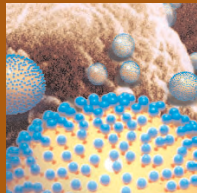


SCIENCE AND THE REGULATION OF BIOLOGICAL PRODUCTS



*From a*

*Rich History*

*to a*

*Challenging*

*Future*

*In memory of Harry M. Meyer, Jr., MD,*

*Former Director, Bureau of Biologics,*

*Food and Drug Administration*

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*Dr. Meyer and Paul D. Parkman, MD,*

*developed the first licensed*

*rubella virus vaccine.*

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Kathryn C. Zoon, PhD  
Director,  
Center for Biologics  
Evaluation and Research

### *Message from the Center Director*

July 1, 2002, marked the Centennial of the 1902 Biologics Control Act, an event of great significance in the history of public health. This year, the Department of Health and Human Services (HHS), Food and Drug Administration (FDA), and Center for Biologics Evaluation and Research (CBER) commemorate passage of the Act and 100 years of biologics regulation. The Act established the authority to regulate biological products and ensure their safety for the American public. Until that time, biologics were not subject to federal oversight and lacked standards for quality, safety, purity, and potency.

As is sometimes the case, the Biologics Control Act was passed as a result of tragedy. In 1901, 13 children died after receiving diphtheria antitoxin contaminated with tetanus. The Act provided, for the first time, a legislative framework for the regulation of biologics and a means to protect Americans from unsafe products.

Since passage of the Act, CBER has established a proud record of regulatory stewardship and research accomplishments. CBER's history illustrates how science and innovative regulation go hand in hand. As part of HHS, CBER works closely with other Department agencies to achieve the goals set forth by HHS to ensure a strong public health safety net for all Americans. I believe that CBER's tradition of integrating innovative science with innovative regulation has enhanced our ability to protect the public health, and has led to safer and more effective biological products.

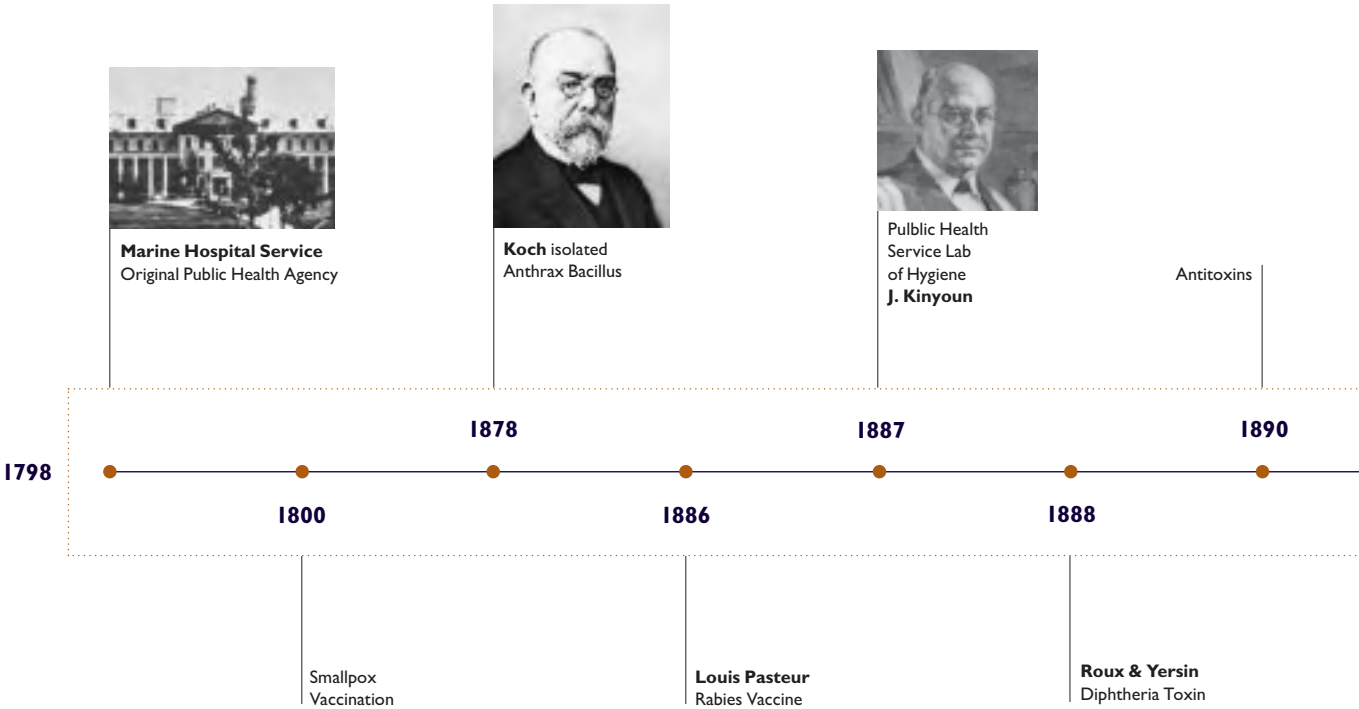
This book describes the rich history of biologics regulation, highlights key research contributions made by CBER scientists over the last 100 years, and offers a glimpse into the exciting and challenging future of biomedical discoveries and regulation. I am humbled, yet very proud to be a part of CBER's legacy and invite you to join me on this historic journey. CBER welcomes the future, its challenges and opportunities, and will build upon its record of success by ensuring another 100 years of safe biological products.

Regulation of FDA Products

Based on Sound Science, Law, and Public Health Impact



H I S T O R Y   O F   B I O L O G I C A L

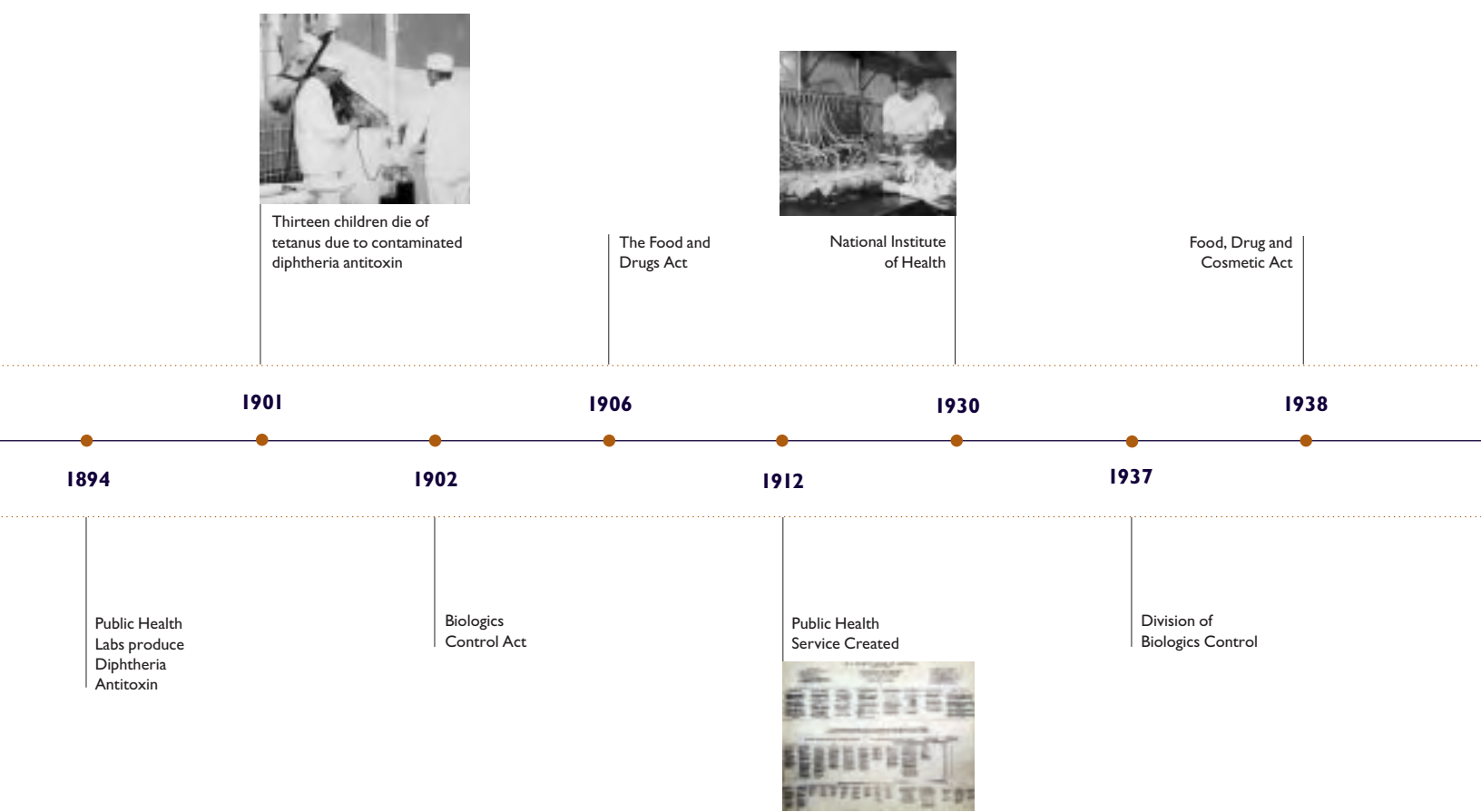


Introduction

The regulation of biologics by CBER is founded on both science and law. Throughout the 20th century, developments in biologics regulation have been made possible by advances in scientific knowledge. As stated by Paul Parkman, MD, a former CBER Director, CBER “is a science-based organization that regulates biological products. It has to have a strong scientific component and a strong regulatory program melded together.” Thus, many CBER staff are both researchers and regulatory reviewers. John Finlayson, PhD, Associate Director for Science, Office of Blood Research and Review, believes that “our excellence in CBER is a direct result of the fact that people are expected to wear many hats at the same time,” and hopes that “the researcher-reviewer model can be preserved into the future.”

This publication chronicles the long scientific history, as well as the 100 years of legislative history, related to biologics. In addition, it emphasizes the importance of the interactive relationship between science and law—a relationship that CBER has used effectively to make life-saving biological products available throughout the 20th century and will continue to use throughout the 21st century.

P R O D U C T S   R E G U L A T I O N



# HISTORY OF BIOLOGICAL

**Cohn Fractionation**  
of Blood

1941

National  
Microbiological  
Institute

1948

**Cutter Polio**  
Vaccine Incident  
Division of Biologics  
Standards created

1955



**BoB** To FDA

1972

1940

Rh Blood  
Group System

1944

The Public Health  
Service Act (Lab of  
Biologics Control)

1950

1st Live Polio  
Vaccine in Humans



1962

**Kefauver-Harris**  
Drug  
Amendments



*Science and Peace will triumph*

*over ignorance and war,*

*nations will unite, not to destroy,*

*but to build, and the future*

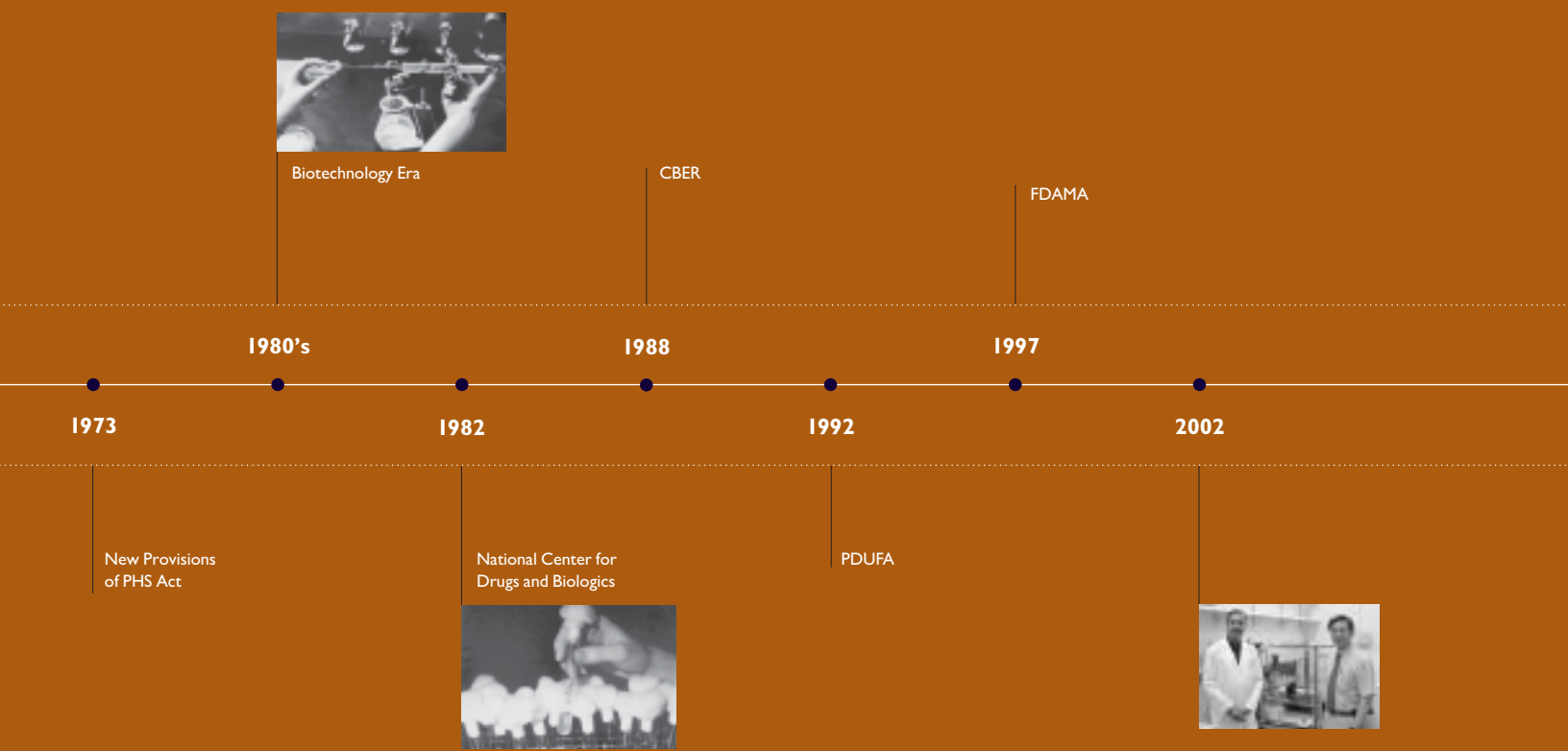
*will belong to those*

*who will have done most*

*for suffering humanity.*

LOUIS PASTEUR

P R O D U C T S   R E G U L A T I O N



# CBER

## THE CENTER FOR BIOLOGICS EVALUATION AND RESEARCH



Division of Biologics  
Standards staff photo

The Center for Biologics Evaluation and Research (CBER) within the Food and Drug Administration (FDA) is responsible for ensuring the safety, purity, potency, and efficacy of biological and related products (biologics) intended for use in the diagnosis, prevention, treatment, or cure of diseases in humans, and for ensuring the safety of the nation’s supply of blood and blood products. Biologics are substances either derived from living organisms—including humans, animals, plants, and microorganisms—or produced by biotechnology. In addition, they can be combinations of these substances. Biologics include vaccines, blood and blood products, antitoxins, allergenic products such as patch tests and extracts, certain tissues, diagnostic devices for HIV and hepatitis, and biotechnology-derived therapeutic products for cancer, arthritis, and other conditions. The number of biologics regulated by CBER is expanding rapidly because of the remarkable growth of research in biotechnology and scientific advances such as completion of the Human Genome Project.

CBER scientists directly support regulatory decisions by carrying out a wide range of activities that begin with premarket product review, continue throughout all aspects of product production, and extend to postmarket review and follow-up.

**To fulfill its regulatory responsibilities, CBER:**

- Conducts premarket review of new products, as well as review of new indications for already approved products, to ensure that they are safe and effective;
- Facilitates establishment of industry-wide standards and methods, and encourages industry-wide adoption of new technologies—activities that contribute to the improvement of existing products and the development of new products;
- Conducts establishment inspections and product surveillance to ensure that licensed products are in full compliance with appropriate laws and regulations;

- Formulates policy through open communication, public dialogue, scientific and regulatory workshops, and participation in scientific, regulatory, and ethics fora;
- Anticipates public needs and supports informed decision-making in prevention of, and response to, public health crises; and
- Demonstrates international leadership in regulation through development of innovative regulatory strategies and standards, coordinated research, and the use of partnerships.

