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Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: December 1, 2010.

**Jill Hartzler Warner,**

*Acting Associate Commissioner for Special Medical Programs.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-2000-N-0163; Formerly Docket No. 2000N-1219]

#### Reclassification of Category IIIA Biological Products, Bacterial Vaccines and Related Biological Products; Implementation of Efficacy Review; Final Order; and Delmont Laboratories, Inc.: Denial of Request for a Hearing, and Revocation of License

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice; final order.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing a final order pursuant to the reclassification procedures under the biologics regulations; denying the request by Delmont Laboratories, Inc. (Delmont), for a hearing on FDA's proposal to revoke Delmont's license based on the proposed reclassification of its product, Polyvalent Bacterial Antigens with "No U.S. Standard of Potency," Staphage Lysate® (SPL) (hereinafter referred to as SPL) into Category II (unsafe, ineffective, or misbranded); and revoking Delmont's U.S. License No. 299. The final order finalizes the proposed order published in the **Federal Register** of May 15, 2000 (65 FR 31003) (May 2000 proposal), to reclassify Category IIIA bacterial vaccines and bacterial antigens into Category I or Category II.

**DATES:** The final order reclassifying Delmont's SPL into Category II, and Sanofi Pasteur Inc.'s (Sanofi's) Tetanus Toxoid Adsorbed and Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (DECAVAC™) into Category I for both primary immunization and booster use is effective December 6, 2010. The revocation of Delmont's license (U.S. License No. 299) is effective December 6, 2010.

**FOR FURTHER INFORMATION CONTACT:** Stephen Ripley, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, 301-827-6210.

#### SUPPLEMENTARY INFORMATION:

##### I. Background on the Efficacy Review Process

In the **Federal Register** of February 13, 1973 (38 FR 4319), FDA issued procedures for the review by independent advisory panels of the safety, effectiveness, and labeling of

biological products licensed before July 1, 1972. These procedures were later codified in § 601.25 (21 CFR 601.25) (38 FR 32048 at 32052, November 20, 1973). Under § 601.25, FDA assigned responsibility for the initial review of each of the biological product categories to a separate independent advisory panel consisting of qualified experts. Each panel was charged with preparing for the Commissioner of Food and Drugs an advisory report which was to: (1) Evaluate the safety and effectiveness of the biological products for which a license had been issued; (2) review their labeling; and (3) identify the biological products that are safe, effective, and not misbranded. Each advisory panel report was also to include recommendations classifying the products reviewed into one of three categories.

- Category I, designating those biological products determined by the panel to be safe, effective, and not misbranded.

- Category II, designating those biological products determined by the panel to be unsafe, ineffective, or misbranded.

- Category III, designating those biological products determined by the panel not to fall within either Category I or Category II on the basis of the panel's conclusion that the available data were insufficient to classify such biological products, and for which further testing was therefore required. Category III products were assigned to one of two subcategories. Category IIIA products were those that would be permitted to remain on the market pending the completion of further studies. Category IIIB products were those for which the panel recommended license revocation on the basis of the panel's assessment of potential risks and benefits.

In accordance with § 601.25, after reviewing the conclusions and recommendations of the review panels, FDA would publish in the **Federal Register** a proposed order containing: (1) A statement designating the biological products reviewed into Categories I, II, IIIA or IIIB; (2) a description of the testing necessary for Category IIIA biological products; and (3) the complete panel report. Under the proposed order, FDA would propose to revoke the licenses of those products designated into Category II and Category IIIB. After reviewing public comments, FDA would publish a final order on the matters covered in the proposed order.

Two original advisory panels reviewed the four Category IIIA products that are the subject of this final order. The advisory panel for Bacterial Vaccines and Bacterial Antigens with

“no U.S. Standard of Potency” (the Original Antigen Panel) reviewed Delmont’s SPL product. The advisory panel for Bacterial Vaccines and Toxoids with Standards of Potency (the Original Toxoid Panel) reviewed Sanofi’s Tetanus Toxoid Adsorbed and Tetanus and Diphtheria Toxoids Adsorbed For Adult Use products. The above definition of Category IIIA was applied at the time of each advisory panel’s review and served as the basis for their recommendations.

