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March 29, 2005

Division of Dockets Management  
Food and Drug Administration  
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Re: Biological Products Review: Bacterial Vaccines and Toxoids  
Docket No. 1980N-0208  
29 Fed. Reg. 78281 (December 29, 2004)

These comments are submitted in response to the proposed regulation and proposed order published by the Food and Drug Administration (FDA) in accordance with the procedures established for the Biological Products Review in 21 C.F.R. 601.25. The comments focus on the historical development of the Biological Products Review process that FDA implemented when it assumed responsibility for biological product licensing from the National Institutes of Health (NIH) in June 1972. The undersigned served as Chief Counsel for FDA during the time that the agency developed the Biological Products Review process, and drafted both the proposed regulations and the final regulations that govern the process.

## Summary

Biological products that were licensed by NIH prior to 1972 explicitly retain their licensed status, without change, for the duration of the Biological Products Review. Once an independent advisory panel and FDA fully analyze a particular licensed product and reach a final determination on the safety, effectiveness, and labeling of such product, FDA determines

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whether any change in the licensing status is necessary. If a change is required for a particular product, that change would be undertaken by a separate and independent licensing proceeding after the Biological Products Review is completed. The Review process itself does not and cannot effect a revocation, suspension, or amendment of any product license.

#### **I. The Biological Products Act of 1902**

The Biological Products Act of 1902<sup>1</sup> was the first national statute regulating all biological products<sup>2</sup> marketed in the United States. This statute was a response to an outbreak of tetanus in Camden in 1901 from a contaminated smallpox vaccine<sup>3</sup> and the death of several children in St. Louis from a lot of tetanus-infected diphtheria antitoxin.<sup>4</sup> The Medical Society of the District of Columbia took the initiative to investigate the problem and to recommend that Congress enact legislation to address it.<sup>5</sup> Zachariah T. Sowers, M.D., then persuaded the leadership in Congress to expand the coverage of the law from the District of Columbia to the entire country.<sup>6</sup> Under the 1902 Act, biological products were licensed by the Treasury

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<sup>1</sup> 32 Stat. 728 (1902). The 1902 Act encompassed “any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention and cure of diseases of man,” and did not use the term “biological product,” but it has been referred to throughout history as the Biological Products Act of 1902 or by the shortened name of the Biologics Act of 1902.

<sup>2</sup> The first federal law to regulate a biological product was the Vaccine Act of 1813, 2 Stat. 806 (1813), repealed by 3 Stat. 677 (1822), but it was intended to cover only smallpox vaccine.

<sup>3</sup> Jonathan Liebenau, Medical Science and Medical Industry 79 (1987).

<sup>4</sup> Ralph C. Williams, The United States Public Health Service 1798-1950 180 (1951).

<sup>5</sup> H.R. Rep. No. 2713, 57th Cong., 1st Sess. (1902).

<sup>6</sup> Bess Furman, A Profile of the United States Public Health Service 1798-1948 251 (1973).

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Department pursuant to standards established in regulations promulgated by a triumvirate consisting of the Surgeons General of the Army, the Navy, and the Marine Hospital Service.<sup>7</sup> The Marine Hospital Service was, at that time, a part of the Treasury Department. Within the Marine Hospital Service, it was the Hygienic Laboratory that had specific responsibility for implementing the 1902 Act.

In 1930, the Hygienic Laboratory of the Marine Hospital Service was renamed the National Institute of Health (NIH). NIH retained responsibility for implementation of the 1902 Act through a series of internal reorganizations, and ultimately established the Division of Biologics Standards (DBS) in 1955 to have responsibility for this function.