*The Mission of the Center for Biologics Evaluation and Research is to protect and enhance the public health through the regulation of biological products, including blood, vaccines, therapeutics, and related drugs and devices, according to statutory authorities. The regulation of these products is founded on science and law to ensure their purity, potency, safety, efficacy, and availability.*

**CBER Leadership**

Between 1887 and today, biologics regulation has been led by the following directors:

Joseph J. Kinyoun, 1887-1899

Milton J. Rosenau, 1899-1909

John F. Anderson, 1909-1915

George W. McCoy, 1915-1937

Walter T. Harrison, 1937-1940

Milton V. Veldee, 1940-1949

William G. Workman, 1949-1955

Roderick Murray, 1955-1972

Harry M. Meyer, Jr., 1972-1987

Paul D. Parkman, 1987-1991

Gerald V. Quinnan, Jr., 1991-1992 (Acting)

Kathryn C. Zoon, 1992-present

FROM THE LABORATORY OF  
HYGIENE TO CBER

The regulation of biologics and the research necessary to support such regulation was delegated to the U.S. Treasury Department’s Hygienic Laboratory of the Public Health and Marine Hospital Service, under the provisions of the Biologics Control Act of 1902. As the Hygienic Laboratory evolved into the CBER of today, its name also evolved to reflect changing responsibilities. The progression of names is given here. These names are used throughout the publication.



Dr. Ida Bengtson, bacteriologist  
in the Hygienic Laboratory, 1916  
Courtesy of National Library of Medicine

1887 Laboratory of Hygiene of the  
Marine Hospital Service (MHS)

1891 Laboratory of Hygiene renamed  
Hygienic Laboratory, still of the MHS

1902 Hygienic Laboratory of the  
Public Health and Marine Hospital Service  
(PH-MHS)

1930 Hygienic Laboratory renamed  
National Institute of Health (NIH)

1937 Division of Biologics Control  
(DBC) formed within NIH

1944 DBC renamed Laboratory of  
Biologics Control (LBC)

1948 LBC incorporated into National  
Microbiological Institute (NMI), NIH

1955 LBC becomes Division of  
Biologics Standards (DBS), an independent  
entity within NIH; NMI renamed the  
National Institute of Allergy and Infectious  
Diseases

1972 DBS transferred from NIH to  
FDA; becomes Bureau of Biologics (BoB)

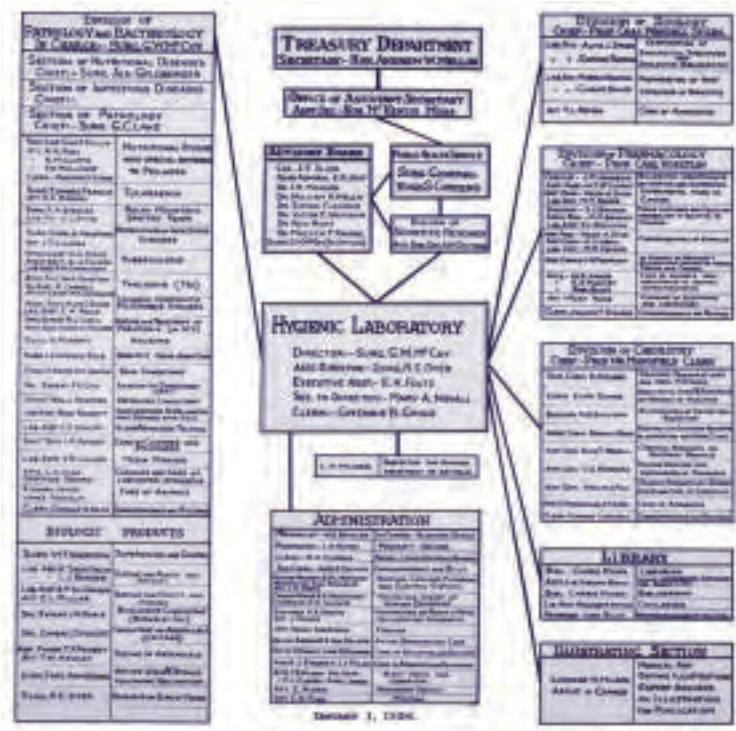
Division of Biologics Standards  
Lab of Viral Immunology



1982 BoB merged with Bureau of  
Drugs to form National Center for Drugs  
and Biologics (NCDB)

1983 Biologics component of NCDB  
renamed Office of Biologics Research and  
Review (OBRR) within Center for Drugs  
and Biologics (CDB)

1988 CDB separated into two Centers;  
Center for Biologics Evaluation and  
Research (CBER) (formerly OBRR) and  
Center for Drug Evaluation and Research  
(CDER)



U. S. Treasury  
Organizational  
Chart, 1926  
Courtesy of National  
Library of Medicine



Dedication ceremony of Building 29.  
Dr. Roderick Murray greets the King and  
Queen of Thailand. DHEW Secretary  
Arthur Flemming looks on.



THE BEGINNING OF BIOLOGICS

Imagine living in the mid-18th century, when infectious disease epidemics were common and survival depended solely on a person’s resistance—the body’s natural ability to fight back against disease-causing bacteria and viruses. Imagine not knowing that tiny, unseen disease agents exist and that, although most are harmless, some are pathogens that cause infectious human diseases such as smallpox, cholera, rabies, diphtheria, plague, typhoid, tuberculosis, and many others. We who live in the 21st century are fortunate that the existence of a pathogen-disease relationship has been recognized, allowing biomedical science to make enormous strides leading to the prevention of many infectious diseases.

Above, right  
**Medieval alchemist**  
Courtesy of National Library of Medicine

Below, right  
**House sign, ca. 1910-1919**  
Courtesy of National Library of Medicine

**Cholera, one of the most feared epidemic diseases of the 19th century**  
Courtesy of National Library of Medicine



**Vaccination from the Calf**  
Courtesy of National Library of Medicine



The Speckled Monster

Smallpox (the “speckled monster”) was a feared infectious disease that was frequently fatal. Smallpox caused about 10 percent of all deaths in 18th-century Europe; in London, about 80 percent of children younger than five who developed smallpox died. Early on, people noticed that those who survived smallpox seemed to be protected against the disease. Based on this observation, they often used the practice of “variolation”—putting pus or ground scabs from a person with mild smallpox into a healthy person, through the nose or skin. The practice of variolation was introduced into England in 1717. In 1721, it was first used in North America to stop a smallpox epidemic in Boston. These variolation efforts were carried out by Zabdiel Boylston, MD, who showed that the risk for death from variolation was about 2%. The risk of death from smallpox was about 15%. Many were reluctant to use the procedure, including Benjamin Franklin, whose 4-year-old son died of smallpox in 1736. However, after seeing the procedure’s effectiveness, Franklin became an advocate for variolation and for educating the public about it through simple written materials.

In 1796, in a historic scientific breakthrough, the English physician Edward Jenner discovered that immunity to smallpox could be achieved by deliberately infecting a person with cowpox, a mild disease that did not have the serious side effects of variolation. This was the first “vaccination.” By 1800, Jenner’s vaccination technique for smallpox had spread to Europe and Benjamin Waterhouse had introduced the technique into the United States, where it became widely used in Boston, New York, Philadelphia, and Baltimore.

To help prevent fake smallpox vaccine from being marketed, James Smith, a Baltimore physician, persuaded Congress to pass The Vaccine Act of 1813—the first federal law for any medical substance. The Act authorized the President to appoint a smallpox “vaccine agent” who would preserve and furnish “genuine vaccine matter” to people who requested it. The Act was repealed in 1822, however, returning smallpox vaccine control to local authorities, after vaccine furnished by Smith (the first and only vaccine agent) was believed to have been the cause of an outbreak of smallpox in North Carolina.

Early Research in Bacteriology

Between 1800 and 1900, many great scientists from various countries conducted innovative, sometimes controversial experiments leading to discoveries that were critical for developing biologics to prevent disease. In the second half of the 19th century, French chemist and microbiologist Louis Pasteur and German

physician Robert Koch laid the foundation for the science of bacteriology and its application. Pasteur showed that microorganisms were required for fermentation and deterioration of foods and beverages. Also, he isolated the bacteria for certain silkworm diseases. In a major advance in 1879, he prepared the first laboratory-produced vaccine by using weakened chicken cholera bacteria to protect fowl against the disease. At about the same time, Koch was investigating the cause of anthrax. He perfected pure-culture techniques to isolate the anthrax bacterium and proved that it caused anthrax disease in laboratory animals. Using



Koch’s discovery to good advantage, Pasteur developed a weakened-bacterium anthrax vaccine in 1881 that protected animals. He then turned his attention to rabies, for which he developed an effective weakened-virus vaccine in 1885.

While Pasteur was doing vaccine research, Koch was concentrating on identifying disease bacteria; he isolated the organisms that caused tuberculosis (1882) and cholera (1883). In 1884, he published a paper on the tuberculosis organism that described the steps necessary to establish its pathogenic nature, steps now known as “Koch’s postulates.” These included: demonstrating the presence (by staining) of the organism in tubercular lesions in various human and animal organs; cultivating the organism in pure culture in blood serum; and producing tuberculosis at will by inoculating guinea pigs with the organism.



**Robert Koch, 1932**  
Courtesy of National Library of Medicine

U.S. scientists also were doing bacteriology research during this period. American bacteriologists Theobald Smith and Edmund Salmon introduced a new vaccine concept by preparing an effective vaccine from hog cholera bacteria killed by heat. Their work on “killed-bacterium vaccines,” published in 1886, led to the development of human “killed” vaccines for typhoid, cholera, and plague by the beginning of the 20th century.

*Right*  
**Edward Jenner**  
Courtesy of Blocker Medical Library, The University of Texas Medical Branch, Galveston, Texas



**Edward Jenner  
prepares to inoculate  
a young woman, 1802**

**The First Smallpox Vaccination Experiment**

*In 1796, Edward Jenner, a rural physician in Gloucestershire, England, made the first scientific attempt to control smallpox by deliberate inoculation—a term we now understand to mean introducing a disease-causing organism into a person to stimulate the production of antibodies protective for the disease. Jenner based his experiment on observations that people who had suffered an attack of cowpox, a harmless disease contracted from cattle, did not later develop smallpox. He used an inoculation procedure that was extremely rudimentary compared with modern-day techniques. He took pus from cowpox lesions on the hand of a dairymaid, Sarah Nelmes, and “inoculated” an 8-year-old boy, Thomas Phipps, by putting the material into two cuts on his arm. The boy became slightly ill over the next nine days and recovered by the tenth day. Six weeks later, Jenner “inoculated” the boy with pus from smallpox lesions. As Jenner had hoped, the boy did not develop smallpox. He concluded that cowpox protected against smallpox. In other experiments, he later showed that cowpox could be deliberately transmitted from person to person as a way of providing protection. Jenner called the cowpox material vaccine, from the Latin vacca (cow), and called the process vaccination. In 1798, he published a book entitled An Inquiry Into the Causes and Effects of the Variolae Vaccinae that described his vaccination results. In his book, Jenner states, “Thus far have I proceeded in an inquiry founded...on the basis of experiment;...I shall myself continue to prosecute this inquiry, encouraged by the hope of its becoming essentially beneficial to mankind.” Despite some opposition and failures caused by not following Jenner’s procedure correctly, vaccination for smallpox quickly became an accepted practice. Dr. Benjamin Waterhouse introduced smallpox vaccination into the United States (Boston) in 1800.*



(German) suggested that antibodies (molecules formed by the body to attack antigens) also have a key role in immunity and later pointed out that active and passive immunity differ. Active immunity is acquired when the body’s own tissues produce antibodies against a disease, resulting from either an attack of or exposure to the disease, or from inoculation of a vaccine consisting of weakened or killed pathogens. Passive immunity is acquired when people are injected with the antibodies themselves, which may be of animal or human origin.

**Investigating Disease Immunity**

During the years when some scientists were identifying bacterial causes of disease and developing disease vaccines, others were trying to explain what happens in the body to produce disease immunity. In 1884, Ilya Metchnikoff (Russian) showed that certain body cells (phagocytes) consumed and destroyed invading bacteria and other foreign proteins (antigens) and proposed his theory of “cellular immunity.” In 1891, Paul Ehrlich



### Louis Pasteur: An Extraordinary 19th Century Scientist

Louis Pasteur, a French chemist and microbiologist, was an extremely skillful scientist who made significant contributions to human health and coincidentally to the 19th-century wine, beer, and silk industries. His experiments helped to lay the groundwork for bacteriology—the science of bacteria and their relationship to medicine, industry, and agriculture. Pasteur proved that microorganisms cause fermentation, a chemical change that produces alcohol and carbon dioxide. He disproved the theory of “spontaneous generation,” the concept that bacterial life arose spontaneously. Also, he developed the process that came to be known as pasteurization, which is the destruction of harmful bacteria by heat, and developed vaccines for chicken cholera, anthrax, and rabies. In 1879, Pasteur left a chicken cholera culture exposed to air over a long summer holiday. He found that the culture, when weakened by exposure to air, protected fowl inoculated with it against chicken cholera. This was the first vaccine developed in a laboratory. At the same time, Pasteur was developing a vaccine for the anthrax bacterium. In a well-controlled experiment in 1881, Pasteur inoculated 24 sheep, one goat, and six cows with weakened anthrax bacteria. All of the animals remained healthy. He then challenged these animals, and others that had not been inoculated, with the virulent anthrax. In this experiment, he showed that all inoculated animals remained alive, whereas the uninoculated animals died. Pasteur’s work with the chicken cholera and anthrax vaccines demonstrated that it was possible to use systematic procedures to make reproducible vaccines. His research on a rabies vaccine began in 1886. Using brain tissue from infected dogs, Pasteur developed a weakened rabies virus that he used in 1886 to inoculate a nine-year-old boy, Joseph Meister, who had been bitten by a rabid dog. Introducing an actual disease virus, even a weakened virus, into a human was highly controversial at the time. However, the experiment with Joseph Meister was a clear success that was confirmed by many subsequent successes and that helped save many others from rabies.



**Louis Pasteur**  
Courtesy of Blocker Medical  
Library, The University of Texas  
Medical Branch, Galveston, Texas



**Production of diphtheria antitoxin**  
Courtesy of National Archives and Records  
Administration

Serum therapy, a practical application of passive immunity, proved to be a valuable approach for fighting diphtheria, a major cause of illness and death before the 20th century. At the Pasteur Institute in 1888, Emile Roux and Alexandre Yersin isolated a powerful toxin from the diphtheria bacterium and showed that it harmed tissues and organs. This paved the way for the work of Emil von Behring and Shibasaburo Kitasato at Koch’s laboratory in Berlin. In 1890, they found that injecting a small dose of diphtheria toxin (an antigen) into animals produced a serum containing antitoxins (antibodies) that provided immunity to people inoculated with the serum. In 1894, Roux reported that large quantities of diphtheria antitoxins could be produced in horses. Large-scale production and use of the antitoxin serum began in Europe at this time. The first biological standard in the world, a diphtheria antitoxin serum reference standard, was prepared by Paul Ehrlich in 1897.



**Production of diphtheria antitoxin by inoculating horses required great care to maintain purity and avoid contamination**  
Courtesy of National Archives and  
Records Administration

### The First Heat-Killed Vaccine

Vaccines made from killed or inactivated microorganisms are safer than attenuated vaccines, which are made from weakened, but live, microorganisms. There is a small chance that an attenuated vaccine might cause the disease it is designed to prevent. Therefore, development of the first heat-killed vaccine—a vaccine prepared from microorganisms killed by elevated temperature—was a major step in vaccine development. This took place in the United States in the mid-1880s, through the efforts of Theobald Smith and Edmund Salmon. They developed a heat-killed vaccine from the bacterium that causes hog cholera. The vaccine, tested by injecting it into pigeons, was found to be effective in protecting the birds against the disease. Smith and Salmon, who were working for the U.S. Department of Agriculture at the time of their discovery, published their work on the heat-killed hog cholera vaccine in 1886. As sometimes happens in research, scientists from Pasteur’s laboratory in Paris independently published an article on heat-killed vaccines in late 1887, about 16 months after the report of Smith and Salmon. The original work on heat-killed vaccines proved to be highly valuable and led to the development of killed vaccines for several human infectious diseases—typhoid, cholera, and plague—in the late 1890s.