In the **Federal Register** of October 5, 1982 (47 FR 44062), FDA revised § 601.25 and codified § 601.26 (21 CFR 601.26) to establish procedures to reclassify those products in Category IIIA into either Category I or Category II based on available evidence of safety and effectiveness. Under § 601.26, Category IIIA products that would be reclassified included products that an advisory panel had recommended be assigned to Category IIIA, that FDA had proposed to place into Category IIIA, or for which FDA had issued a final order reclassifying the products into Category IIIA.

Under the procedures specified in § 601.26, FDA appointed an advisory panel and used existing advisory panels to review Category IIIA products and to make recommendations to reclassify each Category IIIA product into Category I or Category II. FDA assigned the reclassification review of bacterial vaccines and bacterial antigens with “no U.S. standard of potency” to the Vaccines and Related Biological Products Advisory Committee

(VRBPAC). FDA also assigned the reclassification review of bacterial vaccines and toxoids with standards of potency to the VRBPAC.

During the reclassification review process, interested persons were permitted to attend meetings, appear before the advisory panels, and submit data to the panels for review. The advisory panels then submitted reports to FDA that recommended the reclassification of each Category IIIA product into either Category I or II. According to § 601.26, after reviewing the conclusions and recommendations of the advisory panels, FDA must publish in the **Federal Register** a proposed order containing: (1) A statement designating the products as Category I or Category II, (2) a notice of availability of the full panel report, (3) a proposal to accept or reject the findings of the advisory panels, and (4) a statement identifying those products that FDA proposes to permit to remain on the market because of a compelling medical need and because no suitable alternative exists as described in § 601.26(d)(4).

**II. Category IIIA Products Subject to This Final Reclassification Order**

FDA published the May 2000 proposal to reclassify Category IIIA bacterial vaccines and bacterial antigens into Category I or Category II. FDA based the proposed order on its review of all the evidence, and considered the findings and recommendations of the VRBPAC. The proposed order also announced FDA’s intent to revoke the biologics licenses for those bacterial

vaccines and bacterial antigens that FDA proposed reclassifying into Category II.

FDA agreed with VRBPAC’s recommendations and proposed that bacterial vaccines and toxoids with standards of potency be classified into two separate categories based upon their use as either a primary immunogen or as a booster immunogen. FDA proposed that some bacterial vaccines with standards of potency be classified into Category II for use as a primary immunogen, but into Category I for use as a booster immunogen.

FDA further proposed that bacterial vaccines and bacterial antigens with “no U.S. standard of potency” be classified into Category II for all labeled indications, agreeing with the VRBPAC’s recommendations.

*A. Category IIIA Products That FDA Had Proposed To Reclassify Into Category II*

Five manufacturers of Category IIIA products that VRBPAC recommended for reclassification into Category II were subject to the May 2000 proposal (Table 1 of this document). After publication of the May 2000 proposal, four of the five manufacturers voluntarily submitted to FDA requests for revocation of their licenses for the applicable products. Subsequently, FDA revoked these licenses. Therefore, no further action is required on these manufacturers’ products. The reclassification of the Category IIIA product of the remaining manufacturer, Delmont, is discussed in a later section of this document.

TABLE 1—CATEGORY IIIA PRODUCTS THAT FDA HAD PROPOSED TO RECLASSIFY INTO CATEGORY II

| Manufacturer/License No.                    | Product(s)   | Proposed Category II indication |
|---|--|---------------------------------|
| Bioport Corporation, No. 1260 .....         | Diphtheria and Tetanus Toxoids Adsorbed <sup>2</sup> .....   | Primary immunogen.              |
| Delmont Laboratories, Inc., No. 299 .....   | Tetanus Toxoid Adsorbed <sup>2</sup> .....   | All labeled indications.        |
| Hollister-Stier Laboratories LLC, No. 1272. | Polyvalent Bacterial Antigens with “No U.S. Standard of Potency” Staphage Lysate® (SPL).   |                                 |
| Sanofi Pasteur Inc., No. 1725 .....         | Polyvalent Bacterial Vaccines with “No U.S. Standard of Potency” (Bacterial Vaccines Mixed Respiratory (MRV or MRVI), Bacterial Vaccines for Treatment, Special Mixtures) <sup>3</sup> . | All labeled indications.        |
| Wyeth Laboratories, Inc., No. 3 .....       | Tetanus Toxoid <sup>4</sup> .....  | Primary immunogen.              |
|   | Tetanus and Diphtheria Toxoids Adsorbed (Adult Use) <sup>5</sup> .....   | Primary immunogen.              |

