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# Early Developments in the Regulation of Biologics

TERRY S. COLEMAN\*

## I. ABSTRACT

*This article is a history of the policy positions and legal interpretations adopted by the Public Health Service (PHS) under the 1902 Biologics Control Act. PHS generally interpreted the scope of the Act narrowly because it lacked authority to deny marketing licenses for ineffective biologics and wanted to minimize the number of worthless drugs with the imprimatur of a governmental license. In addition, PHS implemented important regulatory strategies not expressly authorized by the Act.*

## II. INTRODUCTION

The Food and Drug Administration (FDA) licenses biologics for marketing under the Public Health Service Act (PHS Act),<sup>1</sup> but it approves other types of drugs as “new drugs” under the Federal Food, Drug, and Cosmetic Act (FDCA).<sup>2</sup> This article is a history of the policy positions and legal interpretations adopted by the Public Health Service (PHS)<sup>3</sup> in the early decades after enactment of the Act of July 1, 1902 (1902 Act), which was the law under which biologics were regulated until the 1902 Act was incorporated into the newly enacted PHS Act in 1944 and was administered by PHS until that responsibility was transferred to FDA in 1972. Many of the policies and interpretations developed during that early period continue to affect how FDA defines and regulates biologics.

The 1902 Act was enacted after contaminated products killed more than two dozen children in widely publicized incidents during 1901. The commercial biologics manufacturers sought a federal stamp of approval in the form of PHS licenses to stave off possible increased production of biologics by state and local health departments and to eliminate substandard manufacturing.

Because the legislation was rushed through Congress to deal with the problem of contamination, it did not address, or address clearly enough, a number of issues that arose as PHS established regulatory controls. Nevertheless, as discussed in this article, PHS implemented potency standards, rules governing manufacturing practices, a

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\* Terry S. Coleman retired from Ropes & Gray LLP.

<sup>1</sup> Public Health Service Act § 351, 42 U.S.C. § 262 (2012).

<sup>2</sup> Federal Food, Drug, and Cosmetic Act § 505, 21 U.S.C. § 355 (2012).

<sup>3</sup> PHS was established in 1798 to provide health services to merchant marine seamen and was called the Marine Hospital Service until 1902, when its name was changed to the Public Health and Marine Hospital Service to recognize the broader functions that it was actually undertaking. In 1912, it became the Public Health Service. For simplicity, this article refers to the Service as “PHS” with respect to all time periods.

system of governmental approval of each product lot before its release to the public, recall procedures, and other regulatory approaches that had no explicit support in the language of the 1902 Act.

The most significant problem that PHS faced in administering the 1902 Act, and the issue dealt with at greatest length in this article, was determining which product classes should be licensed. The statutory descriptions of products subject to licensure were potentially quite expansive, but PHS realized early on that a broad interpretation would lead to licensing many ineffective products because PHS lacked authority to deny marketing licenses for ineffective biologics. To minimize the number of worthless drugs with the imprimatur of a governmental license, PHS interpreted the Act narrowly, generally licensing only those products that were indisputably subject to the law. In a few cases PHS adopted a broader interpretation to regulate potentially unsafe products. After some years, PHS decided that it had the authority to deny licenses for ineffective products, but it nevertheless maintained a restrictive interpretation of the Act, apparently because it had come to disdain involvement in regulatory activities.

In recent years many new products with a biological origin have been introduced, and FDA has licensed some of them as biologics and treated others as new drugs. The legal literature has observed the lack of clear criteria to distinguish biologics from new drugs and has attributed some of the oddities in the criteria to obscure regulatory history.<sup>4</sup> This article shows that PHS's decision to interpret the 1902 Act narrowly except in certain circumstances where safety was an issue accounts for some of the anomalous aspects in the definition of a biologic that persist to this day.

### III. BIOLOGICS BEFORE THE 1902 ACT

At the time of the 1902 Act, the two most important biologics, by far, were smallpox vaccine and diphtheria antitoxin. The products were tremendous medical advances in themselves, and they served as prototypes for additional products. This section briefly reviews their development and suggests how vital they were to the public health and their manufacturers. The crisis of contamination incidents in 1901 involving both of these critical biologics led to passage of the 1902 Act.

#### A. *Smallpox Vaccine*

Smallpox (variola, in medical terminology) is a devastating and often fatal disease. It has been known for centuries that a smallpox survivor has long-lasting and often lifetime immunity from further infection, and this knowledge led to the intentional inoculation of healthy individuals with variola virus (in a procedure later called variolation) in the hope that the virus would cause only a mild case of smallpox and in the process the inoculated individual would gain lifetime immunity.<sup>5</sup> Although variolation typically resulted in only a mild illness (which was nevertheless unpleasant

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<sup>4</sup> See, e.g., Richard Kingham et al., *Key Regulatory Guidelines for the Development of Biologics in the United States and Europe*, in *BIOLOGICAL DRUG PRODUCTS: DEVELOPMENT AND STRATEGIES* 75, 75–77 (Wei Wang & Manmohan Singh eds., 2014); Edward L. Korwek, *What Are Biologics? A Comparative Legislative, Regulatory and Scientific Analysis*, 62 *FOOD & DRUG L.J.* 257 (2007); Edward L. Korwek, *Human Biological Drug Regulation: Past, Present, and Beyond the Year 2000*, 50 *FOOD & DRUG L.J.* 123, 142–43 (1995).

<sup>5</sup> Variolation was invented in Asia and introduced in England from Turkey in 1721. For a history of variolation, see F. FENNER ET AL., *SMALLPOX AND ITS ERADICATION* 246–58 (1988).

and disfiguring), in a small percentage of cases it was unpredictably fatal.<sup>6</sup> Another disadvantage was that variolated individuals were contagious and could pass along the fatal form of the disease to those they contacted.

In 1798, an English physician, Edward Jenner, initially published his finding that immunity against smallpox could also be conferred by inoculating an individual with virus from a person who had cowpox (at the time called vaccinia), a nonfatal disease that was transmitted from cattle to humans, in a process called vaccination to distinguish it from variolation.<sup>7</sup> Vaccination was introduced in the United States shortly after Jenner published his paper. In the early decades, physicians used “humanized” cowpox virus in arm-to-arm transfers. Fluid was taken from the vaccination site of one person, often a healthy child, and applied to the scarified (scratched) arms of other individuals.<sup>8</sup> Using humanized virus sometimes transferred diseases that the source individual had, however, and maintaining an adequate supply of humanized virus was difficult.<sup>9</sup>

The practice of using bovine vaccine to overcome the shortcomings of humanized virus was developed in Europe and introduced in the United States to a limited extent by the army during the Civil War and more broadly in 1871.<sup>10</sup> A calf or heifer was

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<sup>6</sup> By the end of the eighteenth century, the mortality rate was 0.5 percent or lower, but it had been several times higher than that in earlier years. Derrick Baxby, *Edward Jenner, William Woodville, and the Origins of Vaccinia Virus*, 34 J. HIST. MED. & ALLIED SCI. 134, 139 (1979). Smallpox caused by variolation was less severe than the naturally acquired disease presumably because infection occurred through inoculation rather than by breathing the virus.

<sup>7</sup> There are many publications about Jenner’s work. See, e.g., DERRICK BAXBY, JENNER’S SMALLPOX VACCINE: THE RIDDLE OF VACCINIA VIRUS AND ITS ORIGIN (1981); FENNER ET AL., *supra* note 5, at 258–61. That exposure to cowpox provided immunity to smallpox was widely believed in rural Britain, but Jenner methodically collected information about the phenomenon and tested it experimentally. Derrick Baxby, *Edward Jenner’s Role in the Introduction of Smallpox Vaccine*, in HISTORY OF VACCINE DEVELOPMENT 13, 14 (Stanley A. Plotkin ed., 2011). At the suggestion of Louis Pasteur, the term “vaccination” was later applied to all products that similarly provided immunity. Ian Bailey, *Edward Jenner, Benefactor to Mankind*, in HISTORY OF VACCINE DEVELOPMENT 21, 25 (Stanley A. Plotkin ed., 2011).

<sup>8</sup> MICHAEL WILLRICH, POX: AN AMERICAN HISTORY 180–81 (2011).

<sup>9</sup> Cowpox did not occur naturally in the United States, so the virus had to be imported in dried form from England and then maintained in existence through an endless series of vaccinations in which material from the disease vesicles of a vaccinated individual was used to vaccinate someone else. A new individual had to be vaccinated every week or so to maintain the chain, except that virus in dried material could survive for some weeks and allow breaks in the continuous series of vaccinations. Because this process was so demanding, physicians established a few “vaccine institutions” to maintain a supply of cowpox virus. James Smith opened the first vaccine institution in Baltimore in 1802, and in 1809 Maryland granted him the proceeds of a lottery in exchange for providing free vaccine to all residents of the state. Beginning in 1814 Virginia made an annual payment to him for furnishing free vaccine. Smith sought compensation from Congress to provide vaccine to the entire country, and in 1813 Congress passed “An Act to Encourage Vaccination,” 2 Stat. 806, under which he was appointed by the President to provide vaccine nationally. The law gave him no direct compensation, although he got postal franking privileges and could charge for the vaccine. Smith set up a network of twenty deputies, and they vaccinated an estimated hundred thousand people. The law was controversial because of the special rights it gave to Smith’s vaccine institution and questions about its constitutionality. It was repealed in 1822 after an incident in which Smith mailed smallpox material to a deputy who, thinking it was cowpox, used it for inoculations. The variolated individuals were contagious and fatally infected others. See, e.g., WHITFIELD J. BELL, JR., *Dr. James Smith and the Public Encouragement for Vaccination for Smallpox*, in THE COLONIAL PHYSICIAN & OTHER ESSAYS 131 (1975).

<sup>10</sup> *The Relative Immunizing Value of Human and Bovine Vaccine Virus*, 148 BOS. MED. & SURGICAL J. 24 (1903).

infected with vaccinia virus,<sup>11</sup> virus for inoculation of humans was harvested from the vaccinia-caused vesicles, and additional animals were infected from the first to increase the quantity of vaccine produced.<sup>12</sup> Making vaccine was relatively easy; by the mid-1870s many “vaccine farms” had been established around the country, typically by local physicians, and bovine vaccine almost completely replaced humanized virus.<sup>13</sup> In 1876, the New York City Board of Health became the first municipal agency to produce smallpox vaccine.<sup>14</sup>

### B. *Diphtheria Antitoxin*

Diphtheria was a dreaded disease with a high fatality rate, particularly in children. The infecting bacteria secrete a protein toxin (called an exotoxin), which creates a tough membrane in the nasopharyngeal tract that can cause suffocation and spreads through the body causing damage to the heart and nerves. During the 1880s, German and French scientists identified the diphtheria bacterium and determined that its toxin was the cause of the harm.<sup>15</sup> An 1890 article disclosed that animals injected with diphtheria bacteria developed “antitoxins” in their blood, which could be transferred to other animals to prevent the injurious effects of diphtheria toxin. After additional animal and human trials and resolution of production problems, a German company began selling diphtheria antitoxin serum for human use in August 1894.

Diphtheria antitoxin was produced by obtaining diphtheria bacteria from the throat of an infected individual and growing it in the laboratory to produce large quantities of bacteria and toxin.<sup>16</sup> The bacteria were then killed and filtered out to leave only the toxin, which was injected into horses in gradually increasing amounts over weeks or months, during which time antitoxins were formed in the horses’ blood. After test bleedings showed a high antitoxin content, several liters of blood were drawn from a horse and set aside to clot. The clot fell to the bottom of the container, leaving the antitoxin-laden serum to be bottled for distribution. Potency of the batch was calibrated by injecting guinea pigs with a mixture of toxin and varying amounts of antitoxin and assessing the effects of the mixtures on the animals.<sup>17</sup> When injected into

<sup>11</sup> Although Jenner used cowpox virus, at some point vaccine producers unknowingly began using vaccinia virus, thinking that it was cowpox. It was established in 1939 that vaccinia is a virus different from both smallpox and cowpox. WILLRICH, *supra* note 8, at 183.

<sup>12</sup> See, e.g., Joseph McFarland, *Vaccine Virus – Its Preparation and the Complications Attending Its Use*, 38 J. AM. MED. ASS’N 217 (1902); M.J. Rosenau, *Vaccine Virus*, 54 J. AM. MED. ASS’N 250 (1910).

<sup>13</sup> WILLRICH, *supra* note 8, at 182.

<sup>14</sup> WADE W. OLIVER, *THE MAN WHO LIVED FOR TOMORROW: A BIOGRAPHY OF WILLIAM HALLOCK PARK, M.D.* 132–33 (1941). New York had begun production in 1871, but that effort was unsuccessful and the program was restarted in 1876.

<sup>15</sup> For history of the development of diphtheria antitoxin and related issues, see, for example, TERRA ZIPORYN, *DISEASE IN THE POPULAR AMERICAN PRESS* 35–62 (1988); C.H. Browning, *Emil Behring and Paul Ehrlich: Their Contributions to Science*, 175 NATURE 570 (1955); Esteban Rodriguez-Ocaña, *The Social Production of Novelty: Diphtheria Serotherapy*, “Herald of the New Medicine,” 27 DYNAMIS 21 (2007) (introducing a series of articles on diphtheria antitoxin); William H. Welch, *The Treatment of Diphtheria by Antitoxin*, 6 BULL. JOHNS HOPKINS HOSP. 97 (1895).

<sup>16</sup> See, e.g., Fred I. Lackenbach, *Pharmacy in Its Higher Development*, 1 J. AM. PHARM. ASS’N 959, 961–62 (1912); C.F. Nixon, *Antitoxin Serums and Vaccine Virus*, 28 PHARM. ERA 119 (1902); Charles M. Twining, *The Preparation of Serums and Antitoxins*, 5 J. AM. PHARM. ASS’N 21, 21–26 (1916).

<sup>17</sup> The method for determining potency changed over time but in essence involved calculating the amount of antitoxin from a particular batch that was necessary to avoid guinea pig deaths from a known amount of toxin, with the result expressed in immunity units. M.J. ROSENAU, *TREAS. DEP’T, PHS*,

a diphtheria patient, the antitoxin serum ordinarily neutralized the toxin in the patient's body and eliminated the disease.

In 1894, Joseph J. Kinyoun, the Director of PHS's Hygienic Laboratory—a small bacteriology laboratory that Kinyoun had run since its start in 1887<sup>18</sup>—and Herman Biggs from the New York City Board of Health were in Europe to meet with scientists about developments there. Both learned how to make diphtheria antitoxin and brought the information home. New York City began distributing diphtheria antitoxin on January 1, 1895, and the Hygienic Laboratory did the same shortly afterwards for use in the Marine Hospital Service (a governmental medical service for merchant marine seamen).<sup>19</sup> PHS encouraged state and local health departments to produce diphtheria antitoxin, and PHS and New York City provided technical assistance to them and to commercial manufacturers that sought it.<sup>20</sup> A number of city health departments began making diphtheria antitoxin.<sup>21</sup> Commercial manufacturing began about the same time, with Parke, Davis & Co. (Parke-Davis) of Detroit and H.K. Mulford and Co. (Mulford) of Philadelphia being the first, after they had hired academic bacteriologists to help them.<sup>22</sup> By 1896 there were at least five commercial companies selling diphtheria antitoxin and more were starting up.<sup>23</sup> Commercial manufacturers also began making smallpox vaccine and other types of serums.<sup>24</sup>

### C. Contamination Incidents in 1901

Two highly publicized incidents in late 1901 involving fatalities drew attention to unsafe diphtheria antitoxin and smallpox vaccine. The St. Louis Health Department ran a low-budget operation in which a part-time bacteriologist assisted by a janitor from the City Chemist's office used horses stabled on the grounds of the poor house to produce diphtheria antitoxin. One of the horses developed tetanus a few days after it had been bled for serum, but instead of being discarded, the serum was labeled with the date of an earlier bleeding and distributed without having been tested in guinea

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HYGIENIC LAB. BULL. NO. 21, THE IMMUNITY UNIT FOR STANDARDIZING DIPHTHERIA ANTITOXIN 18–24 (1905).

<sup>18</sup> David M. Morens & Anthony S. Fauci, *The Forgotten Forefather: Joseph James Kinyoun and the Founding of the National Institutes of Health*, 3 MBIO (July/August 2012), <http://mbio.asm.org>.

<sup>19</sup> OLIVER, *supra* note 14, at 98–125, 161–90; Ramunas A. Kondratas, *Biologics Control Act of 1902*, in *THE EARLY YEARS OF FEDERAL FOOD AND DRUG CONTROL* 8, 11 (James Harvey Young symp. chairman, 1982).

<sup>20</sup> Jonathan M. Liebenau, *Public Health and the Production and Use of Diphtheria Antitoxin in Philadelphia*, 61 BULL. HIST. MED. 216, 235 (1987).

<sup>21</sup> Kondratas, *supra* note 19, at 11.

<sup>22</sup> LOUIS GALAMBOS WITH JANE ELIOT SEWELL, NETWORKS OF INNOVATION 13–21 (paperback ed. 1997); JONATHAN LIEBENAU, MEDICAL SCIENCE AND MEDICAL INDUSTRY 57–67 (1987); Milton L. Hoefle, *The Early History of Parke-Davis and Company*, 25 BULL. HIST. CHEMISTRY 28, 31–33 (2000).

<sup>23</sup> Kondratas, *supra* note 19, at 12.

<sup>24</sup> Mulford began selling smallpox vaccine in 1898, GALAMBOS WITH SEWELL, *supra* note 22, at 21, and Parke-Davis sometime before 1901, *see* PARKE, DAVIS & CO., PHYSICIANS' MANUAL OF THERAPEUTICS 80–81, 498 (1901) (during 1901 Parke-Davis was selling diphtheria and tetanus antitoxins as well as antistreptococcal and antitubercle serums and smallpox vaccine). The first published list of licensees under the 1902 Act included eight manufacturers of smallpox vaccine. *Operations Under Act Approved July 1, 1902*, 19 PUB. HEALTH REP. 1195 (1904). LIEBENAU, *supra* note 22, at 60, 62 (stating that Mulford began selling tetanus antitoxin in 1895 and by 1898 was making eleven biologics).



pigs because the supply of antitoxin from previous bleedings had been exhausted.<sup>25</sup> The serum was contaminated with tetanus toxin and resulted in the deaths of thirteen children. The incident received national publicity for weeks as the deaths accumulated and the investigation proceeded. Diphtheria fatalities in Chicago increased by one-third in November 1901 as parents refused to allow the use of antitoxin.<sup>26</sup>

The fall of 1901 was also the time of a national smallpox epidemic. Smallpox had been relatively uncommon in the United States for decades until an epidemic began in the South in the winter of 1898-99 and over the next five years spread across the country.<sup>27</sup> Much of the smallpox was a new, milder strain (called variola minor), which had a lower fatality rate, but some of the outbreaks, particularly in the Northeast, were classic smallpox (variola major).<sup>28</sup> The demand for smallpox vaccine surged and, in the rush to get product to the market, some of the vaccine was inactive or contaminated.<sup>29</sup>

Camden, New Jersey, was the site of a disastrous vaccine problem. There were about eighty cases of tetanus including eleven fatalities among individuals who had recently been vaccinated.<sup>30</sup> Many more children died from tetanus than from smallpox. The Camden Board of Health could not find vaccine that was contaminated and concluded that the tetanus cases were the result of infections at the vaccination site when the scabs fell or were rubbed off.<sup>31</sup> Nevertheless, the unusual outbreak of tetanus—“[t]he number of cases observed in 1901 was out of all proportion to what has been observed heretofore”<sup>32</sup>—combined with the fact that almost all of the vaccine came from a single manufacturer (Mulford) led to further investigation and argument over the data and to unresolved concern about vaccine safety with a strong suspicion that the problem was contaminated vaccine.<sup>33</sup> Although the Camden incident was the

<sup>25</sup> CITY OF ST. LOUIS HEALTH DEP'T, TWENTY-FIFTH ANNUAL REPORT OF THE HEALTH COMMISSIONER FOR THE YEAR ENDING MARCH 31ST, 1902, at 257-62 (1902); Ross E. DeHovitz, *The 1901 St. Louis Incident: The First Modern Medical Disaster*, 133 PEDIATRICS 964 (2014).

<sup>26</sup> *Unjustifiable Distrust in Diphtheria Antitoxin*, 37 J. AM. MED. ASS'N 1396 (1901); Kondratas, *supra* note 19, at 14-16.

<sup>27</sup> WILLRICH, *supra* note 8, at 10, 167.

<sup>28</sup> *Id.* at 41-74, 167; *The Vaccination Question*, 37 J. AM. MED. ASS'N 1680 (1901).

<sup>29</sup> WILLRICH, *supra* note 8, at 167; PHS, TREAS. DEP'T, DOC. NO. 2331, ANNUAL REPORT OF THE SURGEON-GENERAL OF THE PUBLIC HEALTH AND MARINE-HOSPITAL SERVICE OF THE UNITED STATES FOR THE FISCAL YEAR 1902, at 446-49 (1903) [hereinafter 1902 PHS ANNUAL REPORT]; *The Vaccination Question*, *supra* note 28 (arguing that the federal government should investigate reports that much smallpox vaccine has been unreliable and that, if it does not, the American Medical Association should do so).

<sup>30</sup> LIEBENAU, *supra* note 22, at 80; WILLRICH, *supra* note 8, at 171-79; Robert N. Willson, *An Analysis of Fifty-Two Cases of Tetanus Following Vaccinia* (pts. 1 & 2), 38 J. AM. MED. ASS'N 1147, 1222 (1902) (reporting eight fatalities in the greater Philadelphia area in the fall of 1901 in addition to eleven fatalities in Camden).

<sup>31</sup> *Vaccination, Antitoxin and Tetanus*, 48 SANITARIAN 32 (1902) (reprinting the report of the Camden Board of Health).

<sup>32</sup> Joseph McFarland, *Tetanus and Vaccination – An Analytical Study of Ninety-Five Cases of This Rare Complication*, 8 MED. 441, 456 (1902); see also *The Relation of Tetanus to Vaccination*, 146 BOS. MED. & SURGICAL J. 441 (1902).

<sup>33</sup> LIEBENAU, *supra* note 22, at 84-87; WILLRICH, *supra* note 8, at 201-06.

most publicized, there were tetanus fatalities related to smallpox vaccine in other cities as well, including Philadelphia, Atlantic City, Bristol (Pennsylvania), and Cleveland.<sup>34</sup>

#### D. Preventing a Recurrence

The 1901 incidents led to discussion about preventing a recurrence, with the options being governmental regulation of biologics manufacturers or governmental manufacture of the products.<sup>35</sup> In speaking to the New York Academy of Medicine in February 1902, Milton Rosenau, the director of PHS's Hygienic Laboratory, reported on his laboratory's tests of vaccine produced by various manufacturers: there was substantial contamination—"immense numbers of bacteria" present in the vaccines, in the words of a journal news report.<sup>36</sup> "Dr. Rosenau said that his opinion, based on the results of this investigation, was that governmental control should be exercised."<sup>37</sup> Some medical publications also called for governmental inspection and licensing of biologics manufacturers.<sup>38</sup> The *Journal of the American Medical Association* editorialized that "[i]f necessary, legislation should be had forbidding the sale or use of any antitoxin not . . . tested and certified by some competent authority."<sup>39</sup> The *New York Times* called for more intensive inspection and supervision of commercial biologics producers.<sup>40</sup> In October 1902, the Conference of State and Provincial Boards of Health of North America recommended that vaccine should be produced either by governments or by private producers "under the closest supervision of qualified government officials."<sup>41</sup>

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<sup>34</sup> WILLRICH, *supra* note 8, at 168. Vaccination in Cleveland was stopped in mid-1901 after three cases of tetanus were attributed to contaminated vaccine. *The Cleveland Experiment*, 87 CIN. LANCET-CLINIC 580 (1902). A letter from Parke-Davis to a medical journal asserted that its vaccine was not involved in tetanus fatalities following vaccination in Camden, Atlantic City, Bristol, Cleveland, and St. John, N.B. Parke, Davis & Co., Letter to the Editor (Dec. 7, 1901), 45 PAC. MED. J. 25 (1902).

<sup>35</sup> WILLRICH, *supra* note 8, at 197-98.

<sup>36</sup> *Vaccination Before the Academy of Medicine*, 75 N.Y. MED. J. 375 (1902); see also John F. Anderson, *Remarks on the Preparation of Vaccine Virus*, 29 PUB. HEALTH PAPERS & REP. 221 (1903) (describing the bacterial contamination of products discovered in the initial inspections under the 1902 Act); M.J. ROSENAU, PHS, TREAS. DEP'T, HYGIENIC LAB. BULL. NO. 16, THE ANTISEPTIC AND GERMICIDAL PROPERTIES OF GLYCERIN 30 (1903) (reporting that, contrary to belief, mixing glycerin with smallpox vaccine cannot be depended on to prevent tetanus transmission).

<sup>37</sup> *Society Reports: New York Academy of Medicine*, 61 MED. REC. 391 (1902).

<sup>38</sup> E.g., *Governmental Control of Therapeutic Serums, Vaccine, Etc.*, 61 MED. REC. 495 (1902) (stating "Government control of [biologics] . . . [is] absolutely imperative."); W.R. Inge Dalton, *The Responsibility for the Recent Deaths from the Use of Impure Antitoxins and Vaccine Virus*, 40 MED. TIMES & REG. 3 (1902) (arguing that boards of health should cease production of their own biologics and cease buying from the lowest bidder and instead enforce regulations leading to reliable products).

<sup>39</sup> *Unjustifiable Distrust in Diphtheria Antitoxin*, *supra* note 26, at 1397.

<sup>40</sup> Editorial, *Commercial Virus and Antitoxin*, N.Y. TIMES, Nov. 18, 1901, at 6.

<sup>41</sup> *Conference of State and Provincial Boards of Health of North America*, 62 MED. REC. 788, 790 (1902). The Surgeon General of PHS attended the conference and referred to the 1902 Act, but as summarized in the report, his comments seem to have been interpreted as meaning merely that a bill had been introduced. *Id.* at 789.

#### IV. ENACTMENT OF THE BIOLOGICS CONTROL ACT OF 1902

On July 1, 1902, President Theodore Roosevelt signed the 1902 Act, which is now called the Biologics Control Act.<sup>42</sup> Broadly speaking, it prohibited the sale, barter, or exchange of any “virus, therapeutic serum, toxin, antitoxin, or analogous product” in interstate or foreign commerce, or in the District of Columbia, unless the product was made in an establishment licensed annually by PHS. In addition, the law prohibited false statements and required the governmental license number and an expiration date in the product label.

Histories of the 1902 Act generally describe it simply as a congressional response to the St. Louis and Camden incidents<sup>43</sup> as if the law was the outcome of some routine congressional process, or as a bill proposed by the Medical Society of the District of Columbia.<sup>44</sup> Neither explanation is correct. As Jonathan Liebenau pointed out, the 1902 Act was an initiative of the large biologics manufacturers,<sup>45</sup> and it was enacted with the secret cooperation of PHS. This section outlines the process by which the 1902 Act became law.

##### A. *The Industry’s Urgent Desire for a Federal Licensing System*

The biologics industry sought passage of the 1902 Act primarily because it feared that the contamination incidents would cause additional state and local health departments to make their own vaccines and antitoxins, wiping out the commercial biologics business.<sup>46</sup> As mentioned above, after the 1901 incidents, discussion focused on the alternatives of governmental production or governmental regulation. Governmental manufacturing had been a threat to the industry since its inception, and the St. Louis and Camden incidents increased the odds of a wholesale takeover of biologics production by health departments.

The production of biologics had begun in the public sector, but once commercial manufacturers learned how to make them, the companies wanted government out of the business.<sup>47</sup> Their main arguments were that the production facilities of local governments were inadequate—an argument with some validity because funding

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<sup>42</sup> Act of July 1, 1902, Pub. L. No. 57-244, 32 Stat. 728, 42 U.S.C. §§ 141–48 (repealed 1944). In the early years, both in correspondence and in internal documents, PHS almost always referred to the legislation as “the Act of July 1, 1902” or in similar terms. PHS started calling it the “Biologics Act” in the 1920s and sometimes the “Biologics Control Act” in the 1930s. *E.g.*, Letter from White, Acting Surgeon Gen., to William E. Docks, United Fruit Co. (June 6, 1926) (on file with the Nat’l Archives, Rec. Grp. 443, Gen. Recs. 1932–1948, File 425S) (“Under the terms of the law of July 1, 1902, usually known as the ‘Biologics Act’ . . .”); Letter from Thomas Parran, Surgeon Gen., to Rep. Edward L. O’Neill (Jan. 15, 1938) (on file with the Nat’l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 725O) (“Biologics Control Act of 1902”).