## **II. The Statutory Authority Under the 1902 Act**

The 1902 Act prohibited any covered biological product unless it had been “propagated and prepared at an establishment holding an unsuspended and unrevoked license issued by the Secretary of the Treasury.” The Treasury Department was given authority to inspect any establishment where a biological product was being manufactured. The Treasury Department was also given authority to promulgate rules and regulations for implementing the statute. The 1902 Act did not, however, state the specific grounds upon which a license would

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<sup>7</sup> There was precedent for the Treasury Department to regulate human drugs. Under the Drug Import Act of 1848, 9 Stat. 237, all imported drugs were required to be examined by the Treasury Department for their “quality, purity, and fitness for medical purposes.” This statute was not repealed until 1922, 42 Stat. 858, 989.

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be granted or denied, i.e., it did not specifically state that such products must be shown to be safe or effective.

When Congress recodified all of the Public Health Service provisions in the Public Health Service Act of 1944,<sup>8</sup> the provisions of the Biological Products Act were included as Section 351.<sup>9</sup> The 1944 statute explicitly used the term “biological products” for the first time. The recodified statute authorized the Surgeon Generals of the Public Health Service, the Army, and the Navy to establish standards “designed to insure the continued safety, purity, and potency” of all biological products. The proposed legislation would have required a showing that a biological product has “efficaciousness” as well as safety, purity, and potency. At the request of the Acting General Counsel of the Federal Security Agency (under which NIH, as well as FDA, was at that time located), the requirement of efficaciousness was deleted.<sup>10</sup> The 1944 recodification required both an establishment license and a product license for each biological product. When Congress recodified the 1902 Act again as part of the Food and Drug Administration Modernization Act of 1997,<sup>11</sup> it combined the two licenses into a single “biologics license” but maintained the criteria for the licensing of a biological product as “safe, pure, and potent.”

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<sup>8</sup> 58 Stat. 682 (1944).

<sup>9</sup> 42 U.S.C. 261.

<sup>10</sup> “Laws Relating to the Public Health Service,” Hearings Before a Subcommittee of the Committee on Education and Labor, United States Senate, 78th Cong., 2d Sess. 48 (1944).

<sup>11</sup> 111 Stat. 2296, 2323 (1997).

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### III. Regulation of Biological Products By the NIH Division of Biologics Standards

In 1955, the NIH Microbiological Institute -- which at that time was charged with implementation of the Biological Products Act -- licensed Cutter Laboratories to manufacture the Salk vaccine for poliomyelitis. As a result of a major manufacturing problem, the Cutter vaccine caused several deaths and a much larger number of cases of paralytic polio. Following this incident, NIH created a new Division of Biologics Standards (DBS) under the leadership of Roderick Murray, M.D., to take responsibility for implementing the Act.<sup>12</sup>

The creation of DBS, under the leadership of Dr. Murray, was followed by fifteen years of relatively routine regulation of the biological products industry. In the early 1970s, however, a dissident employee, J. Anthony Morris,<sup>13</sup> initiated charges that the research and regulatory functions of DBS created an inherent conflict of interest. A young reporter for Science magazine, Nicholas Wade, wrote several articles on this issue, thus increasing its public visibility.<sup>14</sup> At the same time that DBS was under this attack for an inherent conflict of interest,

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<sup>12</sup> The Cutter incident resulted in substantial litigation. E.g., Note, The Cutter Polio Vaccine Incident: A Case Study of Manufacturers' Liability Without Fault in Tort and Warranty, 65 Yale L.J. 262 (1955).

<sup>13</sup> Dr. Morris was subsequently involuntarily removed from government service by FDA, and his removal was upheld after a series of hearings and appeals. June Osborne, In the Matter of Witch Hunts, 240 J.A.M.A. 1616 (October 6, 1978); and General Accounting Office, Answers to Questions on Selected FDA Bureau of Biologics' Regulation Activities, HRD-80-55 (1980).

<sup>14</sup> Nicholas Wade, Division of Biologics Standards: In the Matter of J. Anthony Morris, 175 Science 861 (February 25, 1972); Nicholas Wade, Division of Biologics Standards: Scientific Management Questioned, 175 Science 966 (March 3, 1972); Nicholas Wade, Division of Biologics Standards: The Boat That Never Rocked, 175 Science 1225 (March 17, 1972).