<sup>1</sup> FDA is not relisting in this document the licenses FDA listed in and revoked before the May 2000 proposal.

<sup>2</sup> The licenses for these products were transferred from Michigan Department of Public Health, No. 99, to BioPort Corporation, License No. 1260 on November 12, 1998. The licenses were subsequently revoked by FDA on November 20, 2000, at the request of the manufacturer (66 FR 29148 at 29149, May 29, 2001).

<sup>3</sup> The licenses for these products were transferred from Bayer, Inc., No. 8 to Hollister-Stier, LLC, No. 1272 on June 2, 1999. The licenses were subsequently revoked by FDA on August 3, 2000, at the request of the manufacturer (66 FR 29148 at 29149, May 29, 2001).

<sup>4</sup> The license for this product was transferred from Merrell-National Laboratories Division of Richardson-Merrell, Inc. (License No. 101) to Connaught Laboratories, Inc. (License No. 711) on January 3, 1978; from Connaught Laboratories, Inc. (License No. 711) to Aventis Pasteur, Inc. (License No. 1277) on December 9, 1999; and from Aventis Pasteur, Inc. (License No. 1277) to Sanofi Pasteur Inc. (License No. 1725) on December 19, 2005. The license for this product was subsequently revoked by FDA on July 16, 2009, at the request of the manufacturer.

<sup>5</sup> The license for this product was revoked by FDA on May 30, 2002, at the request of the manufacturer.

Delmont Laboratories, Inc., SPL

On August 9, 2000, Delmont submitted to FDA a response to FDA's May 2000 proposal to reclassify SPL into Category II. Information regarding Delmont's response and FDA's actions are discussed in section III of this document.

*B. Category IIIA Products That FDA Had Proposed To Reclassify Into Category I*

Four manufacturers of Category IIIA products, recommended by VRBPAC for reclassification into Category I for both primary and booster immunization, were subject to the May 2000 proposal (Table 2 of this document). After publication of the May 2000 proposal,

three of the four manufacturers voluntarily submitted to FDA requests for revocation of their licenses. FDA subsequently revoked these licenses. Therefore, no further action is required on these manufacturers' products. The reclassification of the Category IIIA products of the remaining manufacturer, Sanofi, is discussed in this section of this document.

TABLE 2—CATEGORY IIIA PRODUCTS THAT FDA HAD PROPOSED TO RECLASSIFY INTO CATEGORY I FOR BOTH PRIMARY AND BOOSTER IMMUNIZATION <sup>1</sup>

| Manufacturer/License No.  | Product(s)   |
|---|--|
| Lederle Laboratories, Division, American Cyanamid Company, No. 17 | Tetanus Toxoid. <sup>2</sup><br>Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed. <sup>2</sup><br>Diphtheria and Tetanus Toxoids Adsorbed. <sup>2</sup><br>Tetanus and Diphtheria Toxoids Adsorbed (Adult Use). <sup>2</sup><br>Tetanus Toxoid Adsorbed. <sup>2</sup> |
| Sanofi Pasteur Inc., License No. 1725                             | Tetanus Toxoid Adsorbed. <sup>3</sup><br>Tetanus and Diphtheria Toxoids Adsorbed (Adult Use). <sup>3</sup>   |
| Swiss Serum and Vaccine Institute Berne, No. 21                   | Tetanus Toxoid Adsorbed. <sup>4</sup>  |
| Wyeth Laboratories, Inc., No. 3                                   | Diphtheria and Tetanus Toxoids Adsorbed. <sup>5</sup><br>Tetanus Toxoid. <sup>5</sup><br>Tetanus Toxoid Adsorbed. <sup>5</sup><br>Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed. <sup>5</sup>  |

<sup>1</sup> FDA is not relisting in this document the licenses FDA listed in and revoked before the May 2000 proposal.