<sup>43</sup> *E.g.*, FDA, SCIENCE AND THE REGULATION OF BIOLOGICAL PRODUCTS: FROM A RICH HISTORY TO A CHALLENGING FUTURE 13 (2002); William R. Pendergast, *Biologic Drugs*, in FOOD AND DRUG LAW 303, 307 (Richard M. Cooper ed., 1991); Margaret Pittman, *The Regulation of Biologic Products, 1902–1972*, in NAT’L INST. OF ALLERGY & INFECTIOUS DISEASES, INTRAMURAL CONTRIBUTIONS, 1887–1987, at 61 (Harriet R. Greenwald & Victoria A. Harden eds., 1987).

<sup>44</sup> *E.g.*, WILLRICH, *supra* note 8, at 200; John Parascandola, *The Public Health Service and the Control of Biologics*, 110 PUB. HEALTH REP. 774, 774 (1995); Kondratas, *supra* note 19, at 16.

<sup>45</sup> LIEBENAU, *supra* note 22, at 88–89. Liebenau cited no authority for this conclusion but appears to have correctly deduced the origin of the Act based on his thorough study of the industry at that time.

<sup>46</sup> *Id.* at 88.

<sup>47</sup> Liebenau, *supra* note 20, at 235–36.

depended on elected officials—and that governments should not compete against private enterprise.<sup>48</sup> For several years there had been a campaign in the pharmaceutical and medical press, probably generated by biologics manufacturers, against “municipal socialism” and alleged unsanitary conditions in governmental facilities.<sup>49</sup> Mulford sued several times attempting to stop governmental production.<sup>50</sup> A petition circulated by the trade publication *Druggists’ Circular* and signed by over four thousand doctors and druggists asked New York City to stop producing biologics.<sup>51</sup>

After the 1901 incidents, Massachusetts, which already made diphtheria antitoxin, seemed headed toward state production of smallpox vaccine. In January 1902 *The Boston Medical and Surgical Journal* published a long editorial on the history of smallpox vaccine in the United States and Europe that concluded that it was preferable for vaccine to be produced by states and large cities than by sometimes “unscrupulous” commercial entities.<sup>52</sup> The Boston Board of Health asked the Massachusetts legislature to authorize the state Board of Health to produce vaccine,<sup>53</sup> and in June 1902 the state Board recommended to the legislature that it produce vaccine for free distribution.<sup>54</sup>

Moreover, there was an ongoing precedent for biologics manufacturing by the federal government. Biologics manufacturers were at war with the Agriculture

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<sup>48</sup> *Id.* See also Gardner T. Swarts, Sec’y, R.I. State Bd. Health, *Is it Advisable for a State to Provide Vaccine Virus*, 1 SIXTEENTH ANNUAL REPORT OF THE STATE BOARD OF HEALTH AND VITAL STATISTICS OF THE COMMONWEALTH OF PENNSYLVANIA 464 (1901) (setting forth, prior to the St. Louis and Camden incidents, the advantages and disadvantages of governmental production versus governmental regulation of commercial producers).

<sup>49</sup> *E.g.*, Editorial, *Chicago’s Work Against Smallpox*, 3 AM. MED. 331 (1902) (“The state or city as a manufacturer of antitoxin, vaccine, etc., in competition with its own citizens, is such an un-American proceeding that only temporarily and under very exceptional circumstances can it be justified.”); *Governmental Control of Therapeutic Serums, Vaccine, Etc.*, 61 MED. REC. 495 (1902) (“No municipal or State board has any right to manufacture [biologics] for sale, and thus compete with private manufacturers . . . [I]t is the Government’s business to inspect products, but never to manufacture them for sale.”); Editorial, 27 PHARM. ERA 261 (1902) (“The supply of [antitoxin and smallpox vaccine] by municipal authorities subjects private manufacturers who have brought the preparation of serums and lymph to the highest degree of perfection, to an unfair and needless competition.”); *Should Cities Go Into the Drug Business?*, 74 ST. LOUIS MED. & SURGICAL J. 152 (1898) (“From the standpoint of fairness and justice, no municipality should ever try to be a rival of a legitimate manufacturing concern . . .”); *The Manufacture of Serums*, 79 MED. NEWS 825, 826 (1901) (asserting that the risk from commercial production was “greed” and from governmental production was “political influence in appointments” and concluding that competition among private companies was superior to municipal manufacture).

<sup>50</sup> LIEBENAU, *supra* note 22, at 71.

<sup>51</sup> *Against the Sale of Antitoxin and Vaccine by the Board of Health*, 11 MERCK’S REP. 176 (1902); *Topics of the Times*, N.Y. TIMES, Mar. 20, 1902, at 8. New York stopped selling antitoxin outside the city in 1903. *Health Department Stops Selling Antitoxin to Outsiders*, 12 MERCK’S REP. 239 (1903); *Report of Health Commissioner on the Manufacture of Serums*, 63 OIL PAINT & DRUG REP., June 29, 1903, at 10.

<sup>52</sup> *The Production of Vaccine Lymph*, 146 BOS. MED. & SURGICAL J. 22 (1902). *But see* A.M. Phelps, *Boards of Health and the Manufacture of Vaccine Virus and Antitoxins*, 146 BOS. MED. & SURGICAL J. 99 (1902) (letter to the editor opposing the proposal).

<sup>53</sup> S.H. Durgin, *Vaccination and Smallpox*, 146 BOS. MED. & SURGICAL J. 114, 115 (1902).

<sup>54</sup> *State Vaccine Lymph*, 146 BOS. MED. & SURGICAL J. 676 (1902); *The Fly in the Apothecary’s Ointment*, 146 BOS. MED. & SURGICAL J. 701 (1902); *State Manufacture of Vaccine in Massachusetts*, 4 AM. MED. 86 (1902). Massachusetts went on to expand its governmental production of biologics. BARBARA GUTMANN ROSENKRANTZ, *PUBLIC HEALTH AND THE STATE: CHANGING VIEWS IN MASSACHUSETTS, 1842–1936* 124–26 (1972); M.J. Rosenau, *Federal Supervision of Biologic Therapeutic Products*, 18 AM. J. PUB. HYGIENE 126, 126 (1908).

Department over the Bureau of Animal Industry's practice of making and distributing certain veterinary biologics for free; the manufacturers wanted the Bureau to restrict its activities to experimental research.<sup>55</sup> In the late 1890s the Bureau began giving away its hog cholera serum and its vaccine for blackleg, a cattle and sheep disease, which provoked strong opposition from commercial manufacturers.<sup>56</sup> Parke-Davis enlisted Michigan Senator James McMillan, who wrote the Secretary of Agriculture that he was "inclined strongly to the view" of Parke-Davis that the Department "should no more distribute serum than it should distribute pitch-forks,"<sup>57</sup> but the Secretary refused to discontinue the program.<sup>58</sup>

The 1902 Act may also have been motivated by a desire of the large manufacturers to reduce competition by establishing strict governmental standards that small producers would have difficulty meeting. A body of literature argues that companies often seek regulation to eliminate competitors or otherwise gain a business advantage.<sup>59</sup> Shortly after the law was enacted, Parke-Davis wrote to PHS with suggestions for regulations stating, "As you are perhaps aware, the regulations cannot be too stringent for us."<sup>60</sup> It is impossible to disentangle the desire for strict regulations to boost public confidence in biologics from the desire for such regulations to eliminate competitors, but it is noteworthy that several biologics producers went out of business because they were unable to pass PHS inspections.<sup>61</sup>

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<sup>55</sup> ALAN L. OLMSTEAD & PAUL W. RHODE, *ARRESTING CONTAGION* 149–52 (2015).

<sup>56</sup> The National Archives has a large number of letters to the Agriculture Department from Pasteur Vaccine Co., Parke-Davis, and Mulford, and from members of Congress writing on their behalf, complaining about the free vaccine program during the period 1897–1904 (Rec. Grp. 17, Cent. Correspondence 1895–1906, File 3290).

<sup>57</sup> Letter from Sen. James McMillan to James Wilson, Sec'y Agric. (Jan. 6, 1899). Eleven months later McMillan wrote again, this time asking for the Secretary's views on Parke-Davis's complaint that the Agriculture Department was planning to distribute free blackleg vaccine for years. Letter from Sen. James McMillan to James Wilson, Sec'y Agric. (Dec. 6, 1899) (enclosing Letter from Parke-Davis to McMillan (Dec. 1, 1899)) (all on file with the Nat'l Archives, Rec. Grp. 17, Cent. Correspondence 1895–1906, File 3290).

<sup>58</sup> The Department's defense was that its statutory mission was to eradicate animal diseases and that it was testing whether widespread use of blackleg vaccine would accomplish that. Widespread use would not occur with commercial vaccine, the Secretary said, in part because of its "exorbitant" cost and in part because some stock raisers would not use vaccines if any cost was involved. Letter from Sec'y Agric. to Sen. James McMillan (Dec. 9, 1899) (on file with the Nat'l Archives, Rec. Grp. 17, Cent. Correspondence 1895–1906, File 3290).

<sup>59</sup> *See, e.g.*, DONNA J. WOOD, *STRATEGIC USES OF PUBLIC POLICY* (1986); GABRIEL KOLKO, *THE TRIUMPH OF CONSERVATISM: A REINTERPRETATION OF AMERICAN HISTORY, 1900–1916* (1963); Ilyse D. Barkan, *Industry Invites Regulation: The Passage of the Pure Food and Drug Act of 1906*, 75 *AM. J. PUB. HEALTH* 18 (1985); Marc T. Law & Gary D. Libecap, *The Determinants of Progressive Era Reform: The Pure Food and Drugs Act of 1906*, in *CORRUPTION AND REFORM: LESSONS FROM AMERICA'S ECONOMIC HISTORY* 319 (Edward L. Glaeser & Claudia Goldin eds., 2006).

<sup>60</sup> Letter from Chas. A. Cotterill, Parke-Davis, to Supervising Surgeon Gen. (Aug. 9, 1902) (on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 15395) [hereinafter Cotterill Letter]. The phrase "As you are perhaps aware" implies prior discussions between Parke-Davis and PHS regarding the requirements that the company wanted PHS to impose.

<sup>61</sup> Walter Wyman, Surgeon Gen., *President's Address*, 29 *PUB. HEALTH PAPERS & REP.* 1, 2 (1903) ("Ten plants were inspected, six recommended for license and four for refusal. Of the four refused, two were subsequently reinspected, the faults having been remedied. Several establishments, rather than submit to inspection, closed their business. In all, eight establishments in the United States have received licenses from the Secretary of the Treasury.").

*B. The Extraordinary Handling of the Bill by a Congress  
Hostile to Governmental Regulation*

The Senate bill that resulted in the 1902 Act was introduced on April 4, 1902,<sup>62</sup> by John C. Spooner, a Republican from Wisconsin and one of “The Four” (or the “Big Four”) Senators who controlled the Senate’s activities at that time.<sup>63</sup> The Four also controlled the House of Representatives through Speaker David B. Henderson, a congressman from Iowa who was loyal to Iowa Senator William B. Allison, one of The Four.<sup>64</sup> Spooner’s bill was referred to the District of Columbia Committee, chaired by Senator McMillan, a longtime political ally of The Four.<sup>65</sup>

Although the archives have been purged of PHS documents related to the legislation, the circumstantial evidence that the bill was a joint undertaking of the industry and PHS is overwhelming. The Republican-controlled Fifty-Seventh Congress was conservative, allied with big business, and hostile to governmental regulation of business.<sup>66</sup> Nevertheless, the bill flew through Congress with amazing speed and almost invisibly—there were no committee hearings, no request for a report from the Administration, no “active steps” by PHS to further its adoption,<sup>67</sup> no public statements or speeches about the bill, no floor debate, and no recorded votes, and both Houses passed the bill in the closing days of the session in June 1902. It is inconceivable that the Congress of 1902 would have passed a bill that the *New York Times* called “a dangerous expansion of Federal authority” and reflecting “the principle of paternalism”<sup>68</sup> in this extraordinarily expedited manner unless the biologics industry was begging for immediate federal regulation. The actions of The Four with respect to the 1902 Act can be contrasted with their actions with respect to

<sup>62</sup> S. 4960, 57th Cong. (1902).

<sup>63</sup> The Four were Nelson W. Aldrich of Rhode Island, Orville H. Platt of Connecticut, William B. Allison of Iowa, and John C. Spooner of Wisconsin. HORACE SAMUEL MERRILL & MARION GALBRAITH MERRILL, *THE REPUBLICAN COMMAND 1897–1913*, at 4 (1971); *see id.* at 19–20 (indicating that although the position of Majority Leader did not yet exist, Aldrich was often referred to as “the Republican leader in the Senate”); *see also* MICHAEL WOLRAICH, *UNREASONABLE MEN* 34 (2014).

<sup>64</sup> MERRILL & MERRILL, *supra* note 63, at 118.

<sup>65</sup> In the Fifty-First Congress (1889–1891) a small group of Senators, including Aldrich, Allison, and Spooner, often met at McMillan’s house in the evenings to discuss Senate issues, and the close relationship continued in subsequent Congresses. DOROTHY GANFIELD FOWLER, JOHN COIT SPOONER: DEFENDER OF PRESIDENTS 137–38, 201 (1961); *see also* Geoffrey G. Drutchas, *Gray Eminence in a Gilded Age: The Forgotten Career of Senator James McMillan of Michigan*, 28 MICH. HIST. REV. 79, 94–95 (2002).

<sup>66</sup> MERRILL & MERRILL, *supra* note 63, at 3–7, 19, 39, 93; *see also id.* at 25 (“Aldrich [the Republican leader in the Senate] embraced a simple, direct philosophy concerning the role of government. He believed that business and government should combine to run the country. Within that framework he was convinced that business should play the leading role. Government should serve business and exercise great restraint on those who tried to use government to harness the power of business.”).

<sup>67</sup> J.W. Kerr, Ass’t Surgeon Gen., *Address to the Biological Sec.* (Feb. 5, 1917), in PROCEEDINGS OF SIXTH ANNUAL MEETING OF NATIONAL ASSOCIATION OF MANUFACTURERS OF MEDICINAL PRODUCTS 231, 232 (1917) [hereinafter 1917 ANNUAL MEETING] (“But in 1902, without the Bureau taking the active steps, the law which you know as the law of July 1, 1902, was adopted by Congress.”).

<sup>68</sup> Editorial, *Virus, Antitoxins, and Serums*, N.Y. TIMES, Apr. 14, 1902, at 8 (The *Times* nevertheless supported the proposed legislation since it was “aimed to correct an evil yet more dangerous as directly and immediately affecting the public health.”).

the Food and Drugs Act, which was before Congress at the same time but was opposed by some industries. The Four blocked the Food and Drugs Act for years.<sup>69</sup>

Moreover, it is clear that PHS secretly cooperated in passing the bill.<sup>70</sup> Shortly after the bill was introduced, it was endorsed by the District of Columbia Medical Society, which also recommended an amendment to reduce the power of the Secretary of the Treasury and PHS (which was part of the Treasury Department) by requiring rules under the Act to be issued by a board of officials from various agencies, instead of by the Secretary alone, as the bill provided.<sup>71</sup> It said the change would be “more in keeping with the spirit of American institutions to separate the legislative and the executive functions” under the bill.<sup>72</sup> The two physicians who shepherded the endorsement though the Medical Society were members of the public health community and colleagues of the PHS physicians<sup>73</sup> and would not have recommended

<sup>69</sup> Beginning in June 1902, the same month in which the 1902 Act was waved through the Senate, Sen. Aldrich, assisted by Sen. Spooner, held up consideration of the Food and Drugs Act until 1906, when Aldrich changed his mind and allowed the bill to proceed. OSCAR E. ANDERSON, JR., *THE HEALTH OF A NATION* 141, 148, 175–76 (1958); WOLRAICH, *supra* note 63, at 60–61; *see also* FOWLER, *supra* note 65, at 334 (“The bill failed to pass during the Fifty-eighth Congress and Spooner, Platt, and Aldrich (a onetime grocer) were largely responsible for its defeat.”). Moreover, their sentiments about governmental regulation were reflected in how they eventually voted on the bill in 1906, which passed the Senate 63 to 4 with 22 senators not voting. ANDERSON, *supra* at 180. Aldrich abstained, and Spooner, who opposed the bill, was “paired” with Allison, who supported it. MERRILL & MERRILL, *supra* note 63, at 221. Although Spooner introduced the bill that led to the 1902 Act, that action should not be interpreted as meaning that he was a Progressive Era reformer; Spooner led the “Stalwart” faction of the Wisconsin Republican Party, which opposed the faction led by the famous Progressive Robert La Follette. FOWLER, *supra* note 65, at 294–326.

<sup>70</sup> PHS probably acted secretly because it did not have authority for its involvement from the Treasury Secretary. Roosevelt became President on September 14, 1901, after McKinley’s assassination, and McKinley’s Treasury Secretary resigned on January 31, 1902. The new Treasury Secretary, Leslie M. Shaw, a former lawyer-banker who had just ended four years as Governor of Iowa, took office on February 1, and PHS was likely reluctant to raise the issue with an unknown Secretary new to the position since his consideration of the issue might have delayed the effort to see legislation enacted before the congressional adjournment in June. The reason why the industry concealed its role in the legislation is obvious: the objective of reassuring the public that biologics would be safe as a result of the legislation would not be helped if it were known that the bill was an industry initiative.

<sup>71</sup> *Report of the Executive Committee on “A Bill to Regulate the Sale of Viruses, Serums and Analogous Products in the District of Columbia,” &c*, 1 WASHINGTON MED. ANNALS 274 (1902), reprinted in H.R. REP. NO. 57-2713, at 4 (1902) [hereinafter *Executive Committee Report*].

<sup>72</sup> *Id.* As introduced, the bill provided that regulations would be issued by the Secretary of the Treasury on the recommendation of the Supervising Surgeon General of the Marine-Hospital Service. The D.C. Medical Society and the D.C. Commissioners recommended that regulations be issued by a board consisting of the Surgeon General of the Army, the Surgeon General of the Navy, the Supervising Surgeon General of the Marine-Hospital Service, the Chief of the Bureau of Animal Industry of the Department of Agriculture, and the Health Officer of the District of Columbia, and the Senate and House committees both accepted that change. On the Senate floor, immediately prior to passage of the bill, Sen. Jacob H. Gallinger, a member of the District of Columbia Committee, moved to amend the bill by providing that regulations were to be issued by a board composed of the three surgeons general after approval by the Secretary of the Treasury. 35 CONG. REC. 7644 (1902). The amendment was agreed to, the Senate passed the bill, and the House then passed the Senate-passed bill.

<sup>73</sup> The recommendation from the Executive Committee to the full Society was signed by George M. Kober, who was then dean of the Georgetown Medical School but who had spent most of his career working for the Army Surgeon General. In 1895 he conducted an investigation of the causes of typhoid fever in Washington, D.C., at the request of the D.C. Health Officer, and he was a volunteer worker in the Hygienic Laboratory in 1895–96. FRANCIS A. TONDORF, *BIOGRAPHY AND BIBLIOGRAPHY OF GEORGE M. KOBER, M.D., LL.D.* 6 (1920); *HISTORY OF THE MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA 1817–1909*, at 301–02 (1909) [hereinafter *MEDICAL SOCIETY HISTORY*]. Kober’s recommendation was

diluting PHS's authority unless PHS requested that action. PHS would not have sought reduced authority unless the industry insisted on it.<sup>74</sup>

The statement of the Executive Committee of the Medical Society on which the Society based its support for the proposed legislation is also a clue to the bill's origin. The statement referred only to the St. Louis incident involving antitoxin produced by the local board of health and not to the vaccine-related cases of tetanus in Camden and elsewhere<sup>75</sup> even though both incidents were widely reported and discussed in lay and medical publications and a January 1902 PHS article about possible federal legislation referred to both incidents.<sup>76</sup> St. Louis was a one-off debacle caused by the misconduct of the two individuals who ran the operation and did not necessarily have broader public health significance, whereas PHS's post-Camden analysis of smallpox vaccine revealed a substantial industry-wide problem of bacterial contamination. The Camden deaths represented a much larger potential public health problem than those in St. Louis, but if the Medical Society had cited vaccine contamination as a reason for legislation, it would have indiscreetly disparaged the products of the companies enabling its enactment.

Since the bills were being handled by the District of Columbia Committees, the Committees waited for a recommendation from the D.C. Commissioners, who were the governing officials of the District. Based on a report from the D.C. Health Officer (one of the two doctors who had secured the support of the D.C. Medical Society), the Commissioners backed the bills but, in addition to offering the Medical Society's amendment concerning the officials authorized to issue regulations, they recommended deleting the prohibition against using a biologic after its expiration date.<sup>77</sup> This suggestion probably resulted from a belated realization by the Medical Society that the provision was aimed at physicians.

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presented to the Society by William C. Woodward. *Meeting of the Medical Society of the District of Columbia (Apr. 16, 1902)*, in TRANSACTIONS OF THE MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, 1902, at 127 (unpublished minutes) (on file with the Nat'l Library of Med., D.C. Med. Soc'y Papers). Woodward was the D.C. Health Officer and had been in that position since 1894. MEDICAL SOCIETY HISTORY, *supra*, at 342.

<sup>74</sup> It is unclear why the industry saw a need to amend the bill as soon as it was introduced. A possibility is that PHS and the industry had agreed on a board to issue the rules but that a Senate drafter simplified the administrative structure by conferring authority on the Treasury Secretary alone without realizing the importance of the board to the industry.

<sup>75</sup> *Executive Committee Report, supra* note 71.

<sup>76</sup> H.D. Geddings, *Governmental Control of Therapeutic Serums, Vaccine, Etc.*, 17 PUB. HEALTH REP. 93, 93 (1902).

<sup>77</sup> Letter from Henry B.F. Macfarland, President, D.C. Bd. of Comm'rs, to J.W. Babcock, Chairman, H. Comm. on D.C. (June 4, 1902), in H.R. REP. NO. 57-2713, at 1 (1902); same letter to Sen. James McMillan, in S. REP. NO. 57-1980, at 1 (1902). The Commissioners' delayed response appears to have been due to a dispute over whether the D.C. Health Officer should be a member of the board that would issue regulations under the Act. The Health Officer recommended approval of the bill in a report to the Commissioners on April 24, 1902, and the City Solicitor approved the form of the bill on May 3. Memorandum from A.B. Duvall, City Solic., to D.C. Comm'rs (May 3, 1902) (on file with the Nat'l Archives, Rec. Grp. 351, Off. Comm'rs, Letters Received 1897-1933, No. 239097/2). Then nothing happened until May 31, when the Health Officer submitted a supplemental report to the Commissioners stating that "there is some objection" to making the D.C. Health Officer a member of the board on the ground that "the board is national in its character and the Health Officer of the District is a local officer." The Health Officer thought that the objection was "ill-founded," but he nevertheless suggested deleting the Health Officer from the board in the proposed amendment. Memorandum from Wm. C. Woodward, Health Officer, to D.C. Comm'rs (May 31, 1902) (on file with the Nat'l Archives, at *id.*). The Commissioners rejected the suggestion and submitted the proposed amendment as originally drafted. The



A plausible scenario is that the big biologics companies recognized the desirability of federal regulation, and they reached agreement with PHS on terms of the legislation. Parke-Davis then sought help from Senator McMillan, who had previously supported the company in opposing Agriculture's free biologics program. McMillan obtained approval of the bill from The Four, and Senator Spooner introduced the legislation to signal to the rest of the Senate that The Four supported it. It was referred to McMillan's District of Columbia Committee—it rightfully should have gone to the Commerce Committee—so that McMillan could manage the process of obtaining passage in the few remaining weeks before the congressional adjournment. PHS arranged for the D.C. Medical Society to advocate for the bill so that there would be evidence in the record of support from the medical community in the absence of hearings. Through Senator Allison, The Four obtained the help of Speaker Henderson, who created a parallel path for a companion House bill through that body's District of Columbia Committee.<sup>78</sup>

PHS's 1902 annual report stated that both PHS and the D.C. Medical Society had been thinking about such a bill but provided no information about how it came to be enacted.<sup>79</sup> In a speech some years later, a PHS official obliquely confirmed that the 1902 Act was the alternative to governmental manufacture of biologics:

The enactment of this law [the 1902 Act], therefore, was indicated as a change of policy; whereas on a very small and experimental scale viruses, serums and toxins had been manufactured by the [federal] government, this new law substituted rather regulation than manufacture.

. . . .

. . . [I]f the governmental regulation of serums could not be adequately carried out, the result would be that biologicals would be made by governments themselves; if not by the federal government, certainly by state governments.<sup>80</sup>

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amendment on the Senate floor to eliminate the D.C. Health Officer and the Chief of the Bureau of Animal Industry from the board may have been intended to remove the D.C. Health Officer from the board without singling him out.

<sup>78</sup> The House bill, H.R. 13392, 57th Cong. (1902), which was identical to the Senate bill, was introduced April 5, 1902, by Charles A. Russell of Connecticut, who was chairman of the Committee on Expenditures in the Department of War and had no apparent connection to the subject matter of the bill. He may have been asked to introduce the bill by Sen. Orville H. Platt, who was also from Connecticut and was one of The Four.

<sup>79</sup> "The Bureau had been considering for some time the preparation of a bill of this kind and had gathered considerable information necessary for its preparation. The Medical Society of the District of Columbia had also taken up the matter and their representatives consulted the Bureau for advice and information, which was freely given. The bill, as introduced and passed after amendment, was not, however, submitted to the Treasury Department nor to the Marine Hospital Bureau for report. It met, however, the indorsement of the Medical Society of the District of Columbia, and was reported back to the Senate and to the House by the respective committees on the District of Columbia." 1902 PHS ANNUAL REPORT, *supra* note 29, at 28–29.

<sup>80</sup> Kerr, *supra* note 67, at 232, 237. Enactment of the legislation did not stop consideration of governmental manufacture. In 1904 the *Journal of the American Medical Association* editorialized about the "antitoxin trust," which had supposedly raised the price of diphtheria serum to unreasonable levels. *The Price of Diphtheria Antitoxins*, 42 J. AM. MED. ASS'N 249, 249 (1904). The editor asked the Surgeon General whether it would be possible and advisable for the government to manufacture antitoxin, to which he replied, "My present belief is that it is inadvisable for the government to go into the

### C. *The Substantive Provisions of the Legislation*

The 1902 Act's description of the product classes subject to licensing was borrowed from French and Italian statutes. In January 1902, PHS published an article stating that, because of the St. Louis and Camden incidents involving diphtheria antitoxin and smallpox vaccine, "there have been numerous suggestions looking to the control of these materials and analogous products by the National Government" and "it is felt that good might accrue from government supervision and periodical inspection of the laboratories and farms where serums and vaccine virus are produced commercially."<sup>81</sup> The article included the translated text of several European statutes as potential models. The French law applied to "[a]ttenuated viruses, therapeutic serums, modified toxins, and analogous products," and the Italian statute applied to "(a) vaccine; (b) virus; (c) therapeutic serums, and (d) toxins, antitoxins, and other similar preparations."<sup>82</sup> The coverage of the 1902 Act was based on those statutes.

The 1902 Act conferred its authority on the Secretary of the Treasury, except the authority to issue rules, which, subject to the Secretary's approval, were to be issued by a board composed of the PHS Surgeon General and two military surgeons general. In practice, the Act was administered by PHS, which was headed by the Surgeon General. There was a layer of assistant surgeons general under the Surgeon General, one of whom supervised the Hygienic Laboratory and other PHS units (collectively, the Division of Scientific Research).<sup>83</sup> The Hygienic Laboratory conducted the inspections and laboratory tests necessitated by the 1902 Act and made recommendations with respect to licenses. A Sanitary Board, which was composed of several assistant surgeons general and sometimes also the Director of the Hygienic Laboratory, considered the Hygienic Laboratory's recommendations, but the Sanitary Board made the final recommendations to the Surgeon General on whether to issue, suspend, or revoke licenses.<sup>84</sup> The Surgeon General generally made all policy

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manufacture of antitoxin." Telegram from Wyman, to G.H. Simmons (Jan. 26, 1904), replying to Letter from George Simmons, *JAMA*, to Surgeon Gen. Walter Wyman (Jan. 21, 1904) (both on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897-1923, File 3655). In 1907 a bill was introduced in Congress to require PHS to manufacture and sell diphtheria antitoxin at ten percent above cost, H.R. 25126, 59th Cong. (1907), and PHS concluded that it would be feasible to do so, Letter from Acting Treas. Sec'y to William F. Hepburn, Chairman, H. Comm. on Interstate & Foreign Commerce (Feb. 14, 1907) (on file with the Nat'l Archives, Rec. Grp. 233, Accompanying Paper Files, 59th Cong., H. Comm. on Interstate Commerce (H.R. 25126)) (enclosing memorandum from Walter Wyman, Surgeon Gen. to Sec'y Treas. (Feb. 13, 1907)). Beginning in 1913, North Carolina made typhoid vaccine for free distribution within the state and later expanded the program to other vaccines and antitoxins because of the cost of commercial biologics. C.A. Shore, *Distribution of Vaccines and Serums by the State Laboratories*, 9 AM. J. PUB. HEALTH 106, 107 (1919).

