Biologics Centennial: 100 Years of Biologics Regulation

by Suzanne White Junod, Ph.D.

The late 19th century was one of the most exciting times imaginable for physicians and scientists working in biological research arenas around the world. Robert Koch in Germany was investigating and isolating the bacterial organisms responsible for anthrax, rabies, tuberculosis, and cholera. In France, Louis Pasteur was studying the microorganisms causing fermentation and spoilage, and he developed the first laboratory vaccine to protect fowl from chicken cholera. American bacteriologists Theobald Smith and Edmund Salmon introduced the concept of heat-killed vaccines, and used it first to prepare a vaccine against hog cholera. This burgeoning science of immunology was rapidly developing new vaccines and antitoxins that promised to prevent and cure some of the most dangerous and dreaded epidemic diseases afflicting mankind.

For example, researchers in Robert Koch's lab, Emil von Behring and Shibasaburo Kitasato, discovered that animals injected with diphtheria and tetanus toxins produced antitoxins that could be inoculated into other animals to cure these dread diseases and provide future immunity from them. Their serum therapy was tested at Berlin's Charite' hospital at the end of 1891, and the Hoechst chemical company began commercial antitoxin serum production soon after. Mortality rates from diphtheria in Europe dropped dramatically and laboratories in the United States quickly rushed to begin production of these new life-saving biological products.

The Hygienic Laboratory in Washington, D.C., (the early Public Health Service (PHS)) began a program to immunize horses to produce serum in large quantities. Likewise, serum production was begun at the Bacteriological Laboratory of the New York City Health Department. What Europe pioneered, the United States soon mass-produced. Although the first standardized serums were produced in public health departments and state laboratories, commercial manufacturers soon developed expertise in creating the careful temperature controls and sterile conditions required to produce potent sera and vaccines, as well as the injection tools—aseptic syringes—necessary for injecting these early biological drugs directly into the body, a particularly perilous procedure in the early days of the bacteriological revolution.

According to Smithsonian expert, Ray Kondratas, although the medical and popular literature had voiced concern about the need for regulation, standardization, and quality control of these new biological products, nothing lay on the table but talk at the turn of the century.[1] In 1901, however, that changed quickly after a five-year-old girl died from tetanus in a St. Louis city hospital. The admitting physician stated that she had most likely presented at the hospital nine days earlier with spinal meningitis, but was given the diphtheria antitoxin prophylactically. While investigating the case, however, municipal health officials located the horse from which the antitoxin had been

Vacuum Dried Human Serum

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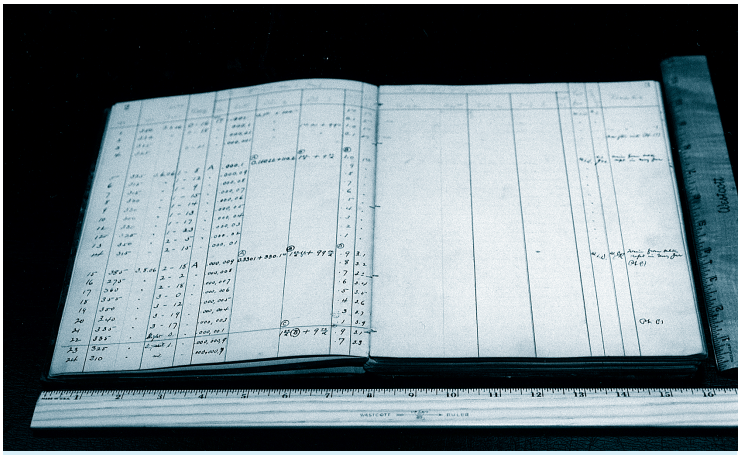
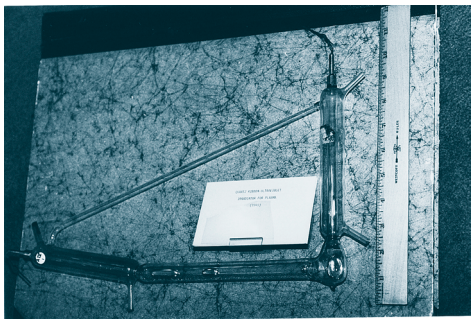
taken and learned that he—a horse named Jim, who had produced over 30 quarts of diphtheria antitoxin in his career—had been destroyed after contracting tetanus. Investigators concluded that, instead of destroying all of Jim's contaminated serum, two officials had allowed some of it to be distributed, resulting in the deaths of twelve more children throughout St. Louis. Soon thereafter, nine children in New Jersey died from contaminated smallpox vaccine, setting the stage for the adoption of rigorous standards for the emerging biological products industry.