<sup>2</sup> The licenses for these products were revoked by FDA on March 4, 1994, July 24, 2002, May 10, 2002, May 10, 2002, and May 22, 2002, respectively, at the request of the manufacturer.

<sup>3</sup> The licenses for these products were transferred from Merrell-National Laboratories Division of Richardson-Merrell, Inc. (License No. 101) to Connaught Laboratories, Inc. (License No. 711) on January 3, 1978; from Connaught Laboratories, Inc. (License No. 711) to Aventis Pasteur, Inc. (License No. 1277) on December 9, 1999; and from Aventis Pasteur, Inc. (License No. 1277) to Sanofi Pasteur Inc. (License No. 1725) on December 19, 2005.

<sup>4</sup> The license for this product was revoked by FDA on August 29, 2000, at the request of the manufacturer.

<sup>5</sup> The licenses for these products were revoked by FDA on May 30, 2002, May 30, 2002, May 30, 2002, and October 15, 2002, respectively, at the request of the manufacturer.

1. Sanofi Pasteur Inc., Tetanus Toxoid Adsorbed

The Original Toxoid Panel recommended that all licensed and marketed tetanus toxoid products be classified into Category I for booster immunization (50 FR 51002, December 13, 1985). The Original Toxoid Panel reviewed Sanofi's Tetanus Toxoid Adsorbed product and recommended that the product be placed into Category I for booster use and Category IIIA for primary immunization (50 FR 51002 at 51029). FDA agreed with the Original Toxoid Panel's recommendations to classify this product into Category I for booster use and Category IIIA for primary immunization (50 FR 51002 at 51105 and 51106). The VRBPAC reviewed the Category IIIA primary immunization indication for Sanofi's Tetanus Toxoid Adsorbed. Based on additional data from a clinical study performed by the firm, the VRBPAC recommended that the product be placed into Category I for primary immunization. (See Ref. 1, at pages 19 and 20). FDA agrees with the Original Toxoid Panel's and VRBPAC's recommendations and is reclassifying Sanofi's Tetanus Toxoid Adsorbed

product into Category I for both primary immunization and booster use.

2. Sanofi Pasteur Inc., Tetanus and Diphtheria Toxoids Adsorbed (Adult Use)

The Original Toxoid Panel reviewed Sanofi's Tetanus and Diphtheria Toxoids Adsorbed (Adult Use) and recommended that the product be placed into Category I for booster immunization and Category IIIA for primary immunization (50 FR 51002 at 51040). FDA agreed with the Original Toxoid Panel's recommendations to classify this product into Category I for booster use and Category IIIA for primary immunization (50 FR 51002 at 51105 and 51106). The VRBPAC reviewed the Category IIIA primary immunization indication for Sanofi's Tetanus and Diphtheria Toxoids Adsorbed (Adult Use). Based on additional data from a human clinical study performed by the firm, the VRBPAC recommended that the product be placed into Category I for primary immunization. (See Ref. 1, at pages 21 and 22). FDA agrees with the Original Toxoid Panel's and VRBPAC's recommendations and is therefore

reclassifying Sanofi's Tetanus and Diphtheria Toxoids Adsorbed For Adult Use product into Category I for both primary immunization and booster use.

**III. Denial of a Hearing on Proposed License Revocation—Delmont Laboratories, Inc.**

*A. Notice of Opportunity for a Hearing*

On August 9, 2000, Delmont submitted to FDA a written comment opposing FDA's May 2000 proposal to reclassify its product, SPL, into Category II. Delmont proposed, instead, reclassifying SPL into Category I and submitted information supporting its proposal. FDA carefully considered the information that Delmont provided and found that the information did not support a reclassification of SPL into Category I.