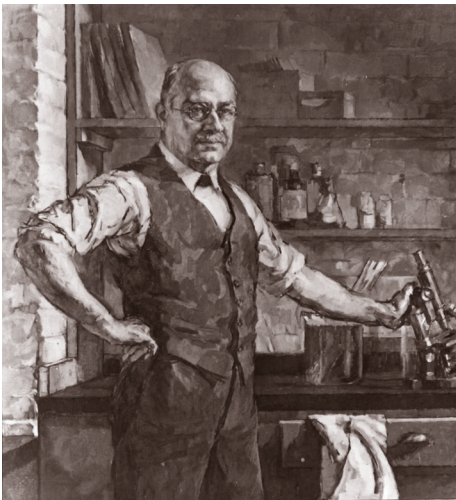
**U. S. Marine Hospital  
No. 21, NY**  
Courtesy of National  
Library of Medicine

**The Public Health Service  
Hygienic Laboratory**

*The Marine Hospital Service (MHS), the original public health agency, was established in 1798 to provide hospital care for merchant seamen. It also protected port cities against diseases such as smallpox, cholera, and yellow fever. Joseph Kinyoun was a young MHS medical officer who toured the research centers of Europe to learn the latest techniques for controlling infectious diseases. Determined to apply his new-found knowledge to improving public health in the United States, he established one of the country's first bacteriological laboratories in 1887 in the MHS Marine Hospital on Staten Island, New York. This one-room "Laboratory of Hygiene," with Kinyoun as director, was the beginning of medical laboratory research in the U.S. Public Health Service. In 1891, the Laboratory of Hygiene was moved to Washington, D.C. and renamed the "Hygienic Laboratory." Soon after, Kinyoun again visited Europe and, at the Pasteur Institute in Paris, learned the procedure for preparing diphtheria antitoxin. On returning to the United States, he prepared an antitoxin serum to be used by the MHS and demonstrated its production to representatives of local and state health boards. In a report to the U.S. Surgeon General in 1895, Kinyoun noted that all serum intended for sale should be made and tested by competent and disinterested persons, making an early plea for the establishment of a regulatory service. Beginning in 1899, under new director Milton Rosenau, the Hygienic Laboratory expanded into a research organization with divisions of chemistry, bacteriology and pathology, zoology, and pharmacology. Recognizing its importance, Congress authorized \$35,000 in 1901 for construction of a new building, in which the Laboratory could investigate "infectious and contagious diseases and matters pertaining to the public health." The Hygienic Laboratory ultimately evolved into the National Institute of Health.*

Officials and scientists in the United States had paid close attention to the compelling evidence presented in Europe that specific microorganisms caused specific infectious diseases and to the vaccination techniques developed to control these diseases. Joseph Kinyoun, a medical officer in the Marine Health Service, played a key role in bringing this new technology to America.

As the end of the 19th century neared, scientists had identified almost two dozen disease pathogens and introduced many fundamental concepts of bacteriology, vaccinology, and immunology to biomedical research. The state of the science at this time provided a strong research base for further development of biologics.

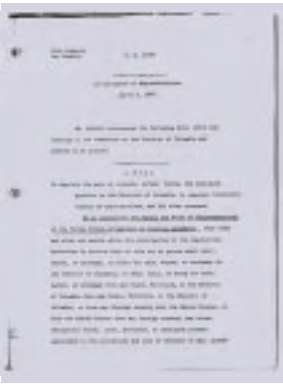


**Joseph J. Kinyoun, MD, founder  
of the Hygienic Laboratory**  
Courtesy of National Institutes of Health



**Refluz Apparatus.**  
Used in 1970's to early 1980's by a team of biochemists under Dr. Darrell Liu to determine the amino acid sequence of proteins, and the structure of bacterial polysaccharides used in vaccines.

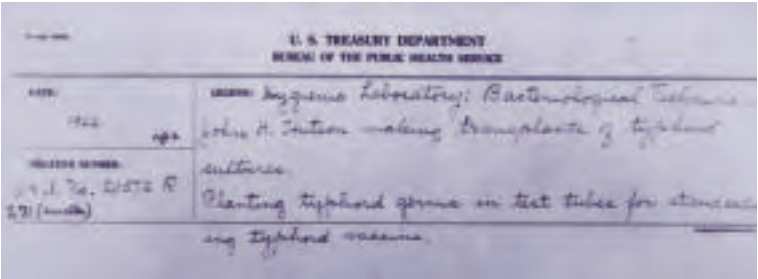
**Virus-Toxin Law (Biologics Control Act), 1902**



THE EARLY YEARS OF BIOLOGICS REGULATION AND DEVELOPMENT

The discoveries in bacteriology, vaccinology, and immunology that were taking place at the brink of the 20th century were tremendously exciting. Equally exciting to many was the

diers had typhoid fever. During World War I, only 1 in 1000 developed this disease. And, in World War I in 1914, tetanus occurred in 8 per 1,000 wounded British soldiers. After development of routine tetanus antitoxin use and careful wound management, however, this rate fell to 1.5 per 1,000. U.S. forces entering the war in 1917 benefited from the British experience, and had a tetanus incidence of only 0.16 per 1,000 wounded.



**Old Public Health Service record of typhoid culture**

prospect of being able to apply these discoveries to prevent and treat dangerous diseases. Live vaccines were being used worldwide for smallpox and rabies, heat-killed vaccines for cholera, typhoid, and plague, and antitoxins for diphtheria and tetanus. The results were dramatic. In large U.S. cities, for example, the number of deaths from diphtheria decreased by 50 to 70 percent between the early 1890s and the early 1900s, and by more than 99 percent by the early 1940s. In the Spanish-American War of 1898, 1 in 5 American sol-

By 1895, laws regulating biologics had been enacted by the governments of France, Germany, Italy, and Russia. In part, these laws dealt with licensing and inspection of products by government-approved laboratories, proper labeling, and the accreditation of manufacturing facilities. In the United States, even though many were concerned about the safety of biologics—because they were injected and could have a rapid adverse effect if contaminated—the rush to use these products proceeded without regulatory safeguards. Legislators acted after a tragedy occurred in October 1901, when 13 children in St. Louis died after being given diphtheria antitoxin that was contaminated with tetanus.

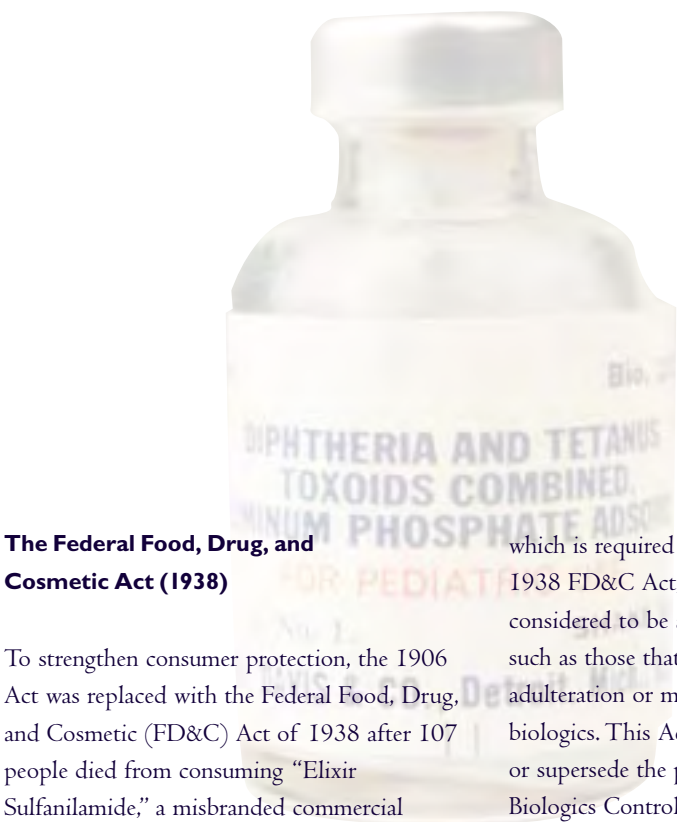


**The Biologics Control Act (1902)**

As a result of the St. Louis tetanus outbreak and similar (but smaller) occurrences of contaminated smallpox vaccine and diphtheria antitoxin, Congress passed the Biologics Control Act on July 1, 1902, only a few months after it was proposed—with virtually no debate or opposition. This Act authorized the Hygienic Laboratory of the Public Health and Marine Hospital Service to issue regulations that governed all aspects of commercial production of vaccines, serums, toxins, antitoxins, and similar products, with the objective of ensuring their safety, purity, and potency. The Laboratory issued its first series of regulations in 1903 and additional regulations in 1909 and thereafter, to strengthen control over biologics production. Further, in 1934, the Hygienic Laboratory—renamed the National Institute of Health in 1930 by the Ransdell Act—issued a regulation stating that licenses to manufacture new biologics would not be granted without evidence that the products were effective. Overall, however, the basic provisions of the 1902 Act served the nation well throughout the 20th century.

**The Federal Food and Drugs Act (1906)**

In 1906, the Federal Food and Drugs Act outlawed adulterated and misbranded foods and drugs, but made no specific reference to biologic drugs. In contrast to the quick passage of the 1902 Act, there had been 25 years of heated debate before Upton Sinclair’s 1906 novel, *The Jungle*, which described the unsanitary conditions in Chicago’s meatpacking industry, caused a public furor that helped pass the law. The 1906 Act had some shortcomings. For example, the Supreme Court, in a case involving “Dr. Johnson’s Mild Combination Treatment for Cancer,” ruled in 1911 that the Act did not prohibit false therapeutic claims, but only false and misleading statements about the ingredients or identity of a drug. As a result, Congress passed the Sherley Amendment in 1912, which prohibited labeling medicines with false therapeutic claims intended to defraud the purchaser, a legal standard difficult to prove.



**The Federal Food, Drug, and Cosmetic Act (1938)**

To strengthen consumer protection, the 1906 Act was replaced with the Federal Food, Drug, and Cosmetic (FD&C) Act of 1938 after 107 people died from consuming “Elixir Sulfanilamide,” a misbranded commercial product that had been made using toxic diethylene glycol as a solvent instead of alcohol,

which is required in an “elixir.” Under the 1938 FD&C Act, a biological product was considered to be a drug, and parts of the Act, such as those that concerned drug or device adulteration or misbranding, were applied to biologics. This Act, however, did not modify or supersede the provisions of the 1902 Biologics Control Act. After 1938, the appropriate provisions of both Acts were used to regulate biologics.

**The St. Louis Tetanus Epidemic**

*Diphtheria antitoxin was a formidable new weapon in the fight against diphtheria, a dangerous infectious disease. But without proper standards to ensure its potency and purity, the antitoxin could be harmful instead of beneficial. Medical workers and the public expressed concern about the poor supervision of antitoxin production, and the lack of inspection and testing of the final product. Even though many believed that federal oversight was necessary, no action was taken until a tragedy occurred. In 1901, when a serious diphtheria epidemic swept St. Louis, Missouri, victims of the disease were given antitoxin serum prepared from horses. In late October, five-year-old Veronica Neill was admitted to the city hospital and received two shots of diphtheria antitoxin. Several days later, on October 26, she died from tetanus, a different infectious disease. Her doctor notified the St. Louis Health Commissioner that her death likely was caused by tetanus-contaminated antitoxin prepared by the city’s Health Department. Distribution of the antitoxin was stopped immediately. An investigation uncovered that a horse named Jim, which had provided diphtheria antitoxin for three years, had contracted tetanus and had been killed. The contaminated serum from this horse should have been destroyed, but was not. Instead, it was accidentally bottled and issued to doctors to use in treating diphtheria patients. Thirteen children died from tetanus as a result of receiving this serum. Although the St. Louis disaster was the worst, it was not the only such incident. Also in the fall of 1901, nine children in Camden, New Jersey, died from tetanus as a result of receiving contaminated smallpox vaccine. These events spurred Congress into action. The Biologics Control Act was passed quickly and without notable opposition, and signed into law by President Theodore Roosevelt on July 1, 1902.*



Courtesy of National Library of Medicine



**First biologics license, Parke, Davis and Company, 1903**  
Courtesy of Pfizer, Inc.



**Second biologics license, H. K. Mulford, Co.**  
Courtesy of Merck & Co., Inc.

**Implementing the Biologics Control Act**

Between 1903 and 1907, the Hygienic Laboratory established standards and issued licenses to pharmaceutical firms for making smallpox and rabies vaccines, diphtheria and tetanus antitoxins, and various antibacterial antiserums. After 1907, many firms also started producing antibacterial vaccines. Beginning in 1917, the Laboratory issued licenses for making toxin products that provided immunity, for example: diphtheria toxin mixed with antitoxin [1917]; scarlet fever toxin [1925]; diphtheria toxoid [1926]; tetanus toxoid [1933]; additional antitoxins such as botulinum [1921], scarlet fever streptococcus [1925], gonococcus [1927], and perfringens and other gas gangrene-causing bacteria [1931-1939]; and human bacterial and viral antisera for pertussis, poliomyelitis, and mumps [1939-1941].

Throughout these early years, as is still true today, the 1902 Act stimulated scientific research by the Hygienic Laboratory to improve existing biologics and find better ways of producing them, to develop standards for new products, and to find immunizing agents for all infectious diseases. Laboratory staff made numerous significant contributions that advanced the state of the science. For instance, staff established the standards for botulinum antitoxins and for gas gangrene antitoxins, developed a practical method for preparing serums to diagnose various types of pneumonia, and developed an improved meningitis serum potency test as well as a serum specific for different types of meningitis bacteria.

**The Biologics Control Act of 1902**

In 1901, there were no mandatory federal manufacturing or product standards for biologics. The deaths of 13 children in St. Louis in 1901 as a result of receiving tetanus-contaminated diphtheria antitoxin, and other similar incidents, prompted quick action by lawmakers. The Biologics Control Act (also called the Virus-Toxin Law) was passed on July 1, 1902, with little comment or publicity. The Act mandated annual licensing of establishments to manufacture and sell vaccines, sera, antitoxins, and similar products in interstate commerce. Biologics had to be labeled with the name of the product, the name, address, and license number of the manufacturer, and an expiration date for potency. Production of biologics had to be supervised by a qualified scientist. The Hygienic Laboratory of the Public Health and Marine Hospital Service was authorized to conduct regular inspections of licensed manufacturing establishments and to sample products on the open market for purity and potency. The Act included provisions for revocation or suspension of licenses and for penalties in cases of violations. Most important, the Act empowered the government to issue rules necessary to enforce the Act. The first regulations under the Act, which dealt with the issuance of licenses and inspection, became effective on August 21, 1903. By 1904, 13 establishments had been inspected and licensed, mostly for the sale of smallpox vaccine and diphtheria antitoxin. The Hygienic Laboratory tested the products of licensed establishments for purity and potency once a month. The Act stimulated the growth of the Hygienic Laboratory. Between 1904 and 1921, the number of staff increased from 13 to 127 and the number of products monitored climbed to 102. Overall, the Act improved the quality of biologic products in the marketplace, helped to restore confidence in these products, stimulated research on biologics, and promoted mutual respect and cooperation between the federal government and the pharmaceutical industry.

**Blood-letting**  
Courtesy of National Library of Medicine





Margaret Pittman and visitors to her lab

Early Blood Research

In addition to vaccines and antitoxins, the Hygienic Laboratory’s regulatory responsibilities extended to blood and any products made from blood. During the first few decades of the 20th century, scientists learned much about how to use blood properly for medical purposes. Early attempts at transfusion led to serious adverse reactions. However, in 1901, Austrian scientist Karl Landsteiner discovered that individuals belonged to one of four different blood groups (O, A, B, and AB), and that transfusions between people in different blood groups could be unsafe. In addition, scientists developed suitable techniques for collecting blood, separating the plasma, and properly storing these products. In 1934, the Laboratory—by then named the National Institute of Health—issued the first licenses to manufacturers for production of a human blood product. The product was a preparation of protein (called immunoglobulin G or IgG in current terminology) from human placental extracts, and was used for prevention of measles.