The Hygienic Laboratory's logbook from 1895 shows the schedule of injections of horses used in the production of diphtheria antitoxin.

Unlike the fanfare that would accompany passage of the Pure Food and Drugs Act of 1906, Theodore Roosevelt's signing of the Biologics Control Act on July 1, 1902, was marked by neither comment nor discussion, much less publicity. The Medical Society of the District of Columbia had proposed the legislation initially, and the D.C. Commissioners shepherded the bill through the District of Columbia Committees of both houses of Congress. Although the PHS had been considering drafting similar legislation, Congress did not consult with the PHS before the legislation was enacted. Instead, it appointed the Surgeon General of the Marine Hospital Service, as well as those of the Army and Navy, to a Board whose members were tasked with promulgating regulations for licensing establishments engaged in the "sale and preparation of viruses, serums, toxins, and anti-toxins and analogous products in international or foreign commerce." Procedures for licensing manufacturing establishments and expiration dates were included in the Act. Under the 1944 PHS Act, both biological products and their manufacturing establishments were to be licensed. Responsibility for biologics rested with the National Institutes of Health in 1948, but biologics control came to the Food and Drug Administration (FDA) in 1972.



Prototype ultraviolet irraditor

FDA's Center for Biologics Evaluation and Research (CBER) is marking the first 100 years of biologics regulation by celebrating the Centennial of the Biologics Control Act. On September 23 and 24, 2002, CBER sponsored a science symposium entitled, "Science and the Regulation of Biological Products: From a Rich History to a Challenging Future." The symposium was dedicated to the memory of Harry Meyer, Jr., co-developer of the first licensed rubella virus vaccine. During the symposium, Meyer's friend, colleague, and co-developer, Paul D. Parkman, delivered the Harry Meyer, Jr. lecture, and a Centennial video was shown.[2]

The Smithsonian Institute's National Museum of American History has opened to the public a case exhibit for the Centennial, entitled "Safety for Millions: The Biologics Control Act of 1902 Centennial." FDA Historian John Swann, the staff of the museum's Division of Medical Sciences (headed by Ray Kondratas), and CBER staff have assembled an interesting array of artifacts exploring the evolution of biologics research and regulation. From early diphtheria antitoxins and a logbook on their testing from the Hygienic Laboratory in 1895, to diphtheria booklets and early licenses, the artifacts give a glimpse into the earliest U.S. regulation of these biological products. Especially timely are the exhibit's addition of a smallpox quarantine sign from 1919 and a vial of smallpox vaccine from the 1960s. Unusual polio artifacts, including a Polio Pioneer card and pin as well as samples of polio vaccine, highlight the exhibit's portrayal of the 1950s safety debate over the killed (Salk) v. live (Sabin) vaccines against polio; also noted is the Cutter Laboratories vaccine incident that raised concerns with the regulation and overall safety of the live polio vaccine. Finally, the exhibit covers the modern day AIDS crisis, focusing on the safety of the blood supply and including examples of old blood irradiation devices as well as one of the first AIDS test kits.

[1] Ramunas A. Kondratas, *Biologics Control Act of 1902*, *in* American Institute for the History of Pharmacy, The Early Years of Federal Food and Drug Control (J.H. Young ed., 1982).

[2] Information on the conference and the Centennial commemorative booklet is available on the CBER website at http://www.fda.gov/cber/inside/centennial.htm.