Accordingly, a Notice of Opportunity for Hearing (NOOH) on a proposal to revoke the license for Delmont's SPL was published in the **Federal Register** of February 26, 2003 (68 FR 8908). In the NOOH, FDA provided a detailed analysis and discussion of the information that Delmont submitted in its response to FDA's May 2000 proposal. Further, in the NOOH, FDA

advised Delmont that a request for a hearing should identify the specific fact or facts that are genuine, substantial, and in dispute (§ 12.24(b)(1) (21 CFR 12.24(b)(1)). FDA put Delmont on notice that mere allegations or denials are not enough to obtain a hearing (§ 12.24(b)(2)). FDA also put Delmont on notice that the Commissioner would deny a hearing request if the Commissioner concluded that the data and information submitted are insufficient to justify the factual determination urged, even if accurate (§ 12.24(b)(3)).

#### B. Delmont's Hearing Request

On April 28, 2003, Delmont submitted to FDA a letter objecting to FDA's proposal to revoke its license and requested a hearing. In the letter, Delmont did not submit any evidence that raised a genuine and substantial issue of fact justifying a hearing. Instead, Delmont resubmitted data on SPL that it previously submitted to FDA and made procedural arguments for why it is entitled to a hearing. Specifically, Delmont argued that FDA applied the wrong effectiveness standard when evaluating the studies that Delmont previously submitted, and that FDA used incorrect procedures when proposing to reclassify SPL and to revoke Delmont's license.

#### C. Commissioner's Determination That Delmont Has Not Justified a Hearing

As explained in subsection 1 in this section of this document, FDA applied the correct effectiveness standard to SPL. In subsection 2 in this section of this document, we explain that SPL does not satisfy that standard. Specifically, this document explains why most of the data on which Delmont relies came from studies that do not meet that standard either because they were not human studies or were not adequately controlled studies. For the few studies that were controlled or even partially controlled, this document explains why they did not show that SPL is effective. Therefore, Delmont fails to raise a genuine and substantial issue of fact regarding the effectiveness of SPL for resolution at a hearing. Moreover, the procedural objections that Delmont raises do not create a basis for a hearing (§ 12.24(b)(1)). These arguments are discussed in subsection 3 of this section of this document.

##### 1. Biologics Effectiveness Standard

Under FDA regulations, codified from the final rule published on February 13, 1973 (38 FR 4319 at 4322), biologics manufacturers, like Delmont, whose products were licensed before 1972,

must prove that their products are effective by submitting data from "controlled clinical investigations" as defined in § 314.126 (21 CFR 314.126) ("Adequate and well-controlled studies"), unless FDA waives that requirement (§ 601.25(d)(2)). To obtain a waiver, the sponsor must show that controlled clinical investigations are "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" (§ 601.25(d)(2)) (emphasis added).

Delmont attempted to argue that FDA should not have applied that standard to SPL. Instead of arguing that controlled clinical investigations are not reasonably applicable to SPL or essential to the validity of SPL investigations, and instead of advancing an alternative method of investigation and explaining why it would be adequate to substantiate SPL's effectiveness, Delmont simply argued that FDA should never require data from controlled clinical investigations for biologics. The basis for its argument is the following statement in the preamble to FDA's proposed reclassification rule for Category IIIA products (46 FR 4634 at 4635, January 16, 1981): "While it is clear \* \* \* that the applicable statutory requirement for potency in the Public Health Service Act has been interpreted as requiring that a product be effective, the specific statutory criteria governing new drugs, 'adequate and well-controlled clinical studies,' have not been applied to biological drugs."

FDA's final reclassification rule for Category IIIA products (47 FR 44062 at 44067, October 5, 1982), however, confirmed that FDA "does indeed consider controlled clinical studies to be the preferred form of evidence for documenting a product's effectiveness." Furthermore, FDA clarified that "unless unusual circumstances justify a special exemption for a particular product," controlled clinical investigations are required to establish effectiveness (47 FR 44062 at 44067).