<sup>81</sup> Geddings, *supra* note 76, at 93.

<sup>82</sup> *Id.* at 93-95.

<sup>83</sup> In 1930 the Hygienic Laboratory was renamed the National Institute of Health (NIH) (which became the plural "Institutes" in 1948) to recognize an expansion of its research capabilities. As NIH grew, the unit directly involved with biologics became the Division of Biologics Control in 1937, the Laboratory of Biologics Control in 1944, and the Division of Biologics Standards in 1955. FDA, *supra* note 43, at 7.

<sup>84</sup> Kerr, *supra* note 67, at 233 ("All questions, executive or scientific in character, are placed before an executive board, consisting of five medical officers. This is known as the Sanitary Board."). Although the Sanitary Board seems to have been technically composed of four assistant surgeons general and the Director of the Hygienic Laboratory, most of the recommendations in the PHS archives are signed by only three or four assistant surgeons general.

decisions related to the 1902 Act, but decisions on controversial issues were sometimes sent to the Secretary or an Assistant Secretary for approval.

Significant improvements resulted from the 1902 Act. It greatly reduced the bacterial contamination of vaccines, made sore arms following vaccination unusual (arms that could be sore to the point of preventing the individual from working for days or weeks had been frequent before the 1902 Act because of bacterial contamination), resulted in improvement of biologics manufacturers' production facilities, and allowed the standardization of certain products.<sup>85</sup>

## V. IMPORTANT REGULATORY POLICIES NOT EXPRESSLY AUTHORIZED BY THE STATUTE

The regulatory structure created by the 1902 Act was skeletal. The law established a mechanism for inspecting and licensing biologics manufacturing facilities and imposed a few requirements on information in product labels but beyond that was largely silent about how and on what terms PHS was to regulate biologics. This structure satisfied the needs of the biologics companies as they saw their problems following the 1901 incidents; they just wanted the federal government to assess the various manufacturers and bless the high-quality operations. But the skimpy provisions of the statute left important regulatory issues unresolved. This section explains how PHS developed potency standards, rules for manufacturing practices, enforcement mechanisms, and lot-release testing procedures—all in the absence of relevant statutory provisions.

### A. Potency Standards

One issue was product potency. The statements in the legislative record by the D.C. Medical Society and the D.C. Health Officer both concentrated on product purity but also mentioned product potency. The Medical Society's statement referred to potency only in passing, stating that federal regulation was the "only feasible method of insuring the purity and strength" of biologics.<sup>86</sup> The Health Officer's statement was stronger, calling the "potency of these remedies . . . of corresponding importance" to their safety since "therapeutic inactivity . . . may cost the life of the patient."<sup>87</sup> The only statutory provisions arguably related to potency, however, were the requirement for an expiration date in the product label and the prohibition against false label statements. As a basis for establishing potency standards, those provisions seem inadequate.

Potency standards nevertheless became a major part of the PHS regulatory program because the affected parties wanted them. Soon after passage of the 1902 Act, antitoxin manufacturers and the American Pharmaceutical Association (the principal pharmacists' professional group) asked PHS to develop a standard diphtheria antitoxin that manufacturers could use in guinea pig testing to determine and label the potency

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<sup>85</sup> John F. Anderson, *Federal Control of Vaccine Virus*, 30 PUB. HEALTH PAPERS & REP. 201 (1905); John F. Anderson, *The Results of the Federal Control of the Manufacture of Viruses, Serums, Toxins, and Analogous Products*, 19 AM. J. PUB. HYGIENE 722 (1909); Rosenau, *supra* note 54; *supra* note 12.

<sup>86</sup> H.R. REP. NO. 57-2713, at 4 (1902).

<sup>87</sup> *Id.* at 2.

of their products.<sup>88</sup> PHS prepared such a standard and issued it to manufacturers beginning April 1, 1905.<sup>89</sup> PHS eventually developed standards for many other biologics, although it was slow going in the early years with only standards for diphtheria and tetanus antitoxins and a tentative standard for antityphoid vaccine in existence by 1917.<sup>90</sup>

### B. Manufacturing Practices

A second question about the legislation was whether the government could mandate specific manufacturing practices. The statute authorized rules “to govern the issue, suspension, and revocation of licenses,” but it was not clear whether that authority was limited to procedural rules or allowed substantive standards.

Parke-Davis assumed that the statute permitted substantive rules. Only a few weeks after the bill was enacted, the company wrote PHS with a list of suggested requirements for staff expertise (“expert, skillful and scholarly scientists” and an expert veterinarian), examination of animals, modern sanitary physical facilities, and “very rigid and searching tests for purity and safety” prior to product release.<sup>91</sup>

Either the government was not prepared to identify specific standards or it believed its authority was limited to procedural rules. The board of surgeons general adopted regulations, effective August 21, 1903, which set forth procedures for issuing, suspending, and revoking licenses, inspecting production facilities, and examining product samples but did not establish substantive standards.<sup>92</sup> A 1906 regulation established the first manufacturing requirement by ordering licensees to test every lot of smallpox vaccine for microbial contamination, with a special examination to determine the absence of tetanus.<sup>93</sup> In 1909 additional regulations governing manufacturing practices were promulgated<sup>94</sup> after approval by the Treasury Department Solicitor, who held that “while the act does not expressly regulate the manufacture of viruses, etc., it clearly implies that such manufacture must necessarily be under the supervision and control of the Treasury Department” and that regulations designed “to secure additional safeguards in the manufacture and sale” of biologics were therefore authorized.<sup>95</sup> The rules on manufacturing practices were substantially expanded in subsequent years.

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<sup>88</sup> PHS, TREAS. DEP’T., DOC. NO. 2354, ANNUAL REPORT OF THE SURGEON-GENERAL OF THE PUBLIC HEALTH AND MARINE-HOSPITAL SERVICE OF THE UNITED STATES FOR THE FISCAL YEAR 1903 325–26 (1904).

<sup>89</sup> ROSENAU, *supra* note 17.

<sup>90</sup> G.W. McCoy, *Standardization of Serums and Vaccines*, 69 J. AM. MED. ASS’N 378, 378 (1917).

<sup>91</sup> Cotterill Letter, *supra* note 60.

<sup>92</sup> PHS, TREAS. DEP’T, REGULATIONS FOR THE SALE OF VIRUSES, SERUMS, TOXINS, AND ANALOGOUS PRODUCTS IN THE DISTRICT OF COLUMBIA, ETC. (1903) [hereinafter 1903 REGULATIONS].

<sup>93</sup> TREAS. DEP’T, 1906 CIRCULAR NO. 31, AMENDMENT TO THE REGULATIONS FOR THE SALE OF VIRUSES, SERUMS, TOXINS, AND ANALOGOUS PRODUCTS (Mar. 13, 1906); *see* PHS, TREAS. DEP’T, DOC. NO. 2498, ANNUAL REPORT OF THE SURGEON-GENERAL OF THE PUBLIC HEALTH AND MARINE-HOSPITAL SERVICE OF THE UNITED STATES FOR THE FISCAL YEAR 1907 25 (1908).

<sup>94</sup> *Regulations for the Sale of Viruses, Serums, Toxins, and Analogous Products*, 24 PUB. HEALTH REP. 629 (1909) [hereinafter 1909 Regulations].

<sup>95</sup> Memorandum from Maurice D. O’Connell, Solic., to Sec’y Treas. (Apr. 5, 1909) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

### C. Enforcement Mechanisms

The 1902 Act had only one enforcement mechanism if a licensed manufacturer sold a product that was contaminated or the manufacturer otherwise violated the Act—PHS could suspend or revoke its license. Moreover, on the face of the statute, there was no means other than facility inspection by which PHS might detect defective biologics.

The initial regulations addressed the issue of detecting problems by imposing a duty on PHS to purchase products of licensed manufacturers in the open market and test them for purity and potency.<sup>96</sup> Adverse results were to be reported to the manufacturer, which had fifteen days to correct the problem or face license suspension or, after sixty days, license revocation.

The disposition of defective product was initially handled outside the regulations; PHS requested manufacturers to recall contaminated or subpotent product.<sup>97</sup> In 1919 a recall provision was added to the regulations: if a company did not recall defective product, PHS could publicize the lot numbers involved.<sup>98</sup>

### D. Lot-Release Testing

Under the lot-release system, a biologics manufacturer tests each lot of product and submits the results of those tests (its “protocols”) together with samples from the lot to the government. The manufacturer is prohibited from distributing product from the lot until the government releases it based on review of the manufacturer’s protocols and, often, on the results of the government’s own tests on the samples submitted.

The lot-release system has a surprising origin—the fear during World War I that German spies or disloyal Americans might contaminate biologics during their manufacture. On July 5, 1917, a few months after the United States entered the war, the Surgeon General sent a letter to biologics manufacturers warning them of the risk of sabotage and urging them to take precautions.<sup>99</sup> The Director of the Hygienic Laboratory, George McCoy, reviewed the manufacturers’ responses to that letter for suggestions regarding governmental action and did not find any he thought useful, but he did suggest to the Surgeon General that PHS could invite manufacturers to send samples of products intended for the military to the Hygienic Laboratory for confirmatory testing.<sup>100</sup>

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<sup>96</sup> 1903 REGULATIONS, *supra* note 92, Inspection, para. 9; *see also* PHS, TREAS. DEP’T, DOC. NO. 2378, ANNUAL REPORT OF THE SURGEON-GENERAL OF THE PUBLIC HEALTH AND MARINE-HOSPITAL OF THE UNITED STATES FOR THE FISCAL YEAR 1904, at 376–77 (1904) (stating that smallpox vaccine from each manufacturer was purchased and examined for impurities and that arrangements were being made to check potency by observing vaccinations at District of Columbia children’s asylums).

<sup>97</sup> PHS, TREAS. DEP’T., DOC. NO. 2427, ANNUAL REPORT OF THE SURGEON-GENERAL OF THE PUBLIC HEALTH AND MARINE-HOSPITAL SERVICE OF THE UNITED STATES FOR THE FISCAL YEAR 1905, at 221 (1906) (stating that the Surgeon General had taken steps to require the recall of all bottles from lots of diphtheria antitoxin found to be subpotent in tests of product purchased in the open market).

<sup>98</sup> PHS, TREAS. DEP’T, MISC. PUBL’N NO. 10, REGULATIONS FOR THE SALE OF VIRUSES, SERUMS, TOXINS AND ANALOGOUS PRODUCTS para. 80 (1919) [hereinafter 1919 REGULATIONS].

<sup>99</sup> The Surgeon General’s letter is not available, but the archives contain numerous replies from manufacturers. *E.g.*, Letter from Eli Lilly & Co. to Rupert Blue, Surgeon Gen. (July 17, 1917) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655) (stating that it had doubled its night watch).

<sup>100</sup> Memorandum from G.W. McCoy, Dir., Hygienic Lab., to Surgeon Gen. (July 30, 1917) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

The Surgeon General was taken with that idea and asked whether the opportunity for testing by the Hygienic Laboratory should be extended to all production, not just the portion intended for military use.<sup>101</sup> After three weeks of what he called “prolonged and attentive consideration,” and probably out of concern about the workload that the testing of all lots would entail, McCoy said he thought that the normal procedures were sufficient to safeguard the purity of biologics “even in these abnormal times.”<sup>102</sup> He went on, however, to identify three products—antimeningococcus, antipneumococcus, and antidysentery serums—which he thought should be subject to mandatory lot-release testing by PHS. This suggestion was not based on a fear of intentional contamination but on the inability of commercial manufacturers to make those products as well as the Rockefeller Institute for Medical Research had made the original versions. PHS had not been able to develop official standards for the three products that the manufacturers could use, but McCoy thought that the Hygienic Laboratory could compare the commercially prepared products to samples obtained from the Rockefeller Institute.

McCoy recognized in his memo that there was a serious question about PHS’s legal authority to require lot-release testing, and his suggestion was apparently rejected for that reason.<sup>103</sup> Several months later, however, he recommended that manufacturers of the three serums be *requested* to submit samples of each lot and to withhold distribution until the lots were cleared by PHS, and that revised recommendation was accepted by the Surgeon General and the Secretary’s office.<sup>104</sup> Both internally<sup>105</sup> and in letters to manufacturers,<sup>106</sup> the purpose of the new policy was explained as “exercising every possible precaution to safeguard the purity and potency” of the products—language that seemed to reflect a wartime concern even though that was not the underlying issue. Manufacturers complied with the request, and apparently the legal concerns faded, because when the regulations were revised in 1919, the option for PHS to impose *mandatory* lot-release testing was included.<sup>107</sup>

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<sup>101</sup> Memorandum from Rupert Blue, Surgeon Gen., to G.W. McCoy, Dir., Hygienic Lab. (Aug. 1, 1917) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>102</sup> Memorandum from G.W. McCoy, Dir., Hygienic Lab., to Surgeon Gen. (Aug 21, 1917) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File, 1897–1923, File 3655).

<sup>103</sup> Memorandum from G.W. McCoy, Dir., Hygienic Lab., to Surgeon Gen. (Dec. 6, 1917) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>104</sup> *Id.*; Memorandum from Sanitary Bd. to Surgeon Gen. (Dec. 10, 1917) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655) [hereinafter Sanitary Board Memorandum] (endorsed by Surgeon Gen., approved by J.H. Moyle, Ass’t Treas. Sec’y).

<sup>105</sup> Sanitary Board Memorandum, *supra* note 104.

<sup>106</sup> *See, e.g.*, Letter from J.H. Moyle, Ass’t Sec’y Treas., to Parke-Davis (Dec. 14, 1917) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655). *See also* PHS, TREAS. DEP’T., ANNUAL REPORT OF THE SURGEON GENERAL OF THE PUBLIC HEALTH SERVICE OF THE UNITED STATES FOR THE FISCAL YEAR 1918, H.R. DOC. NO. 65-1457, at 66 (1919) (describing the lot-release system); ANNUAL REPORT OF THE SURGEON GENERAL OF THE PUBLIC HEALTH SERVICE OF THE UNITED STATES FOR THE FISCAL YEAR 1919, H.R. DOC. NO. 66-436, at 58 (1919) (stating that the testing of the three serums “grew out of war conditions” but “will have to be continued indefinitely”).

<sup>107</sup> 1919 REGULATIONS, *supra* note 98, para. 68 (“Samples of special lots of products, or of all lots of particular products, may be required to be sent to the Hygienic Laboratory of the United States Public Health Service for examination prior to being placed in interstate commerce or on sale in the District of Columbia.”).

Although PHS considered lot-release testing to be valuable, it also saw routine testing as interfering with its research activities. McCoy expressed his quandary in a 1921 speech to the drug manufacturers' association as follows:

There is one further question . . . and that is how much longer the government should go along testing the anti-bacterial serums which are now tested, each batch from each plant and factory prior to putting them on the market; whether that particular way of controlling products should be extended or discontinued.

We would very much like to discontinue it entirely. It takes up a large share of our appropriation; we have people working on that who, from a purely research point of view, might be much better working on some other problems.

But when we reflect on the very unsatisfactory state in which antipneumococcic and antimeningitis serum were prior to this method of control, I am very reluctant to suggest to the Surgeon General any change. I would like very much to have the manufacturers' attitude on this. The suggestion has been made that the method affords such an effective way of control and increases the government's responsibility so definitely that it ought to be extended.<sup>108</sup>

Evidently the manufacturers were fine with lot-release testing because it was expanded; a universally applicable lot-release requirement was in effect by 1932, if not earlier.<sup>109</sup> PHS nevertheless continued to see routine testing as detracting from its research and resisted testing that it saw as unnecessary. In 1928 the Navy Department asked whether PHS could test the insulin it was buying, and McCoy told the Surgeon General that the Hygienic Laboratory could do so only "at the expense of the research work of the Division of Pharmacology."<sup>110</sup> He also argued that to accept the Navy's request would logically lead to testing all of the insulin procured by the government and for that matter all insulin period, which "would encroach on the time and effort required for other, and more important, investigations."

Lot release became a contentious legal issue within the government. After PHS was transferred from the Treasury Department to the Federal Security Agency and the 1902 Act was replaced by the PHS Act, the PHS lawyers opined that PHS lacked authority to require lot release because the PHS Act authorized only "standards, designed to insure the continued safety, purity, and potency" of products, which the lawyers viewed as inadequate language to support the mandatory lot-release system.<sup>111</sup> PHS

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<sup>108</sup> AM. DRUG MFRS.' ASS'N, TENTH ANNUAL MEETING 351 (1921). McCoy had said essentially the same thing in an earlier speech to the American Medical Association. G.W. McCoy, *Official Methods of Control of Remedial Agents for Human Use*, 74 J. AM. MED. ASS'N 1553, 1554–55 (1920).

<sup>109</sup> See Letter from R.E. Dyer, Acting Dir., NIH, to Solon Ayers (Apr. 25, 1932) (on file with the Nat'l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 725A) ("The National Institute of Health tests each batch of a product manufactured by a licensed establishment . . . and if it meets with the requirement of the 'Regulations' . . . it is released to the manufacturer for distribution.")

<sup>110</sup> Memorandum from G.W. McCoy, Dir., Hygienic Lab., to Surgeon Gen. (July 16, 1928) (on file with the Nat'l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 1973, "Old" Investigations).

<sup>111</sup> Memorandum from Joel M. Mangel to Gen. Couns. Files (Oct. 18, 1968) (on file with the Nat'l Archives, Rec. Grp. 235, Off. Gen. Couns. Op. Files 1942–1963, File PS8000) [hereinafter Mangel Memorandum] (recounting that the authority to require governmental approval for lot release was questioned in a Harrison to Parran opinion dated Nov. 23, 1945). The lawyers subsequently decided that it

argued that, because of the complexity of the tests required, check tests by an independent laboratory were essential to ensure the safety, purity, and potency of the product,<sup>112</sup> but the lawyers held to their legal position and the regulation imposing the lot-release requirement was deleted.<sup>113</sup> PHS nevertheless continued to operate the system in defiance of the lawyers' view that it was illegal.<sup>114</sup> The issue was finally resolved in 1960 when the General Counsel of the Department of Health, Education, and Welfare overruled the PHS lawyers and allowed issuance of a regulation that officially reestablished lot-release requirements.<sup>115</sup>

### *E. Attempt to Amend the Statute*

In 1914 a bill was introduced in Congress at the request of PHS to address some of the statutory deficiencies just discussed.<sup>116</sup> The bill would have established criminal penalties for the preparation, sale, or exchange of "any contaminated, dangerous, or harmful" biologic (even if it was produced in a licensed facility), and it would have authorized regulations governing production and distribution to prevent the marketing of such biologics. It would also have authorized standards of purity and potency and closed a loophole in the statute that allowed an unlicensed biologic to be imported if

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would be permissible to require manufacturers to submit samples from each lot to PHS thirty days before distribution, thus giving PHS an opportunity to analyze the samples and object to distribution of the lot. Memorandum from Gladys Harrison, Off. Gen. Couns., to James A. Crabtree, PHS (Feb. 20, 1946) (on file with the Nat'l Archives, Rec. Grp. 235, Gen. Classified Files 1944–1950, Gen. Decimal Series, File 950). Ultimately, the regulations were issued without the thirty-day provision, probably because PHS had decided to continue the lot-release system in spite of the lawyers' ruling and consequently saw the delay as unnecessary.

<sup>112</sup> Memorandum from Surgeon Gen. to Off. Gen. Couns. (Nov. 13, 1945) (on file with the Nat'l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 470-132).

<sup>113</sup> When PHS was transferred to the Federal Security Administration, the biologics regulations were reissued, and the lot-release regulation became 42 C.F.R. § 22.102. 5 Fed. Reg. 4107, 4111 (Oct. 11, 1940). The regulation was not included in the regulations implementing the PHS Act. 12 Fed. Reg. 411 (Jan. 21, 1947).

<sup>114</sup> PHS continued the program under the purported authority of 42 C.F.R. § 73.71: "Samples of any lot of any licensed product, together with the protocols showing the results of applicable tests, may at any time be required to be sent to the Institute for examination." See Memorandum from Chief, Gen. Methods Staff, to Surgeon Gen., § IX (July 27, 1955) (on file with the Nat'l Archives, Rec. Grp. 235, Gen. Classified Files 1951–1955, Gen. Decimal Series, File 960). The same memo noted that in 1954 almost two-thirds of the lot-release actions (1187 out of 1831) were based partially on PHS tests.

<sup>115</sup> 26 Fed. Reg. 5752, 5754 (June 28, 1961) (to be codified at 42 C.F.R. § 73.76); 25 Fed. Reg. 11,182, 11,185 (proposed Nov. 24, 1960). The chief PHS lawyer later attempted to clean up the record by supplying a rationale for the General Counsel's 1960 action approving lot release. In a 1968 memo to the file he said,

In light of the complex nature of the testing required for many products, we think it is not an unreasonable standard to require the last step in the process to be conducted by DBS [the Division of Biologics Standards]. This is particularly true in light of the expertise developed within DBS which is not otherwise available to the manufacturers. Presumably that is the basis upon which G.C. [General Counsel] finally cleared the regulations containing "prior approval" provisions.

Mangel Memorandum, *supra* note 111.

<sup>116</sup> H.R. 13040, 63d Cong. (1914); see 53 CONG. REC. 501 (1916) ("I have introduced it twice at the earnest recommendation of the department . . .") (statement of Rep. Adamson).



the sale of the biologic took place before importation.<sup>117</sup> The Treasury Secretary, rather than the board of surgeons general, would have the power to issue the newly authorized regulations and standards.

In most respects, the amendments would not have been significant changes from how PHS was administering the law, but the drug manufacturers association strongly opposed the legislation, mainly on the grounds that it would allow PHS to deny licenses for ineffective products and, by regulating methods of production, compel the disclosure of trade secrets.<sup>118</sup> There was, however, nothing in the bill about product effectiveness. In the week between the introduction of the bill and the association's annual meeting, at which the association adopted a resolution opposing the legislation, executives of the association apparently assumed erroneously that the bill carried out PHS's previous statements that it wanted authority to deny licenses for ineffective products.<sup>119</sup>

The bill languished in Congress for over two years, probably due to the industry opposition, until the biologics companies withdrew their objections,<sup>120</sup> after which a House committee issued a perfunctory favorable report and the House passed the bill on a voice vote in December 1916. The long delay may have doomed the legislation. For whatever reasons (possibly preoccupation with war-related legislation), the Senate did not take up the bill, and the 1902 Act was never amended, thus leaving its shortcomings in place.

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<sup>117</sup> The Attorney General had ruled that the 1902 Act did not prohibit the importation of an unlicensed biologic by a person intending to use it in his own practice and not to sell it. *Importation of Viruses, Serums, Toxins and Analogous Products*, 29 Op. Att'y Gen. 340 (1913).

<sup>118</sup> *Memorial Respecting the Operation of the Federal Serum Laws*, PROCEEDINGS OF 3D ANNUAL MEETING OF NATIONAL ASSOCIATION OF MANUFACTURERS OF MEDICINAL PRODUCTS 56–57 (1914) [hereinafter *1914 Memorial*]. As its example of how an effectiveness requirement could keep valuable medicines from the public, the report used diphtheria antitoxin, which it said “was introduced wholly by the private enterprise of manufacturers . . . and had the power then been exercised which the authorities . . . now claim to possess, diphtheria antitoxin might have been kept out of this country altogether and hundreds of thousands who have been saved by its use might have perished.” It is astonishing that less than twenty years after PHS and the New York City Board of Health introduced diphtheria antitoxin to the United States and provided technical assistance to commercial manufacturers wanting to make it, the history of the serum had been entirely rewritten in the minds of the manufacturers' representatives. *See also* Letter from Charles M. Woodruff, Sec'y, Nat'l Ass'n Mfrs. Medicinal Prods., to J.F. Anderson, Hygienic Lab. (Aug. 3, 1914) (on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655) (elaborating on the Association's objections to the bill and adding the objection that the bill would give too much power to the Treasury Secretary). Opposition to the legislation was expressed again at the Association's February 1915 meeting. PROCEEDINGS OF THE 4TH ANNUAL MEETING OF NATIONAL ASSOCIATION OF MANUFACTURERS OF MEDICINAL PRODUCTS 30–31 (1915).

<sup>119</sup> ANNUAL REPORT OF THE SURGEON GENERAL OF THE PUBLIC HEALTH SERVICE OF THE UNITED STATES FOR THE FISCAL YEAR 1913, H.R. DOC. NO. 63-392, at 44 (1914) [hereinafter 1913 PHS ANNUAL REPORT]; John F. Anderson, *Federal Control over the Manufacture of Serums and Vaccines*, 61 J. AM. MED. ASS'N 661, 661 (1913).

<sup>120</sup> The bill was originally introduced in February 1914 and was reintroduced in the new Congress in December 1915. H.R. 199, 64th Cong. (1915). The drug manufacturers association publicly withdrew its opposition at its annual meeting in February 1917, at which it stated that the bill “should give our biological people little concern. There are no provisions in it seriously affecting the producer that are not contained in the present law.” 1917 ANNUAL MEETING, *supra* note 67, at 76. It seems likely that the association actually changed its views some months earlier, allowing the bill, which then became noncontroversial, to be favorably reported by a House committee in June 1916 and passed by the House in December 1916. H.R. Rep. No. 64-845 (1916); 53 CONG. REC. 502 (1916).

## VI. EARLY EFFORTS TO DEAL WITH INEFFECTIVE BIOLOGICS

### A. *The Problem of Licensing Ineffective Products*

The 1902 Act had an important unanticipated effect: governmental licensing of a product, with the license number printed on its label, potentially gave the product a marketing advantage. This was the era of patent medicines—thousands of drugs with extravagant or wholly false claims were on the market<sup>121</sup>—and a governmental license implied governmental endorsement, distinguishing it from the mass of marketed drugs. At the same time, there was nothing on the face of the 1902 Act that required a licensed biologic to be safe and effective. PHS seemed to be in the position that it would have to confer a marketing advantage on worthless drugs. This section describes how PHS struggled in the early years to reconcile the terms of the statute with its desire to avoid implying governmental approval of ineffective products.

Two weeks before the regulations implementing the 1902 Act went into effect, PHS received a license application for a “serum” made from urea (a byproduct of the metabolism of proteins in animals) and mercury.<sup>122</sup> PHS saw the product, which was taken orally and advertised to the general public as a cure for “blood poison,”<sup>123</sup> as a quack drug. It contrived the theory that the drug was not eligible for a license because the applicant purchased the urea and mercury from others and therefore was not an establishment that “propagated and prepared” biologics, as the statute specified. In seeking approval of this position from the Treasury Department Solicitor, the Surgeon General asserted, “To grant this company a Treasury license would be of very material assistance to them in prosecuting a business which, to say the least, is believed to be not above suspicion.”<sup>124</sup> Without articulating a legal theory, the Solicitor agreed with the Surgeon General that a license should not be granted.<sup>125</sup>

The resolution of that specific application did not address the larger question of what types of products should be given the marketing edge of a governmental license when the statute did not require licensed products to be effective. It is evident from PHS’s subsequent actions that it decided to license only those products for which it thought that the law gave it no choice in order to minimize the number of licensed but ineffective products. For safety reasons, in a few cases it adopted expansive readings of the statute to subject a small number of products to regulation.

The Act required licenses for the “maintenance of establishments for the propagation and preparation of [biologics],” which might imply that PHS was to consider only the condition of the establishment, not also the identity of the products being made there. Some of the early licenses authorized companies to manufacture whole classes of biologics, but PHS soon changed its policy and licensed companies

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<sup>121</sup> See, e.g., JAMES HARVEY YOUNG, *THE TOADSTOOL MILLIONAIRES* (1961).

<sup>122</sup> Memorandum from Walter Wyman, Surgeon Gen., to Sec’y Treas. (Aug. 12, 1903) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655) [hereinafter Wyman Memorandum].

<sup>123</sup> E.g., Advertisement of the International Serum Toxin Co., *CHI. TRIB.*, July 23, 1902, at 11.

<sup>124</sup> Wyman Memorandum, *supra* note 122.

<sup>125</sup> Memorandum from F.A. Reeve, Acting Solic., to Sec’y Treas. (Aug. 17, 1903), approved in Memorandum from Acting Sec’y Treas. to Walter Wyman, Surgeon Gen. (Aug. 19, 1903) (both on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

for specific products, a practice that the industry thought was illegal.<sup>126</sup> The change may have had multiple purposes, but by allowing PHS to control which specific products would bear a governmental license number with its implied seal of approval, it was essential to PHS's policy of not licensing ineffective products to the extent possible.<sup>127</sup>

### B. Initial Interpretation of the Statutory Terms

To minimize the number of licensed but ineffective drugs, PHS narrowly interpreted each of the statutory terms describing a product class subject to licensure—"virus," "antitoxin," "toxin," "therapeutic serum," and "analogous product." These interpretations first appeared in the regulations in 1919 (as clarified in 1923) and codified decisions, as described in this section, that PHS had previously made in adjudicating license applications.<sup>128</sup>

#### I. Viruses

The 1919 regulations defined a "virus" as "a product containing the minute living cause of an infectious disease," which conformed to the meaning of the term at that time.<sup>129</sup> Smallpox vaccine contained live vaccinia virus and was the first virus product.