The considerable progress made in effectively regulating and developing biologics during the first four decades of the 20th century was put to the test with the entry of the United States into World War II in 1941.



Karl Landsteiner  
Courtesy of National Library of Medicine



Pioneering Work on Haemophilus influenzae

*Haemophilus influenzae* bacteria cause infections in humans ranging from asymptomatic respiratory infections to serious diseases such as meningitis. Children are particularly susceptible to this pathogen. In the early 1930s, Margaret Pittman, who retired from the Division of Biologics Standards in 1971 after 35 years of making significant scientific contributions, was doing postgraduate work at the Rockefeller Institute (RI) for Medical Research. While at the RI, she conducted pioneering research on the microbiology and immunology of infections caused by *H. influenzae*. She found that these bacteria existed in two forms—encapsulated (with a special coating) and unencapsulated. The unencapsulated bacteria, which generally caused either no illness at all or relatively mild respiratory infections and mucosal infections (such as sinusitis), frequently were found in the upper respiratory tract of adults. Pittman discovered six different varieties of the encapsulated *H. influenzae* organism and observed that only the type b encapsulated variety seemed to cause serious diseases in children, for example, meningitis, pneumonia, and septic arthritis. She identified the material forming the coating of the type b encapsulated variety as a certain polysaccharide, information that would be useful in developing future vaccines. Pittman’s work formed the basis for development of an antiserum for invasive *H. influenzae* type b disease by Hattie Alexander and colleagues at the Columbia University College of Physicians and Surgeons, in the late 1930s. The antiserum was the first effective therapy for this potentially fatal infection. The 1985 licensing of a polysaccharide vaccine for *H. influenzae* type b, for use in preschool-aged children, was a long-term outcome of Pittman’s early research on this pathogen. Research by John Robbins, MD, and colleagues, conducted at the Bureau of Biologics in the 1970s – 1980s, led to development and licensing in 1987 of a polysaccharide-protein conjugate vaccine for *H. influenzae* type b that provided protection for infants, the group most at risk for disease. In 1996, Robbins and Rachel Schneerson, MD, received the Albert Lasker Award for Clinical Medical Research for their work on the conjugate vaccine.



Above  
John Robbins and Rachel Schneerson, winners of the Lasker Award, 1996  
Courtesy of National Institutes of Health



Bernice Eddy, PhD

Early Research on Influenza Vaccine

*The influenza (flu) epidemic of 1918-19 caused an estimated 20 million deaths worldwide. There was little progress, however, in flu research until a flu virus called Type A was finally isolated in England in 1933 and in the United States in 1934. This advance came from the use of embryonated chicken eggs for recovering the virus—a new breakthrough that allowed the preparation of vaccines. The most common varieties of flu are caused by the Type A flu virus. Researchers discovered a second kind of flu virus (Type B) in the 1940 flu epidemic. Flu vaccines made in the late 1930s and early 1940s were not always effective, because no accurate test was available to measure their potency. Even though flu vaccine was not yet licensed for marketing, commercial laboratories produced large amounts of flu vaccine for the U.S. Army during World War II. Because this vaccine was of variable quality, Bernice Eddy, a scientist at the Division of Biologics Control, concentrated on developing the first reliable potency test for flu vaccine, so that manufacturers could make a uniform product with the desired effectiveness. The vaccine produced during World War II was effective against both Type A and Type B influenza viruses. The flu vaccine was licensed in 1945 and, after World War II, it was also used for civilians. Producing effective flu vaccine is complicated because the Type A virus has a number of subtypes and, as new subtypes appear and circulate in the human population, vaccine formulations must be changed to protect people against the new subtypes. Today's flu vaccines are 70 to 90 percent effective in reducing a person's chances of getting the flu.*



WORLD WAR II AND THE  
POSTWAR PERIOD

Many of the scientific advances in the early 1940s were driven by the need to provide U.S. military personnel in World War II with the best medical care possible, including ready access to safe blood products and the best possible protection against disease.

Developing Essential Blood Products

In 1940, shortly after the start of the German offensive in Europe and at the request of American Red Cross, American biochemist Edwin Cohn and his Harvard colleagues began to develop methods for blood fractionation, the separation of blood plasma proteins. By the summer of 1941, using alcohol-water mixtures, they were able to prepare albumin, globulins, fibrinogen, and fibrin—all useful blood proteins. The albumin was particularly important, because it could be given to the wounded to restore blood volume, reducing the risk of shock resulting from blood loss. On December 7, 1941, a small supply of albumin was on hand, which was immediately flown to Pearl Harbor where it proved to be extremely beneficial to people suffering from shock and low blood protein as a result of severe burns.





During World War II, the Division of Biologics Control established standards for manufacturing plasma and albumin, and supervised their production in commercial establishments. The Division issued licenses for several blood fractionation products, including albumin, globulins useful for blood grouping, immune globulins (called gamma globulin at the time), fibrin foam and thrombin (clotting agents used to control bleeding during surgery), and fibrin film (used in surgery as a substitute for the outermost membrane covering the brain).

In 1940, almost four decades after the discovery of the A, B, O, and AB blood groups, Karl Landsteiner and Alexander Wiener found another important characteristic of blood—a protein called the Rh (rhesus) factor—in the blood of rhesus monkeys. The Rh factor is also present in humans in 85 percent of Caucasians, and in an even larger percentage of African Americans and Asians. If blood from a person with the Rh factor (Rh positive) is transfused into a person without the Rh factor (Rh negative), antibodies can form in the Rh-negative person that cause the Rh-positive blood cells to clump together and eventually

be destroyed. If the Rh-negative person is given additional transfusions of Rh-positive blood, the concentration of antibodies may become high enough to cause a serious or fatal reaction. Thus, in addition to knowing a person's A, B, O, or AB blood group, it is important to know whether the Rh factor is present. The Laboratory of Biologics Control issued the first licenses for Rh typing serums in 1947.



**Elimination of Jaundice Virus From Blood Plasma**

*During World War II, the demand for human blood plasma (the liquid portion of the blood in which the solid components are suspended) for America’s military personnel was huge. The Division of Biologics Control (DBC) had responsibility for setting up safety standards and supervising the production of blood products by commercial laboratories. Blood plasma, blood serum (plasma in which fibrinogen, a clotting agent, has been “used up” by clotting the blood), and serum albumin (a protein) were among these products. Although blood products without doubt saved many lives, they were found to have potential hazards. In 1942, 28,000 military personnel, injected with a yellow fever vaccine prepared with human blood serum as a stabilizing agent, developed a disease then named jaundice. Obvious symptoms were yellowing of the skin and eyes. One hundred people died. There was a strong possibility that some unknown factor in human blood was causing the disease. Thus, in the middle of wartime production of blood plasma on a massive scale, the DBC was faced with the urgent need to find a way to guarantee its safety. By conducting careful research, three DBC scientists, John Oliphant, Alexander Gilliam, and Carl Larson, showed that people who were inoculated with blood serum from jaundice-infected patients also developed jaundice, but that the disease was not spread by personal contact. The cause of the jaundice appeared to be an unidentified virus. The yellow fever vaccine likely had been contaminated by the blood serum of donors who either had unrecognized disease or were simply carriers of the virus. Because blood plasma from individual donors was generally “pooled,” one donor infected with the virus could contaminate an entire batch of either plasma or serum derived from the plasma. The DBC scientists found that the jaundice-causing virus was heat resistant. Also, it was too small to be removed from blood products by using filters. Next, Oliphant, working with biophysicist Alexander Hollaender, conducted research in which ultraviolet radiation appeared to kill the virus in blood serum and plasma. In April 1949, regulations were issued by the Laboratory of Biologics Control (LBC) requiring that human blood plasma and serum be irradiated. Studies conducted by Oliphant and Roderick Murray in the LBC in the early 1950s, however, showed that some jaundice (renamed hepatitis) cases were still being transmitted through transfusions. In later years, researchers identified both hepatitis B virus and hepatitis C virus as possible contaminants in blood products. Today, all blood donors are tested for hepatitis B and C to prevent contaminated blood from being used for transfusions or for the manufacture of blood products.*



**American troops wait for medical treatment, Normandy, 1944**  
Courtesy of National Archives and Records Administration



**Wounded soldier after receiving blood plasma, 1944**  
Courtesy of National Archives and Records Administration



**World War II soldier receiving blood plasma infusion, 1945**  
Courtesy, National Archives and Records Administration

### Improving Existing Biologics

During the war years, all U.S. military personnel received shots for tetanus, typhoid fever, and smallpox. Also, tremendous quantities of vaccines for typhus, yellow fever, cholera, diphtheria, and plague as well as antitoxins and serums for various other diseases had to be manufactured to immunize those who served in areas where these diseases occur. The Division of Biologics Control had to be certain that the requirements for each product helped ensure that it would be safe, pure, and effective against the disease. In some cases, this meant improving existing products by refining standards, developing better potency tests, or finding new ways to purify a product. For instance, in 1941, the Division licensed a new vaccine for typhus—a disease caused by a kind of bacteria called rickettsia. The vaccine was given to U.S. military personnel in southern

Europe and North Africa. Typhus had caused devastating epidemics in World War I, but only 64 cases occurred among U.S. military personnel in World War II.

The typhus vaccine was the first rickettsial vaccine; it was produced by growing the bacteria in fertilized hen’s eggs (chick embryo), a new technique at the time. This technique was also used to make vaccines for viral diseases such as mumps. In the general effort to improve biologics, the Division of Biologics Control also conducted important research on pertussis (whooping cough) vaccine, rabies vaccine, methods for sterility testing (to assure that biologics were not contaminated by bacteria), and causes of pyrogenicity (fever reactions), particularly as related to blood products.

### The Public Health Service Act (1944)

In 1944, laws relating to the Public Health Service (PHS) were revised and consolidated into the PHS Act, which helped to define the shape of medical research after World War II. The 1902 Biologics Control Act was incorporated into Section 351 of the 1944 Act with



Courtesy of National Library of Medicine



Child coughing from Pertussis infection  
Courtesy of World Health Organization

### Testing the Potency of Pertussis Vaccine

*Pertussis, also known as “whooping cough,” is a potentially deadly respiratory infection that most commonly affects children. The illness can last for weeks and is characterized by a severe cough; some infected children are left with permanent neurological damage, and some die. Although scientists had been trying to develop a pertussis vaccine since the early 1900s, the difficulty in assessing its potency was a major stumbling block. Scientists had not been able to develop a potency test for pertussis vaccine, because they were unable to establish pertussis infection in a laboratory animal. In 1944, Margaret Pittman, at the Laboratory of Biologics Control, found that she could infect mice with pertussis by injecting pertussis bacteria into the mouse brain. She then used this knowledge to test the potency of a pertussis vaccine. Pittman first gave vaccine to mice in small, medium, and large doses. Several days later, she injected them with a greater than lethal quantity of pertussis bacteria. This procedure provided the data she needed to set up a vaccine potency standard based on a “50 percent dose”—that is, the dose of vaccine that would result in the survival of 50 percent of mice infected with a certain number of pertussis bacteria. On January 1, 1949, manufacturers began using this “mouse protection test” for determining pertussis vaccine potency. Further, to make vaccine preparation easier, Pittman prepared an opacity standard for pertussis vaccine that could be used to estimate the number of bacteria in a vaccine, instead of laboriously counting the bacteria under a microscope. To do this, she adjusted the cloudiness of a suspension of glass particles until it exactly matched, as measured with an optical instrument, the cloudiness of a standard vaccine in which bacteria had been directly counted. The glass particle preparation was designated as the U.S. Opacity Standard and later was used as the International Opacity Reference Preparation. Margaret Pittman was “a woman scientist ahead of her time” and was considered a “world-renowned expert on the subject of pertussis,” according to John Robbins, formerly with the Bureau of Biologics.*



Pyrogenicity Testing for Blood Products

*In the early 1940s, intravenous therapy using blood and blood products increased significantly because of the many wounded soldiers who needed treatment during World War II. Occasionally, pyrogenic (fever) reactions occurred after this therapy. At that time, scientists already knew that distilled water could contain pyrogens—fever-producing substances—of bacterial origin and that intravenous solutions prepared using contaminated distilled water could produce fever. In fact, by November 1942, a U.S. Public Health Service regulation required that all distilled water must be pyrogen-free. To investigate pyrogenicity in blood products, Margaret Pittman and Thomas Probey, at the Division of Biologics Control, studied the pyrogenicity of 28 types of bacteria isolated from blood plasma by using a rabbit pyrogen test. They injected the material to be tested into the ear of the rabbit. If the animal’s temperature rose over the next few hours, the material was judged to be pyrogenic. Pittman and Probey found that all of the bacteria were capable of producing fever, but because the effects of various types of bacteria differed widely, simply measuring the number of bacteria in plasma could not predict the pyrogenicity of the plasma. Gram negative bacteria were the most pyrogenic of those tested. Their study also showed that bacterial growth in plasma enhanced pyrogenicity. Based on these findings, Pittman and Probey collaborated with manufacturers to help define production techniques that resulted in pyrogen-free blood products.*



Laboratory of Biologics Control came from Section 351 of the 1944 Act and from certain sections of the 1938 FD&C Act. Further, the 1944 Act provided new authority for the PHS to manufacture biologics, should such a need arise. In 1948, the Laboratory of Biologics Control became part of the National Microbiological Institute within the National Institutes of Health.

A Significant Advance

One postwar research advance that significantly influenced the future of biologics was made in 1949 at Boston Children’s Hospital, where scientists successfully grew a human virus—the Lansing Type II poliovirus—in human tissue cell culture. The ability to grow human viruses easily and safely outside of a living host was a breakthrough that led to an explosion of research in vaccinology, beginning in the 1950s. This advance might be considered a forerunner of the almost unimaginable discoveries and changes relevant to biologics that would occur in the second half of the 20th century.