In this case, Delmont did not attempt to show that SPL meets the criteria for a special exemption, namely, that an alternative method of investigation is adequate to substantiate SPL's effectiveness, and that controlled clinical investigations are either inapplicable to SPL or not essential to the validity of the investigation. In fact, Delmont sponsored a controlled clinical trial of SPL (in patients suffering from the disease hidradenitis suppurativa), but as FDA explained at length in the February 26, 2003, NOOH, the data showed no statistically significant

difference between SPL and a placebo. Therefore, the data were inadequate to demonstrate that the product was effective. See 68 FR 8908 at 8909.

Clearly, FDA applied the correct standard when evaluating SPL.

##### 2. Application of the Standard to SPL

Since FDA's biologics review began, Delmont has submitted to FDA data on SPL at four different times: (a) Before 1978, as part of FDA's initial biologics review process; (b) between January and May 1978, to convince FDA to classify SPL into Category IIIA rather than IIIB so that Delmont could continue marketing SPL while obtaining data from effectiveness studies; (c) in 1983, as part of FDA's reclassification procedures; and (d) in 1994, to supplement its reclassification data with the results of studies that were incomplete in 1983. As discussed in turn below, none of the data are sufficient to demonstrate that SPL is effective.

###### a. Pre-1978 Data

As part of FDA's initial biologics review process, Delmont submitted data to the Original Antigen Panel. The Original Antigen Panel issued a report, which is published in the **Federal Register** of November 8, 1977 (42 FR 58266 at 58270), that analyzed in detail all the studies that Delmont had submitted, and described deficiencies in each one. Based on that analysis, the Original Antigen Panel concluded that Delmont had provided "no substantial evidence of safety or effectiveness," and "no evidence presumptive of safety" (42 FR 58266 at 58285). Consequently, the Original Antigen Panel recommended that FDA classify SPL into Category IIIB and revoke Delmont's license (42 FR 58266 at 58285). In the **Federal Register** of November 8, 1977, FDA issued a proposed order notifying Delmont that it agreed with the Original Antigen Panel's findings and that it intended to revoke Delmont's license (42 FR 58266 at 58318). As discussed in subsection b.iii of this section of this document, FDA ultimately classified SPL into category IIIA based on additional safety data that Delmont submitted (44 FR 1544 at 1548, January 5, 1979), but FDA agreed with the Original Antigen Panel's criticisms of SPL's effectiveness data (44 FR 1544 at 1546, comment 5) and ordered Delmont to complete and submit the effectiveness testing that the Original Antigen Panel had recommended (44 FR 1544 at 1548).

## b. January to May 1978 Data

## i. Delmont's Hearing Request

In response to FDA's revocation proposal (42 FR 58266), Delmont requested a hearing on whether FDA should classify SPL into Category IIIA or IIIB, and submitted to FDA additional data on January 8, 1978, February 7, 1978, March 31, 1978, and May 26, 1978. Those submissions are all currently in the public docket relating to this matter, Docket No. 2000N-1219, as attachments to Delmont's April 28, 2003, hearing request. None of the data satisfied the controlled clinical investigations standard for proving effectiveness, as discussed in subsection b.iii of this section of this document, even though FDA eventually determined that the safety data were sufficient to classify SPL into Category IIIA to allow Delmont to continue marketing SPL while obtaining effectiveness data.

## ii. Deficiencies in Delmont's Data

## (1). January 8, 1978, Submission

In a letter dated January 8, 1978 (Docket No. 2000N-1219, Item SUP1, Tab C to Delmont's April 28, 2003, hearing request), Delmont submitted to FDA additional study reports. Delmont stated that the reports "show that no risk to human safety can result from continued marketing of SPL for a limited period while further studies are conducted." As to effectiveness, however, Delmont said only that the study reports "demonstrate that further studies of SPL in accordance with FDA requirements for clinical investigations will very likely provide substantial evidence that the product is effective for its labeled indications \* \* \*." Therefore, Delmont admitted that the data it was submitting were collected from studies that were not conducted in accordance with FDA requirements for clinical investigations.