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<sup>126</sup> "The license is issued . . . for a specific product." Rosenau, *supra* note 12, at 249. Initially, Parke-Davis and Mulford were licensed for "[v]accine virus, serums, and toxins" and the Pasteur Institute was licensed for "viruses (other than vaccinia), serums, toxins, and analogous products," while other companies were licensed for specific products. *Operations Under Act Approved July 1, 1902*, 19 PUB. HEALTH REP. 1195 (1904) (listing licenses as of June 1904). By fiscal year 1908, all licenses were issued for specific products, except for bacterial vaccines and tuberculin. PHS, TREAS. DEP'T, DOC. NO. 2539, ANNUAL REPORT OF THE SURGEON-GENERAL OF THE PUBLIC HEALTH AND MARINE-HOSPITAL SERVICE OF THE UNITED STATES FOR THE FISCAL YEAR 1908, at 44 (1909) [hereinafter 1908 PHS ANNUAL REPORT]. Licenses for bacterial vaccines and tuberculin were also eventually issued for specific products. The biologics industry argued that Congress intended for PHS "to license the laboratory rather than the product issued from the laboratory." *1914 Memorial*, *supra* note 118, at 57. When the 1902 Act was incorporated into the PHS Act in 1944, the statute was reworded to require both the manufacturing establishment and "the products for which a license is desired" to meet specified standards, PHS Act § 351(d), 58 Stat. at 702, and PHS implemented that provision by creating a system of separate product and establishment licenses, 12 Fed. Reg. 411, 412 (Jan. 21, 1947) (to be codified at 42 C.F.R. §§ 22.4–22.5). The system was changed to a single, product-specific license by the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 123, 111 Stat. 2296, 2323 (1997).

<sup>127</sup> See Letter from Surgeon Gen. to Parke-Davis (Feb. 12, 1907) (on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655) [hereinafter Surgeon Gen. Letter] (stating that the license number must not appear on licensee's products that are not subject to the 1902 Act). See also G.W. McCoy, *Control and Standardization of Biological Products*, in THE NEWER KNOWLEDGE OF BACTERIOLOGY AND IMMUNOLOGY 947, 947 (Edwin O. Jordan & I.S. Falk eds., 1928) ("In the United States the law is interpreted as requiring a license for each product falling in the group of biological products. This at once brings to the fore the question of issuing licenses for preparations which the licensing authorities consider valueless or of doubtful worth.").

<sup>128</sup> 1919 REGULATIONS, *supra* note 98, para. 7; PHS, TREAS. DEP'T, MISC. PUBL'N NO. 10, REGULATIONS FOR THE SALE OF VIRUSES, SERUMS, TOXINS, AND ANALOGOUS PRODUCTS, para. 7 (1923) [hereinafter 1923 REGULATIONS]. The 1909 regulations included a nonexhaustive list of products subject to the 1902 Act but did not categorize them. 1909 Regulations, *supra* note 94, para. 16.

<sup>129</sup> 1919 REGULATIONS, *supra* note 98, para. 7-I. The pathogens we now call viruses were known as filterable viruses because they passed through all of the filters then in use. The current regulatory definition is substantively the same as the 1919 version although examples have been added: "A virus is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa." 21 C.F.R. § 600.3(h)(1) (2016).

Only a small number of other vaccines containing live viruses were licensed prior to 1919.

In addition to vaccines, PHS licensed suspension of lactic acid bacilli, which contained live microbes and therefore presumably had to be licensed.<sup>130</sup> It was applied externally to wounds and lesions.

## 2. Antitoxins

With diphtheria antitoxin as the model, an “antitoxin” was defined in the 1919 regulations as a product made in an immunized animal that neutralizes the toxin against which the animal was immunized.<sup>131</sup> Based on the stunning success of diphtheria antitoxin, it was at first thought that cures for other diseases could similarly be made by injecting horses with toxins from various bacteria.<sup>132</sup> Tetanus acts through exotoxins like diphtheria, but most bacterial infections do not and thus antitoxins could not be created to treat most types of infections.<sup>133</sup>

PHS did, however, license two antitoxins that were not related to infectious diseases—antitoxins to snake venom<sup>134</sup> and to a plant toxin.<sup>135</sup> Those serums were not only antitoxins but they were made by injecting horses with toxins in the same manner as diphtheria antitoxin was produced. PHS saw them as subject to the 1902 Act.

## 3. Toxins

“Toxin” was included in the 1902 Act as a product class subject to licensing to cover tuberculins, which were prepared by culturing tuberculosis bacteria in the laboratory for several weeks and then filtering out the bacteria to make an ostensibly curative antituberculosis serum out of what was left behind in the culture medium.<sup>136</sup> Production did not involve horses or other animals. It was thought that the bacteria

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<sup>130</sup> 1909 Regulations, *supra* note 94, para. 16 (listing suspension of lactic acid bacilli as subject to licensing); *see also* WM. CECIL BOSANQUET & JOHN W.H. EYRE, *SERUMS, VACCINES AND TOXINS IN TREATMENT AND DIAGNOSIS* 74–75 (3d ed. 1916).

<sup>131</sup> “An antitoxin is a product containing the soluble substance in the serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune.” 1919 REGULATIONS, *supra* note 98, para. 7-IV.

<sup>132</sup> Simon Flexner, *Biologic Therapy: General Considerations Regarding Serum and Vaccine Therapy*, 76 J. AM. MED. ASS’N 30, 33 (1921).

<sup>133</sup> Several additional antitoxins were licensed in the 1920s and 1930s. Pittman, *supra* note 43, at 63.

<sup>134</sup> Pasteur Institute was licensed for sérum antivenimeux in 1909, *Establishments Licensed for the Propagation and Sale of Viruses, Serums, Toxins, and Analogous Products*, 25 PUB. HEALTH REP. 3 (1910), but the Pasteur antitoxin was based on cobra venom, and snake antivenin is effective only for the type of snake whose venom was used to produce the antitoxin, Joseph McFarland, *Serum Therapy*, in 11 A SYSTEM OF PHYSIOLOGIC THERAPEUTICS 17, 50–52 (Solomon Solis Cohen ed., 1906). Antivenins that PHS considered effective against the venom of North American snakes were not approved until the late 1920s. *See Establishments Licensed for the Propagation and Sale of Viruses, Serums, Toxins, and Analogous Products*, 43 PUB. HEALTH REP. 2108, 2109 (1928) (Mulford).

<sup>135</sup> In 1912 PHS licensed jequiritol serum, which was an antitoxin produced by administering the plant poison abrin (obtained from jequiritol seeds) to horses in the same manner as diphtheria antitoxin was made. Jequiritol serum counteracted an overdose of abrin, which was used in ophthalmology. Letter from Merck & Co. to Surgeon Gen. (Apr. 17, 1912) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>136</sup> BOSANQUET & EYRE, *supra* note 130, at 68, 271–78; Edward R. Baldwin, *General Principles of Tuberculin Diagnosis and Treatment*, 54 J. AM. MED. ASS’N 260, 260 (1910) (“Tuberculin represents the toxin of the tubercle bacillus.”).

generated intracellular toxins (endotoxins, rather than exotoxins like diphtheria bacteria secreted), which were released when the bacteria died and remained in the culture medium, and that the toxins would act against the disease in a tuberculosis patient. In 1890 Robert Koch, the German scientist who discovered the tubercle bacillus, invented the first tuberculin, which proved to be dangerous and ineffective.<sup>137</sup> Many variations followed as researchers attempted to find a safe and effective version. Tuberculins were licensed by PHS because as toxins they were plainly meant to be regulated, but they were all ineffective.<sup>138</sup>

Bacterial vaccines (or bacterins) were similar to tuberculins in that they were made from bacteria grown in the laboratory, although bacterins consisted of killed bacteria, whereas tuberculins generally consisted of material remaining in the culture media after the bacteria had been filtered out.<sup>139</sup> The medical rationale for bacterins was the theory that the anti-infective action of white blood cells depended on the presence of “opsonins,” which facilitated the ability of the cells to destroy bacteria. The killed bacteria in the vaccines, which were generally administered in a long series of injections to patients with chronic bacterial infections, would supposedly cause the patient’s body to produce additional opsonins.<sup>140</sup> Interestingly, Mulford, a major biologics manufacturer, began marketing bacterins without seeking a license, presumably because it believed that the 1902 Act did not apply. (It may have thought that the Act applied only to biologics produced in animals.) When the Director of the Hygienic Laboratory saw an advertisement for the Mulford bacterins, however, he wrote the Surgeon General that the products were “nothing more or less than toxins and apparently come under the law of July 1, 1902.”<sup>141</sup> PHS licensed bacterial vaccines

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<sup>137</sup> See, e.g., GEORGINA D. FELDBERG, *DISEASE AND CLASS* 55–80 (1995); Christoph Gradmann, *Locating Therapeutic Vaccines in Nineteenth-Century History*, 21 *SCI. CONTEXT* 145, 155 (2008); R.A. Young, *The Position To-Day of Tuberculin in Treatment*, 1932 (vol. 2) *BRIT. MED. J.* 1091, 1091 (“The introduction of tuberculin was one of the great tragedies of medical research.”).

<sup>138</sup> *AM. MED. ASS’N, NEW AND NONOFFICIAL REMEDIES*, 1918, at 325–30 (1918) (listing marketed tuberculins); see also *Friedmann’s Tuberculosis Vaccine*, 1912 (vol. 2) *BRIT. MED. J.* 1615, 1615 (“Attempts to produce a tuberculin that is both potent and non-toxic have failed hitherto . . .”). Tuberculins did have an important use as diagnostic agents. Baldwin, *supra* note 136.

<sup>139</sup> See, e.g., Ilana Löwy, *Biotherapies of Chronic Diseases in the Inter-War Period: From Witte’s Peptone to Penicillium Extract*, 36 *STUD. HIST. & PHIL. BIOLOGICAL & BIOMEDICAL SCI.* 675, 685–88 (2005).

<sup>140</sup> Peter Keating, *Vaccine Therapy and the Problem of Opsonins*, 43 *J. HIST. MED. & ALLIED SCI.* 275 (1988).

<sup>141</sup> Memorandum from M.J. Rosenau, Dir., Hygienic Lab., to Surgeon Gen. (Aug. 5, 1907). A few months earlier, PHS had told Parke-Davis that bacterial vaccines had to be licensed. Surgeon Gen. Letter, *supra* note 127.

for a wide range of conditions,<sup>142</sup> although they came to be viewed as largely ineffective.<sup>143</sup>

PHS also licensed a product consisting of erysipelas and prodigious toxins, which purportedly cured cancer.<sup>144</sup> Unlike most biologics, this product was not related to the immune system or infection, but it was clearly a toxin and therefore subject to licensure.

As discussed later in this article, PHS's definition of "toxin" changed when it considered the status of rattlesnake venom and pollen extracts. By the time of the 1919 regulations, tuberculins and bacterins were no longer toxins but had become "analogous products."

#### 4. Therapeutic Serums

The statutory terms "virus," "antitoxin," and "toxin" had relatively clear meanings, but "therapeutic serum" and "analogous product" have no definite boundaries, and PHS had great discretion to interpret them expansively or narrowly. PHS interpreted them restrictively.

Although, based on European statutes, PHS had recommended licensing "therapeutic serums," it found the term troublesome. "Serum" usually means blood serum, the liquid that is left after the blood cells and clot components have been removed from blood. The word, however, can also refer to fluids more generally. Medical dictionaries of the time defined "serum" as including, besides blood serum, "[a]ny clear fluid resembling the serum of the blood"<sup>145</sup> and the "watery portion of an organic fluid."<sup>146</sup> Moreover, "therapeutic serum" seems an odd way to refer exclusively to blood serum if that was the intent; the term looks more like a catch-all category. The mercury-and-urea product in the 1903 license application that first raised the issue of licensing ineffective products was called a serum, but PHS did not reject the application on the ground that the product was not a serum. An indication of

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<sup>142</sup> AM. MED. ASS'N, *supra* note 138, at 330–50; Pittman, *supra* note 43, at 6 ("Some 30 bacterial species, representing practically all of those associated with bacterial disease, had been [licensed] by the 1930s when the sulfa drugs, followed by the antibiotics, were introduced."). PHS also licensed two variations of bacterins. So-called sensitized bacterial vaccines (or serobacterins) were "prepared in the same manner as bacterial vaccines, except that the bacterial suspensions [were] treated with the serum of an animal which has been immunized to some extent against the species of bacterium in hand." AM. MED. ASS'N, *supra* note 138, at 348. Phylacogens, called "modified bacterial vaccines" by PHS, were solutions of the material left behind in the culture media of two or more species of bacteria after the bacteria had been filtered out. PARKE, DAVIS & CO., *MANUAL OF THERAPY* 72–75 (1923).

<sup>143</sup> PHS thought that, with the exception of antityphoid vaccine, "evidence of value [of the bacterial vaccines] is meager . . ." McCoy, *supra* note 90, at 380. "Efficacy of only a few of the many bacterial vaccines licensed before the advent of antibacterial drugs was encouraging but variable." Pittman, *supra* note 43, at 64.

<sup>144</sup> 1909 Regulations, *supra* note 94, para. 16 (listing erysipelas and prodigious toxins as products subject to licensing); *see also* PARKE, DAVIS & CO., *supra* note 24, at 222 (describing the product as "[u]nfiltered toxins from the bacillus of erysipelas and the *bacillus prodigosus*, including therefore the dead bodies of the germs themselves"); Leo Loeb, *The Treatment of Inoperable Sarcoma by Erysipelas and Prodigious Toxins*, 54 J. AM. MED. ASS'N 262, 262 (1910) (concluding that the therapy results in a favorable outcome in a small percentage of sarcoma cases).

<sup>145</sup> GEORGE M. GOULD, *THE PRACTITIONER'S MEDICAL DICTIONARY* 871 (1907).

<sup>146</sup> SMITH ELY JELLIFFE & CAROLINE WORMELEY LATIMER, *APPLETON'S MEDICAL DICTIONARY* 749 (1915).

PHS's uncertainty about what to do with the statutory term is that the regulations always said "serum," not "therapeutic serum," until 1947.

In the end, PHS adopted the narrowest possible definition of "serum" by limiting it in the 1919 regulations to "the product obtained from the blood of an animal by removing the clot or clot components and the blood cells."<sup>147</sup> PHS licensed normal horse serum as an agent (applied locally or injected) to stop bleeding<sup>148</sup> and other animal-blood serums.<sup>149</sup>

### 5. *Analogous Products*

The 1902 Act required licenses for products that were "analogous" to viruses, therapeutic serums, toxins, and antitoxins, and PHS could have used that authority to cover many other types of products. For example, it could have developed a functional definition of an "analogous product" similar to a provision in the British biologics law, which allowed the administering agencies to require licensing of "therapeutic substances . . . the purity or potency of which cannot be adequately tested by chemical means."<sup>150</sup> Instead, the products that PHS licensed as "analogous products" prior to the 1919 regulations appear to have fallen into only three categories: (a) antibacterial serums, (b) tuberculins and bacterins (and similar products), which, as noted above, started out as "toxins" but were reclassified by PHS as "analogous products," and (c) leukocyte extract. In light of the potential breadth of the term "analogous product," this was an extremely restrictive implementation.

Antibacterial serums were made in horses in the same manner as antitoxins, but because the bacteria being used did not generate exotoxins, manufacturers injected horses with living and dead bacteria rather than toxins.<sup>151</sup> The horses were bled in the same manner as for antitoxins, and the resulting products were thought to transfer antibodies to human patients or to be directly bactericidal. PHS no doubt licensed antibacterial serums as "analogous products" because the manufacturing method so closely resembled that of diphtheria antitoxin.

The 1919/1923 regulations provided that products "prepared from a virus, including microorganisms actually or potentially virulent" were analogous to viruses and that products intended "for the prevention of treatment of disease through specific immunization" were analogous to toxins or antitoxins.<sup>152</sup> Those definitions overlap, but it appears that the combination was intended to sweep in a range of microbe-related

<sup>147</sup> 1919 REGULATIONS, *supra* note 98, para. 7-II.

<sup>148</sup> 1909 Regulations, *supra* note 94, para. 16 (listing normal horse serum as subject to licensing); *see also* AM. MED. ASS'N, *supra* note 138, at 312–13.

<sup>149</sup> For example, in 1918 PHS licensed thyroidectomized horse serum, normal sheep serum, and normal goat serum. *Establishments Licensed and Products for Which Licenses Have Been Issued*, 33 PUB. HEALTH REP. 870 (1918).

<sup>150</sup> Therapeutic Substances Act, 1925, 15 & 16 Geo. 5, c. 60. In addition to permitting the licensing of substances meeting the functional definition, the Act explicitly applied to vaccines, sera, toxins, antitoxins, antigens, Salvarsan and analogous substances, insulin, and injectable preparations of the posterior lobe of the pituitary gland.

<sup>151</sup> BOSANQUET & EYRE, *supra* note 130, at 43–44; B.A. THOMAS & R.H. IVY, APPLIED IMMUNOLOGY 38–41 (1915); Twining, *supra* note 16, at 27–28.

<sup>152</sup> 1919 REGULATIONS, *supra* note 98, para. 7-V; 1923 REGULATIONS, *supra* note 128, para. 7-V. The 1919 regulations provided that products "intended for specific immunization or therapy" were "analogous products." The implication that any product "intended for specific . . . therapy" had to be licensed was inadvertently broad, and the provision was reworded in 1923 as quoted in the text.

products, including those made from live or killed bacteria, endotoxins, etc. The definition of “analogous product” thus encompassed antibacterial serums, tuberculins, bacterins, and similar products but did not extend beyond that relatively circumscribed group. The one exception, leukocyte extract, is discussed later in this article.

### C. *Licensing of Biologics Whether or Not They Were Effective*

If a product fell into one of the classes of products that PHS felt compelled to license, PHS licensed it even if it was probably ineffective. For example, the Hygienic Laboratory’s review in 1909 of a license application for a product made of goat serum drawn from the animal’s renal vein recommended approval despite the lack of evidence that it would work or had a valid medical rationale:

I know but little of the therapeutic value of blood collected from the renal vein of a goat in the treatment of certain forms of nephritis. It was considered at one time that the kidney had an important internal secretion affecting metabolism in some way, but recent work has cast a doubt upon this hypothesis. As other serums, such as antistreptococcus serum, whose therapeutic efficiency is not generally recognized have been licensed, I can see no special reason why this serum should be refused a license.<sup>153</sup>

Effectiveness mattered only if a product failed in vitro testing for biological activity. PHS collected samples of products during prelicensing inspections<sup>154</sup> and at least in some circumstances assessed effectiveness to a limited extent by subjecting the samples to laboratory tests.<sup>155</sup> In vitro biological activity, of course, does not demonstrate clinical effectiveness.

PHS became concerned about physician acceptance of biologics that were probably ineffective and wrote articles pointing out that licensing did not imply effectiveness. In a 1910 article, the Director of the Hygienic Laboratory noted that a number of serums “of weak and doubtful efficiency” and “substances in the experimental stage” had been licensed and warned that a licensed product “may have little or no therapeutic value.”<sup>156</sup> In 1913, a new Director wrote that the law “does not give specific authority to refuse to issue a license for a product of unknown or doubtful therapeutic value” and that federal licensure of a product “does not mean that the government recognizes such a product as valuable for curative or prophylactic purposes.”<sup>157</sup> The standard that PHS was applying was:

Unless it can be shown by satisfactory tests that such preparations are directly harmful or are based on demonstrated false premises, their sale

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<sup>153</sup> Memorandum from John F. Anderson, Ass’t Dir., Hygienic Lab., to Surgeon Gen. (May 17, 1909) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>154</sup> Anderson, *supra* note 119, at 660.

<sup>155</sup> See, e.g., Letter from H.A. Taylor, Sec’y Treas., to Bristol Lab. Co. (Apr. 6, 1905) (denying license for purported antisyphilitic serum); Memorandum from M.J. Rosenau, Dir., Hygienic Lab., to Surgeon Gen. (Mar. 8, 1905) (reporting the results of laboratory tests that failed to show any in vitro activity of the product against the bacillus that the company claimed was the cause of syphilis and that showed greater agglutination in the blood serum of normal individuals than in the blood serum of syphilis patients—the opposite of what should have been seen if the product was active against syphilis) (both on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>156</sup> Rosenau, *supra* note 12, at 250.

<sup>157</sup> Anderson, *supra* note 119, at 659, 661.



cannot be prevented under existing law, though they may have no therapeutic value and may even do harm to a patient because of his generally lowered resistance to toxic substances.<sup>158</sup>

In its annual report for 1913, PHS wrote, “Manufacturers are constantly placing on the market new biological products the therapeutic efficiency of which has not yet been demonstrated. Certain other products are offered for sale which seem to be prepared and recommended for use with reference to no definite scientific principles.”<sup>159</sup> The Director of the Hygienic Laboratory railed against the widespread use of biologics that often lacked any scientific evidence of effectiveness, asserting that the parenteral method of administration “appears to have cast a spell not only over the laity . . . but also on some physicians who seem easily persuaded to ascribe virtue to parenteral administration of almost any preparation.”<sup>160</sup> A 1916 internal memo assessing which biologics had “known value” set forth a very short list—diphtheria and tetanus antitoxins, smallpox vaccine, “probably” rabies and typhoid vaccines, and “possibly certain other agents.”<sup>161</sup>

In sum, PHS knowingly licensed products that were likely ineffective because it thought that the statute gave it no choice. Officials published articles pointing out that a governmental license did not imply effectiveness, but the articles had little effect. PHS became increasingly dismayed that dubious products did not quickly fade away but enjoyed considerable use by physicians.

## VII. EXCLUSION OF VARIOUS CATEGORIES OF PRODUCTS FROM LICENSURE EVEN THOUGH THEY WERE ARGUABLY SUBJECT TO THE 1902 ACT

In the early decades of the 1902 Act, there were drugs on the market that were arguably subject to licensing—even under the narrow interpretations that PHS had ascribed to the statutory classes—but that PHS nevertheless concluded were outside its jurisdiction. Those decisions were driven in large part by a view that the products were probably ineffective and declaring them to be outside the Act avoided licensing any more ineffective products than necessary. The decisions may also have been based in part on conclusions that the products were probably safe and that the inspection and licensing mechanism of the 1902 Act was unnecessary to protect the public. This section of the article describes situations in which PHS decided that certain classes of products were not subject to licensure.

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<sup>158</sup> *Id.* at 660.

<sup>159</sup> 1913 PHS ANNUAL REPORT, *supra* note 119, at 44.

<sup>160</sup> John F. Anderson, *Some Unhealthy Tendencies in Therapeutics*, 63 J. AM. MED. ASS’N 1, 1 (1914).

<sup>161</sup> Memorandum from Dir., Hygienic Lab., to Surgeon Gen. (Jan. 20, 1916) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655); *see also, e.g.*, G.W. McCoy, *The Prophylactic and Therapeutic Value of Vaccines*, 9 J. AM. PHARM. ASS’N 573, 573 (1920) (assessing various vaccines); Frederick P. Gay, *The Use of Antiserums in the Treatment of Disease*, 81 J. AM. MED. ASS’N 283, 284 (1923) (assessing various serums).

### A. Oral and Other Nonparenteral Products

PHS initially ruled that oral products were not subject to licensure. That policy was formed in early 1907 when a major biologics manufacturer applied for a license for Antithyroidin, which was made from the blood serum of sheep whose thyroid glands had been removed and was used to treat the thyroid condition Grave's (or Basedow's) disease.<sup>162</sup> The underlying medical theory was that Grave's disease was caused by excess thyroid toxins and that antitoxins in the sheep blood would neutralize those toxins. It was administered as an oral liquid because the original researcher found that oral administration worked better than the subcutaneous administration he initially tried. The Director of the Hygienic Laboratory recommended against licensing Antithyroidin. He wanted to limit licensing to conventional injectable biologics because licensing an orally administered antitoxin serum seemed to imply that all serums should be licensed, and if PHS did that, it would give commercially useful governmental licenses to products of questionable medical value:

[A]ntithyroidin is exhibited by mouth and, so far, no serum or analogous products intended for use in this way has [*sic*] been licensed under the law of July 1, 1902 . . . .

In my opinion, therefore, this letter brings up the question whether all serums . . . shall be submitted to surveillance under the law. While official control of the potency and purity of this class of products is desirable, the technical difficulties of such a control are very great; in fact, there is no satisfactory test for the majority of these substances. Many of them are experimental and will not linger long. There is no test, for instance, for antithyroidin which, taken by the mouth, is doubtless harmless.

So it is difficult to see how the licensing of this remedy under the law would result in benefit except to those who exploit the substance in giving it the dignity of official recognition.<sup>163</sup>

PHS told the applicant that "after due consideration of its characteristics and method of administration," the product was not subject to the 1902 Act.<sup>164</sup>

PHS gave the application "due consideration" because the product was an antitoxin and thus seemed to be squarely within the terms of the 1902 Act. Nevertheless, in implementing the Act, PHS added a nonstatutory exclusion of oral products, which it thought were likely safe but ineffective and did not pose problems that could be addressed by licensing them.<sup>165</sup> In 1910, the Hygienic Laboratory implicitly suggested

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<sup>162</sup> Letter from Merck & Co. to Surgeon Gen. with enclosed pamphlet on Antithyroidin (Apr. 4, 1907) (on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897-1923, File 3655) [hereinafter Merck Letter]. The American Medical Association later said of antithyroidin products: "The value of these preparations is very doubtful. The reported improvements may only be psychical or due to associated measures, as is often seen in this disease." AM. MED. ASS'N, *supra* note 138, at 37.

<sup>163</sup> Endorsement from M.J. Rosenau, Dir., Hygienic Lab., to Surgeon Gen. (Apr. 15, 1907), on back of Merck Letter, *supra* note 162 [hereinafter Rosenau Endorsement].

<sup>164</sup> Letter from A.H. Glennan, Acting Surgeon Gen., to Merck & Co. (Apr. 25, 1907) (on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897-1923, File 3655).

<sup>165</sup> See also, e.g., Letter from A.H. Glennan, Acting Surgeon Gen., to Pasteur Vaccine Co. (Sep. 24, 1908) (oral scarlet fever serum not subject to the 1902 Act); Letter from Walter Wyman, Surgeon Gen., to Abbott Alkaloidal Co. (Aug. 10, 1909) (pills of bulgarian bacillus not subject to licensure) (both on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897-1923, File 3655).

review of the policy when it sent the Surgeon General information about a pill being sold as a tuberculosis cure through advertising that implied it was a tuberculin (i.e., a product that would be licensed if in injectable form). The Surgeon General's response shut down any reconsideration of the policy by answering that, as an "ordinary pill . . . , it is not at the present time considered to be a vaccine, serum, or toxin within the meaning of the law."<sup>166</sup>

PHS later expanded the exclusion to include all nonparenteral products, not just oral products. For a few years, PHS licensed lactic acid bacilli and Pyocyanase, both of which were applied externally, but in 1912 or 1913 PHS stopped licensing them even though at least lactic acid bacilli continued to be sold.<sup>167</sup>

As an exception to its general rule, PHS regarded any product that contained horse serum to be subject to the 1902 Act, regardless of method of administration,<sup>168</sup> due to the risk of anaphylaxis.<sup>169</sup> Wound dressings containing horse serum were regulated, said PHS, because the Act "specifies serums but without any statement as to how they are to be used,"<sup>170</sup> a position that was of course irreconcilable with the policy of generally not licensing oral serums.