Discovery and Change:  
1950 Through 1980

The 1950s, 1960s, and 1970s were dynamic years for biologics regulation, characterized by exciting scientific advances as well as legislative and organizational changes. Vaccine research flourished because of the new techniques for growing viruses in tissue culture. The polio vaccine developed by Jonas Salk in 1954 was the first licensed vaccine made using a virus grown in this way. Preparation of vaccines for other viral diseases soon followed, including measles, mumps, rubella (German measles), and rabies. In addition, many important changes took place in testing and regulating blood and blood products. In 1972, the authority for biologics control moved from NIH to FDA. During these 30 years, the number and variety of biologics—and the challenges of regulating them—continued to grow.

few changes. One important change was that the Laboratory of Biologics Control was now authorized to license biological products as well as the establishments in which they were produced. After 1944, the authority of the



Jonas E. Salk and  
Edward R. Murrow  
Courtesy of National  
Library of Medicine



**President Franklin D. Roosevelt and three polio patients in Warm Springs, Georgia, 1925**  
Courtesy of National Archives and Records Administration

### The Cutter Incident

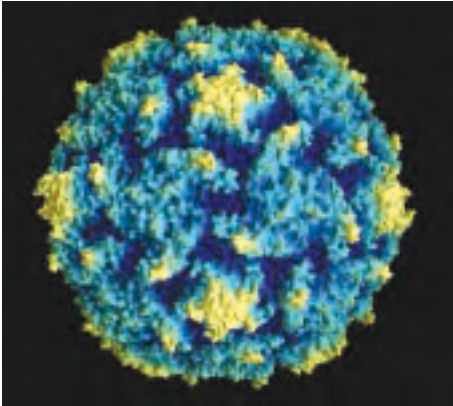
*U.S. President Franklin D. Roosevelt, who suffered the paralytic effects of poliomyelitis (also called polio or infantile paralysis), initiated a “War on Polio” during his administration. He created the National Foundation for Infantile Paralysis (NFIP), a fund-raising organization, to ensure that money was available for scientists to conduct research on the cause and prevention of polio. Concerted efforts were directed toward finding a vaccine for this incurable, infectious disease. Poliovirus was successfully grown in tissue cell culture in 1949, and live poliovirus vaccine produced from virus grown by this method was successfully tested in humans in 1950. Jonas Salk, funded by NFIP, began his polio vaccine research in 1951. By 1954, a large field trial of vaccine developed by Salk, using inactivated (killed) poliovirus, was conducted in American children. Trial data showed the vaccine to be both safe and effective. On April 12, 1955, the Public Health Service issued licenses for commercial manufacture of polio vaccine to six companies that had already been producing vaccine for the field trials. Written protocols for vaccine production and safety testing, submitted to the Laboratory of Biologics Control by the companies, were the only legal requirement for licensing. Over the next two weeks, approximately 40 batches of manufactured vaccine were released by the government for distribution. Unexpectedly, on April 25, polio was reported in a vaccine recipient. One day later, five more cases were reported. All cases had received vaccine produced by Cutter Laboratories. On April 27, the Laboratory of Biologics Control requested that Cutter Laboratories recall all vaccine and the company did so immediately. On May 7, the Surgeon General recommended that all polio vaccinations be suspended pending inspection of each manufacturing facility and thorough review of the procedures for testing vaccine safety. The investigation found that live polio virus had survived in two batches of Cutter vaccine. In fact, Cutter Laboratories had discarded a number of other vaccine batches because live virus was present, but there was no requirement for them to report such difficulties. Overall, 260 cases of polio were attributed to Cutter vaccine; these included 94 vaccinees and 166 close contacts of vaccinees, with 192 cases being paralytic. Reappraisal of virus inactivation and safety testing procedures led to improved production techniques, and development of more sensitive and better-controlled testing methods to ensure consistently safe vaccine. Large-scale polio vaccinations resumed in the fall of 1955.*

*The Cutter Incident was a defining moment in the history of the manufacture and government oversight of vaccines. It occurred because the rigorous safety precautions that were used in the field trials—which included repeating all vaccine safety tests in three different laboratories and confirming all manufacturers’ ability to prepare consistently safe vaccine—were not required for the production of commercially-produced licensed vaccine. In addition, the protocols provided by the manufacturers did not provide enough information for safety evaluation. Clearly, the government needed to strengthen its role in biologics regulation. The Cutter Incident led directly to an expansion of the Public Health Service’s biologics control function. By order of the Surgeon General in 1955, regulation of biologics, which had resided in the Laboratory of Biologics Control, was transferred to the newly created Division of Biologics Standards, an independent entity within the National Institutes of Health. Also, regulations were strengthened, requiring more precise experimental testing to assess the safety of vaccines.*

### The Story of Polio Vaccine

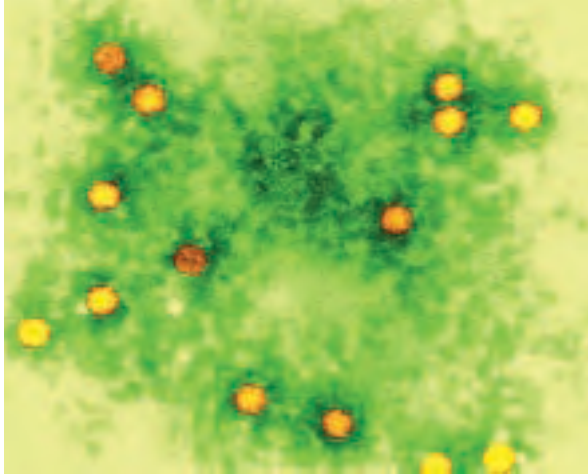
A great deal of research was devoted to finding a vaccine to prevent polio. This highly contagious disease, which often had paralytic effects, affected more than 20 people per 100,000 in the United States in 1953. Anyone who was a child or a teenager before or during the early 1950s may remember not being allowed to go to crowded places such as swimming pools or movie theaters during summer or early fall, when the chances of “catching” polio were greatest. Polio was a highly publicized and greatly feared disease. The American public was extremely eager to have a vaccine.

As with all new vaccines, Salk’s polio vaccine (a “killed” vaccine given by injection) had to be tested in human trials to show that it was safe and effective before it could be licensed. The National Foundation for Infantile Paralysis (NFIP) took on the responsibility for testing the polio vaccine. The Laboratory of Biologics Control had no legal role in the testing. Because of the large amount of polio vaccine needed, it was manufactured by several pharmaceutical firms. And, because these



**Poliovirus Type I Mahoney**  
Copyright Grasp Image J. Y. Sgro, 2002





**Polio Virus**

Copyright Dennis Kunkel Microscopy, Inc.

firms had problems producing consistently safe vaccine—some batches of vaccine contained live virus—strict safety requirements were put into place by the NFIP, as recommended by its Vaccine Advisory Committee, a group of eminent physicians and researchers. All commercial vaccines had to be tested in three different laboratories. Also, the manufacturer had to be able to produce 11 consecutive batches of vaccine that did not contain live virus; otherwise, none of the vaccine could be used.

The field trial to test the Salk vaccine began in April 1954 in more than 1,800,000 children, the largest test using human subjects in the history of medical science. Thomas Francis, a highly respected scientist, was chosen by NFIP to design and direct the trial, and evaluate the trial results. On April 12, 1955, he reported the vaccine to be 80 to 90 percent effective, and stated that the Salk vaccine's safety was "powerfully affirmed." The Public Health Service immediately issued licenses allowing polio vaccine distribution. Unfortunately, the strict safeguards used in producing vaccine for field testing were not required in commercial

production. The only legal requirement for licensing was submission of a company's written protocols for vaccine production and for safety testing to the Laboratory of Biologics Control. The rush to distribute vaccine proved to be a tragic mistake that resulted in the loss of many lives, an event known as the "Cutter Incident." Afterwards, improved production and testing procedures were implemented to ensure the safety of Salk's vaccine and, beginning in fall 1955, it was used widely in the United States.

Even though the Salk vaccine was generally successful in preventing polio, some scientists, including Albert Sabin, believed that a weakened, live-virus vaccine would provide longer-lasting immunity. Sabin developed a live polio vaccine in the mid-1950s. His vaccine, which was given by mouth, was tested in a large field trial in the Soviet Union between 1957 and 1959. By 1962, the Sabin oral polio vaccine was licensed in the United States and endorsed by the American Medical Association. It became the primary vaccine for polio prevention worldwide by the end of the 1960s. One drawback of the Sabin vaccine was a small possibility of paralysis from the live virus. By the mid-1970s, data showed that about 10 Americans per year developed paralytic polio



**Albert B. Sabin**

Courtesy of National Library of Medicine

from the live vaccine. Even so, Sabin oral vaccine continued to be used, primarily because it was the most effective means of protection for the population, but also because its oral administration was convenient. With wild polio on the brink of eradication throughout the world, in 1999 the decision was made to revert to use of an inactivated polio vaccine for routine childhood polio vaccination in the United States.



**Girl with polio  
in leg brace**



## Organizational Changes

In 1955, as a result of the Cutter Incident, the Laboratory of Biologics Control was raised to division status within NIH, to strengthen and expand its biologics control function. It became the Division of Biologics Standards, an independent entity composed of seven laboratories. The Division continued to oversee the control and release of biologics until 1972, when, in reaction to its not having instituted an effectiveness review equivalent to that performed for drugs, it was moved from NIH to FDA and renamed the Bureau of Biologics. The merger with FDA was logical, because a “biological product” under the 1944 PHS Act also falls within the jurisdiction of the 1938 FD&C Act. The appropriate provisions of both Acts were skillfully used to regulate biologics.

## Amendments to the Food, Drug, and Cosmetic Act

Certain amendments to the 1938 FD&C Act during these years affected biologics. In 1951, the Durham-Humphrey Amendment defined the kinds of drugs that could not be used safely without medical supervision and required them to be sold “by prescription only.” And, in 1962, Congress passed the Kefauver-Harris Amendments after thalidomide, a new sleeping pill used widely in Europe, was found to cause birth defects. It has been claimed that there were between 10,000 and 20,000 babies born disabled in Europe as a consequence of the drug, but numbers vary among sources. FDA had kept

thalidomide from being marketed in the United States. But, as part of a pharmaceutical company’s investigational trial, physicians gave the drug to more than 20,000 U.S. patients, 624 of whom were pregnant. There were 17 documented cases of American children born with defects caused by thalidomide—ten from the U.S. trial and seven from thalidomide obtained in Europe. To prevent similar calamities, the 1962 amendments strengthened the regulations for drug safety and for testing drugs in clinical trials. Also, they required manufacturers to provide “substantial evidence” that their drugs were effective for the intended use. Further, they required that drugs must be manufactured using “good manufacturing practices,” required inspection of commercial manufacturers once every two years, and required annual registration of manufacturers. These amendments also applied to blood banks.

## Testing Blood for Hepatitis B

*Hepatitis B is a viral disease that occurs worldwide. The virus is found in body fluids of people who clearly have infections, as well as people who are carriers of the virus but show no hepatitis symptoms. Unlike hepatitis A virus, which is commonly spread by ingesting the virus in contaminated food, hepatitis B virus is transmitted mostly through injection—for example, by blood transfusion or by sharing needles among drug users. Research in the 1950s confirmed that post-transfusion hepatitis can be caused by either whole blood or plasma from virus carriers. Around 1970, methods for the detection of hepatitis B virus surface antigen (HBsAg) were developed that could be used to screen blood for the virus. Test kits for HBsAg were first licensed by the Division of Biologics Standards (DBS) in February 1971 and, in November 1971, DBS published a requirement that all blood collected under license must be tested for HBsAg. Licensing by DBS was initially required for blood banks engaged in interstate shipment of blood, but not for blood banks that operated only within state borders. On July 1, 1972, the requirement that the HBsAg test be performed on all blood collected under license became effective. As technology improved, more sensitive tests for HBsAg were developed and licensed. By December 1975, all registered blood establishments were required to use these more sensitive tests. This requirement was more comprehensive than the one that became effective in 1972, because “registered” establishments included those involved in interstate shipment of blood and those operating only within state borders. In the early 1970s, the risk of contracting some form of hepatitis from a unit of blood was as high as six to eight percent. Now, the risk of contracting hepatitis B from a pint of blood is about 1 in 200,000.*

Legal Action Against Blood Banks

*The first prosecution of a licensed blood bank occurred in 1962, when the Division of Biologics Standards brought suit against John Calise and the Westchester Blood Bank in New York, for altering the expiration dates on whole blood to dates that were beyond the 21-day expiration date requirement. This was the first litigation brought against a manufacturer under the Biologics Control Act of 1902. 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 forbidden to take part in the manufacture, distribution, or sale of any biologics, including blood products. This case represented the first time a court had declared that blood was a drug, as defined by the FD&C Act of 1938. There were other prosecutions of blood banks in the 1960s. For instance, in 1963, an outbreak of hepatitis was linked to the commercial Paterson Blood Bank, Inc., (PBB) in Paterson, New Jersey. Investigators traced the likely sources of the contamination to tattooing and to blood sold by known narcotics addicts to a local unlicensed blood bank, that sold the blood to PBB. In July 1964, the president of PBB was found guilty of selling blood from an unlicensed bank in interstate commerce, as well as falsely labeling blood with dates past the 21-day expiration date. The PBB also was convicted of numerous charges, including mislabeling blood that was reactive for syphilis as being nonreactive.*

The Challenge of Regulating Blood Products

The Laboratory of Biologics Control issued the first blood bank license and the first license for interstate shipment of blood to the Philadelphia Blood Bank in 1946. Regulating blood products posed considerable challenges for the Laboratory and, after 1955, for the Division of Biologics Standards. For example, they licensed only facilities that shipped blood between states; thus, they had no control over blood banks operating within states. Also, mislabeling blood products and altering the expiration dates (to increase profits) was easy for commercial blood banks. And, interpretation by the courts of the laws regulating blood products was not entirely consistent. For



instance, in 1968, a Dallas blood bank was found guilty of mislabeling Whole Blood and Red Blood Cells shipped in interstate commerce. A Court of Appeals overturned the guilty verdict on the basis that Citrated Whole Blood (blood containing an anticoagulant) and Red Blood Cells were not products similar to a therapeutic serum and so could not be regulated under the 1944 PHS Act. Because of this decision, the terms “blood, blood components, and derivatives” were inserted into the 1944 PHS Act in October 1970.

After establishment of the Bureau of Biologics within FDA in 1972, the agency reviewed the safety, effectiveness, and labeling of all previously licensed biologics. Regulatory activity increased, especially for blood and blood products. Interstate blood banks were still licensed under the 1944 PHS Act, but all intrastate blood banks (operating only within states) were subject to the 1962 Kefauver-Harris Amendments. By 1973, the Bureau had oversight of almost 7,000 blood facilities. In

**Andrew Young** performs ultracentrifugation studies to detect changes that occur during the storage of blood derivatives, 1964

addition, regulations were published in 1973 that required licensing of all establishments that collected blood plasma by plasmapheresis, that is, by harvesting the plasma and returning the cells to the donor. And new regulations in 1975 established standards (good manufacturing practices) for the operation of all blood banks. By December 1975, all registered blood establishments were required to test for hepatitis B with tests of third-generation (meaning the highest) sensitivity.

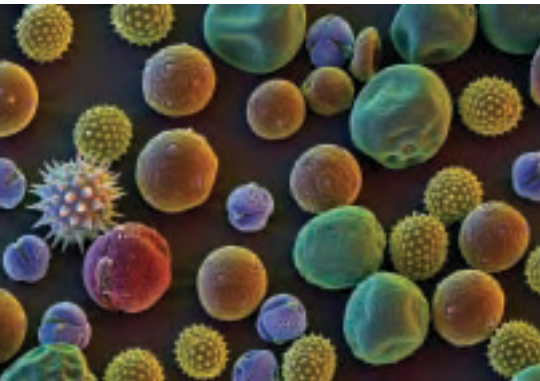


**John S. Finlayson, PhD,** CBER Office of Blood Research and Review. In the 1950s–1980s he conducted research on plasma proteins.



**Ensuring Effectiveness of Allergenic Products**

Allergenic products include allergen patch tests—diagnostic tests applied to the surface of the skin, and allergenic extracts—injectable products, made from natural substances, used to diagnose and treat allergic diseases such as “hay fever,” food allergy, and bee venom allergy. Very important research on allergenic products, particularly allergenic extracts, began in the 1970s in the Bureau of Biologics. As explained by Harold Baer, former Chief of the Laboratory of Allergenic Products, “although there were hundreds of allergenic products, and many were injected into numerous people, these were the only products for which there were no standards.” To address this issue, Bureau scientists developed laboratory techniques for measuring the activity of allergenic extracts, linked these results to effectiveness of



**Mixed pollen grains**  
Copyright David Scharf Photography



**DNA molecule**  
Courtesy of National Institutes of Health

the extracts in humans, and established standards for the extracts that had to be met by manufacturers. A scientific review of the hundreds of allergenic extracts that were being marketed in the United States in the 1980s found that about 240 products had no allergenic activity. These ineffective products were gradually removed from the market over the course of a decade.

**Noteworthy Achievements**

Several events of global significance that occurred between 1951 and 1980 deserve mention. First, in 1953, James Watson (American) and Francis Crick (British) determined that the structure of DNA, the molecule that holds genetic information, is a “double helix.” They also realized that this structure could make copies of itself. Because genes are made of DNA, these discoveries were the foundation for the development of biotechnology—the manipulation of genes and genetic characteristics of living things. In the early 1970s, scientists discovered how to insert foreign genes into bacteria, a huge scientific advance that set the stage for producing biologics by using “biotech” methods.

The development of hybrid cells, commonly called hybridomas, by Georges Köhler (German) and Cesar Milstein (Argentine) in 1975 was another scientific advance that had significant consequences for biologics and for modern medicine. These scientists physically fused cancerous mouse plasma cells (plasmacytoma cells) with mouse lymphocytes (cells responsible for immunity) to form the hybrid cells, which could survive indefinitely in tissue culture and produce specific antibodies. Their research laid the foundation for large-scale production of monoclonal antibodies. In this process, plasmacytoma cells are fused with spleen cells from a mouse that has been immunized against an antigen of interest. Only a few of the hybridomas (about 1 in 500) will produce antibodies to the antigen. Once a hybridoma “clone” is selected, however, it can be grown in large quantities and an unlimited amount of specific “monoclonal” antibodies can be made for the diagnosis and treatment of disease.