Most of those studies failed to satisfy FDA's controlled clinical investigations standard because they were preclinical studies not performed on humans, and therefore, were not clinical investigations. Specifically, those reports were as follows: "Chronic Toxicity Test of SPL in Rats" (Fujino, *et al.*) (Ref. 2); "Acute and Subacute Toxicity Tests of SPL" (Fujino, *et al.*) (mice and rats) (Ref. 3); "Teratogenicity Study of SPL in Rats and Rabbits" (Hachihiko Hirayama) (Ref. 4); "Effect of SPL on the Development of Skin Lesion in Mice after Inoculation with Herpes Simplex Virus" (Department of Microbiology, School of Medicine, Kyushu University) (Ref. 5); "Chemotactic Accumulation of

Macrophages in the Peritoneal Cavity after Inoculation of SPL and their Antitumor Activity" (Department of Microbiology, School of Medicine, Kyushu University) (mice) (Ref. 6); and "S-27: Summary of Results of Tests Conducted at Fuji-Zoki Pharmaceutical Research Division" (safety tests in mice and guinea pigs) (Ref. 7).

Two other studies that Delmont included in its January 8, 1978, submission, "Susceptibility of Staphylococcus aureus Clinical Isolates to Gratia Bacteriophage" (Shigeno, *et al.*) (Ref. 8) and "Influence of Staphage Lysates (SPL) on Immune Responses In Vitro" (Mitsuma, *et al.*) (Ref. 9), do not qualify as controlled clinical investigations because they were in vitro studies. Moreover, the limited data contained in the abstracts that Delmont submitted to FDA on these two studies limit their usefulness for any purpose. Therefore, they are not adequate to support reclassifying SPL into Category I.

Delmont also submitted two reports on studies of SPL in humans, "Immunopotiator Activity of Staphage Lysate (Mudd)" (Azuma, *et al.*) (Ref. 10) and "Immunochemotherapy for Infections—With Particular Reference to Staphage Lysate" (Tsuda, *et al.*) (Ref. 11). Neither of those qualifies as a controlled clinical investigation, for a number of reasons. First, neither study was controlled as required in FDA's 1979 final order, which included Delmont's product in Category IIIA (44 FR 1544 at 1548). A fundamental characteristic of controlled clinical investigations is that they "use a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect" (§ 314.126(b)(2)). A control is necessary to "distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation" (§ 314.126(a)). While different types of controls are permitted under different conditions, neither study reports that the investigators used controls.

Second, both a protocol and a study result report should contain a clear statement of the objectives of the investigation and a summary of the methods of analysis (§ 314.126(b)(1)). Delmont did not submit the protocol for either study, and the resulting reports for the two studies did not explain how the investigators measured or analyzed the results of treating their study subjects with SPL. Although the Tsuda study report (*see* Ref. 11) contains a summary of clinical results in Table 8, which lists the investigators' assessments of subjects' responses to

SPL—either "Excellent," "Greatly improved," or "Unimproved"—the study does not state what criteria were used to reach those assessments. Moreover, as the report itself admits, "no conclusive statement can be made here because of the relatively small series studied." Clearly, the reports do not provide "sufficient details of the study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present" (§ 314.126(a)).

The studies also failed to meet other characteristics of a controlled investigation. The study reports fail to show that the "method of selection of subjects provides adequate assurance that they have the disease or condition being studied or evidence of susceptibility and exposure to the condition against which prophylaxis is directed" (§ 314.126(b)(3)). In the Tsuda study (*see* Ref. 11) the diseases being studied were chronic intractable staphylococcal infections or other viral infections. In the Azuma study (*see* Ref. 10), the condition being studied was defensive capacity against infection generally. However, neither study report showed how the subjects were selected to meet these criteria. Similarly, the studies fail to show that the "method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables" (§ 314.126(b)(4)); fail to show that "[a]dequate measures [were] taken to minimize bias on the part of the subjects, observers, and analysts of the data" (§ 314.126(b)(5)); fail to demonstrate that the "methods of assessment of subjects' response [were] well-defined and reliable" (§ 314.126(b)(6)); and fail to provide "an analysis of the results of the study adequate to assess the effects of the drug" (§ 314.126(b)(7)). Clearly, then, these two studies do not meet the criteria for controlled clinical investigations.