At some point in the 1920s or early 1930s, PHS began licensing nonparenteral products. A 1931 memo providing an overview of product developments noted:

Probably the most striking development is in products intended to be administered by other than the hypodermic method. Thus, we have diphtheria toxoid and bacterial vaccines and antigens to be administered by inunction [rubbing the product on the skin]; colon bacillus vaccine, incorporated in suppositories, to be given by the rectum; antipyogenic

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<sup>166</sup> Memorandum from A.H. Glennan, Acting Surgeon Gen., to J.F. Anderson (Nov. 11, 1910), responding to Memorandum from John F. Anderson, Dir., Hygienic Lab., to Surgeon Gen. (Nov. 9, 1910) (both on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>167</sup> Pyocyanase and suspension of lactic acid bacilli first appeared in the list of products licensed as of Jan. 1, 1910. *Establishments Licensed for the Propagation and Sale of Viruses, Serums, Toxins, and Analogous Products*, 25 PUB. HEALTH REP. 3 (1910). Pyocyanase was no longer on the list of products licensed as of Jan. 1, 1913, see *Establishments Licensed for the Propagation and Sale of Viruses, Serums, Toxins, and Analogous Products*, 28 PUB. HEALTH REP. 61, and suspension of lactic acid bacilli was gone from the list of licenses as of July 1, 1913, see *Establishments Licensed for the Propagation and Sale of Viruses, Serums, Toxins, and Analogous Products*, 28 PUB. HEALTH REP. 105 (1913). At least suspension of lactic acid bacilli continued to be marketed. AM. MED. ASS'N, *supra* note 138, at 187. Pyocyanase was made from weeks-old cultures of *Bacillus pyocyanus*; it killed bacteria in vitro and supposedly had a similar effect when applied to humans. HOWARD TAYLOR RICKETTS, *INFECTION, IMMUNITY AND SERUM THERAPY* 172, 422–24 (2d ed. 1913); *Pyocyanase* (undated brochure) (on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655 (1909–1912)).

<sup>168</sup> See Memorandum from Acting Surgeon Gen. to Chief, Div. of Customs (Feb. 14, 1920) (on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655) (tablets); Letter from G.W. McCoy, Dir., Hygienic Lab., to Charles A. Darius (Feb. 26, 1924) (on file with the Nat'l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 0725D) [hereinafter McCoy Letter] (locally applied wound dressing); Letter from L.R. Thompson, Dir., NIH, to Spicer & Co. (Jan. 22, 1938) (on file with the Nat'l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 1973S) (revoking previous determination that a product was not subject to the 1902 Act upon discovering that it contained a residue of horse serum and that sequential doses of the product in test animals resulted in anaphylactic shock and death).

<sup>169</sup> See M.J. ROSENAU & JOHN F. ANDERSON, PHS, TREAS. DEP'T, HYGIENIC LAB. BULL. NO. 29, A STUDY OF THE CAUSE OF SUDDEN DEATH FOLLOWING THE INJECTION OF HORSE SERUM 7 (1906).

<sup>170</sup> McCoy Letter, *supra* note 168.

vaccine and antigen for vaginal administration, and “bacteriophage” preparations for application to the skin, or to open lesions.<sup>171</sup>

During the same period, PHS began licensing oral bacterial vaccines for typhoid and colds.<sup>172</sup>

The PHS regulations distinguished among product classes with respect to method of administration. There was no reference to parenteral administration until the 1923 regulations, which made parenteral administration a prerequisite for licensing products *analogous* to serums, toxins, and antitoxins, but not to viruses or to serums, toxins, and antitoxins themselves.<sup>173</sup> In 1947, the limitation no longer applied to products analogous to toxins and antitoxins but applied for the first time to serums (and continued to apply to products analogous to serums).<sup>174</sup> The current regulations include no limitations based on method of administration.

The basis for applying or not applying the parenteral-administration limitation is unclear but was presumably related to PHS’s changing views about the possible effectiveness of the products. Under the usual rules of statutory interpretation, an agency lacks the discretion to regulate or not regulate products based on ad hoc considerations not supported by the statutory text,<sup>175</sup> but that seems to be what PHS did in the case of oral and externally applied products.

### B. Plant-Derived Products

A factor that led to PHS defining “serum” in the 1919 regulations as meaning only blood serum was that a broader definition could include products derived from plants. Plant-derived serums would not likely pose the risk of microbial contamination that a serum produced in an animal would, and like many of the plant-derived drugs then on the market, plant-derived serums would often be ineffective. Prior to defining “serum” as limited to blood serum, PHS tested products for the presence of protein, which implied an animal source, and if there was no protein present, it was not subject to the 1902 Act.<sup>176</sup>

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<sup>171</sup> Memorandum from G.W. McCoy, Med. Dir., NIH, to Surgeon Gen. (Sep. 1, 1931) (on file with the Nat’l Archives, Rec. Grp. 90, Gen. Subject File 1924–1935, Gen. Files, File 470-132).

<sup>172</sup> Answer on “Cold Vaccines”, *Actively Sought in NIH Laboratories, Seems Likely to Ban Oral Products, Based on Findings to Now*, FOOD-DRUG-COSMETIC REP. (DRUG & COSMETIC ED.), Mar. 31, 1945, at 1 (supp.) (on file with the Nat’l Archives, Rec. Grp. 443, Gen. Recs. 1930-1948, File 1850). Oral cold vaccines became something of a scandal in 1945 when FDA took enforcement action against alleged cold cures only to discover that some of the products making extravagant claims were licensed by PHS. PHS defended the situation by arguing that the products had been approved based on in vitro studies showing apparent effectiveness before issuance of the 1934 regulation requiring proof of effectiveness. Memorandum from R.E. Dyer, Dir., NIH, to Mary E. Switzer (Aug. 4, 1945) (on file with the Nat’l Archives, Rec. Grp. 235, Gen. Classified Files 1944–1950, Gen. Decimal Series, File 950).

<sup>173</sup> 1923 REGULATIONS, *supra* note 128, para. 7.

<sup>174</sup> 12 Fed. Reg. 411, 412 (Jan. 21, 1947) (to be codified at 42 C.F.R. 22.1(g)).

<sup>175</sup> Cf. Memorandum from Edward J. Rourke, Ass’t Gen. Couns., to Luther L. Terry, Surgeon Gen. (Apr. 23, 1962) (on file with the Nat’l Archives, Rec. Grp. 235, Off. Gen. Couns. Op. Files 1942–1963, File PS8000) (“As we have thus previously noted, the Service or Department has no authority under section 351 to choose to exclude or include a product which otherwise is, respectively, included or excluded by the statute merely because of judgments of administrative feasibility or of importance of a product to the public health.”).

<sup>176</sup> See, e.g., Letter from A.H. Glennan, Acting Surgeon Gen., to Collector of Customs, San Juan, P.R. (Mar. 4, 1911); Memorandum from Walter Wyman, Surgeon Gen., to S.B. Grubbs, Chief Quarantine

### C. Glandular Products, Including Hormones

A prominent regulatory curiosity is that hormones are not licensed as biologics.<sup>177</sup> PHS did not want to license products derived from glands because it thought that most of them were worthless, although basically safe, and that a license would be seen as a governmental determination that they were effective.

The interest in using glandular extracts for therapeutic purposes (known as “organotherapy” or “opotherapy”) began with the announcement in 1889 by Charles-Édouard Brown-Séquard, a French academic physician, that he had found beneficial effects from injections of animal testicle extracts.<sup>178</sup> In 1891 researchers found that injections of animal thyroid extract could cure myxedema (a condition caused by an underactive thyroid gland), which led physicians to believe that glandular extracts could be medically useful in many conditions. During the 1890s physicians and laboratories assessed the effects of many types of animal tissues, but only thyroid and adrenal extracts proved valuable during that time.<sup>179</sup> Nevertheless, many organotherapeutic products continued to be sold.

In 1907-1908 PHS attempted to develop standards for glandular products, and its 1908 annual report seemed to say that they were subject to the 1902 Act.<sup>180</sup> The effort to develop standards was largely unsuccessful, however, and the Hygienic Laboratory came to see most of the products as useless. Its position was summarized in the following 1909 note to the Surgeon General, which opposed licensing glandular products:

[M]ost of these organo-therapeutic preparations are in the experimental stage; but few of them are really useful and but a few of them are occasionally harmful; with the exception, perhaps, of adrenalin, these glandular extracts cannot be standardized; to license them would give respectability to a class of drugs some of which are on the borderline of

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Officer (Apr. 3, 1911); Memorandum from John F. Anderson, Dir., Hygienic Lab., to Surgeon Gen. (Sep. 22, 1911) (all on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897-1923, File 3655).

<sup>177</sup> In addition to covering the products subject to the 1902 Act, the French statute on which the 1902 Act was based applied to “injectable substances of organic origin not chemically defined,” a provision that was intended to encompass organotherapy products. Jonathan Simon, *Quality Control and the Politics of Serum Production in France*, in *EVALUATING AND STANDARDIZING THERAPEUTIC AGENTS, 1890-1950*, 89, 95-96 (Christoph Gradmann & Jonathan Simon eds., 2010). The provision was translated as “injectable substances of organic origin, of undefined composition” in PHS’s 1902 article on foreign biologics statutes. Geddings, *supra* note 76. For unknown reasons, the language did not make it into the 1902 Act; it may have encompassed products that the industry or PHS, or both, were not interested in licensing, or, conceivably, they viewed the statutory term “analogous products” as covering glandular products.

<sup>178</sup> For history of organotherapy, see, for example, WALTER SNEADER, *DRUG DISCOVERY: A HISTORY* 151-52 (2005); Merriley Borell, *Brown-Séquard’s Organotherapy and Its Appearance in America at the End of the Nineteenth Century*, 50 *BULL. HIST. MED.* 309 (1976); Merriley Borell, *Organotherapy, British Physiology, and Discovery of the Internal Secretions*, 9 *J. HIST. BIOLOGY* 235 (1976); Merriley Borell, *Organotherapy and the Emergence of Reproductive Endocrinology*, 18 *J. HIST. BIOLOGY* 1 (1985); Robert Tattersall, *Pancreatic Organotherapy for Diabetes, 1889-1921*, 39 *MED. HIST.* 288 (1995).

<sup>179</sup> *The Scientific Basis of Organotherapy*, 35 *J. AM. MED. ASS’N* 1483, 1483 (1900).

<sup>180</sup> 1908 PHS ANNUAL REPORT, *supra* note 126, at 47 (“In order to satisfactorily administer the law regulating the manufacture and sale of [biologics] in interstate traffic, it is imperative to establish standards by which they may be measured. The necessity of such standards especially applies to organo-therapeutic products, some of which are now recognized as of great value in the treatment of disease.”).

being non-ethical; to license these preparations would serve little or no useful purpose, and it is doubtful if they may be properly considered as either viruses, serums, toxins or analogous products under the Law of July 1, 1902.<sup>181</sup>

This rationale was essentially the same as that advanced two years earlier in opposition to licensing oral serums: organotherapeutic products were largely safe but ineffective, licensing would not address any problems, and licensing would imply governmental endorsement. Following this 1909 note, PHS consistently took the position that glandular products were outside the scope of the 1902 Act and did not require licensing.<sup>182</sup>

By the 1920s, it was evident to mainstream medicine that the hoped-for benefits of glandular therapy were not going to materialize except for a small number of products. The *Journal of the American Medical Association* editorialized that much of the “organotherapeutic craze” lacked a sound medical rationale and also presented “positive dangers.”<sup>183</sup> It urged that further experimentation be confined to the laboratory and that experimental products not be used in the clinic.<sup>184</sup>

In 1947 the regulations were amended to exclude hormones from licensure.<sup>185</sup> This was a codification of PHS’s longstanding policy and clarified that the regulation requiring licensure of products made from constituents of blood did not require hormones to be licensed even though hormones are found in blood.

#### D. Amino Acids

The 1947 regulation that excluded hormones from licensure also excluded amino acids.<sup>186</sup> This provision was likely a codification of a decision made years earlier. In the mid-1930s research found that amino acids seemed to be effective in treating certain muscular diseases,<sup>187</sup> and the published articles reporting that research probably led to a PHS determination that, like other questionable products, amino acids were not subject to the 1902 Act.

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<sup>181</sup> Endorsement by John F. Anderson, Ass’t Dir., Hygienic Lab., to Surgeon Gen. (Apr. 7, 1909), on back of Letter from Morgenstern & Co. to Surgeon Gen. (Mar. 31, 1909) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>182</sup> E.g., Letter from A.H. Glennan, Acting Surgeon Gen., to Morgenstern & Co. (Apr. 21, 1909) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655); Letter from W. Wyman, Surgeon Gen., to Schering & Glatz (Nov. 4, 1910) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655) [hereinafter Wyman Letter]; Letter from W.F. Draper, Ass’t Surgeon Gen., to J.D. Nevius, Div. Customs (Feb. 26, 1923) (on file with the Nat’l Archives, Rec. Grp. 90, Gen. Subject Files 1924–1938, Gen. Files, File 470-95); Letter from G.W. McCoy, Dir., NIH, to Randolph Cautley (Oct. 28, 1933) (on file with the Nat’l Archives, Rec. Grp. 443, Gen. Recs. 1930-1948, File 0725G) (stating that sex hormones are not subject to the 1902 Act).

<sup>183</sup> *Limitations of Organotherapy*, 82 J. AM. MED. ASS’N 1048, 1048 (1924).

<sup>184</sup> *Id.*

<sup>185</sup> 12 Fed. Reg. 411, 412 (Jan. 21, 1947) (to be codified at 42 C.F.R. § 22.1(g)(5)(ii)).

<sup>186</sup> *Id.*

<sup>187</sup> E.g., Walter M. Boothby, *Myasthenia Gravis*, 102 J. AM. MED. ASS’N 259, 260 (1934); J.G. Reinhold et al., *The Effects of Glycine (Glycocol) in Muscular Dystrophy*, 102 J. AM. MED. ASS’N 261, 261 (1934); Carlo J. Tripoli et al., *Muscular Dystrophy, Muscular Atrophy, Myasthenia Gravis and Strabismus: Clinical and Biochemical Studies of the Effects of Amino Acid Therapy*, 103 J. AM. MED. ASS’N 1595, 1595 (1934).

### *E. Nonspecific Protein Therapy*

In the mid-teens of the twentieth century, articles began appearing in the literature about a new treatment known as nonspecific protein therapy and by other names.<sup>188</sup> An agent such as a protein was injected into a patient to cause fever and chill and an increase in the leukocyte count, supposedly alleviating a wide variety of conditions, including arthritis and infections.

In 1919 the Hygienic Laboratory learned that a company was marketing “Proteogens” for this type of therapy and in a memo to the Surgeon General stated that it was “disposed to believe” that they should be considered subject to the 1902 Act as “analogous products.”<sup>189</sup> Proteogens were proteins extracted from plants, administered by intramuscular injection, and recommended for treating many diseases.<sup>190</sup> A few months after the Hygienic Laboratory’s recommendation, the American Medical Association’s Council on Pharmacy and Chemistry found no evidence that Proteogens were effective and no rational theory for their use.<sup>191</sup> A competitor of the Proteogens manufacturer then asked PHS whether they were subject to the 1902 Act and was told that the matter was under consideration.<sup>192</sup> Evidently the Surgeon General decided that the proteins were outside the scope of the 1902 Act, since no action was taken. A series of review articles in 1921 found that there were sometimes favorable results from the use of nonspecific proteins, but an accompanying editorial noted that there was no scientific explanation for the effects and urged that the therapy should be used only under experimental conditions.<sup>193</sup>

In 1921 an academic physician asked about the legal status of his “pure protein,” which was made by splitting up ox-blood fibrin with pepsin and hydrochloric acid and was administered by injection for treatment of arthritis.<sup>194</sup> The Hygienic Laboratory wrote the Surgeon General that “up to the present time such material has not been held to come under the terms of the law,” and the physician was advised that his “nonspecific hemoprotein” could be sold interstate without a license.<sup>195</sup> The position

<sup>188</sup> *E.g.*, Joseph L. Miller, *Foreign Protein Therapy in the Acute Infections*, 76 J. AM. MED. ASS’N 308, 308 (1921) (reviewing the literature).

<sup>189</sup> Memorandum from G.W. McCoy, Dir., Hygienic Lab., to Surgeon Gen. (Feb. 25, 1919) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>190</sup> A.S. Horovitz, *The Non-Specific Plant Protein Therapy*, 11 NAT’L ECCLECTIC MED. ASS’N Q. 65, 65 (1919).

<sup>191</sup> *Proteogens of the Wm. S. Merrell Company*, 73 J. AM. MED. ASS’N 128, 128 (1919).

<sup>192</sup> Letter from Milton Campbell, President, Mulford, to Surgeon Gen. Off. (Nov. 7, 1919); Letter from Ass’t Surgeon Gen. to Campbell (Nov. 18, 1919) (both on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>193</sup> David Murray Cowie, *Nonspecific Protein Therapy in Arthritis*, 76 J. AM. MED. ASS’N 310, 310 (1921); Harry Culver, *Intravenous Protein Injections in Urology and Dermatology*, 76 J. AM. MED. ASS’N 311, 311 (1921); Miller, *supra* note 188; W.F. Petersen, *The Nonspecific Reaction*, 76 J. AM. MED. ASS’N 312, 313 (1921); Editorial, *Foreign Protein Therapy*, 76 J. AM. MED. ASS’N 315, 316 (1921).

<sup>194</sup> Letter from Clyde Brooks, Dean, Univ. Ala. Sch. Med., to George W. McCoy, Dir., Hygienic Lab. (June 20, 1921) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655); Clyde Brooks & F.M. Stanton, *Nonspecific Hemoprotein Antigen for the Treatment of Arthritis*, 109 N.Y. MED. J. 452, 452 (1919).

<sup>195</sup> Memorandum from G.W. McCoy, Dir., Hygienic Lab., to Surgeon Gen. (June 24, 1921); Letter from J.W. Schereschewsky, Ass’t Surgeon Gen., to Clyde Brooks (June 29, 1921) (both on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

was reaffirmed in 1929.<sup>196</sup> A 1931 review article found the case for nonspecific protein therapy still unproven and predicted that it would soon be abandoned.<sup>197</sup>

Nonspecific protein therapy seems to have been a difficult case for PHS as indicated by the many months it took to resolve the therapy's status. In 1919 the Hygienic Laboratory probably saw the proteins as "analogous products" because they increased a patient's leukocyte count. A few years earlier, that mechanism of action might have been sufficient to require licensure, but as described later in this article, by 1919 PHS was to some extent considering evidence of a product's effectiveness. Here the evidence of effectiveness was confusing because, while the therapy seemed to work at times, it lacked any scientific rationale. The end result was a decision not to imply governmental approval of the therapy through licensure of the proteins.

### F. *Products Made from Live Bacteria*

In November 1912 Friedrich F. Friedmann announced to the Berlin Medical Society that he had created a cure for tuberculosis by passing tuberculosis bacteria through turtles, a cold-blooded animal. Attempts to make a safe and effective tuberculin had failed, but Friedmann claimed to have made a nonvirulent product. The drug was a suspension of live bacteria and was administered by intramuscular injection. Friedmann's announcement created a sensation and resulted in a message from President Taft to Congress providing information about it.<sup>198</sup> Friedmann came to the United States to treat patients with his serum, and the Treasury Department Solicitor ruled that use of an unlicensed biologic to treat a patient was not a violation of the 1902 Act.<sup>199</sup>

In March 1913 PHS decided to investigate the treatment and in a preliminary report published in May 1913 stated that although its investigation was continuing, "we are in a position to state that the effects thus far observed do not justify that confidence in the remedy which has been inspired by widespread publicity."<sup>200</sup> A final report issued the following year determined that Friedmann's claims for his product were not substantiated and that there was evidence patients were harmed by it.<sup>201</sup>

While PHS's investigation of Friedmann's treatment was taking place, Mulford applied for a license for various products, and the license issued by PHS did not include cultures of *Staphylococcus aureus* as Mulford had requested. When Mulford inquired about the omission, PHS replied that "for the present" it would not license

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<sup>196</sup> Letter from G.W. McCoy, Dir., Hygienic Lab., to Edgar B. Carter, Swan-Myers Co. (June 4, 1929) (on file with the Nat'l Archives, Rec. Grp. 443, Gen. Recs. 1930-1948, File 425F-L) (stating that a solution of nonspecific plant-derived proteins for intramuscular injection advertised as a hay fever remedy is not subject to the 1902 Act).

<sup>197</sup> Ernest E. Irons, *Facts and Fallacies Concerning Foreign Protein and Vaccine Therapy*, 96 J. AM. MED. ASS'N 1289, 1293 (1931).

<sup>198</sup> DR. FRIEDMANN'S NEW TREATMENT FOR TUBERCULOSIS, S. DOC. NO. 62-1018, at 7 (3d Sess. 1913).

<sup>199</sup> Memorandum from W.T. Thompson, Solic., to Sherman Allen, Ass't Sec'y Treas. (Apr. 17, 1913) (on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897-1923, File 3655).

<sup>200</sup> John F. Anderson & A.M. Stimson, *The Friedmann Treatment for Tuberculosis*, 28 PUB. HEALTH REP. 937, 939 (1913); but cf. William J. Beattie & Edward E. Myers, *The Relative Value of Turtle Tuberculin in the Treatment of Tuberculosis*, 98 N.Y. MED. J. 500, 502 (1913) (describing the treatment in favorable terms).

<sup>201</sup> JOHN F. ANDERSON & ARTHUR M. STIMSON, THE FRIEDMANN TREATMENT FOR TUBERCULOSIS, H.R. DOC. NO. 63-1406, at 63 (1914); Anderson, *supra* note 160, at 1-2.



any cultures of living organisms<sup>202</sup>—even though a product composed of live bacteria would seem to have been a “virus” under the statute. Although PHS had previously licensed a nonparenteral culture of live bacteria, this new position was probably a preemptive move to avoid any possibility of having to license Friedmann’s therapy. The interim policy of not licensing cultures of live bacteria may have become permanent. A later publication of a biologics company stated that PHS prohibited the use of living bacteria in bacterial vaccines because of the danger involved.<sup>203</sup> Although nothing in the 1902 Act explicitly barred products that are inherently unsafe, the concern about product safety that led to its enactment may have encouraged PHS to believe that it had authority to deny licenses for such products.<sup>204</sup>

### G. Diagnostic Biologics

PHS excluded biologics used for diagnostic purposes from licensing on the ground that they were not “applicable to the prevention and cure of diseases,” in the words of the 1902 Act.<sup>205</sup> That conclusion may have been simply a legal interpretation not motivated by the desire to avoid licensing ineffective products, although that assessment is thrown in doubt by the recommendation of the Hygienic Laboratory to the Surgeon General in 1920 to regulate additional products, including “diagnostic agents.”<sup>206</sup> Whatever the reason for the original policy, PHS reversed its position in 1947 and applied the Biologics Control Act to diagnostics.<sup>207</sup>

### H. Surgical Sutures and Ligatures

In response to a manufacturer’s request, bills were introduced in Congress in 1937 to require licenses under the 1902 Act for surgical sutures and ligatures.<sup>208</sup> The

<sup>202</sup> Letter from Rupert Blue, Surgeon Gen., to A. Parker Hitchens, Mulford (Feb. 3, 1914), responding to Letter from A. Parker Hitchens, Dir., Mulford, to Surgeon Gen. Rupert Blue (Jan. 28, 1914) (both on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>203</sup> ELI LILLY & CO., *THE ELEMENTS OF BIOLOGICS* 98 (1917). (Although the available version of the publication is dated 1917, it contains material from the 1930s.)

<sup>204</sup> The only instance in the early years in which PHS expressly refused to license a product because it was inherently unsafe appears to have been a license application for normal human serum, which was declined “because of the great liability of the transmission of disease, should such serum be handled commercially.” 1917 ANNUAL MEETING, *supra* note 67, at 235.

<sup>205</sup> Letter from Surgeon Gen. to Parke-Davis (Feb. 12, 1907) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655) (stating that a diagnostic agent is not subject to the 1902 Act because it is not a “therapeutic remedy for the prevention and cure of diseases of man”); Memorandum from H.D. Geddings to Surgeon Gen. (June 24, 1912) (on file with the Nat’l Archives, Rec.d Grp. 90, Cent. File 1897–1923, File 3655); Letter from John W. Kerr, Ass’t Surgeon Gen., to Arlington Chem. Co. (July 20, 1916) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655); Letter from Rupert Blue, Surgeon Gen., to W.B. Hamilton, U.S. Customs Serv. (Apr. 7, 1919) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655); Letter from G.W. McCoy, Dir., NIH, to Arthur Stull, Roosevelt Hosp. (July 28, 1933) (on file with the Nat’l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 1973S).

<sup>206</sup> Memorandum from G.W. McCoy to Surgeon Gen. (June 1920) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655) [hereinafter McCoy Memorandum].

<sup>207</sup> 12 Fed. Reg. 411, 412 (Jan. 21, 1947) (to be codified at 42 C.F.R. § 22.1(i)). Some diagnostic agents were licensed before the regulation was issued. *Establishments Licensed for the Propagation and Sale of Viruses, Serums, Toxins, and Analogous Products*, 57 PUB. HEALTH REP. 1775, 1776–81 (1942) (listing licenses for meningococcus typing serum and pneumococcus typing serum).

<sup>208</sup> H.R. 6359, 75th Cong. (1937); S. 1629, 75th Cong. (1937). See Letter from L.R. Thompson, Dir., NIH, to Olin West, Sec’y & Gen. Manager, Am. Med. Ass’n (Feb. 7, 1938) (on file with the Nat’l

Treasury Department's report to Congress on the bills noted that catgut ligatures are "very apt to be contaminated with dangerous bacteria, notably those causing tetanus," and that the "manufacturing processes and final product must be carefully controlled to insure absence of such organisms."<sup>209</sup> The report also stated that the issue of regulating sutures and ligatures "has been before this Department upon numerous occasions, looking to the possibility of control of these products under the Biologics Act of July 1, 1902 . . . , but it has always been held that suture materials do not come within the scope of the Act." The Department supported the legislation, provided that it was limited to material sold as sterile.

In other words, PHS repeatedly considered regulating catgut sutures and ligatures as "analogous products" under the 1902 Act but rejected doing so even though they posed a risk of infection from contaminating tetanus bacteria that could be mitigated by controlling the manufacturing process—the same risk that led to the 1902 Act and that inspection and licensing were intended to address. The form of the product seems to have been an insurmountable obstacle to asserting jurisdiction. Moreover, despite acknowledging the risk, PHS never took the initiative to seek a statutory amendment.

### VIII. EXPANSIVE INTERPRETATIONS OF THE 1902 ACT TO SUBJECT CERTAIN PRODUCTS TO REGULATION

The preceding section of this article discussed product classes that PHS declined to regulate even though they arguably fell within the ambit of the 1902 Act. This section describes product classes that were not obviously subject to licensure but that PHS reached out to regulate.

#### A. *Crotalin (Rattlesnake Venom)*

Under the current regulations, which are essentially unchanged on this point since 1919, a "toxin" is defined as a substance that (a) is poisonous in doses of one milliliter or less, and (b) when injected into an animal, produces an antitoxin that neutralizes the substance.<sup>210</sup> The important element of the definition is its second part—a toxin differs from an ordinary poison because a toxin produces an antitoxin. Although this definition did not appear in the regulations until 1919, it seems to have been settled on by PHS in 1914 as it considered the status of two products—rattlesnake venom to treat epilepsy and pollen extract to treat hay fever.

In 1907 an individual who had had epileptic fits for fifteen years was bitten by a rattlesnake and was said to have had no further epileptic attacks. A Philadelphia physician learned of the incident, conducted clinical trials, and concluded that rattlesnake venom, also called crotalin, reduced the severity and frequency of attacks

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Archives, Rec. Grp. 90, Gen. Classified Recs. 1936–1944, File 470) ("The bill was introduced at the instigation of one of the manufacturers and without consulting with us [PHS]."). The bill was reported out by the Senate Committee on the District of Columbia, S. REP. NO. 75-1174 (1937), and passed the Senate but failed to pass the House. The risk was serious enough that sutures were licensed under the British version of the 1902 Act. R.G. Penn, *The State Control of Medicines: The First 3000 Years*, 8 BRIT. J. CLINICAL PHARM. 293, 302 (1979).

<sup>209</sup> Letter from Sec'y Treas. to Mary T. Norton, Chairman, H. Comm. on D.C. (June 1, 1937) (on file with the Nat'l Archives, Rec. Grp. 90, Gen. Classified Recs. 1936–1944, File 470).

<sup>210</sup> 21 C.F.R. § 600.3(h)(3) (2016); 1919 REGULATIONS, *supra* note 98, para. 7-III.

in a certain kind of epilepsy.<sup>211</sup> Consistent with its general approach of narrowly interpreting the purview of the 1902 Act, PHS ruled in 1912 that crotalin did not require a license on the ground that the Act applied only to “manufactured products produced by biologic methods”; merely collecting and purifying venom did not meet that test.<sup>212</sup> Several companies began marketing crotalin.

The Hygienic Laboratory purchased crotalin products on the market for its own study, which found that, of the samples, thirty-nine percent of the solutions and all of the tablets sold for hypodermic use were contaminated with bacteria.<sup>213</sup> In addition, there were dangers of secondary infection because the venom destroyed the body’s ability to combat infection while at the same time causing injection-site tissue damage that allowed infection. Finally, the strength of the venom varied greatly. PHS determined that there had been multiple fatalities from crotalin use.