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a General Accounting Office<sup>15</sup> report of March 1972 concluded that ineffective biologics could have been licensed under the Biological Products Act because DBS had failed to apply the requirements for proof of effectiveness of new drugs added to the Federal Food, Drug, and Cosmetic Act (FD&C Act) by the Drug Amendments of 1962.<sup>16</sup> Although DBS and NIH defended its actions, this incident cast further doubt on the ability of DBS adequately to regulate biological products.<sup>17</sup> To add to the turmoil, NIH announced in April 1972 a search for a successor to Dr. Murray two years before his mandatory retirement.<sup>18</sup>

In anticipation of the GAO findings, Secretary of HEW Elliott L. Richardson formally re delegated authority to administer the new drug provisions of the FD&C Act for all biological products and new drugs concurrently to both DBS and FDA.<sup>19</sup> NIH then issued a notice announcing its intention to review the effectiveness of all licensed biological products, using the same standard used by FDA.<sup>20</sup> That announcement called for manufacturers to submit “substantial evidence of effectiveness” of their products to DBS.

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<sup>15</sup> General Accounting Office, Problems Involving the Effectiveness of Vaccines, B-164031(2) (1972).

<sup>16</sup> 76 Stat. 780, 781 (1962), Section 505(d) of the FD&C Act, 21 U.S.C. 355(d).

<sup>17</sup> Nicholas Wade, DBS: Agency Contravenes Its Own Regulations, 176 Science 34 (April 7, 1972).

<sup>18</sup> Id.

<sup>19</sup> 37 Fed. Reg. 4004 (February 25, 1972).

<sup>20</sup> 37 Fed. Reg. 5404 (March 15, 1972).

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As it turned out, however, this was not sufficient to settle the matter. At a hearing held by the Senate Government Operations Committee on May 2, 1972 on the pending Consumer Safety Act of 1972, HEW Secretary Richardson was asked by Senator Ribicoff whether the regulatory function of DBS should be consolidated with those of FDA. To the complete surprise of both DBS and FDA, Secretary Richardson announced that they should be consolidated.<sup>21</sup> Responsibility for implementation of the Biological Products Act was formally transferred to FDA a short time later, at the end of June 1972.<sup>22</sup>

#### **IV. Regulation of Biological Products by FDA**

When FDA assumed responsibility for the regulation of biological products in June 1972, it was immediately apparent to FDA Commissioner Charles C. Edwards, M.D., that FDA must promptly and comprehensively address the charges that DBS had possibly been licensing ineffective biological products. There was a clear and recent precedent for handling this matter. Under the Drug Amendments of 1962, Congress had required FDA to review all new drug applications that had become effective between 1938 and 1962, in order to verify that they were effective as well as safe.<sup>23</sup> For ten years, FDA had failed to implement this requirement with respect to nonprescription (commonly called over-the-counter, or OTC)

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<sup>21</sup> "Consumer Safety Act of 1972," Hearings before the Subcommittee on Executive Reorganization and Government Research of the Committee on Government Operations, United States Senate, 92d Cong., 2d Sess. 198 (1972).

<sup>22</sup> 37 Fed. Reg. 12865 (June 29, 1972).

<sup>23</sup> Prior to 1962, the FD&C Act required premarket notification with respect to the safety of a new drug. Following 1962, the statute required premarket approval of both safety and effectiveness.

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drugs.<sup>24</sup> In 1972, however, FDA established comprehensive procedures for the OTC Drug Review, under which each of seventeen panels of independent experts reviewed all OTC drug active ingredients within a given pharmacological category and issued a report on the safety, effectiveness, and labeling for OTC drug products containing those ingredients. Each active ingredient reviewed was classified as Category I (safe, effective, and properly labeled), Category II (unsafe or ineffective for any use), or Category III (needs more testing to determine safety, effectiveness, or labeling). The OTC Drug Review procedures were proposed in January 1972<sup>25</sup> and promulgated in final form in May 1972,<sup>26</sup> just before FDA assumed responsibility for the Biological Products Act.