**Arcadia, California newcomers receive vaccination against smallpox, 1942**  
Courtesy of National Archives and Records Administration

In addition, the global eradication of smallpox was accomplished during this period, an effort that had its beginnings in 1950 when the Pan American Sanitary Organization made a commitment to eradicate smallpox in the western hemisphere. The World Health Organization (WHO) undertook an initial global eradication program in 1959, but the results were disappointing. Then, in December 1966, encouraged by the commitment of the Centers

for Disease Control (CDC) of the PHS to wipe out smallpox in Africa, WHO funded an intensified, well-organized global program to eliminate smallpox worldwide within ten years. CDC staff directed the worldwide effort and also conducted the program in Africa. The last naturally occurring case of smallpox was reported in Somalia in October 1977. In May 1980, WHO announced that worldwide elimination of the disease had been achieved. The elimination of smallpox illustrates how effective international collaboration can be in improving human health.



**Roderick Murray, Division of Biologics Standards, 1955-1972**



**Barbara Jackson, Laboratory of Viral Immunology, worked with the Meyer-Parkman team**

### Protection Against Rubella

*Rubella (German measles) is a usually mild viral disease that most often affects children and young adults. But, it is a very dangerous disease for pregnant women, particularly during the first three months of pregnancy. The virus can be transmitted to the unborn child, resulting in abnormalities such as cataracts, deafness, heart defects, and mental retardation. A global epidemic of rubella that started in Europe in 1962 spread to the United States in 1964, causing an estimated 12.5 million cases in this country and birth defects in about 20,000 children. The need for a rubella vaccine was clear, and many in the scientific community were working on the problem. In 1963, Roderick Murray, MD, the founding Director of the Division of Biologics Standards (DBS), hired Paul Parkman, MD, who had discovered rubella virus while working at the Walter Reed Army Institute of Research, to start a rubella program. Dr. Parkman teamed with Harry Meyer, Jr., MD, already at DBS. By 1966, they were able to report that they had developed the first effective experimental vaccine for rubella. They had weakened the rubella virus by subjecting it to 77 passages in primary African green monkey kidney cell cultures over two years and then tested its effectiveness in rhesus monkeys. When the monkeys were inoculated with the weakened, live virus, none of them developed rubella or transmitted the disease to monkeys that had not been inoculated, and they were solidly protected against infection with the wild virus. Based on these results, Parkman and Meyer prepared a weakened, live vaccine for human testing and inoculated 34 children. None of the children developed rubella; also, the children did not transmit the vaccine virus infection to any of their 30 playmates who had not been inoculated. Parkman and Meyer made the weakened virus, the first successful experimental rubella vaccine, available to other scientists interested in rubella research. Based on their success, 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.*



**Paul Parkman and Harry Meyer, developers of the rubella vaccine, 1966**



Discovery and Change:  
1981 through 2000

During these years, scientific achievements and challenges related to biologics came fast and furiously. To keep pace with rapidly changing technology, new discoveries, and the difficulty of regulating an ever-growing number of biologic products, organizational changes transformed the Bureau of Biologics into CBER, as it exists today.

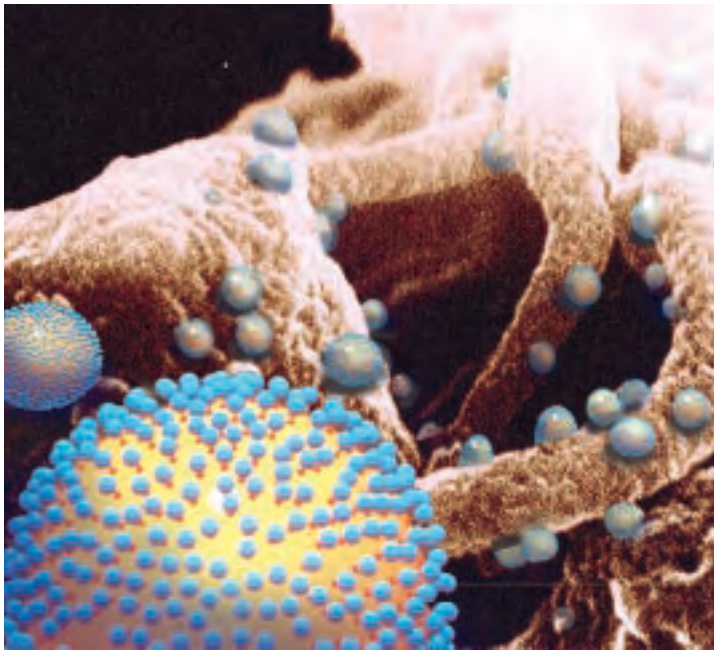
A New Era in Biologics

During the latter part of the 20th century, research in biotechnology and genetics revolutionized methods for making biologics. Additionally, advances in biotechnology led to the identification of many biological molecules important in disease processes, and thus to the identification of many potential new biological products. These new technologies and products raised important new regulatory challenges. Working with the broader scientific community, CBER scientists and physicians helped ensure that new production and testing methodologies were developed and implemented in a manner that produced safe, pure, and potent biologics. While leading to important further advances in vaccine development and blood safety, these advances also led to development of a range of biologic products that have made major contributions to all branches of medicine. Biologic therapeutics licensed in recent years have revolutionized the treatment of heart disease, cancer, serious infections, arthritis, anemia, hemophilia, multiple sclerosis, and many other diseases.

As the 21st century approached, CBER licensed a broad array of new biologic products. Examples of these products include new biotechnology-based drugs; new vaccines for typhoid, rabies, hepatitis A, and chickenpox; acellular pertussis vaccines, which cause fewer adverse side effects than whole-cell pertussis vaccines; and combination vaccines, such as the ones that protect against Haemophilus b disease, diphtheria, tetanus, and pertussis. During this time CBER also licensed the first HIV test system for which blood samples may be collected at home; a device that concentrates adult blood stem cells from bone marrow; and Rh<sub>0</sub> (D) Immune Globulin Intravenous, the first human blood product approved for both intravenous and intramuscular use.

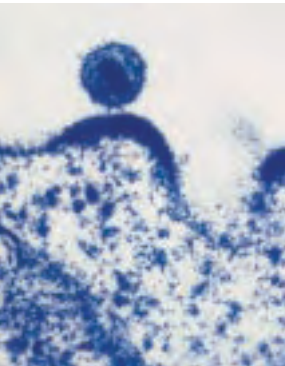
HIV virus

Courtesy of National Institutes of Health



Screening Blood for HIV

The blood supply plays a vital role in the American health system, and CBER is responsible for ensuring the safety of that supply. The appearance of AIDS in the United States in 1981 threatened the safety of the U.S. blood supply, because 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 people who have been exposed to the virus but who are not yet ill. HIV was not identified as the cause of AIDS until 1984. There are two types of HIV: HIV-1, found worldwide, and HIV-2, found mostly in West Africa. Once HIV was identified and characterized, scientists were able to develop tests to detect HIV in blood. In 1985, CBER licensed the first test kit to screen donated blood for antibodies to HIV-1 (the presence of antibodies means the individual has been exposed to HIV-1) and licensed a more accurate test, the Western Blot Test, in 1987. Since the mid-1980s, screening tests for both HIV-1 and HIV-2 have been continually improved. CBER published regulations in 1987 that required HIV screening, with tests that detect HIV antibodies, of all blood and blood plasma collected in the United States. “With the advent of the screening tests for HIV, enforcement and compliance activities focused on ensuring that blood establishments were conducting the screening tests properly...,” according to Steven Masiello, Director of CBER’s Office of Compliance and Biologics Quality. In March 1996, the first antigen test kit for screening blood for HIV-1 was licensed. It is used in addition to HIV antibody tests. HIV antigen appears in the blood of an HIV-infected person about one week earlier than HIV antibodies, which usually appear within three months after infection. Thus, an HIV-antigen test reduces the “window” period, when blood could be HIV-infected, but still have negative antibody tests. It has been estimated that HIV-1 antigen screening prevents five to ten cases of AIDS per year. In 1985, the risk of HIV infection from a blood transfusion was 1 in 2,500. By the mid-1990s, the risk had decreased to only about 1 in 500,000. In February 2002, CBER licensed the first nucleic acid-based test for HIV and Hepatitis C virus, decreasing the risk further to only about 1 in 2 million. So, even though blood products are not completely risk-free, the risk of contracting HIV infection from receiving a blood transfusion is very small.



HIV virus

Courtesy of National Institutes of Health

The Biotechnology Revolution in Medicine

In recent years, biotechnology has facilitated the identification, development, and production of new biologic therapeutic products that have substantially advanced nearly all areas of medicine. The mortality rate due to heart attacks, a leading killer of Americans, was substantially reduced by the use of several fibrinolytic agents, licensed by CBER, that help clear clots from coronary arteries. An anti-platelet agent licensed by CBER, abciximab, has significantly reduced the morbidity from platelet aggregation that complicates many coronary procedures.

In oncology, biologic therapeutics have ushered in a new era of therapies that target specific tumor cells. Monoclonal antibodies including trastuzumab, which targets antigens on some breast tumors, and rituximab and alemtuzumab, which target antigens on some lymphomas and leukemias, have become valuable and important cancer therapies. Ibritumomab tiuxetan is the first CBER-approved biologic employing a monoclonal antibody to target a lethal radioisotope to a tumor. Biologic agents also have been critically important in adjunctive therapy of cancer patients. Colony stimulation factors, such as sargramostim and filgrastim, are used alone and with stem cell transplants, for example, bone marrow transplants, to increase white blood cell production and thereby decrease the risk of infections associated with cancer therapy. Erythropoietins regulate red blood cell production and have an important role in the treatment of anemia associated with renal failure or cancer.

Treatment of rheumatoid arthritis, a debilitating disease, has been revolutionized by biologic agents that bind tumor necrosis factor, an endogenous substance involved in joint destruction. These and other anti-inflammatory agents are now under study for the treatment of many rheumatologic and autoimmune diseases. Antibodies that suppress immune responses by targeting T lymphocytes play an important role in preventing and treating rejection of organ grafts.

New biologics have provided benefits for patients with many previously untreatable diseases. Interferon beta products prevent exacerbations and slow progression of multiple sclerosis, and alteplase, a fibrinolytic agent, helps restore circulation to the brain in patients with stroke. Interferon alfa products were the first approved therapies for hepatitis C, an important cause of morbidity, and remain the backbone of therapeutic regimens for Hepatitis C.

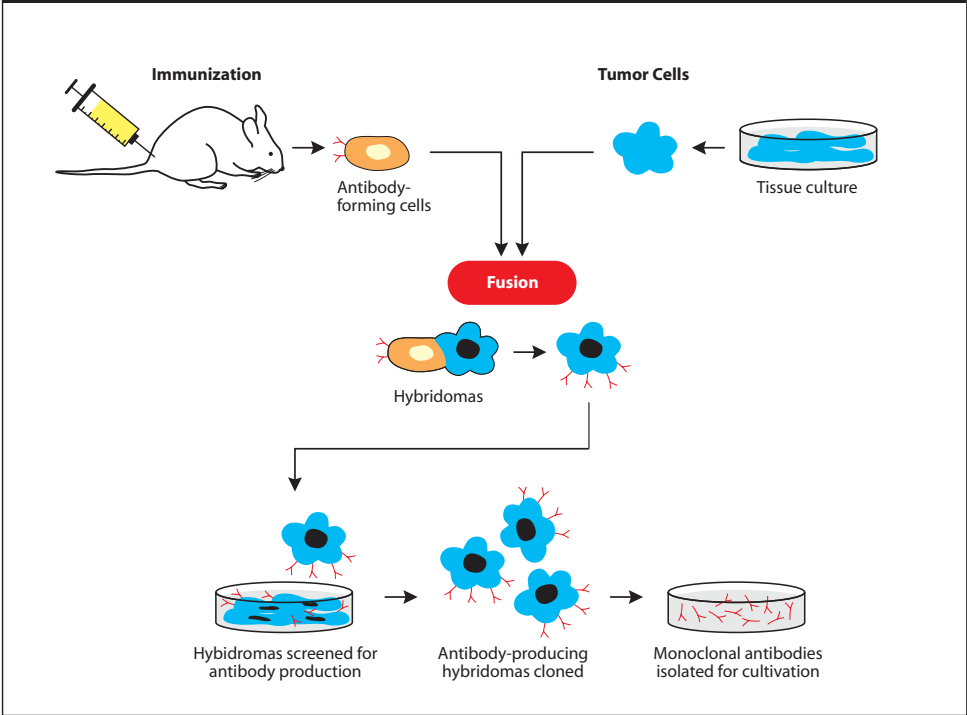
Despite the use of antibiotics, severe sepsis has been fatal in more than 30% of cases. Drotrecogin alfa, a genetically-engineered activated protein C, is the first drug shown to reduce the mortality associated with the most severe forms of sepsis. Infliximab, an antibody against tumor necrosis factor, was the first therapy specific for Crohns’ disease, an inflammatory bowel disease. Dornase alfa is an enzyme that helps clear the thick lung secretions that impair breathing in patients with cystic fibrosis. Interferon gamma is a cytokine that helps correct the immunodeficiency of chronic granulomatous disease, and delays disease progression in severe malignant osteopetrosis.



The Challenge of AIDS

The blood supply plays a vital role in the American health system. Almost four million Americans receive transfusions of blood products every year. The emergence of acquired immunodeficiency syndrome (AIDS) and discovery of the human immunodeficiency virus (HIV) that causes AIDS had serious implications for the safety of the U.S. blood supply. In August 1981, there were 108 reported cases of AIDS in the United States.

Monoclonal Antibody Production



Between 1981 and December 2000, a total of 774,467 cases of AIDS were reported to CDC. The growing presence of AIDS and HIV meant that CBER had to protect the public against unsuitable blood and blood products by strengthening existing safeguards and developing new safeguards specific for HIV.

In 1985, soon after HIV was identified as the cause of AIDS, CBER licensed the first test kit to screen donated blood for HIV. As technology progressed, improved test kits were licensed and became available for use. In 1988, CBER started to inspect regulated blood and plasma donor facilities every year, rather than every two years. Today's general safety measures



Quality control testing on blood grouping and typing reagents, 1967

for protecting the U.S. blood supply include screening donors by interview, checking donors against a list of persons not eligible to donate blood, testing all blood donors for HIV, human T-lymphotropic virus (HTLV), hepatitis B and C, and syphilis before making the products available for use, and reviewing and monitoring any problems reported by blood establishments. As the operations of blood establishments have become more complex, CBER's oversight has adapted to the times. For example, CBER now regulates blood establishment computer software as a medical device, because of its critical role in managing and storing blood-related and donor-related information.