In 1913, Swan-Myers Co. applied for a license to manufacture crotalin and, instead of ruling that a license was unnecessary as it had done a year earlier, PHS denied the license. The denial was based on conclusions “that the therapeutic value of the substance has not been demonstrated, that it is highly toxic, and that no satisfactory method of standardization has been devised . . . .”<sup>214</sup>

Swan-Myers returned to PHS a year later, this time arguing that, as a “natural secretion,” crotalin should be treated like glandular products, which, even if toxic, were not subject to licensure.<sup>215</sup> The letter prompted a careful review of the legal issue within PHS. The 1902 Act had been drafted to apply to “toxins” in order to cover tuberculins, which were made from the endotoxins left in culture media after tuberculosis bacteria died. With crotalin now the issue, however, PHS relied on the definition of a toxin enunciated by the renowned German scientist Paul Ehrlich and concluded that rattlesnake venom was a toxin, which had to be licensed, principally because it resulted in the production of antitoxins in animals that are injected with venom.<sup>216</sup> Since it would have been easy to declare crotalin to be a “therapeutic serum”

<sup>211</sup> Ralph H. Spangler, *Crotalin Treatment for Epilepsy*, 94 N.Y. MED. J. 517 (1911); Ralph H. Spangler, *The Treatment of Epilepsy with Hypodermic Injections of Rattlesnake Venom (Crotalin)*, 92 N.Y. MED. J. 462, 462 (1910).

<sup>212</sup> Letter from Rupert Blue, Surgeon Gen., to James B. Woodruff (Aug. 13, 1912) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>213</sup> The results of the PHS study were later published. John F. Anderson, *Danger in the Subcutaneous Injection of Solutions of Crotalin*, 62 J. AM. MED. ASS’N 893, 894 (1914). An accompanying editorial called the use of crotalin for epilepsy “an unnecessary risk with the life of [the] patient” and saw “no justification” for its use in other conditions. *Further Light on the Use of Rattlesnake-Poison in Therapy*, 62 J. AM. MED. ASS’N 934, 935 (1914). See also ANNUAL REPORT OF THE SURGEON GENERAL OF THE PUBLIC HEALTH SERVICE FOR THE FISCAL YEAR 1914, H.R. DOC. NO. 63-1393, at 86 (3d Sess. 1914) (summarizing the results of the study); Memorandum from John F. Anderson, Dir., Hygienic Lab., to Surgeon Gen. (Sept. 15, 1914) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655) [hereinafter Anderson Memorandum] (reporting two fatal cases in addition to the one reported in the *Journal of the American Medical Association*).

<sup>214</sup> Letter from C.S. Hamlin, Acting Sec’y Treas., to Swan-Myers Co. (Sept. 25, 1913) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>215</sup> Letter from Henry R. Albright, Swan-Myers Co., to Sec’y Treas. (Sept. 1, 1914) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>216</sup> Letter from B.R. Newton, Ass’t Sec’y Treas., to Swan-Myers Co. (Sept. 16, 1914) (ruling that rattlesnake venom is a toxin under the 1902 Act); Anderson Memorandum, *supra* note 213 (concluding that rattlesnake venom is a toxin under the Ehrlich criteria) (both on file with the Nat’l Archives, Rec.

or an “analogous product,” the decision to define the product as a “toxin” must have been motivated by a desire to portray its decision as compelled by the 1902 Act (perhaps to make the ruling less vulnerable if litigated) or, alternatively, by an unwillingness to create an undesirable precedent by regulating it under one of the broad categories.

Adopting Ehrlich’s definition meant abandoning the characterization of tuberculins as toxins because tuberculins do not create antitoxins (since tuberculosis bacteria do not secrete exotoxins). The 1919/1923 regulations based their definition of “toxin” on the Ehrlich criteria, and tuberculins became “analogous” to toxins.<sup>217</sup>

The issue of crotalin lingered for years. When, in 1917, PHS refused to license another company to sell crotalin, and litigation seemed possible, it sought a legal opinion from the Treasury Department Solicitor, who upheld the denial of the license but did so without reference to statutory provisions or case law. He simply declared that if rattlesnake venom was unsafe and ineffective as PHS asserted, “[T]he action taken by the Service was fully authorized by the statute and the regulations.”<sup>218</sup> The implication of this exceptionally weak legal analysis is that there was no identifiable authority to deny licenses for unsafe and ineffective biologics but that the lawyers were not going to stand in the way of PHS keeping such products off the market.

The decision on crotalin is noteworthy because PHS’s interpretation of the 1902 Act stemmed from its desire to remove the product from the market. It could have maintained its 1912 position that rattlesnake venom was not the kind of product that Congress intended to license, but because PHS had come to see crotalin as dangerous, it reinterpreted the Act to allow banning it.

### B. Allergenic Products

The first biologic to treat hay fever was Pollantin, which was produced in the same manner as a bacterial antitoxin; pollen was injected into horses to produce blood serum that presumably contained antitoxins to neutralize the pollen.<sup>219</sup> It was administered to patients by drops in the eye or nose. After seeing an advertisement for Pollantin in a medical journal, in August 1906 the Hygienic Laboratory told the Surgeon General that sale of the unlicensed product was a “direct infraction” of the 1902 Act.<sup>220</sup> No

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Grp. 90, Cent. File 1897–1923, File 3655); *see also* RICKETTS, *supra* note 167, at 176–77 (setting forth Ehrlich’s multifactor definition of a toxin).

<sup>217</sup> “A product is analogous . . . (c) to a toxin or antitoxin, if intended, by parenteral administration, for the prevention or treatment of disease through specific immunization.” 1923 REGULATIONS, *supra* note 128, at para. 7-V.

<sup>218</sup> Memorandum from F.A. Reeve, Acting Solic., to Byron R. Newton, Ass’t Sec’y Treas. (July 31, 1917), responding to Memorandum from Rupert Blue, Surgeon Gen., to Sec’y Treas. (July 27, 1917) (both on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655). PHS held a hearing in 1919 on yet another license application, after which the application was denied. *See* Report of Hearing on Crotalin [Wolf Labs.] (Dec. 18, 1919); Memorandum from Sanitary Bd. to Surgeon Gen. (Feb. 18, 1920) (approved by Acting Surgeon Gen. and Ass’t Sec’y Treas.) (recommending that no license be issued because evidence “shows that the drug is without specific action and in some instances gives unfavorable results”) (both on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>219</sup> *See* Felix Semon, *A Demonstration of Some Experiments on the Nature and Specific Treatment of Hay Fever*, 1903 (vol. 1) BRIT. MED. J. 713, 713. A leading treatise summarized the literature on Pollantin by concluding that sometimes it worked and sometimes it didn’t. RICKETTS, *supra* note 167, at 426–27.

<sup>220</sup> Memorandum from J. F. Anderson, Ass’t Dir., Hygienic Lab., to Surgeon Gen. (Aug. 31, 1906) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

action was taken against the product, however, apparently because, upon further review, Pollantin was seen, like glandular products, as not the type of product that was meant to be licensed.<sup>221</sup> A few years later, nonparenteral products were excluded from licensure, and Pollantin was also excluded from licensure on that basis.<sup>222</sup>

In 1914, Mulford asked PHS about license requirements for its pollen extract solutions, which differed from Pollantin in that they were not produced in animals and were administered by subcutaneous injection.<sup>223</sup> The Director of the Hygienic Laboratory analyzed the question of jurisdiction and concluded that under a “strict interpretation” of the 1902 Act a pollen extract would be licensable if it was a “true toxin,” and it would be a true toxin if it generated antitoxins when injected into humans or animals (i.e., the Ehrlich definition).<sup>224</sup> The scientific literature, he said, was inconclusive on whether pollen generated antitoxins although the literature leaned toward a finding that it did. Regardless of the literature, however, he rejected a “strict interpretation” of the Act and recommended against licensing pollen extracts because, he asserted, the 1902 Act was meant to cover only those toxins (like tuberculins) that were prepared by growing bacteria in artificial culture media. The Surgeon General accepted his recommendation and told Mulford that its pollen extract products were not subject to licensure.<sup>225</sup>

This analysis illustrates the approach that PHS took in the first decade of the 1902 Act. As in the cases of oral and plant-derived serums, it did not want to license a product class unless the statutory language clearly applied, and even then PHS sometimes laid on further tests not evident in the statutory text, such as method of administration or method of manufacture, to determine whether the product was the kind of product intended to be regulated.

Eight months later, PHS reversed its position and told two manufacturers that injectable pollen extract intended for treatment of hay fever had to be licensed.<sup>226</sup> The first, terse internal memo recommending that revised position stated that although the question of whether pollen caused the production of antitoxin “is a matter of dispute, it is accepted by authorities in sufficient number to render necessary the licensing” of the products.<sup>227</sup> The second memo, written two weeks later, said that even if pollen extract was not a true toxin, “there is no doubt that such a product would be included

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<sup>221</sup> Rosenau Endorsement, *supra* note 163 (stating that Merck’s letter about the legal status of Antithyroidin, an oral thyroid serum, raised the question “whether all serums, such as Dunbar’s Pollantin and organotherapeutic products” should be regulated under the 1902 Act).

<sup>222</sup> Letter from B.R. Newton, Ass’t Sec’y Treas., to Fritzsche Bros. (Feb. 5, 1914) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655) (stating that Pollantin, “not being intended for internal administration, is not one of the class of products the sale of which is regulated by the act of July 1, 1902”).

<sup>223</sup> Letter from A. Parker Hitchens, Mulford, to Rupert Blue, Surgeon Gen. (Mar. 17, 1914) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>224</sup> Memorandum from John F. Anderson to Surgeon Gen. (Mar. 25, 1914) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>225</sup> Letter from Rupert Blue, Surgeon Gen., to A. Parker Hitchens, Mulford (Apr. 1, 1914) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>226</sup> Letter from Rupert Blue, Surgeon Gen., to J.C. Missildine (Jan. 5, 1915); Letter from Rupert Blue, Surgeon Gen., to Lederle Antitoxin Labs. (Jan. 18, 1915) (both on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>227</sup> Memorandum from John F. Anderson, Dir., Hygienic Lab., to Surgeon Gen. (Dec. 29, 1914) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

as an ‘analogous product’ equally with tuberculin,”<sup>228</sup> which is the status that tuberculin had assumed as a result of the crotalin consideration.

PHS appears to have made this abrupt about-face in policy to reconcile its position on pollen extract with its position on rattlesnake venom, which it had adopted between its initial position on pollen extract and its reversed position. Having relied solely on Ehrlich’s criteria to define a toxin for purposes of crotalin, it likely occurred to PHS that a failure to apply the same criteria to pollen extract could undermine its legal position on crotalin. Since neither snake venom nor pollen extract was produced in laboratory culture media, PHS could not impose that qualification on the definition of “toxin” in the case of pollen extract while continuing to assert that snake venom was a toxin.

In 1970, “allergenic product” was added to the Biologics Control Act as a clarification of the classes of products covered by the Act.<sup>229</sup> If it had not been for the dangers of rattlesnake venom used as a drug, PHS might never have ruled that pollen extracts were subject to the Act and consequently allergenic products might have remained exempt from licensing as biologics.

### C. *Leukocyte Extract and Constituents of Blood*

In the early twentieth century, the method by which leukocytes<sup>230</sup> (white blood cells) acted against infecting microbes was not fully understood. One thought was that leukocytes contained substances that enabled the cells to destroy bacteria and, especially, to neutralize the poisons that the bacteria created. Researchers thought that these substances could be extracted from animal leukocytes and administered to humans to bolster their infection-fighting capability.<sup>231</sup>

Leukocyte extract was prepared by injecting an irritant into the chest cavity of an animal—typically a rabbit—which caused leukocytes to flood to the scene. About twenty-four hours later, the accumulation of leukocytes was removed from the animal, and their active substances were extracted by heating and freezing the leukocytes.<sup>232</sup> Experiments with leukocyte extract in animals seemed to show significant effectiveness, and there was some evidence that the extract worked against human infections.<sup>233</sup>

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<sup>228</sup> Memorandum from John F. Anderson, Dir., Hygienic Lab., to Surgeon Gen. (Jan. 13, 1915) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>229</sup> Heart Disease, Cancer, Stroke, and Kidney Disease Amendments of 1970, Pub. L. No. 91-515, § 291, 84 Stat. 1297, 1308 (1970).

<sup>230</sup> The word was often spelled “leucocyte” at the time, but this article uses the spelling that is more common today.

<sup>231</sup> See, e.g., Philip Hanson Hiss, Jr., *The Curative Influence of Extracts of Leucocytes upon Infections in Animals*, 19 J. MED. RES. 323, 323–30, 396–97 (1908).

<sup>232</sup> See, e.g., *id.* at 333; D. Moore Alexander et al., *The Use of Leucocytic Extracts in Infective Processes*, 31 LIVERPOOL MEDICO-CHIRURGICAL J. 150 (1911); Arthur R. Meinhard, *Leucocytic Extract – Its Preparation and Uses*, 4 J. AM. PHARM. ASS’N 1463 (1915). After a few years, researchers developed a method of extracting leukocytes directly from the blood of animals. R.A. Archibald & Gertrude Moore, *A Preliminary Report on the Production, Action and Therapeutic Effects of Leucocytic Extracts*, 14 ARCHIVES INTERNAL MED. 120, 123 (1914).

<sup>233</sup> See, e.g., Philip Hanson Hiss Jr. & Hans Zinsser, *Experimental and Clinical Studies on the Curative Action of Leucocyte Extracts in Infections*, 19 J. MED. RES. 321 (1908); Archibald & Moore, *supra* note 232, at 131 (“It is believed, however, from our experience in the treatment of animal diseases,

In 1914 PHS routinely issued a license to a manufacturer for leukocyte extract without any internal comment about its statutory classification.<sup>234</sup> A few months later, a different company asked PHS about the status of leukocyte extract and was told that a license was required.<sup>235</sup> The company protested, arguing that leukocyte extract was no different than glandular extracts, which PHS did not license. PHS's response was, in effect, that leukocyte extract was an "analogous product" because of three differences from glandular products: leukocyte extracts were anti-infectious agents and were therefore similar to viruses, serums, toxins, and antitoxins; they were derived from blood and therefore were analogous to normal horse serum, which was licensed; and they were subject to deterioration if exposed to excessive heat, which glandular products were generally not.

Licensing leukocyte extract deviated from how PHS otherwise implemented the 1902 Act. The extract was not intended to confer immunity, and it was not a virus, toxin, or antitoxin. The odd nature of leukocyte extract is illustrated by the fact that an American Medical Association publication listed leukocyte extract as a glandular product—as the protesting company had argued—and not in its section on serums and vaccines.<sup>236</sup> Since leukocyte extract purported to supply additional anti-infective power, PHS may have seen it as a typical biologic and been influenced by the favorable literature produced by distinguished scientists,<sup>237</sup> including George McCoy before he joined the Hygienic Laboratory.<sup>238</sup> Based on this evidence of effectiveness, PHS may not have focused on the product's statutory classification at the time of first licensing.

Leukocyte extract proved to be a therapeutic disappointment. It was eventually determined that leukocyte extract at most acted like a nonspecific protein.<sup>239</sup>

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that leukocytic extracts have a wide range of therapeutic application and that their use is warranted in all acute infections at least.”).

<sup>234</sup> Memorandum from Sanitary Bd. to Surgeon Gen. (May 26, 1914) (recommending, without comment, issuance of license to E.R. Squibb & Sons and showing approvals of Surgeon General and Assistant Secretary); Memorandum from J.P. Leake, Hygienic Lab., to Surgeon Gen. (Apr. 29, 1914) [hereinafter Leake Memorandum] (recommending, without comment, issuance of license) (both on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655). Another company was later told that a license was required to sell leukocyte extract. Letter from Rupert Blue, Surgeon Gen., to Int'l Labs. (Jan. 21, 1915) (on file with *id.*).

<sup>235</sup> See Letter from W. Labs. to PHS (Jan. 9, 1915); Letter from Rupert Blue, Surgeon Gen., to W. Labs. (Jan. 18, 1915); Letter from W. Labs. to Rupert Blue, Surgeon Gen. (Jan. 29, 1915); Memorandum from J.F. Anderson, Dir., Hygienic Lab., to Surgeon Gen. (Feb. 26, 1915); Letter from Rupert Blue, Surgeon Gen., to W. Labs. (Mar. 1, 1915) (all on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>236</sup> AM. MED. ASS'N, *supra* note 138, at 234–35.

<sup>237</sup> The applicant that received a license submitted a summary of the literature and concluded that leukocyte extract “has thus been demonstrated by Biological [*sic*] tests and by clinical tests to be a most important measure.” Leake Memorandum, *supra* note 234 (enclosing the literature summary prepared by Squibb). A 1910 treatise by one of the early researchers of leukocyte extracts stated that many infected animals were cured by injections of the extract and that there had been “distinctly beneficial results” in some human infections. PHILIP HANSON HISS, JR. & HANS ZINSSER, A TEXT-BOOK OF BACTERIOLOGY 290-91 (1910).

<sup>238</sup> Hans Zinsser, George W. McCoy, & C.W. Chapin, *On the Protective Influence of Leucocytic Substances Upon Experimental Plague Infection in Rats*, 24 J. MED. RES. 483 (1911) (reporting curative results in studies involving administration of leukocyte extracts to plague-infected rats).

<sup>239</sup> The 1922 edition of a textbook that in 1910 had been favorable to leukocyte extracts had a much more limited conclusion, stating that leukocyte extracts “exerted a distinct though not very powerful therapeutic effect” on animals and “a certain degree of beneficial effect in human beings suffering from

When the regulations were amended in 1919 to include definitions of each of the statutory product classes, leukocyte extract, which was still being licensed, could plausibly only fit into the categories of serums or products analogous to serums. Since “serum” was defined in the regulations as blood serum, the definition of an “analogous product” was drafted to include products “prepared from some constituent of blood.”<sup>240</sup> This provision was apparently made for the sole purpose of codifying the decision on leukocyte extract, since there seems to have been no other product licensed on that basis before 1919 or for many years afterwards.<sup>241</sup>

#### D. Certain Arsenic Compounds

In 1944, the 1902 Act was repealed and its content was incorporated, along with other public health statutes, into the new PHS Act.<sup>242</sup> The description of the products subject to licensing remained the same with one exception: “arsphenamine or its derivatives (or any other trivalent organic arsenic compound)” was added as a new class of products that had to be licensed—even though they were not of biological origin.<sup>243</sup> This change codified a policy that had been in effect since 1917, first under a wartime statute and, since 1919, on the theory that arsphenamine and related products were analogous to virus, therapeutic serum, toxin, or antitoxin products.<sup>244</sup>

In 1910, Paul Ehrlich announced the discovery of an arsenic-based compound that was far superior in treating syphilis than previous remedies. A German company obtained United States patents covering the drug, called Salvarsan, and, through an American distributor, began marketing it in the United States.<sup>245</sup> It quickly became an

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various infections,” which it attributed to the leukocyte extracts “act[ing] in more or less the same way as do other non-specific proteins . . .” HANS ZINSSER, *A TEXTBOOK OF BACTERIOLOGY* 346 (5th ed., 1922). See also *Commercial Aspects of Bacteriophage Therapy*, 100 J. AM. MED. ASS’N 1603, 1604 (1933) (“Perhaps a million doses of leukocytic extract were injected before any quantitative tests were attempted to prove that such injection causes anything more than a borderline reaction of negligible therapeutic value.”).

<sup>240</sup> 1919 REGULATIONS, *supra* note 98, para. 7–V. The Bureau of Chemistry, which had only limited authority over unsafe and ineffective drugs under the Food and Drugs Act, pounced on this amendment and sought a PHS ruling that the regulation barred oral drug products that contained blood. PHS rejected the suggestion, however, saying that various products including blood sausage contained blood and were “more or less articles of commerce,” not products intended to be licensed. PHS also said that oral drugs were generally safe and not subject to the 1902 Act. Letter from Alsberg, Chief, Bureau of Chemistry, to Surgeon Gen. (Sep. 27, 1919); Letter from Rupert Blue, Surgeon Gen., to Chief, Bureau of Chemistry (Oct. 4, 1919) (both on file in the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655). In 1923, the regulation was amended to cover products “prepared from some protein constituent of the blood and intended for parenteral administration . . .” 1923 REGULATIONS, *supra* note 128, para. 7–V. The limitation to parenteral products was obviously intended to address the Bureau of Chemistry’s argument. The reference to a “protein” constituent was apparently just a clarification.

<sup>241</sup> FDA, *supra* note 43, at 15 (indicating that the 1934 licenses for immunoglobulin G (now called IgG) were the first licenses for a human-blood product).

<sup>242</sup> PHS Act, Pub. L. No. 78-410, 58 Stat. 682 (1944).

<sup>243</sup> PHS Act, § 351(a), 58 Stat. at 702; 42 U.S.C. § 262(a). The definition of a biologic is now codified at 42 U.S.C. § 262(i)(1).

<sup>244</sup> See generally Dale Cooper, *The Licensing of German Drug Patents Confiscated During World War I: Federal and Private Efforts to Maintain Control, Promote Production, and Protect Public Health*, 54 PHARM. HIST. 3 (2012); Dale Cooper, *The Trading with the Enemy Act of 1917 and Synthetic Drugs*, 47 PHARM. HIST. 47 (2005).

<sup>245</sup> LIEBENAU, *supra* note 22, at 110–12.



extremely important drug.<sup>246</sup> A modified version called Neosalvarsan, which was easier to prepare for administration, was introduced later. (This article will refer to both as Salvarsan.)

After World War I began in August 1914, the supply of Salvarsan became irregular, and there were frequent shortages and supply interruptions.<sup>247</sup> When the United States entered the war in April 1917, physicians realized that shipments of Salvarsan from Germany would cease and sought an alternative source. Bills were introduced in Congress to grant licenses under the Salvarsan patents to American manufacturers,<sup>248</sup> but consideration of those Salvarsan-specific bills was overtaken by enactment of a broader law, the Trading with the Enemy Act (TWEA). TWEA authorized the President to grant U.S. companies licenses under enemy-owned or enemy-controlled patents, trademarks, and copyrights, subject to such conditions as the President might prescribe, and to prohibit importation of articles specified by the President.<sup>249</sup> Licensees had to pay the U.S. Treasury a royalty, which the patent holder could sue to obtain after the end of the war.

The President delegated his patent-licensing authority under TWEA to the Federal Trade Commission (FTC),<sup>250</sup> which, in consultation with PHS and the National Research Council of the National Academy of Sciences, established conditions for licenses under the German-owned patents for Salvarsan, Novocaine, and other drugs.<sup>251</sup> PHS wanted the FTC to impose conditions on Salvarsan similar to the conditions imposed on biologics under the 1902 Act because Salvarsan was “varyingly toxic and for the detection of this toxicity biologic tests are required,” but it saw no need for such conditions for the other drugs.<sup>252</sup>

The FTC’s regulations, issued in November 1917, adopted PHS’s recommendation for Salvarsan licenses.<sup>253</sup> Although the licenses were issued by the FTC, PHS inspected the licensee’s facilities, tested the products, and otherwise regulated the manufacture of Salvarsan in the same manner as it regulated biologics. Because the U.S. trademark for Salvarsan was owned by the U.S. distributor, it was not subject to TWEA, and the FTC established the generic name “arsphenamine” for use instead.<sup>254</sup>

<sup>246</sup> See, e.g., Patricia Spain Ward, *The American Reception of Salvarsan*, 36 J. HIST. MED. 44, 44 (1981).

<sup>247</sup> *Salvarsan: Hearings on S. 2178 and S. 2363 Before the Sen. Comm. on Patents*, 65th Cong. 4–5 (1917) [hereinafter *Salvarsan Hearings*] (statement of Mayo Clinic physicians); Cooper (2012), *supra* note 244, at 4.

<sup>248</sup> H.R. 4190, 65th Cong. (1917) (would abrogate Salvarsan patents); H.R. 4243, 65th Cong. (1917) (would suspend Salvarsan patents during the war and authorize U.S. entities to make and sell it); S. 2178, 65th Cong. (1917) (same as H.R. 4243); *Salvarsan Hearings*, *supra* note 247.

<sup>249</sup> Trading with the Enemy Act, Pub. L. No. 65-91, §§ 10–11, 40 Stat. 411 (1917).

<sup>250</sup> Exec. Order No. 2729A, paras. XVII–XXI (Oct. 12, 1917).

<sup>251</sup> Cooper (2012), *supra* note 244, at 4–9.

<sup>252</sup> Letter from Rupert Blue, Surgeon Gen., to FTC (Nov. 1, 1917) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>253</sup> *Arsphenamine (Salvarsan): Licenses Ordered and Rules and Standards Prescribed for Its Manufacture*, 32 PUB. HEALTH REP. 2071 (1917). The regulations included a toxicity test: at least four rats had to be injected with a specified dose of arsphenamine, and at least seventy-five percent had to survive at least forty-eight hours.

<sup>254</sup> Cooper (2012), *supra* note 244, at 8–11.

In 1918 Congress amended TWEA to authorize the President to sell German-owned patents to American companies.<sup>255</sup> It was thought that there were strong connections between the German government and German companies, and as the Alien Property Custodian, A. Mitchell Palmer, later explained, the amendment was made “with the purpose in mind that the German industrial army on American soil should be captured and destroyed” and that it was important to “secur[e] American industrial independence by dislodging the hostile Hun within our gates, whose methods are such as to unsettle the peace of the world.”<sup>256</sup> After the sale of many German-owned patents to a single company resulted in a highly criticized monopoly over products covered by those patents, the government established a nonprofit corporation, the Chemical Foundation, Inc., to buy the remaining drug and chemical patents, including the patents for Salvarsan, and to issue nonexclusive licenses under them to U.S. companies. Salvarsan licenses previously issued by the FTC, with their conditions for PHS control, remained in effect because they had been issued for the remaining term of the patents, but there was concern that new Salvarsan licenses issued by the Chemical Foundation would not be conditioned on PHS supervision. The Chemical Foundation, however, agreed to impose the same requirements under its licenses as had been imposed under the FTC licenses.<sup>257</sup>

The situation seemed to be settled until February 1919 when the War Trade Board told PHS that it was winding down its import controls and could no longer prohibit the importation of Salvarsan.<sup>258</sup> Although imports would presumably violate the Chemical Foundation’s patents, patent infringement was not a basis to block products at the border, and arsphenamine that had not been tested for toxicity could therefore be imported. To prevent that, PHS sought a legal opinion that arsphenamine was subject to licensing under the 1902 Act as an “analogous product,” thereby prohibiting importation of unlicensed versions. The Treasury Department Solicitor agreed with PHS that arsphenamine was an “analogous product” because, in essence, it was an injectable drug that required a biological test to preclude toxicity.<sup>259</sup>

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<sup>255</sup> TWEA was initially amended to allow the government to sell to the highest American bidder any “property” acquired under TWEA. Act of Mar. 28, 1918, Pub. L. No. 65-109, 40 Stat. 459, 460 (1918) (amending sec. 12 of TWEA). After the Attorney General ruled that “property” did not include patents, TWEA was further amended to explicitly apply the sale provisions to patents. Act of Nov. 4, 1918, Pub. L. No. 65-233, 40 Stat. 1020, 1020-21 (1918) (amending sec. 7(c) of TWEA).

<sup>256</sup> ALIEN PROPERTY CUSTODIAN REPORT: A DETAILED REPORT BY THE ALIEN PROPERTY CUSTODIAN OF ALL PROCEEDINGS HAD BY HIM UNDER THE TRADING WITH THE ENEMY ACT DURING THE CALENDAR YEAR 1918 AND TO THE CLOSE OF BUSINESS ON FEBRUARY 15, 1919, at 15, 17 (1919).

<sup>257</sup> Cooper (2012), *supra* note 244, at 20.

<sup>258</sup> PHS urged that the prohibition against imported Salvarsan be continued or that importation be limited to product from PHS-licensed facilities, Letter from J.C. Perry, Acting Surgeon Gen., to Karl De Laitre, Dir., Bureau of Res., War Trade Bd. (Apr. 29, 1919), but the War Trade Board’s policy was to maintain import restrictions only for war-related purposes, Memorandum from George O. May, Treas. Rep. War Trade Bd., to Ass’t Treas. Sec’y Moyle (May 2, 1919) (both on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655). It was many months until import controls were actually discontinued. *See* Letter from Chief, Bureau of Imports, War Trade Bd. to Surgeon Gen. (Dec. 13, 1919) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655) (stating that all import controls will be discontinued when legislation pending in Congress is enacted and that the Board desires to discontinue licensing of arsphenamine and related products at the current time because they are now regulated by PHS).