Commissioner Edwards concluded that the OTC Drug Review was the correct model for conducting a comparable review of all biological product licenses issued during the past seventy years. As with the OTC Drug Review, I was given the responsibility for preparing the regulations to implement this decision. It was apparent that the basic concept and structure of the Biological Products Review should parallel those of the OTC Drug Review. Thus, the Biological Products Review employed six advisory panels of independent experts who also classified all previously licensed products within a given category into Category I, II, or III,

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<sup>24</sup> FDA implemented this requirement for prescription drugs through the review of these new drug applications by the National Academy of Sciences and the FDA Drug Efficacy Study Implementation (DESI) program.

<sup>25</sup> 37 Fed. Reg. 85 (January 5, 1972).

<sup>26</sup> 37 Fed. Reg. 9464 (May 11, 1972).

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using the same process. FDA was fortunate to recruit out of retirement a highly respected microbiologist and virologist, Morris Schaffer, M.D., to serve as Director of the Review. The Biological Products Review procedures were proposed in August 1972<sup>27</sup> and promulgated in final form in February 1973.<sup>28</sup> There were two significant FDA policy decisions that were highlighted in these procedures and the preambles that accompanied them.

First, FDA determined that, because of the special nature of biological products, it would not always be practicable to apply the same requirement of adequate and well controlled clinical trials that the Drug Amendments of 1962 imposed to establish the effectiveness of a new drug. Accordingly, the preamble to the proposed regulations for the Biological Products Review explicitly recognized this:

“The Commissioner of Food and Drugs is aware of the unique problems involved in applying the requirement of ‘substantial evidence of effectiveness’ to biological products under the Federal Food, Drug, and Cosmetic Act. Where adequate and well-controlled studies are not feasible, and acceptable alternative scientific methods of demonstrating effectiveness are available, the latter will be sufficient.”<sup>29</sup>

In response to public comment, this point was underscored by FDA through a provision in the final regulations inviting information to be submitted to the advisory panels on why controlled studies are not considered to be feasible for a particular biological product or category of

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<sup>27</sup> 37 Fed. Reg. 16679 (August 18, 1972).

<sup>28</sup> 38 Fed. Reg. 4319 (February 13, 1973).

<sup>29</sup> 37 Fed. Reg. at 16679. The OTC Drug Review similarly recognized that alternative methods of demonstrating effectiveness could be appropriate. 21 C.F.R. 330.10(a)(4)(ii).

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biological products.<sup>30</sup> In the final regulations, FDA specifically recognized the types of alternative procedures that may be considered satisfactory under these circumstances:<sup>31</sup>

“Proof of effectiveness shall consist of controlled clinical investigations as defined in § 314.126 of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the biological product or essential to the validity of the investigation, and that an alternative method of investigation is adequate to substantiate effectiveness. Alternative methods, such as serological response evaluation in clinical studies and appropriate animal and other laboratory assay evaluations may be adequate to substantiate effectiveness where a previously accepted correlation between data generated in this way and clinical effectiveness already exists. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing.”<sup>32</sup>

This definition of effectiveness has not since been changed.

Second, because FDA had presumptive evidence of the safety of each licensed biological product in the form of an unrevoked product license,<sup>33</sup> and no evidence that any particular licensed product was ineffective, FDA determined that there was no basis for taking any product off the market either at the beginning of the Biological Products Review or, indeed, until after that Review was fully completed. This decision was implemented in two different ways.

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<sup>30</sup> 38 Fed. Reg. at 4320; 21 C.F.R. 601.25(b)(3)(vii).