**The Recombinant Factor VIII Breakthrough**

*Factor VIII is a protein found in small quantities in the blood; it helps blood to clot. A deficiency of Factor VIII causes hemophilia A, a disease characterized by spontaneous bleeding that is difficult to control. Traditionally, human blood plasma was used as a source of Factor VIII concentrates used to treat hemophilia A. In 1984, however, scientists identified and isolated the gene—the part of human DNA—that contains the instructions for production of Factor VIII. Once they were able to copy this gene in the laboratory, it was possible to produce the Factor VIII protein by using a “recombination” process, referred to as recombinant DNA technology. Scientists linked the Factor VIII gene into a circular strand of DNA (a plasmid) and then inserted the plasmid into a nonhuman host cell that was very similar to a human cell and that was genetically engineered in the laboratory for this purpose. The plasmid moved to the host cell’s nucleus, where genetic information is stored, and merged or recombined with the DNA already in the nucleus. Thus, the human Factor VIII gene became part of the host cell’s genetic makeup. Host cells containing the Factor VIII gene were placed in a large vat called a bioreactor, and given nutrients to promote growth. As the cells grew, they produced Factor VIII. Scientists separated the Factor VIII from the host cells by using several purification steps. Finally, they sterilized the pure Factor VIII, dispensed it into sterile vials, and freeze-dried it to form a powder. Recombinant Factor VIII was first introduced in 1992. Because this product does not use blood plasma as its source, there is no risk of contamination from viruses found in human blood. Recombinant Factor VIII is one example of a biologic that can now be manufactured by biotechnology.*

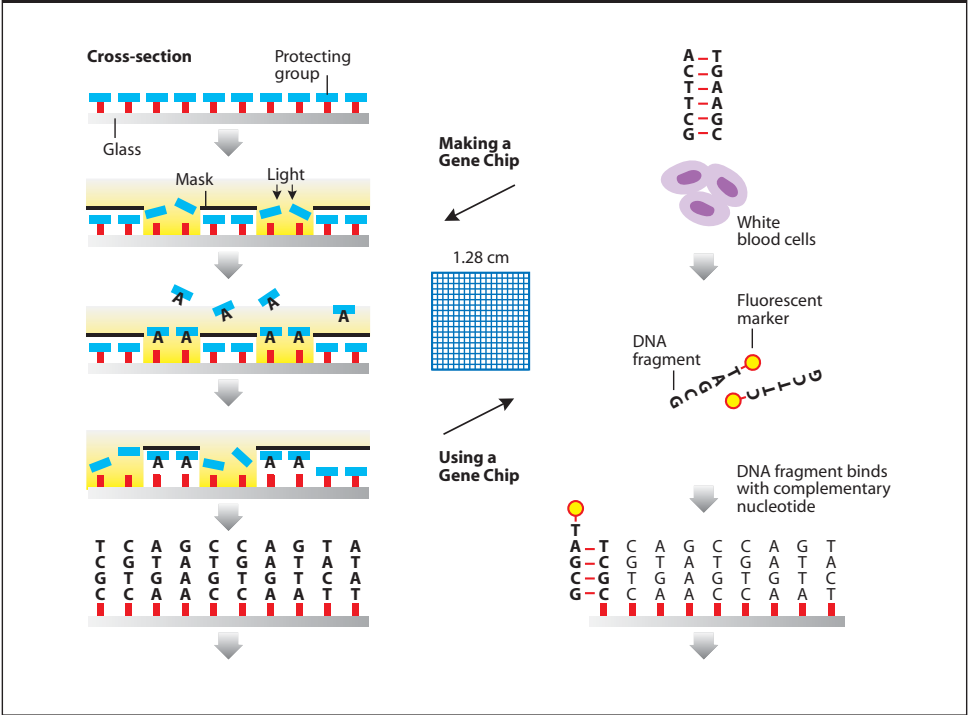
**From the Bureau of Biologics to CBER**

During the 1980s and 1990s, an unprecedented number of organizational changes took place in transforming the Bureau of Biologics to CBER. These changes all were aimed at achieving the most efficient regulation of rapidly-evolving biologic products. In 1982, the Bureau of Biologics was merged with the Bureau of Drugs to form the National Center for Drugs and Biologics (NCDB). In 1983, the biologics component of NCDB became the Office of Biologics Research and Review (OBRR) within the Center for Drugs and Biologics (CDB). It soon became clear that the regulatory programs for biologics and drugs could be managed more effectively if the programs were housed in separate organizations. So, in 1988, CDB was divided into two new Centers, CBER and the Center for Drug Evaluation and Research (CDER). At the close of the 1980s, it was evident that CBER's traditional workload of blood and vaccine products was changing to include biotechnology-derived products, as well as therapeutic products such as cytokines (non-antibody proteins that are part of the immune response to an antigen) and monoclonal antibodies (antibodies, for specific antigens of interest, produced by hybridoma clones grown in tissue culture). To streamline operations, CBER was reorganized in 1993 with separate program offices for vaccines, blood, and therapeutic products. Each office had both research and review responsibilities for their product areas. Also, separate offices were established to deal with manufacturer compliance and establishment licensing; these offices provided support to the product offices.

As a result of additional reorganizations since 1993, CBER now oversees biologics regulation through the coordinated efforts of eight offices: Office of Vaccines Research and Review, Office of Blood Research and Review, Office of Therapeutics Research and Review, Office of Cellular, Tissue, and Gene Therapies, Office of Compliance and Biologics Quality, Office of Communication, Training, and Manufacturers Assistance, Office of Biostatistics and Epidemiology, and Office of Management. In addition, the CBER Facility for Biotechnology Resources



Making a Gene Chip and Using a Gene Chip



(FBR) began operation in 1995. The FBR can be used by all CBER staff, and has the scientific expertise and sophisticated equipment needed to provide specialized reagents and services to CBER scientists and to support CBER’s evaluation of methods used by biotechnology companies.

Also, CBER is part of the National Vaccine Program (NVP), created by Congress in 1986 to coordinate immunization activities. This program is a collaborative effort among all of the groups that have key roles in immunization, including federal agencies, the public, state and local governments, health care providers, and vaccine manufacturers. Major NVP goals are to develop and implement strategies for achieving the highest possible level of prevention of human diseases through immunization, as well as the highest possible level of prevention of adverse reactions to vaccines.

The Potential of Human Gene Therapy

Human gene therapy, an exciting and controversial area of biomedical research, refers to using normal genes or genetic material to either replace or cancel out defective genes in a person’s body, in an effort to treat or cure the disease or medical condition caused by the defective genes. Gene therapy is likely to be most successful in diseases that are caused by defects in single genes—for example, hemophilia, cystic fibrosis, and hemoglobin disorders. Instead of giving Factor VIII, a protein that helps blood coagulate, to a person with hemophilia, it may be possible to replace the defective Factor VIII gene in the person’s cells with a Factor VIII gene that works. The cells would then produce Factor VIII and the hemophilia would be cured. “Of course, that’s a long way off,” cautions Philip Noguchi, MD, Acting Director of the Office of Cellular, Tissue, and Gene Therapies at CBER, who also declares that such cures are “really the promise of what gene therapy hopes to offer.”

Most current gene therapy research is being done using somatic cells (nonreproductive cells); the genes in these cells are not passed on to the next generation. NIH researchers W. French Anderson, MD, R. Michael Blaese, MD, and colleagues used the first approved gene therapy procedure to treat a four-year-old girl, in September 1990, and a nine-year-old-girl, in January 1991, both of whom had a disease called severe combined immune deficiency (SCID). This disease is caused by a gene defect that results in defective T cells, which are one type of white blood cells responsible for immunity. Children with SCID usually develop overwhelming infections and rarely survive to adulthood. The researchers removed T cells from the girls, grew the T cells in the laboratory, inserted the normal gene into the T cells, and then injected the genetically modified T cells into the girls’ bloodstreams. This procedure strengthened the girls’ immune systems, enough so that they had only an average number of infections and could attend public school. But, it was not a cure. The modified T cells only worked for a number of months, so the procedure had to be repeated periodically. This research illustrates just one way to replace defective genes; many other techniques can possibly be used and are being studied, as appropriate for the particular disease. As Dr. Noguchi explains, gene therapy techniques and vaccination techniques have something in common —“It is the whole idea of taking that which causes the disease, changing it into something that you can control, and using that entity itself to try to treat the disease.” Gene therapy research is growing rapidly. Presently, CBER is overseeing more than 200 gene therapy studies, but has not yet licensed any human gene therapy product.



Fast Performance Liquid Chromatography for purification of recombinant proteins

CHALLENGES FOR THE  
21ST CENTURY

Enormous challenges face CBER in its role as steward for the many diverse and innovative biological products, generated by combining biomolecular research and sophisticated technologies, that are being submitted by manufacturers for approval to enter the marketplace. More than 650 new biological products were developed in 2000, compared with 350 in 1990. More than half of the new products now being developed have their origin in biotechnology. In regulating new product areas, CBER's scientists must routinely develop appropriate laboratory and clinical methods to ensure the safety and effectiveness of new products. To do this, they must keep up to date with the rapid progress taking place in cutting-edge science. Even in older product areas, the technologies for production and testing continue to advance, and regulatory approaches must evolve to meet new challenges.

Challenging Areas of Research

Biomedical research areas that are receiving much attention include:

- **human gene therapy**—using normal genes or genetic material to either replace or cancel out the defective genes in a person's body that are responsible for a disease or medical problem
- **human cell and tissue transplantations**—for example, hematopoietic stem cell transplantation

- **xenotransplantation**—transplanting organs or tissues from animals into humans
- **emerging/re-emerging infectious diseases**—HIV, tuberculosis, Mad Cow
- **development of genetically-engineered (transgenic) plants and animals**—that are able to produce vaccines and drugs
- **production of vaccines and blood clotting factors**—from genetic material such as DNA

- **genomics**—the study of genes and their relationship to disease
- **proteomics**—the study of all proteins in living cells, especially protein changes in disease.

The rapidly growing number and variety of cellular and tissue-based products, and the regulation of these products will pose a continuous challenge for CBER in the 21st century. For many years, tissues have been transplanted in a wide range of procedures, such as skin replacement after severe burns, repair of injuries with tendons and ligaments, replacement of defective heart valves, restoration of eyesight using corneas, and use of human semen and implantation of eggs to help infer-

tile couples have children. In recent times, scientists have developed innovative methods, some derived from biotechnology, that hold promise for enhancing and expanding the use of human cells and tissue in therapies for serious diseases and conditions such as cancer, diabetes, Parkinson's Disease, AIDS, hemophilia, and anemia. Existing cellular and tissue-based products and their potential uses are too diverse for a single set of regulatory requirements to be appropriate for all. Therefore,



Emmanuel F. Petricoin, PhD  
CBER



Lance A. Liotta, MD, PhD  
National Institutes of Health

The NCI-CBER/FDA Clinical Proteomics Program

*Proteomics is the study of all proteins in living cells. A new program, the Clinical Proteomics Program, announced in July 2001 by the Food and Drug Administration (FDA) and the National Cancer Institute (NCI), will apply proteomics directly to patient care. Led by Lance Liotta, MD, from NCI's Center for Cancer Research, and Emmanuel Petricoin, PhD, from CBER, the Program will use new, powerful technologies in an innovative approach that could possibly revolutionize cancer detection and care. Liotta and Petricoin have identified more than 130 proteins in cells of the breast, ovary, prostate, and esophagus that change in amount when the cells grow abnormally. This information may help to provide new ways of diagnosing and treating cancer in earlier stages of the disease, when there often is a better chance of cure. Specialized equipment was developed in Liotta's laboratory that can scan cells for hundreds of proteins at once and generate protein "fingerprints" for the cells. The scientists are analyzing protein patterns in normal and precancerous cells to find clues about why and how precancerous cells develop, and are examining tumor cells before and after treatment to determine how the treatment affects cell protein patterns. In addition, they are looking for protein patterns in blood that might signal the presence of cancer. In February 2002, the researchers reported that, using a special computer program, they have been able to recognize blood protein patterns that readily distinguish between women with and without ovarian cancer; they correctly identified 50 out of 50 ovarian cancer patients and 63 out of 66 women without cancer. An exciting finding in this study was the ability to correctly identify early-stage ovarian cancer, difficult to detect by other means. Currently, four out of five ovarian cancer patients are diagnosed at a late stage of disease; these women have, at best, only a 20 percent chance of living for five years after diagnosis, compared with 95 percent for women who are diagnosed with early-stage disease. In addition to diagnosing cancer, and possibly other diseases, at earlier stages than is now possible, potential benefits of the Clinical Proteomics Program include: developing individualized treatments that have been predetermined to be effective for the patient; determining toxic side effects and beneficial effects of treatments in the laboratory before using them on patients; and improving the understanding of tumors at the protein level, leading to development of better treatments. Clinical trials using proteomics to help make decisions about patients' experimental treatments have begun recently as part of this "bench-to-bedside" clinical research program. According to Dr. Petricoin, proteomics could "change the shape of how medicine is practiced."*

CBER has developed a new framework for cell and tissue regulation that will provide a unified approach to the regulation of both traditional and new products. CBER’s goal is twofold: to ensure that innovation and product development can proceed in the rapidly growing area of cell and tissue research without being hindered by excessive regulation, and to ensure that cell and tissue-based products provide the assurance of safety that the public has come to expect from products regulated by CBER.

Vaccine research and regulation also will continue to be a challenge in the 21st century. At the end of the 20th century, the number of new technologies available for making vaccines increased dramatically, building on rapid advances in many areas, including molecular biology, recombinant DNA technology, polysaccharide chemistry, protein chemistry, purification methods for large molecules, analytical techniques, virology, bacteriology, and immunology. As a result, CBER must regulate a wide variety of vaccine types, ranging from vaccines made by using the whole cell of an organism to vaccines that are essentially pure chemicals.

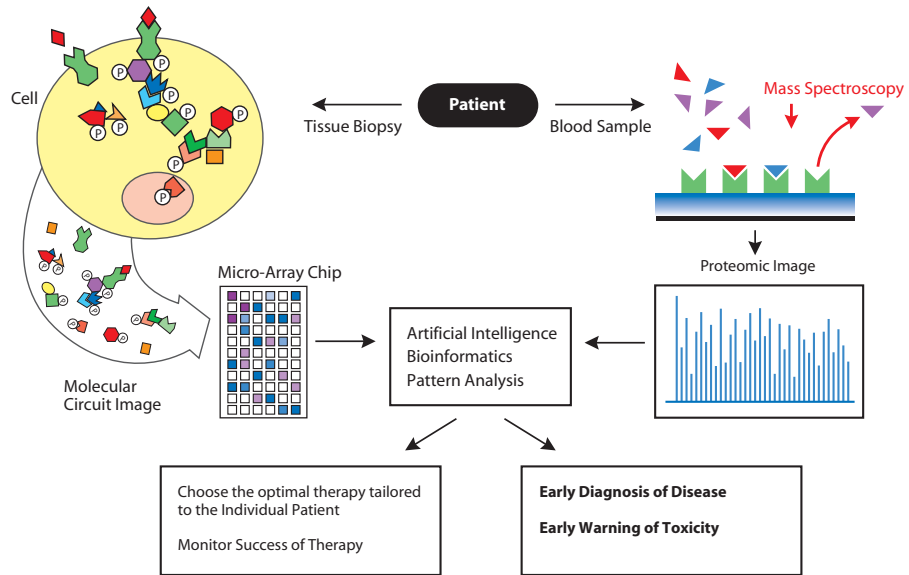
New microorganisms are constantly emerging and known microorganisms are constantly changing. Emerging infectious diseases—those that have newly appeared or have existed but are rapidly increasing in incidence or geographic range—include tuberculosis, malaria, hepatitis C, Lyme disease, AIDS, hantavirus pulmonary syndrome, ebola, and West Nile virus disease, among others. Vaccines have yet to be produced for many of these diseases. Even influenza can be considered an emerging infectious disease, because influenza viruses change from year to year. The effort to protect people against new and changing infectious microorganisms is “a never-ending battle,” according to Neil Goldman, PhD, CBER’s Associate Director for Research.

Mad Cow Disease

The scientific name for “mad cow disease” is bovine spongiform encephalopathy (BSE). BSE belongs to a group of diseases called transmissible spongiform encephalopathies (TSEs). There are no validated treatments or preventive vaccines for TSEs; they appear to be invariably fatal. In these diseases, which occur in both animals and in people, the brain develops a sponge-like appearance. Also, a unique abnormal form of a normal protein called the prion protein is found in the brain tissues. Abnormal prion proteins are believed by many authorities to be the agents that cause TSEs, but little is known about how they work. TSEs can be transmitted between animals, for example, cow-to-cow or sheep-to-cow, and between animals and humans. BSE was discovered in cattle in the United Kingdom in the mid-1980s. It appears that the disease was spread by feeding cattle with supplements containing infected animal tissues and byproducts. In 1996, a new kind of TSE was found in people in the United Kingdom; this disease is now called vCJD because it is a variant of Creutzfeldt-Jakob disease (CJD), a known TSE that affects people worldwide, about one case per million people each year. Investigation revealed that the likely cause of vCJD in people was eating contaminated beef products made from cattle with BSE. At present, more than 115 people in Europe, mostly in the United Kingdom, have died from vCJD. It can take many years for symptoms of vCJD to become noticeable, so it is not known how many more people may be infected with the disease agent. TSE agents are exceptionally resistant to destruction. They are not completely destroyed by the same methods that destroy bacteria and viruses. Fortunately, there is no evidence of either BSE or human cases of vCJD contracted in the United States. As part of its mission to protect the public, CBER is evaluating methods for preventing exposure of Americans to agents of these diseases, especially as a result of blood transfusions or tissue transplantation.