<sup>259</sup> PHS’s full argument relied on the following five reasons: “1. Unless properly supervised, arsphenamine is likely to be highly toxic in ordinary doses, being capable of causing death either immediately or within a few days. 2. Like viruses, serums, and toxins, arsphenamine is administered either

Despite the Solicitor's concurrence, PHS was never comfortable with the determination that arsenic products were subject to the 1902 Act. PHS ensured that subsequent appropriations acts included a specific reference to arsphenamine so that those acts could be viewed as independent authority to regulate the products<sup>260</sup> until the arsenic compounds were explicitly added to the Biologics Control Act in the 1944 codification.<sup>261</sup>

The history of Salvarsan exemplifies how PHS was willing to depart from its generally narrow interpretation of the 1902 Act when it wanted to deal with a safety issue. Here, the departure was so extreme that PHS wanted backup legislation confirming its position. Salvarsan also illustrates that the Solicitor was willing to accommodate a very broad interpretation of "analogous product" if that was what PHS wanted. PHS's restrictive interpretation was the result of its own decisions, not a constraint imposed by its lawyers.

## IX. APPLYING AN EFFECTIVENESS REQUIREMENT TO ALL BIOLOGICS

As discussed in preceding sections, PHS's narrow interpretation of the scope of the 1902 Act was driven largely by its conclusion that it lacked authority to deny licenses for ineffective products. This section describes PHS's changing views on whether licensed biologics had to be effective.

PHS at first assumed that it lacked authority to require biologics to be effective and, as mentioned earlier, in 1913 it stated its desire for legislation that would allow it to deny licenses for ineffective products.<sup>262</sup> A few years later, however, PHS decided that it did have such authority, at least in some circumstances. The first instance of

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intravenously or intramuscularly. 3. Freedom from undue toxicity is found by testing biologically laboratory animals in a fashion similar to that in the case of viruses, serums, and toxins. 4. Arsphenamine is dispensed in sealed glass containers in the same way as in the case of viruses, serums and toxins. 5. Arsphenamine exerts a specific action." Letter from F.A. Reeve, Acting Solic., to J.H. Moyle, Ass't Sec'y Treas. (June 13, 1919) (on file with the Nat'l Archives, Rec. Grp. 90, Gen. Subject File 1924-1935, Gen. Files, File 410) (paragraph breaks omitted).

<sup>260</sup> See, e.g., Act of Mar. 4, 1921, Pub. L. No. 66-389, 41 Stat. 1367, 1377 (appropriating funds for fiscal year 1922 "[t]o regulate the propagation and sale of viruses, serums, toxins, and analogous products, including arsphenamine . . ."); Act of July 2, 1942, Pub. L. No. 77-647, 56 Stat. 562, 583 (appropriating funds for fiscal year 1943 "for regulating the propagation and sale of viruses, serums, toxins, and analogous products, including arsphenamines and other organic arsenic compounds therapeutically analogous thereto . . ."). After PHS was transferred to the Federal Security Agency, a lawyer there ruled that arsphenamine and related products were *not* "analogous products" under the 1902 Act but could continue to be regulated as biologics under authority of the appropriations acts. Memorandum from Stanley L. Drexler, Off. Gen. Couns., to Thomas Parran, Surgeon Gen. (Sep. 8, 1942) (on file with the Nat'l Archives, Rec. Grp. 90, Gen. Classified Recs., Gov't Establishments, File 1850 (FSA-Gen. Couns.)) (monthly report for Aug. 1942).

<sup>261</sup> In the House hearing, the Surgeon General stated that many syphilis drugs were regulated by FDA but "because of the difference in the method of testing and the historical call upon the National Institute of Health, to deal with this subject, it has been agreed that in this particular field the control shall continue to rest in the Institute of Health." *Public Health Service Code: Hearing on H.R. 3379 Before a Subcomm. of the H. Interstate & Foreign Commerce Comm.*, 78th Cong. 136 (1944) [hereinafter *1944 House Hearing*] (statement of Thomas Parran). See also H.R. REP. NO. 78-1364, at 23 (1944) ("The control would be extended to arsphenamines and other trivalent organic arsenic compounds, as has been done, though with less precision, in appropriations acts.").

<sup>262</sup> See *supra* note 119.

requiring a traditional biologic to be effective occurred in January 1917 when PHS disposed of an application for a bacterial vaccine for typhus fever, which the applicant knew was questionable but wanted to sell to meet customer requests.<sup>263</sup> PHS deferred the application indefinitely “in view of the slender evidence to show that the Plotz organism is the cause of typhus fever and the lack of proof as to its immunizing properties.”<sup>264</sup> The applicant challenged the decision on the ground that the statute did not require a showing of therapeutic efficacy and pointed out that PHS had licensed other products of questionable effectiveness. PHS’s response was that it had not denied the application; it had only deferred its consideration pending the accumulation of additional evidence.<sup>265</sup>

The second instance occurred during the influenza pandemic of 1919 when PHS refused to license lipovaccines for influenza. In a letter to the *Journal of the American Medical Association* responding to an attack on this policy by the *Chicago Tribune*, the Surgeon General defended his decision on the ground that PHS had conducted extensive clinical and experimental investigations of lipovaccines and found them not desirable for general use.<sup>266</sup> More broadly, the Surgeon General asserted that PHS required biologics to be safe and effective:

The U.S. Public Health Service has always made it a rule to license only such biologic products as are safe for general use, and within recent years has added the restriction that for original license satisfactory evidence of

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<sup>263</sup> Letter from John F. Anderson, E.R. Squibb & Sons, to George W. M’Coy, Dir., Hygienic Lab. (Jan. 24, 1917) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>264</sup> Memorandum from Sanitary Bd. to Surgeon Gen. (Jan. 27, 1917) (showing approvals by the Surgeon Gen. and B.R. Newton, Ass’t Sec’y Treas.); *see also* Letter from Rupert Blue, Surgeon Gen., to E.R. Squibb & Sons (Feb. 3, 1917) (deferring action on the application); Letter from Surgeon Gen. to Lederle Antitoxin Labs. (Feb. 2, 1917) (deferring action on its application for the same product); Memorandum from G.W. McCoy, Dir., Hygienic Lab., to Surgeon Gen. (Jan. 19, 1917) (reviewing the literature on the relation of the *Plotz* organism to typhus fever and concluding that the “evidence in favor of the organism being most intimately associated with typhus is very strong, but scarcely conclusive” and that the “evidence of the value of a vaccine made from the organism rests upon a single set of observations, and unfortunately figures as to control material are wanting”). PHS said that it was inclined to be “very conservative on this subject” in part because it had conducted its own guinea pig studies that “were negative so far as showing any protective property on the part of the organism used for the injection.” Letter from Dir., Hygienic Lab., to John F. Anderson, E.R. Squibb & Sons (Jan. 26, 1917) (all documents on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>265</sup> Letter from Rupert Blue, Surgeon Gen., to John F. Anderson, E.R. Squibb & Sons (Feb. 5, 1917), responding to Letter from J.F. Anderson to George W. M’Coy, Dir., Hygienic Lab. (Jan. 31, 1917) (both on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>266</sup> Rupert Blue, *Lipovaccines as Influenza Prophylactic*, 73 J. AM. MED. ASS’N 1302, 1302 (1919). It was difficult to make a lipovaccine sterile and “oil suspensions of organisms were definitely less effective in provoking measurable immunity response in laboratory animals (and presumably in man) than were saline suspensions of the organisms.” George W. McCoy, *Application of Vaccines in Public Health Work*, 10 AM. J. PUB. HEALTH 666, 668 (1920). The advantage of a bacterial vaccine suspended in oil was that it could be given in a single dose, whereas bacterial vaccines suspended in saline had to be given in multiple injections. Eugene R. Whitmore, *Lipovaccines, with Special Reference to Public Health Work*, 9 AM. J. PUB. HEALTH 504, 506 (1919) (explaining that the army preferred lipovaccines because of the impracticality of administering multiple doses of multiple vaccines). Influenza vaccines were based on the erroneous belief that the disease was caused by bacteria, and none of them were effective. *E.g.*, John M. Eyler, *The State of Science, Microbiology, and Vaccines Circa 1918*, 125 PUB. HEALTH REP., SUPP. NO. 3 27, 32, 34 (2010); G.W. McCoy, et al., *The Failure of a Bacterial Vaccine as a Prophylactic Against Influenza*, 71 J. AM. MED. ASS’N 1997, 1997 (1918).

efficiency must be presented as well, if it is possible to secure such evidence.<sup>267</sup>

This letter seems to be first time that PHS publicly asserted that newly licensed biologics had to be effective. It repeated the position, together with the same hedge about the ability to secure evidence of effectiveness, in its 1920 annual report.<sup>268</sup> The need to show evidence “if it is possible” meant that “[w]hen it is possible to secure experimental evidence within a reasonable time, this is insisted on.”<sup>269</sup> If the only way to show effectiveness was through controlled clinical trials, however, PHS would license the product even if it believed that the product was likely useless:

[The PHS officer reviewing license applications] may feel that [the products] are worthless, but he cannot prove it, and, on the contrary, he is confronted by a mass of uncontrolled clinical data which indicate the usefulness of the agent. As a result, in order to avoid the possibility of doing harm by depriving people of an agent which it is barely possible may be of value, he recommends the granting of a license, though he may be reasonably certain that the preparation is not of value, though probably harmless.<sup>270</sup>

PHS never articulated a legal theory of how the 1902 Act required biologics to be safe and effective. The closest it came may have been the article just quoted from, in which the Director of the Hygienic Laboratory asserted that, whereas the 1906 Food and Drugs Act was intended to allow physician discretion in choosing drugs,

[t]he wording of the [1902 Act] clearly indicates that it was the intention of Congress to restrict the use of preparations coming under this law to such as had therapeutic or prophylactic activity; in other words, it was intended to prevent the deception, even on the physician, as well as to guarantee safety.<sup>271</sup>

His view that the 1902 Act mandated “therapeutic or prophylactic activity” may have been based on the law’s requirement for an expiration date in the package label “beyond which the contents can not be expected beyond reasonable doubt to yield their specific results.” But the vague requirement that biologics must “yield their specific results” seems far short of a prohibition against unproven therapeutic claims.

PHS took ineffectiveness into account in developing potency standards. Concerned that “establishment of an official standard is likely to be regarded as setting the stamp of governmental approval on claims made for the usefulness of the preparations”—something it did not want to do unless there was a sound scientific basis—PHS declined to issue standards for products it regarded as still experimental.<sup>272</sup> Under the

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<sup>267</sup> Blue, *supra* note 266, at 1303.

<sup>268</sup> ANNUAL REPORT OF THE SURGEON GENERAL OF THE PUBLIC HEALTH SERVICE OF THE UNITED STATES FOR THE FISCAL YEAR 1920, H.R. DOC. NO. 66-864, at 75 (1920) (“[T]he policy has been adopted of recommending original license for biologic products only when there is evidence of value, in cases where it is possible to secure this . . .”).

<sup>269</sup> G.W. McCoy, *Official Methods of Control of Remedial Agents for Human Use*, 74 J. AM. MED. ASS’N 1553, 1554 (1920).

<sup>270</sup> *Id.*

<sup>271</sup> *Id.*

<sup>272</sup> McCoy, *supra* note 90, at 379.

1919 regulations, if PHS had not established a potency standard for a product, it had to be labeled “No U.S. standard of potency,”<sup>273</sup> a requirement that PHS imposed as a hint to physicians that the product had not been shown to be effective, although PHS admitted that the labeling requirement was legally questionable.<sup>274</sup>

Although PHS’s statements in 1919 and 1920 seem to have set forth a coherent position, the uncertain state of its policy on licensing ineffective biologics was on display in 1924 congressional hearings on bills that, in various ways, would have prohibited false or misleading therapeutic claims for biologics. George McCoy, the Director of the Hygienic Laboratory, was very negative about PHS’s authority to deny licenses for ineffective biologics, stating that PHS lacked the authority to withhold a license from an ineffective product, that PHS was required by law to license influenza vaccines even though it “know[s] they are worthless,” and that PHS applied the consensus of medical opinion when considering whether a biologic was effective, even if it thought the consensus was wrong.<sup>275</sup> His analysis probably deviated from PHS’s previous public statements because he was pushing for new discretionary authority to deny or cancel licenses when in the “public interests” and was making the case indirectly that such authority was necessary to deal with ineffective products.<sup>276</sup>

On a subsequent hearing day, one of McCoy’s subordinates took a much different approach and emphasized PHS’s control over ineffective products, testifying that PHS routinely considered whether product claims were “medically sound” and “valid” when a manufacturer applied for a license; that a “bogus vaccine” was barred from being licensed; and that PHS had refused to license purported cures for tuberculosis, cancer, and diabetes.<sup>277</sup> In 1928, McCoy summarized PHS’s policy as establishing a standard of effectiveness that was relatively easy to satisfy: “While no hard-and-fast rule can be followed, the practice in general is that of withholding a license unless either experimental or clinical evidence is available at least strongly suggestive that the preparation has prophylactic or therapeutic value.”<sup>278</sup>

Despite earlier industry objections, PHS’s insistence in the 1920s on effectiveness data for new products apparently met little resistance because in 1934 the regulations were amended to provide that “[l]icense for new products shall not be granted without

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<sup>273</sup> 1919 REGULATIONS, *supra* note 98, para. 59. See *Regulation of Sale of Viruses, Serums, Toxins and Analogous Products, Etc.: Hearings on H.R. 5845, H.R. 7366, and H.R. 8618 Before the Subcomm. of the H. Comm. on D.C., 68th Cong. 110, 112 (1924)* [hereinafter *1924 Rathbone Hearings*] (“By putting ‘No U.S. standard of potency’ on such material it shows all who are intelligent that that has not yet been shown to be an effective remedy. It might have value, and it might not have value.”) (statement of William H. Park, Dir. Bureau of Labs., N.Y.C.).

<sup>274</sup> 1924 Rathbone Hearings, *supra* note 273, at 113 (“We have been in doubt whether, if the matter was tested in the courts, it would be upheld.”).

<sup>275</sup> *Id.* at 53.

<sup>276</sup> *Id.* at 49. Rep. Rathbone subsequently introduced a bill that would have allowed PHS to refuse or revoke licenses based on the public interests. H.R. 7366, 68th Cong. (1924). The provision was opposed by the industry on the ground that it would permit arbitrary action. 1924 Rathbone Hearings, *supra* note 273, at 57-60 (statement of Carson Frailey, Sec’y, Am. Drug Mfrs.’ Ass’n). In response to a request for comment from the chairman of the committee considering the bill, the Justice Department said that the provisions “might result in a question being raised as to the constitutional power of Congress to delegate to the Secretary of the Treasury the discretionary right to determine what constitutes ‘the public interest’ . . . .” Letter from Ass’t Att’y Gen. to Rep. Clarence J. McLeod (Mar. 21, 1924), in 1924 Rathbone Hearings, *supra* note 273, at 141, 142.

<sup>277</sup> 1924 Rathbone Hearings, *supra* note 273, at 149-52 (statement of W.T. Harrison).

<sup>278</sup> McCoy, *supra* note 127, at 947.

satisfactory evidence of therapeutic or prophylactic efficiency.”<sup>279</sup> Manufacturers of previously licensed products could continue to obtain annual license renewals without showing that the products worked. After issuance of the 1934 regulation, PHS seems to have demanded more proof of effectiveness than the “strongly suggestive” evidence that it was asking for in 1928; a PHS official stated in 1938 that “an earnest attempt is made to determine whether or not the claims for effectiveness are based upon scientific evidence” and that “[i]n many instances the claims have been found insufficiently grounded, and in a few apparently fraudulent, and licenses have been refused.”<sup>280</sup> The 1934 regulation was potentially important to the scope of products subject to licensing, because, at least on its face, it eliminated the longstanding concern that expanding the list of products subject to licensure would lead to approval of ineffective medications. What actually happened is discussed later in this article.

The regulation requiring evidence of effectiveness was short-lived. When the 1902 Act was being consolidated into the PHS Act in 1944, PHS proposed to modify the statute to authorize standards “to insure the continued safety, purity, potency and efficaciousness of such products,” which it said did not constitute a significant change from the 1902 Act,<sup>281</sup> and the House-passed bill included that language.<sup>282</sup> Discussions between the Federal Security Agency and the biologics industry followed, however, and as a result the Agency recommended in the Senate that the reference to “efficaciousness” be deleted, which it was.<sup>283</sup> After the PHS Act became law, the PHS lawyers regarded this history as definitively establishing that the statute did not require

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<sup>279</sup> PHS, TREAS. DEP’T, MISC. PUBL’N NO. 10: REGULATIONS FOR THE SALE OF VIRUSES, SERUMS, TOXINS AND ANALOGOUS PRODUCTS para. 2 (1934).

<sup>280</sup> A.M. Stimson, *A Brief History of Bacteriological Investigations of the United States Public Health Service*, SUPP. NO. 141 TO PUB. HEALTH REP. 15 (1938).

<sup>281</sup> H.R. 3379, 78th Cong. § 351 (1943). Thomas Parran, the Surgeon General, asserted that, with respect to biologics, the bill included “no important changes in existing law,” and Alanson W. Willcox, Assistant General Counsel of the Federal Security Agency, stated his understanding that the bill’s proposed provision “to insure the continued safety, purity, potency, and efficaciousness” of biologics “accords with present practices.” *1944 House Hearing*, *supra* note 261, at 45, 138. The House committee report stated that the provisions on biologics would be “a reenactment of present law . . . with only slight changes.” H.R. REP. NO. 78-1364, at 23 (1944).

<sup>282</sup> *See* S. REP. NO. 78-1027, at 4 (1944) (recommending that the reference to “efficaciousness” be struck from the House-passed bill).

<sup>283</sup> *Laws Relating to the Public Health Service: Hearings on H.R. 4624 Before a Subcomm. of the Sen. Comm. on Educ. & Labor*, 78th Cong. 48-49 (1944) (statement of Alanson W. Willcox); S. REP. NO. 78-1027, at 4 (1944).

license applicants to establish that their products were effective.<sup>284</sup> The 1934 regulation requiring a showing of effectiveness was rescinded.<sup>285</sup>

In 1962 a bill was introduced in Congress to require new drugs and new biologics to be effective,<sup>286</sup> but a House committee removed the provision related to biologics, stating that the issue would be considered in the next Congress.<sup>287</sup> As enacted, the legislation amended only the FDCA and applied only to new drugs. Bills were later introduced to require biologics to be effective, but they did not pass.<sup>288</sup>

The PHS lawyers tried to find a legal basis to require that biologics be effective. In 1958 they suggested that, depending on the particular facts, action could be taken under the FDCA against an ineffective biologic on the ground that the product was misbranded because of false or misleading claims.<sup>289</sup> After the FDCA was amended in 1962, the lawyers suggested that the FDCA's requirement for the effectiveness of new drugs could also be imposed on new biologics,<sup>290</sup> and they repeated the suggestion in 1969.<sup>291</sup> The Division of Biologics Standards (DBS), which was the PHS unit directly regulating biologics, did not want to rely on the FDCA for its legal authority, however, because it worried that the concurrent administration of the FDCA by both DBS and FDA would invite consolidation of DBS into FDA.<sup>292</sup>

The situation blew up in 1971 when a DBS employee who had been harassed for years by his superiors retaliated by charging DBS with various acts of mismanagement, including knowingly allowing the distribution of subpotent and

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<sup>284</sup> See Memorandum from Edward J. Rourke, Ass't Gen. Couns., to Roderick Murray, Dir., Div. Biologics Standards (Sep. 3, 1958) (on file with the Nat'l Archives, Rec. Grp. 235, Off. Gen. Couns. Op. Files 1942-1963, File PS4000) [hereinafter Rourke Memorandum] (referring to a 1946 memo, which concluded that "because of the legislative history in 1944 when section 351 was enacted, it was clear that the authority to adopt standards as to 'potency' did not include authority to adopt standards as to 'efficacy'" and reaffirming the conclusion that the PHS Act does not require a licensed biologic to be therapeutically effective). Shortly after the PHS Act was enacted, and before the lawyers weighed in, PHS took the position that the 1934 regulation requiring new biologics to demonstrate effectiveness had become an interpretation of the "potency" requirement adopted in the 1944 Act. Letter from Thomas Parran, Surgeon Gen., to W.Y. Elliott, War Production Bd. (Nov. 7, 1944) (on file with the Nat'l Archives, Rec. Grp. 443, Gen. Recs. 1930-1948, File 470).

<sup>285</sup> After PHS was transferred to the Federal Security Agency, the PHS regulations were reissued, and paragraph 2 of the 1934 regulations, which included the effectiveness requirement, became 42 C.F.R. § 22.2. 5 Fed. Reg. 4107, 4108 (Oct. 17, 1940). The regulations to implement the 1944 PHS Act did not contain a comparable provision. 12 Fed. Reg. 410 (Jan. 21, 1947).

<sup>286</sup> H.R. 11581, 87th Cong. (1962). Section 107(a) of the bill would have amended section 351 of the PHS Act to authorize licenses for "new products" only upon a showing that the products are "efficacious under the conditions prescribed, recommended, or suggested by the manufacturer . . . ."

<sup>287</sup> H.R. REP. NO. 87-2464, at 7 (1962).

<sup>288</sup> H.R. 6788, 88th Cong. § 401 (1963); S. 2580, 88th Cong. § 401 (1964).

<sup>289</sup> Rourke Memorandum, *supra* note 284.

<sup>290</sup> Memorandum from Edward J. Rourke, Ass't Gen. Couns., to Luther L. Terry, Surgeon Gen. (Feb. 21, 1963) (on file with the Nat'l Archives, Rec. Grp. 235, Off. Gen. Couns. Op. Files 1942-1963, File PS4000), in *Consumer Safety Act of 1972: Hearings on Titles I and II of S. 3419 Before the Subcomm. on Exec. Reorganization and Gov't Res. of the Sen. Comm. on Gov't Operations*, 92d Cong. 482 (1972) [hereinafter *1972 Hearings*].

<sup>291</sup> Memorandum from Joel M. Mangel, Off. Gen. Couns., to Roderick Murray, Dir., Div. Biologics Standards (Feb. 28, 1969), in *1972 Hearings*, *supra* note 290, at 474.

<sup>292</sup> GEN. ACCT. OFFICE, B-164031(2), PROBLEMS INVOLVING THE EFFECTIVENESS OF VACCINES 13 (Mar. 28, 1972), *reprinted in 1972 Hearings*, *supra* note 290, at 436, 451.



ineffective influenza vaccine.<sup>293</sup> The ensuing General Accounting Office (GAO) investigation found that twenty-eight percent of licensed products were not generally recognized as effective.<sup>294</sup> DBS defended its actions on the ground that it lacked authority to deny licenses for ineffective products, but GAO pointed to the lawyers' opinions that DBS had such authority under the FDCA.<sup>295</sup> The episode led to the regulatory control of biologics being transferred to FDA in 1972.

Soon after it obtained authority over biologics, FDA issued a proposed regulation requiring new and previously licensed biologics to be effective, citing as authority "the effectiveness and misbranding" provisions of the FDCA as well as the Biologics Control Act.<sup>296</sup> In response to comments questioning the legality of using the FDCA's new-drug provisions to regulate biologics, FDA said that it was permissible to combine the FDCA and PHS Act provisions "to develop a comprehensive regulatory program," and that, in any event, the effectiveness requirement was authorized by the misbranding provisions of the FDCA.<sup>297</sup>

Relying on the FDCA as authority to require biologics to be effective was legally questionable, and, because of that, GAO later recommended enactment of clarifying legislation.<sup>298</sup> Critical to the outcome of the issue in 1972 was the decision of the drug manufacturers association to acquiesce in FDA's administrative imposition of the new policy.<sup>299</sup> The effectiveness requirement might thus be better characterized as the product of a government-industry accommodation—an echo of the process that led to the 1902 Act—than as a conventional statutory interpretation. FDA itself seems to have become concerned about relying on the FDCA as authority; it now asserts that the effectiveness requirement derives from the "potency" requirement in the PHS Act,<sup>300</sup> even though that interpretation is inconsistent with the legislative history of the

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<sup>293</sup> Nicholas Wade, *Division of Biologics Standards: In the Matter of J. Anthony Morris*, 175 SCI. 861, 861 (1972); Nicholas Wade, *Division of Biologics Standards: Scientific Management Questioned*, 175 SCI. 966, 966, 968 (1972); Nicholas Wade, *DBS: Officials Confused Over Powers*, 175 SCI. 1089, 1089 (1972); Nicholas Wade, *Division of Biologics Standards: The Boat That Never Rocked*, 175 SCI. 1225, 1225, 1228 (1972); Nicholas Wade, *DBS: Agency Contravenes Its Own Regulations*, 176 SCI. 34, 34 (1972).

<sup>294</sup> GEN. ACCT. OFFICE, *supra* note 292, at 14, *reprinted in 1972 Hearings, supra* note 290, at 452.

<sup>295</sup> GEN. ACCT. OFFICE, *supra* note 292, at 11–13, *reprinted in 1972 Hearings, supra* note 290, at 449–51.

<sup>296</sup> Biological Products: Procedures for Review of Safety, Effectiveness, and Labeling, 37 Fed. Reg. 16679, 16679 (proposed Aug. 18, 1972).

<sup>297</sup> Biological Products: Procedures for Review of Safety, Effectiveness and Labeling, 38 Fed. Reg. 4319, 4319 (Feb. 13, 1973).

<sup>298</sup> GEN. ACCT. OFFICE, HRD 80-55, B-198648, ANSWERS TO QUESTIONS ON SELECTED FDA BUREAU OF BIOLOGICS' REGULATION ACTIVITIES (June 6, 1980), app. I, at 18–21. If the new-drug provisions of the FDCA applied to biologics, the implication would seem to be that a biologic required both a PHS Act license and an approved new drug application, but that result would be a dubious interpretation of congressional intent. Section 351(j) of the PHS Act, added in 1997, provides that a licensed biologic is not required to have an approved new drug application. Although false claims about the therapeutic effectiveness of a biologic would clearly violate the misbranding provisions of the FDCA, it is questionable whether FDA can reverse the burden of proof under those provisions and require a manufacturer to prove that its product's therapeutic claims are true as a precondition to licensing.

<sup>299</sup> 1972 *Hearings, supra* note 290, at 151 (statement of C. Joseph Stetler, President, Pharm. Mfrs. Ass'n).

<sup>300</sup> FDA, GUIDANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS 4 (May 1998) ("Potency has long been interpreted to include effectiveness (21 C.F.R. 600.3(s)."). The cited regulation states: "The word *potency* is interpreted to

PHS Act and contrary to the position asserted by the government for decades after the “potency” provision became law.

In sum, the legal basis for requiring proof of effectiveness as a prerequisite for licensing is arguably as unclear now as it was a century ago when the uncertainty influenced PHS’s policies on which product classes were subject to licensure. Today, however, FDA unequivocally requires license applicants to show that their biologics are effective, and thus any uncertainty about legal authority does not shape the agency’s definition of a biologic as it did in the early years.

## **X. ATTEMPTS TO RECONSIDER THE NARROW INTERPRETATION OF THE SCOPE OF THE ACT**

### *A. Rejection of Broader Scope by the Surgeons General*

Several times during the life of the 1902 Act, there were discussions inside PHS about licensing additional classes of biologics, especially hormonal products, but the idea was rejected every time. An early reevaluation was reflected in a 1910 letter from PHS, which stated that “organo[-]therapeutic preparations have not thus far been licensed under the Act of July 1, 1902, but the matter of requiring the license of such products is being considered.”<sup>301</sup> No change in policy resulted from that consideration.

A more significant review of the issue occurred in 1919-1920. In 1919, PHS revised its regulations implementing the 1902 Act, and a poorly drafted provision seemed to say that any drug was an “analogous product” subject to the Act if it was “intended for specific . . . therapy.”<sup>302</sup> The Bureau of Chemistry of the Agriculture Department (the predecessor of FDA) wrote PHS in July 1919 to suggest that various imported drugs made from animal organs and glands were described by that provision.<sup>303</sup> After reviewing the letter, the Hygienic Laboratory told the Surgeon General that such products “have not, heretofore, been regarded as coming under the provisions of the biologics law but it is believed that a somewhat broader interpretation of the law than has previously been held is justifiable and in the public interest.”<sup>304</sup> The Hygienic Laboratory also noted that implementing its recommendation would “involve much labor in the establishing of standards and the securing of evidence as to their therapeutic efficiency or lack thereof.” The Surgeon General—at the time Rupert

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mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.” That regulation was adopted in 1947 at the same time that the PHS lawyers refused to approve any regulations that imposed an effectiveness requirement in light of the legislative history of the PHS Act. FDA’s current interpretation cannot be reconciled with the legal turmoil between 1944 and 1972 over the absence of any provision in the PHS Act requiring a showing of effectiveness. In 1997 the PHS Act provisions on biologics were reenacted with changes, and under the doctrine of congressional ratification, administrative interpretations of the Act were arguably endorsed by Congress in the process. If the effectiveness requirement applicable to biologics derives from the FDCA, however, it is questionable whether congressional ratification even arguably occurred.

<sup>301</sup> Wyman Letter, *supra* note 182.