<sup>31</sup> 38 Fed. Reg. at 4321; 21 C.F.R. 601.25(d)(2).

<sup>32</sup> 21 C.F.R. 601.25(d)(2).

<sup>33</sup> 38 Fed. Reg. at 4320.

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- (1) FDA clearly stated in the preamble to the proposed regulations that all existing licenses for biological products subject to the Review “will not be revoked until such time as the Commissioner has published the final order establishing standards for the safety, effectiveness, and labeling of the particular category of biological products.”<sup>34</sup>
  
- (2) A conscious decision was made to conduct the Biological Products Review as a scientific evaluation, not in the form of a licensing proceeding. FDA considered and rejected the possibility of establishing the Review in the form of a licensing proceeding (to determine whether each of the existing licenses should or should not be revoked, suspended, or amended). The agency concluded that the Review should instead be in the form of a scientific review, with the final result an FDA order establishing the biological products that are and are not safe, effective, and properly labeled. FDA concluded that a separate and independent license proceeding would then be instituted following the completion of the

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<sup>34</sup> 38 Fed. Reg. at 4320. No such determination was made in the OTC Drug Review procedures, and FDA has in fact taken interim action to remove OTC drugs from the market.

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scientific review, if such a proceeding was needed to implement the final order promulgated by FDA under the Review.<sup>35</sup>

Thus, all existing licenses were specifically determined by FDA to remain in effect during the pendency of the Biologics Review, through publication of a final order. The conclusions of the Biological Products Review were not self-executing. If revocation, suspension, or amendment of any license was necessary to implement the conclusions reached in a final order, FDA was required to initiate a separate licensing proceeding for that specific biological product license. If a final order under the Biological Products Review classified a product as Category I (safe, effective, and properly labeled), no licensing proceeding would be initiated.

These policy decisions were embodied in the proposed regulations published in August 1972 and the final regulations promulgated in February 1973. The final regulations, now codified in 21 C.F.R. 601.25, have not been changed in any pertinent respect since that time.<sup>36</sup>

## V. Conclusion

The Biologics Review was established by FDA to evaluate and settle two allegations raised in early 1972 about the licensing of biological products by DBS: (1) DBS had

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<sup>35</sup> Under the OTC Drug Review, in contrast, the final regulation (called a monograph) is itself a legally enforceable requirement without any further administrative proceeding.

<sup>36</sup> Following a court decision questioning the continued marketing of active OTC drug ingredients after a final regulation that has placed them in Category III, FDA revised not only the OTC Drug Review regulations but also the Biological Products Review regulations to require that these ingredients be classified either in Category I or Category II. 21 C.F.R. 601.26.

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an inherent conflict of interest in both developing and regulating biological products and thus could not be trusted to make unbiased decisions regarding the licensing of biological products and (2) DBS had failed to apply the FDA standard for effectiveness in its licensing decisions.

When the FDA was delegated responsibility in June 1972 for implementing the Biological Products Act and restoring public confidence in the biological products licensing system, the agency recognized that many of the previously licensed biological products were safe, effective, and important to American medicine and to patient health. The regulations governing the Biological Products Review were therefore prepared to accomplish two objectives. First, all existing licenses granted by DBS for biological products were explicitly retained without change for the duration of the Biological Products Review, until both the independent advisory panels and FDA could conduct a full evaluation and reach a final determination on the safety, effectiveness, and labeling of each licensed product. Second, a final order resulting from the Biological Products Review did not, by itself, result in any change in an existing license for a biological product. FDA determined that any change in an existing license, if needed to reflect a final order under the Biological Products Review, would be undertaken after full completion of the Biological Products Review, through a separate and independent licensing proceeding to revoke, suspend, or amend each particular license in accordance with the Biological Products Act and the implementing regulations. If the final order under the Biological Products Review

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determined that a product is safe, effective, and properly labeled, the product license would remain in place and no further action would be taken by FDA.

  
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