FDA-NCI Clinical Proteomics Program

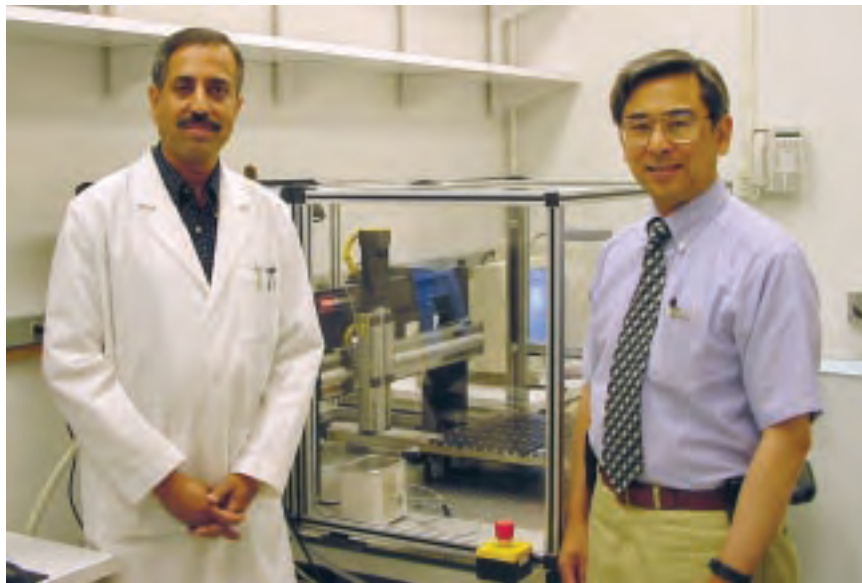
Molecular Imaging of Cells and Blood: Individualized Molecular Medicine



Most genetic vaccines being investigated are made using DNA. Many of these vaccines consist of plasmids (small rings of DNA) that have been altered to carry genes that specify one or more antigens made by the disease-causing organism. The vaccines can be delivered by injection. Once inside the body's cells, the plasmids travel to the cell nucleus and instruct the cell to produce the antigens. Then, these antigens trigger the body's immune system.

Innovative vaccine research is making progress in the development of "edible vaccines" and genetic (DNA) vaccines. Both edible vaccines and genetic vaccines have several advantages over traditional vaccines. They are unable to cause infection, are relatively easy to generate in large quantities, and are stable during storage. Edible vaccines are produced by genetically altering the edible parts of plants. Antigens have been produced in plants for rabies (in tomato), Norwalk virus (in potato), hepatitis B virus (in potato), and cholera (in potato), and testing in humans is under way. Banana is being investigated as a possible vaccine delivery food because it can be eaten raw and appeals to children.

Cancer vaccines are another promising area of vaccine research. There are various tumor-associated antigens (TAAs) present on tumor cells that are absent or present in only very small amounts on normal cells. One example is carcinoembryonic antigen (CEA), produced by colon, breast, lung, gastric, and pancreatic cancers. When used to vaccinate cancer patients, the TAAs can elicit a response from the immune system that is directed at the tumor cells. Some gene therapy studies involving cancer are actually based on the principle of cancer vaccines. Researchers have introduced genes that code for immune hormones into tumor cells to make the cells more reactive to the patient's immune system.



**Raj K. Puri, MD, PhD, and Philip D. Noguchi, MD, CBER, conduct DNA analyses on microarray system**

The new analytical methods of DNA microarray technology, which provide scientists with information on thousands of genes simultaneously, and proteomics, the study of all proteins in living cells, are powerful new research tools. They have tremendous potential for clarifying the complex causes of infectious disease, providing new diagnostic tests, contributing to the discovery of innovative medicines and vaccines, and assisting in the standardization of biologics. Because of advancements in genomics and proteomics research and technology, it is likely that biologics in the 21st century will be tailored on a molecular basis.

## Ethical Concerns

Several current clinical research areas have raised ethical and societal concerns that lie outside of CBER's primary responsibility for safety, purity, potency, and efficacy of biologics. For example, many believe that gene therapy is acceptable if applied to somatic (nonreproductive) cells, but are less willing to accept gene therapy if applied to germ (reproductive) cells, because germ cells carry the genes that are passed on to the next generation. Others believe that any kind of gene manipulation is wrong, including development of genetically engineered plants and animals, because of possible unforeseeable long-term effects that may be harmful to either human health or the environment. Stem cell research using human embryos also has raised concerns. A stem cell is a human cell that may be derived from an embryo, fetus, or adult. Human embryonic stem cells are unique in that they are capable of continuous self-renewal and have the ability to give rise to most cell types that constitute the human body. It is important that research using human embryonic stem cells proceed responsibly and ethically, especially when used in clinical trials. Xenotransplantation also has raised ethical dilemmas because of the risks of transmitting infectious agents from animals to humans, particularly certain viruses that may remain inactive or hidden for many years before they cause disease. Ethical and societal issues such as these lie beyond CBER's legal responsibility. However, CBER clearly has a role to play in the public discussion of these issues. For example, CBER has *ex officio* membership on the NIH Recombinant DNA Advisory Committee (RAC) and the HHS Secretary's Advisory Committee on Xenotransplantation (SACX). CBER has restructured its own Biological Response Modifiers Advisory Committee (BRMAC) to discuss issues such as the above in the context of clinical trials using experimental products. CBER is committed to continued public participation in discussions of novel products that have enormous potential clinical impact, yet also present novel ethical issues.



Stem Cell Research

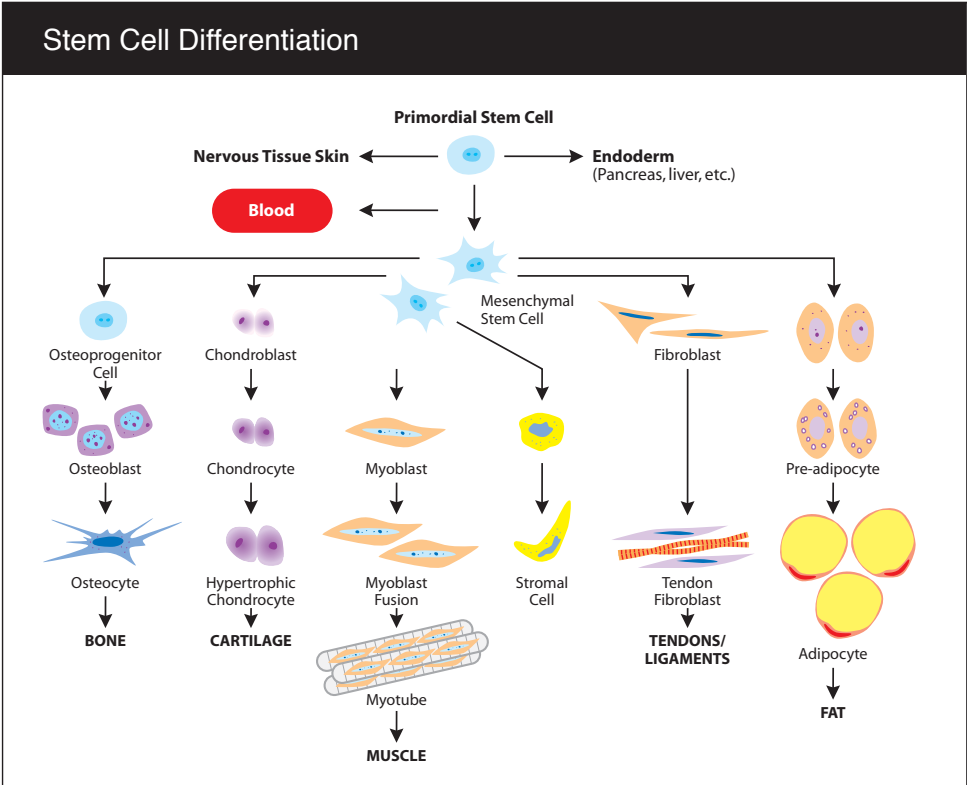
Stem cell research is creating great excitement among scientists because of its potential for developing new ways to prevent and treat disease. Stem cells are cells that grow well in the laboratory and can differentiate into specialized cells for practically every kind of tissue in the body—for example, skin cells, heart muscle cells, or blood cells. Stem cell research is important to science and to advances in health care for several reasons. Understanding how stem cells differentiate can help scientists understand why cells sometimes develop in abnormal ways, as in cancer or birth defects. Also, stem cell lines could be used to test the safety and effectiveness of new drugs before the drugs are tested in animals and people. Finally, and perhaps most important, stem cells could be stimulated to change into specialized cells that could be used for “cellular therapies.” The specialized cells could be used to treat diseases and conditions such as Parkinson’s and Alzheimer’s diseases, spinal cord injury, burns, heart disease, diabetes, and arthritis. For example, in diabetes, specialized cells in the pancreas called islet cells cannot make insulin normally, so insulin injections are needed. Now, there is evidence that if “good” islet cells are transplanted into the pancreas, enough insulin is produced so that injections become unnecessary. Currently, stem cell products are regulated by CBER as biologics. As stem cell research continues, CBER will continue to develop standards and regulations appropriate for stem cell products.

Quality and Safety Issues

Quality and safety issues related to biologics will continue to have high priority in the 21st century. For instance, the need to identify, detect, and either remove or inactivate harmful, infectious agents (such as bacteria, viruses, or parasites) in biological products will remain a challenge. Fortunately, the availability of sophisticated analytical tools is making it easier to identify and detect contaminants, and to characterize products. An example is the “mutant assay by polymerase chain reaction and restriction enzyme cleavage” (MAPREC) that was developed at CBER. This assay can detect a specific molecule in the poliovirus that determines whether the virus will cause the paralytic form of polio. The assay is being made part of the World Health Organization’s testing requirements for live oral polio vaccine to help ensure a consistently safe vaccine.



Konstantin M. Chumakov, PhD, CBER, conducts MAPREC research on polio vaccine

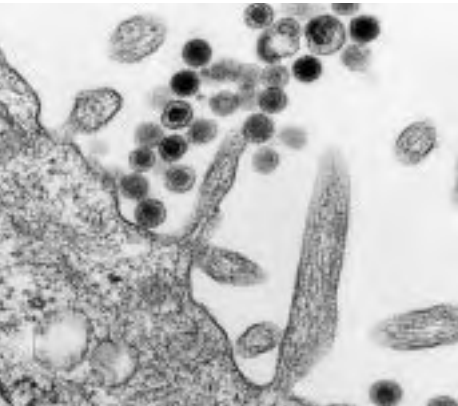


Global Considerations

The world-wide elimination of smallpox in the late 1970s was a major victory for international public health efforts. However, there is much more work to be done on the global scale. For instance, elimination of paralytic polio in all countries presents technical and logistical challenges. Also, safe and effective vaccines that can be used in global immunization efforts to prevent major infectious diseases such as tuberculosis, malaria, and AIDS are urgently needed, but are difficult to devel

op. Even if safe and effective vaccines for these diseases become available, the process of making the vaccines accessible for everyone, especially in developing countries, will be fraught with major challenges, both fiscal and logistical. Public health organizations worldwide, including CBER, will be working to meet such challenges.

International harmonization of regulatory requirements for medicinal products, including biologics, is essential. Without harmonization, different technical requirements among countries make it necessary for industry to conduct numerous similar tests on new products before the products can be marketed internationally. This increases the time that it takes to move discoveries from the laboratory to products that benefit the public. Since 1990, the International Conference on Harmonisation has coordinated international efforts to achieve common or compatible approaches to regulation. CBER takes part in numerous international harmonization activities in the areas of developing international standards, providing technical assistance, providing education and information, and participating in the development of trade policy and free trade agreements. The Center will continue to take an active role in addressing challenges presented by the harmonization of biologics regulation in the 21st century.



**Porcine Endogenous Retrovirus (PERV) isolated in fresh pig lymphocytes by Carolyn Wilson, PhD, and colleagues at CBER**

**Xenotransplantation**

*Xenotransplantation is any procedure in which live cells, tissues, or organs from a nonhuman animal source are transplanted, implanted, or infused into a human. In addition, procedures that use human body fluids, cells, tissues, or organs that have had contact with live nonhuman animal cells, tissues, or organs are defined as xenotransplantation. The increasing interest in xenotransplantation is partly because the demand for human organs for transplantation is much greater than the supply. Today, in the United States, 13 patients die each day while waiting for organ transplants. Also, evidence suggests that transplantation of cells and tissues may be beneficial for certain diseases—for instance, epilepsy, diabetes, and degenerative neurological diseases such as Parkinson’s disease—and human cells and tissues are not usually available. Although the potential benefits of xenotransplantation are great, there are also risks. For example, animal cells, tissues, or organs might harbor infectious agents such as bacteria or viruses that could cause disease in the transplant recipient and/or contacts of the recipient. Philip Noguchi, MD, Acting Director of the Office of Cellular, Tissue and Gene Therapies at CBER, emphasizes that in xenotransplantation, “the first question is, how do you test for what’s infectious?” Some infectious agents may remain dormant for many years, before they finally cause noticeable disease. Further, an infectious agent that does not cause disease in an animal may cause serious disease in a human transplant recipient or even be fatal. Research conducted at CBER has been important for understanding the safety issues associated with xenotransplantation. CBER scientists are conducting studies on known and emerging infectious agents, and on problems related to organ and tissue rejection that need to be solved before xenotransplantation products can be used safely and effectively.*

**Countering Bioterrorism**

CBER has had, and will continue to have, a key role in countering bioterrorism. The Center is responsible for the development and licensing of biological products to prevent, diagnose, and treat outbreaks from exposure to pathogens that have been identified as possible biological warfare agents. CBER staff must guide these products through the review and approval process before marketing is permitted. CBER coordinates its activities in countering bioterrorism with those of the Department of Defense and other components of the Department of Health and Human Services. Developing effective means that can be quickly put into use to protect the public against bioterrorism in the 21st century is critical.

**CONCLUSION**

If Joseph Kinyoun, the first director of the Hygienic Laboratory, could view CBER now, he might consider it to be a creation of science fiction—the changes in technology during the 20th century have been that remarkable. But then again, he might merely smile and reflect on CBER’s remarkable achievements and on how the Biologics Control Act, and the union of scientific research, law, and regulation, have made CBER what it is today.

Although today’s thoroughly modern CBER bears little physical resemblance to the modest Hygienic Laboratory of the late 19th century, its approach to protecting the public health is just the same as that used by the Hygienic Laboratory and the other organizations that were part of the evolution leading to CBER. This approach, based on science and law, has

succeeded admirably over the past 100 years and provides the bedrock foundation for CBER’s march into the next century.

Dr. Zoon predicts, "The next century will be very exciting and very challenging. There will be an explosion of new products—new drugs, new therapies—even cures, that, until recently, were only the dreams and aspirations of physicians and scientists. In the next 100 years, or sooner, we can expect to have an AIDS vaccine, a safer blood supply, perhaps synthetic blood, and safer tissue products. Advances in tissue engineering will lead to bio-engineered replacement parts. We will have new and more effective treatments for cancer, Alzheimer’s, and other devastating diseases. The fruits of proteomics and genomics research will produce customized medicines that have maximum therapeutic benefit and less harmful side effects.

Our biggest challenge will be to make sure that when we repair, replace, restore, or regenerate normal body function, we do so in the safest, most effective, and most ethical way possible. In the last ten years, CBER has laid the groundwork to meet the regulatory challenges posed by these new and potentially profound biomedical discoveries. CBER’s role in the next 100 years is to continue to advance the public health, do the very best job it can, involve the public, and always do the right thing. We welcome the future and look forward to continuing to fulfill our mission to protect and enhance the public health."

U.S. DEPARTMENT OF HEALTH  
AND HUMAN SERVICES

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September 2002

ACRONYMS USED IN THIS PUBLICATION

BCA	Biologics Control Act of 1902
BOB	Bureau of Biologics
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
DBC	Division of Biologics Control
DBS	Division of Biologics Standards
FDA	Food and Drug Administration
FD&C Act	Food, Drug, and Cosmetic Act of 1938
LBC	Laboratory of Biologics Control
MHS	Marine Health Service
NFIP	National Foundation for Infantile Paralysis
NIH	National Institute(s) of Health
NMI	National Microbiological Institute
PHS	Public Health Service
PH-MHS	Public Health and Marine Hospital Service
WHO	World Health Organization