<sup>302</sup> 1919 REGULATIONS, *supra* note 98, para. 7-V.

<sup>303</sup> Letter from W.G. Campbell, Acting Chief, Bureau of Chemistry, to Surgeon Gen. (July 28, 1919) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>304</sup> Memorandum from G.W. McCoy, Dir., Hygienic Lab., to Surgeon Gen. (July 29, 1919) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

Blue—sat on the Hygienic Laboratory's recommendation until the Bureau of Chemistry wrote a follow-up letter five months later, to which the Surgeon General replied by stating that PHS had not yet reached a decision on whether the 1902 Act applied to glandular products.<sup>305</sup>

In June 1920, still having received no final answer from PHS, the Bureau of Chemistry raised the same question with respect to a different group of glandular products being imported.<sup>306</sup> By that time, there was a new Surgeon General, Hugh S. Cumming. In a memo to the Surgeon General, the Director of the Hygienic Laboratory repeated his recommendation from the previous year for a “somewhat broader interpretation of the biologics law” and, in light of PHS's recent statements that it required biologics to be effective, expanded it to refer explicitly to the value of a broader definition as a means to remove ineffective products from the market:

It is believed that not only opotherapeutic products, but also diagnostic agents and other substances of organic nature used by physicians in the handling of human diseased conditions might properly be regarded as biologic products when it is deemed desirable to exercise general control over such products and to prohibit interstate commerce in those which do not present satisfactory evidence of efficiency, in accordance with the letter of the Surgeon General published in the *Journal of the American Medical Association* October 25, 1919 [the letter on lipovaccines].<sup>307</sup>

At the same time that this was happening, the Council on Health and Public Instruction of the American Medical Association (AMA) was following up on resolutions that had been adopted at the AMA's annual meeting, one of which related to the “promiscuous use of potent glandular derivatives.” PHS prepared a memorandum for the Council stating that glandular products should in some manner be regulated by PHS:

It seems probable that there is need of some method for controlling the use of such derivatives. Since these are biologic products and the Public Health Service is charged with the control of viruses, serums, toxins, and analogous products, it would seem that the Public Health Service is the logical federal agency to administer such control of these products as may seem necessary. The extent and control of such control, however, would need very careful study. The Service would be glad to cooperate with the Council on Health and Public Instruction in studying the question and in making an appropriate report in the premises.<sup>308</sup>

The Council met in December 1920 to consider the issue, and Director McCoy of the Hygienic Laboratory presented a resolution that was adopted by the Council. It endorsed the regulation of glandular products but implied, presumably based on

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<sup>305</sup> Letter from Rupert Blue, Surgeon Gen., to Chief, Bureau Chemistry (Dec. 30, 1919), responding to Letter from W.G. Campbell, Chief, Bureau Chemistry, to Surgeon Gen. (Dec. 10, 1919) (both on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>306</sup> Letter from P.B. Dunbar, Chief, Bureau Chemistry, to Surgeon Gen. (June 15, 1920) (on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655).

<sup>307</sup> McCoy Memorandum, *supra* note 206.

<sup>308</sup> Memorandum Prepared for AMA (Council Health & Pub. Instruction) (June 1920) (on file with the Nat'l Archives, Rec. Grp. 90, Gen. Classified Recs. 1936–1944, Gen. Files, File 1575 (Old Correspondence 1915–1918)).

McCoy's advice, that legislation would be necessary: "RESOLVED, That the Council on Health and Public Instruction considers it desirable that organo-therapeutic preparations be placed on the same basis, for government administrative purposes, as are serums, viruses and toxins, and that proper legislative provision to this end be provided."<sup>309</sup> Despite the urgings of the Hygienic Laboratory and the AMA Council, PHS took no steps to regulate glandular products, either administratively or through new legislation.

There was one more significant attempt to persuade the Surgeon General to expand the types of products covered by the 1902 Act. In 1935, the Sanitary Board, which was composed of four assistant surgeons general, recommended that hormonal products and potentially additional biologics should be licensed:

The Board also considered informally the general question of what biological products should be included under the Biologics Act.

The Board was agreed that the Service had in the past been too restrictive in limiting the products which might be considered as coming under the provisions of the Act. Many biologic products similar to those specified in the Act were not known at the time of the passage of the Act in 1902. It was felt that it was the intent of the law to regulate a new class of products which were of a biological nature. The Board feels, therefore, that newer classes of such products as, for example, insulin and similar endocrine products, should have regulatory law applied to them.

The question arose, however, as to whether or not the Act of 1902 was sufficiently broad to include such products. It was felt that the General Counsel of the Department should be asked to give an opinion in the matter.<sup>310</sup>

The Sanitary Board's recommendation did not refer to the regulation, issued a year earlier, barring licenses for ineffective new products, but that policy was surely part of the rationale for the Board's action. Under the regulation, PHS could deny licenses for endocrine and other products that were not shown to be effective, and the lack of that authority had been a crucial reason why such products had been declared to be outside the scope of the 1902 Act.

Although the recommendations in 1919 and 1920 to expand coverage came from the Hygienic Laboratory and might be seen as serving that unit's parochial interests, the four assistant surgeons general on the 1935 Sanitary Board (half of the total of eight assistant surgeons general) represented a large part of PHS. Nevertheless, nothing came of their recommendation.

Finally, an even more dramatic expansion of PHS's authority over drugs was broached in 1937 by the Chief of the Division of Biologics Control in response to a question from the Director of the National Institute of Health (NIH) (the renamed and expanded Hygienic Laboratory) about which arsenicals in addition to arsphenamine should be regulated under the 1902 Act. The Chief stated that "it is extremely difficult

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<sup>309</sup> Letter from Frederick R. Green, Sec'y, AMA Council Health & Pub. Instruction, to Surgeon Gen. Hugh S. Cumming (Dec. 7, 1920) (on file with the Nat'l Archives, Rec. Grp. 90, Cent. File 1897-1923, File 4202) (enclosing a copy of the resolution).

<sup>310</sup> Memorandum from L.R. Thompson, F.A. Carmelia, C.E. Waller & R.C. Williams to Surgeon Gen. (Nov. 29, 1935) (on file with the Nat'l Archives, Rec. Grp. 90, Gen. Subject File 1924-1935, Gen. Files, File 470-132).

to lay down a definite policy which should be followed in this regard” and suggested that there were potential safety problems with all injectable drugs:

From a broad public health standpoint, however, it would appear to be good practice to include under some type of federal control (supervised by the Public Health Service) all products for human use intended for injection, either subcutaneously, intramuscularly, or intravenously. This would open a tremendous field and call for a large expansion of the Division of Biologics Control, but there is little doubt that much of the uncontrolled material now being used intravenously is prepared in a manner which may permit contamination.<sup>311</sup>

While there is no evidence that this suggestion was taken seriously, it again indicates that the opposition to expanding the scope of the 1902 Act was located high in the PHS hierarchy and not in the units directly administering the Act.

With one exception, the 1919 regulations as clarified in 1923 froze the scope of the Biologics Control Act until the administration of the Act was transferred to FDA in 1972. By 1972 PHS had issued about 1300 licenses covering some 300 products, and those products all fit within the 1919/1923 definitions with the exception of whole blood, which, not being “prepared from some constituent of blood,” was outside those regulations.<sup>312</sup>

### *B. PHS’s Opposition to Regulating Insulin as a Biologic*

PHS’s policy that the scope of the 1902 Act would be almost completely limited to the scope set forth in the 1919/1923 regulations was effectively cast in regulatory concrete in 1941. In that year it became necessary to decide whether FDA would regulate insulin as a new drug or whether, instead, PHS would regulate it as a biologic. The required regulatory supervision included the need to test samples from every lot of product before it was released for distribution.

The case for regulating insulin as a biologic was strong. Insulin was derived from animal pancreases, it was an important and proven-effective product and, like licensed biologics, each lot had to be tested in animals before release to the public. The basis for regulating it as a biologic and the manner in which it would be regulated seemed barely distinguishable from licensed products. Nevertheless, PHS strongly resisted licensing insulin; its excuse was that it did not appear to have the legal authority for

<sup>311</sup> Memorandum from W.T. Harrison to Dir., NIH (Oct. 25, 1937) (on file with the Nat’l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 425P).

<sup>312</sup> As categorized by one of the NIH scientists involved in regulating biologics, the pre-1972 biologics could be classified as “allergenic extract[s], antisera, antitoxins, bacterial vaccines, toxins, toxoids, viral and rickettsial vaccines, blood and blood derivatives, immune serum globulins, diagnostic skin tests, venoms, and antivenoms,” Pittman, *supra* note 43, at 63, all of which, except for “blood,” seem to be encompassed by the 1919/1923 regulations. (Note that she did not include the arsenic-based products in her list.) Whole blood for transfusion was first licensed during World War II, and in 1947 the definition of a product analogous to a therapeutic serum was revised to include “whole blood or plasma.” 12 Fed. Reg. 411, 411 (Jan. 21, 1947) (to be codified at 42 C.F.R. § 22.1(g)(5)(ii)). See *United States v. Steinschreiber*, 219 F. Supp. 373, 375 (S.D.N.Y. 1963), *aff’d*, 326 F.2d 759 (2d Cir. 1964) (holding that human blood plasma was subject to licensure under the PHS Act); *United States v. Calise*, 217 F. Supp. 705, 705–07 (S.D.N.Y. 1962) (holding that whole blood was also subject to licensure). *But see* *Blank v. United States*, 400 F.2d 302 (5th Cir. 1968) (holding that whole blood was not covered by the PHS Act). The PHS Act was amended in 1970 by adding “vaccine, blood, blood component or derivative, allergenic product” to the list of products that had to be licensed. Act of Oct. 30, 1970, Pub. L. 91-515, § 291, 84 Stat. 1297, 1308.

lot-release testing—even though it had been conducting lot-release testing for many years and continued to do so afterwards. This section describes how in 1941 PHS firmly rejected expanding the scope of the 1902 Act and, as a practical matter, effectively terminated any further possibility of a broadened interpretation.

In 1922 researchers at the University of Toronto isolated the hormone insulin from animal pancreases.<sup>313</sup> The University patented its discovery and, after resolving problems in scaling up production to commercial quantities, granted nonexclusive licenses to several U.S. manufacturers to make and sell insulin products to treat diabetes.

There is no evidence that the discovery of insulin caused PHS to reconsider its policy that glandular products were not covered by the 1902 Act. In November 1922 and January 1923 letters, PHS wrote that insulin “is not at present declared to be analogous to serums, viruses, toxins and antitoxins, and hence is not controlled under the Act of July 1, 1902.”<sup>314</sup> In letters to potential insulin manufacturers in July and August 1923, PHS stated definitively that insulin was not subject to the 1902 Act.<sup>315</sup> From a regulatory perspective, there was no incentive for PHS to license insulin manufacturers: under its patent licenses, the University of Toronto imposed strict standards on manufacturers, including the requirement that no product from a lot could be distributed until the University had tested samples from the lot and cleared it for release. PHS could not have done more itself. After the FDCA was enacted in 1938, FDA treated insulin as subject to the new-drug provisions of that Act.<sup>316</sup>

The Committee on Revision of the *United States Pharmacopoeia (USP)* issued monographs with standards for drugs when their patents neared expiration, and the Committee began working with FDA on a monograph for insulin in the fall of 1941 in anticipation of the University of Toronto’s patent expiring on December 23, 1941.<sup>317</sup> The Committee became convinced that the *USP* monograph for insulin should include a requirement for lot-release testing by an independent laboratory, but it was not clear how such a requirement could be effected. FDA was willing to conduct the testing but lacked legal authority to impose a lot-release requirement.<sup>318</sup>

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<sup>313</sup> For history of the discovery and development of insulin and its control by the University of Toronto in the early years, see, for example, MICHAEL BLISS, *THE DISCOVERY OF INSULIN* (1982); Insulin Comm. Univ. Toronto, *Insulin: Its Action, Its Therapeutic Value in Diabetes, and Its Manufacture*, 80 J. AM. MED. ASS’N 1847 (1923).

<sup>314</sup> Letter from G.W. McCoy, Dir., Hygienic Lab., to R.L. DeSaussure, Comm’r Health, Glynn County, Ga. (Nov. 4, 1922) (on file with the Nat’l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 1973D, “Old” Investigations); Letter from A.M. Stimson, Ass’t Surgeon Gen., to Julius Leibovitz (Jan. 11, 1923) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655); see also Letter from Ass’t Surgeon Gen. to Sadie M. Campbell (Aug. 13, 1923) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 3655) (“insulin . . . is an organo-therapeutic preparation”).

<sup>315</sup> Letter from G.W. McCoy, Dir., Hygienic Lab., to Digestive Ferments Co. (Aug. 9, 1923); Letter from G.W. McCoy, Dir., Hygienic Lab., to Armour & Co. (July 2, 1923) (both on file with the Nat’l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 1973, “Old” Investigations).

<sup>316</sup> Kingham et al., *supra* note 4, at 77.

<sup>317</sup> Interview by Fred L. Lofsvold with Lloyd C. Miller in Escondido, Cal., (Jan. 27, 1981), at 26–27, U.S. FDA Oral History Collection, <http://oculus.nlm.nih.gov/2935167R>.

<sup>318</sup> Letter from W.G. Campbell, Comm’r Food & Drugs, to E. Fullerton Cook, Chairman, USP Revision Comm. (Dec. 1, 1941) (on file with the Nat’l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 1614). About thirty years later the head of the biologics staff at PHS stated that his predecessor had “persuaded” FDA to assume regulatory responsibility for hormones and antibiotics. John C. Petricciani, *Reinventing the Biologics Approval Process*, 51 FOOD & DRUG L.J. 139, 140 (1996) (relating a 1970

On December 1, 1941, the Revision Committee released its proposed monograph for insulin, flagging the need for lot-release testing and FDA's lack of legal authority to conduct it.<sup>319</sup> The head of the Committee wrote PHS suggesting that there was an immediate need for congressional authorization of lot-release testing by FDA or PHS, which were both units of the Federal Security Agency.<sup>320</sup> Inside NIH a memo was prepared for the Director of NIH to send to the Surgeon General presenting the case that insulin was an "analogous product" under the 1902 Act, but it appears that the memo was not sent.<sup>321</sup> Instead, an alternative memo was drafted, probably by the PHS lawyers, which, although also not sent, explained the necessity for lot-release testing but stated that the 1902 Act "does not provide authority" to require it.<sup>322</sup>

Meanwhile, FDA drafted legislation amending the FDCA to require the Administrator of the Federal Security Agency to certify each batch of insulin. FDA forwarded the draft bill to the Administrator for approval, at which time the Administrator's office asked whether the certification-related testing should be conducted by PHS or FDA. In a December 10 memo to the Administrator, the Surgeon General argued that new legislation would be required whether it was FDA or PHS that did the testing because the 1902 Act "does not appear" to authorize lot-release testing.<sup>323</sup> The Surgeon General's "does not appear [to authorize]" formulation was weaker than the lawyers' definitively negative opinion, presumably because PHS was in fact conducting lot-release testing. Since FDA was already regulating all other aspects of insulin, PHS argued, FDA should also be responsible for the testing. PHS prevailed, and the proposed legislation to amend the FDCA was submitted to Congress and enacted on an emergency basis as the December 23 patent expiration date approached.<sup>324</sup> PHS had passed up its last opportunity to regulate hormones as biologics.

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conversation with Roderick Murray). FDA's letter demonstrates, however, that FDA was quite willing to conduct lot-release testing of insulin, and it was otherwise already regulating hormonal products.

<sup>319</sup> *USP Circular 256, Proposed U.S.P. XI Supplement for Insulin Injection* (Dec. 1, 1941) (on file with the Nat'l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 1614).

<sup>320</sup> Letter from E. Fullerton Cook, Chairman, USP Comm. of Revision, to Lewis R. Thompson, Dir., NIH (Dec. 3, 1941) (on file with the Nat'l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 1614).

<sup>321</sup> Draft memorandum from L.R. Thompson, Dir., NIH, to Surgeon Gen. (Dec. 5, 1941) (on file with the Nat'l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 1614). The factors cited in the memo supporting classification of insulin as an "analogous product" were (1) it is of animal origin, (2) it requires standardization for safety reasons, (3) it is administered by injection, (4) a biological assay is required to determine identity and potency, (5) it must be sterile, and (6) it exerts a specific pharmacological action. There are several unsigned copies of the memo in the archives file, one of which has an attached routing slip with the notation "not used."

<sup>322</sup> Draft memorandum to Surgeon Gen. (undated, but noting in the margin that it was given to the NIH Director on Dec. 9, 1941) (on file with the Nat'l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 1614). We know that the lawyers viewed the PHS Act as not authorizing lot-release testing, so the lawyers would certainly have taken the same position as to the 1902 Act, which lacked even the reference to "standards" that the PHS Act had.

<sup>323</sup> Memorandum from Thomas Parran, Surgeon Gen., to Adm'r, Fed. Sec. Agency (Dec. 10, 1941) (on file with the Nat'l Archives, Rec. Grp. 90, Gen. Classified Recs. 1936–1944, Gen. Files, File 470).

<sup>324</sup> Act of Dec. 22, 1941, Pub. L. No. 77-366, 55 Stat. 851 (1941) (to be codified at 21 U.S.C. §§ 352(k), 356).

The precedent established by the insulin legislation was followed a few years later when penicillin, which is arguably a biologic, was introduced and required lot-release testing.<sup>325</sup> Congress placed the authority over penicillin in the FDCA.<sup>326</sup>

### *C. Rationale for the Refusal to Expand Licensing to Hormonal and Other Products*

A succession of four Surgeons General, acting over a period of three decades, rejected recommendations to cover more products, such as hormones, under the 1902 Act.<sup>327</sup> The inability to deny licenses for ineffective products was certainly the reason why expanded regulation did not result from the 1909 consideration, as contemporaneous documents reflect. After the Surgeon General's 1919 letter to the *Journal of the American Medical Association* asserted that new biologics had to be effective, however, the individuals directly involved in regulating biologics wanted to expand the classes of products subject to licensure, but the Surgeons General repeatedly refused.

Budget does not seem to have been determinative. Hygienic Laboratory officials complained that routine testing of biologics detracted from its research capacity, and additional products subject to licensure would have worsened the problem, but the trade-off between regulation and research would have been well understood by the Hygienic Laboratory and the Sanitary Board, yet they recommended expanded coverage. Moreover, licensing insulin in 1941 would have required relatively few additional resources.<sup>328</sup> If the PHS staff did not see the budget issue as critical, it is hard to see why the Surgeons General would have seen the issue completely differently.

The decisive factor seems to have been an institutional objection in the upper levels of PHS to the Service's having regulatory duties. An early indication of this view was Surgeon General Hugh Cumming's opposition in 1924 to legislation that would have required prior approval of therapeutic effectiveness claims by the board of surgeons general that issued regulations under the 1902 Act. Cumming saw this review process, which would have fallen mainly on PHS to administer, as "chiefly of a police nature" and a task that should be assigned to some agency other than PHS.<sup>329</sup> Another sign of PHS's attitude was that, despite repeatedly recognizing that catgut sutures posed a risk of tetanus unless properly manufactured, as discussed above it made no attempt to regulate them either through administrative interpretation of the 1902 Act or by

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<sup>325</sup> See H.R. REP. NO. 79-702, at 10-11 (1945) (reproducing a May 15, 1945 letter from the Federal Security Agency stating that in September 1943 the War Production Board devised a plan for FDA to assay samples from each batch of penicillin before release to the military, which used the country's entire production, and that, with product now available for civilian use, lot-release testing by FDA was necessary because "[p]enicillin is produced by a biological process and is subject to the vagaries inherent in all such processes"); S. REP. NO. 79-410, at 10-11 (1945) (same).

<sup>326</sup> Act of July 6, 1945, Pub. L. No. 79-139, 59 Stat. 463 (to be codified at 21 U.S.C. §§ 352(l), 357). The provision was later expanded to cover additional antibiotics.

<sup>327</sup> The Surgeons General were Walter Wyman (1891-1911), Rupert Blue (1912-1920), Hugh S. Cumming (1920-1936), and Thomas Parran, Jr. (1936-1948).

<sup>328</sup> In 1956 FDA's Insulin Branch consisted of the branch chief, one chemist, two laboratory technicians, and one secretary. The costs were largely covered by user fees. R. Lorimer Grant, *Certification of Insulin*, 71 PUB. HEALTH REP. 600, 602 (1956).

<sup>329</sup> Letter from H.S. Cumming, Surgeon Gen., to Sen. Royal S. Copeland (Feb. 16, 1924) (on file with the Nat'l Archives, Rec. Grp. 90, Gen. Subject File 1924-1935, Gen. Files, File 470-132).



seeking new statutory authority. In 1939, PHS (which had been transferred to the Federal Security Agency) analyzed the possibility of incorporating FDA (which was then still in the Department of Agriculture).<sup>330</sup> The memo advocated moving FDA into PHS by adducing numerous advantages, but under the heading “Possible Objections” it also stated, “As an administrative policy, there has in times past been a reluctance on the part of the Public Health Service to assume duties which involve regulatory functions.” The writer argued that this was a misplaced concern because PHS had long been involved in quarantine and biologics regulatory matters, but the memo demonstrates that the objection within PHS to involvement in regulatory matters was entrenched. In 1966, FDA sought NIH’s assistance in evaluating the effectiveness of drugs that had been cleared for marketing on the basis of safety alone, but NIH refused because, in the words of FDA Commissioner, “[t]hey didn’t want to become involved in regulatory kinds of activity.” The Director of NIH “consistently rejected any collaborative arrangements with FDA on the basis that we were a regulatory agency, and he didn’t want to get NIH tarred with that brush.”<sup>331</sup>

The antipathy to regulation in the senior ranks of PHS may also have influenced how biologics were regulated. In the early years, interaction with biologics manufacturers had been a cooperative effort to produce better biologics,<sup>332</sup> but that approach was combined with a willingness to decline or suspend licenses for lack of competent scientific management, misconduct, or moral turpitude.<sup>333</sup> By 1939 the attitude had so evolved that when the Chief of the Division of Biologics Control had to threaten license cancellation to force a company to withdraw a new version of smallpox vaccine, the official apparently felt obliged to explain himself in a memo to the NIH Director: “As you know, the enforcement of the Biologics Act is accomplished almost altogether by negotiation and it is very seldom that it becomes necessary to use compulsion. It is believed, however, that in this instance compulsion was necessary in the public interest.”<sup>334</sup> A trade press article noted the difference between the cultures at the Division of Biologics Standards and FDA, stating,

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<sup>330</sup> Memorandum from K.E. Miller, Senior Surgeon, to Surgeon Gen. (Oct. 17, 1939) (on file with the Nat’l Archives, Rec. Grp. 90, Gen. Classified Recs., Gov’t Establishments, File 1575).

<sup>331</sup> Interview by James Harvey Young with James L. Goddard in Atlanta, Ga. (Apr. 30–June 19, 1969), at 279, U.S. FDA Oral History Collection, <http://oculus.nlm.nih.gov/2935166R>.

<sup>332</sup> The provision of the 1902 Act relating to inspection of biologics manufacturing facilities “has been interpreted to mean not only that inspectors shall inspect establishments but that they shall act as advisers . . . Whenever it has been possible to do so, the attention of manufacturers has been directed to means that would improve and safeguard their preparations, and on request officers have been detailed to advise in respect to laboratory methods.” Kerr, *supra* note 67, at 232, 233–34.

<sup>333</sup> *Id.* at 234. In 1909 PHS suspended the licenses of Parke-Davis and Mulford because of an outbreak of foot and mouth disease. PHS, TREAS. DEP’T DOC. NO. 2567: ANNUAL REPORT OF THE SURGEON-GENERAL OF THE PUBLIC HEALTH AND MARINE-HOSPITAL SERVICE OF THE UNITED STATES FOR THE FISCAL YEAR 1909, at 30–34 (1910). In 1915 PHS suspended the license of E.R. Squibb & Sons until it replaced its entire scientific management with a “trustworthy” staff (because of false affidavits to inspectors apparently) and destroyed the animals and products under suspicion. Memorandum from Sanitary Bd. to Surgeon Gen. (Aug. 3, 1915) (on file with the Nat’l Archives, Rec. Grp. 90, Cent. File 1897–1923, File 15401).

<sup>334</sup> Memorandum from W.T. Harrison to Dir., NIH (June 2, 1939) (on file with the Nat’l Archives, Rec. Grp. 443, Gen. Recs. 1930–1948, File 725L).

“Historically, DBS scientists—even if engaged in regulatory chores—looked down on FDA enforcement people, regarding them as cops engaged in a kind of dirty work.”<sup>335</sup>

While it remains uncertain why the high officials in PHS repeatedly rejected recommendations to license additional types of products, an institutional preference to devote the Service’s efforts to research and traditional public health activity rather than regulation of drug products seems to be the most likely explanation. The 1902 Act had stuck PHS with a duty that the higher echelons no longer wanted, and their response was to keep that duty as small as possible. The 1935 recommendation for expanded regulation from half of the assistant surgeons general shows that there was a split of opinion within PHS, but the outcome of that debate, as well as the 1941 decision by a relatively new Surgeon General to oppose licensing of insulin by PHS, demonstrates that the institutional opposition to involvement in product regulation was strong enough to prevail.

## XI. CONCLUSION

The 1902 Act was drafted and enacted in only a few months through the cooperative efforts of the commercial biologics industry, which feared for its continued existence after more than two dozen children died from tetanus-contaminated biologics in the fall of 1901, and PHS, which suddenly had the opportunity to obtain federal regulatory control over potentially dangerous drugs. But the Act’s singular focus on preventing contamination made it ill-designed to deal with all the issues that arose in regulating biologics. As a result, PHS established a number of policies that lacked express support in the statutory text, including potency standards, rules governing manufacturing practices, and lot-release testing.

The most difficult regulatory issue not addressed in the statute was whether PHS was obligated to license ineffective products—not just “experimental” drugs of unproven value that might theoretically work, but also patently worthless products that lacked any scientific rationale. From the time in 1903 when an applicant sought a license for a bogus “serum” made from urea and mercury, PHS realized that it faced the prospect of licensing many dubious products, thereby implicitly endorsing them, because it lacked apparent authority to deny licenses for ineffective biologics.

PHS’s initial approach was to license only those products that it saw as being clearly within the language or intent of the statute. Where the Act allowed broad discretion, such as its authority to license “analogous products,” PHS did not develop a functional definition that might encompass many additional types of products but instead adhered to its restrictive approach by licensing only those products that closely resembled the biologics named in the statute. In theory, PHS could have decided that licensing potentially ineffective products was an acceptable price to pay for stricter safety regulation. Instead, PHS considered the safety concerns to be relatively small, and its priority was not giving implicit governmental approval to worthless drugs. It declared large classes of drugs, including oral and other nonparenteral drugs, plant-derived serums, and glandular products, to be outside the scope of the 1902 Act to reduce the number of ineffective drugs that it licensed. PHS’s belief that even the biologics it licensed were often of questionable effectiveness, yet widely used by physicians, undoubtedly colored its attitude toward the possibility of licensing additional drug

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<sup>335</sup> *Edwards Will Quickly Pick a New Head for DBS, Probably From Outside Govt.*, F-D-C REP., May 29, 1972, at 21, 22.

classes. At the same time, however, it adopted an expansive interpretation of the Act in limited circumstances where necessary to address significant safety issues, as in the cases of crotalin, arsphenamine, and nonparenteral products containing horse serum.

After the first decade of the 1902 Act, PHS became bolder in refusing licenses for ineffective products. In 1913 it denied a license for rattlesnake venom based on a combination of safety and effectiveness reasons; in 1917 it postponed indefinitely consideration of licenses for a bacterial vaccine that was likely ineffective; in 1919 it announced that all newly licensed biologics had to be safe and effective, although the standard of proof was fairly undemanding. In 1934 the regulations were revised to require new biologics to be effective, and it appears that PHS at least somewhat increased the amount of evidence necessary.

Several times during the life of the 1902 Act, the PHS staff directly involved in regulating biologics wanted to loosen PHS's restrictive implementation of the Act and license additional classes of biologics, particularly hormones. The Surgeons General, however, always rejected their recommendations. The 1934 regulation requiring that newly licensed products had to be effective should have ended the prior concern about having to license ineffective products, but by that time a different rationale for narrowly interpreting the 1902 Act seems to have taken hold. PHS apparently resisted an expansive interpretation for bureaucratic reasons: the 1902 Act had been assigned to a governmental agency that by the 1930s, if not earlier, had little interest in regulating drug products.

FDA, which was given responsibility for enforcing the Biologics Control Act in 1972, had no inhibitions against engaging in regulatory activity, but it inherited the definition of a biologic that PHS had developed over the years based on its lack of authority to deny licenses for ineffective biologics and, later, its disinclination to regulate products. Anomalies in the current FDA definition of a biologic can be traced in part to that history.