Finally, Delmont submitted what it described as a protocol for "a study based on short- and long-term surveillance of patients receiving SPL therapy under the care of Arthur G. Baker, M.D." The study had not begun, and Delmont had no results to report at that time. Therefore, it did not contribute to the effectiveness assessment.

In summary, none of the submissions that Delmont included with its January 8, 1978, letter constituted controlled clinical investigations. Thus, they were insufficient to establish SPL's effectiveness at that time.

## (2). February 7, 1978, Letter

On February 7, 1978, Delmont sent to FDA additional data to support its request for a hearing on whether to classify SPL into Category IIIA or IIIB (Docket No. 2000N-1219, Item SUP1, Tab D to Delmont's April 28, 2003, hearing request). Delmont categorized much of the data and reports as safety data, but did include a set of attachments that it labeled "Effectiveness Data." Delmont divided those attachments into "Controlled Studies," and "Other Efficacy Data." The Controlled Studies section contains only a protocol for a study that was then in early stages, and does not contain a report on the results of that study. Thus, Delmont admitted that its February 7, 1978, submission did not contain effectiveness data that met the controlled clinical investigations standard.

The "Other Efficacy Data" section was divided into two subsections: "Studies in Humans" and "Studies in Animals." The first paper in the human studies subsection, Salmon G.G. and M. Symonds, "Staphage Lysate Therapy in Chronic Staphylococcal Infections," (Ref. 12), is a duplicate of a published article that Delmont had submitted to the Original Antigen Panel in 1977. The Original Antigen Panel rejected that article, stating that in the article "patients are said to have recovered because of antibody induction but no data demonstrating such responses are provided" (42 FR 58283). The next three reports were duplicates of reports that Delmont had submitted with its January 8, 1978, letter, which are deficient for the reasons discussed previously in this section of this document. Finally, Delmont submitted two summaries of case studies, "Immune Stimulation Therapy for Inflammatory Disease of the Gut," (Ref. 13) and "Immune Stimulation for Aphthous (Herpetic) Stomatitis & Rhinitis," (Ref. 14) that Dr. Dale Rank had sent to Delmont. These reports contain little information, and therefore do not "provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present" (§ 314.126(a)). Moreover, the terse case reports of Dr. Rank's patients contain no indication that any type of control was used.

Therefore, none of Delmont's February 7, 1978, submissions satisfied the controlled clinical investigations standard.

## (3). March 31, 1978, Letter

On March 31, 1978, Delmont sent to FDA another letter (Docket No. 2000N-1219, Item SUP1, Tab E to Delmont's April 28, 2003, hearing request). That letter served primarily to answer questions that FDA had raised about the animal studies in Delmont's January 8, 1978, submission. The letter also included three new reports. One reported on tests in rabbits and another reported the results of in vitro assays, neither of which constituted controlled clinical investigations in humans. The letter also included a one-page "report of a double blind, placebo controlled trial for evaluation of SPL as a treatment for warts, dated March 7, 1978." The one-page summary clearly did not "provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present," as § 314.126(a) requires, for many reasons. Among them are that it provided: No patient recruitment details on their diagnoses, as § 314.126(b)(3) requires; no explanation of patient inclusion and exclusion criteria (§ 314.126(b)(3)); no description of patient randomization procedures (if performed), as § 314.126(b)(4) requires; and no clinical descriptions or associated clinical measurements for the endpoints of "Excellent," "Good," and "No change," as § 314.126(b)(6) and (b)(7) require. Thus, Delmont's March 31, 1978, submissions did not satisfy the controlled clinical investigations standard.

## (4). May 26, 1978, Letter

In a letter dated May 26, 1978 (Docket No. 2000N-1219, Item SUP1, Tab F to Delmont's April 28, 2003, hearing request), Delmont submitted one last supplement to its comments on FDA's proposal to classify SPL into Category IIIB. The letter stated that "[t]his information further supports Delmont's position, set out in its January 8, 1978, comments, that SPL is safe and that an opportunity should be provided for the completion of clinical studies to provide additional information demonstrating the product's effectiveness." Thus, Delmont acknowledged that its May submissions did not demonstrate SPL's effectiveness.

The first set of documents contains case reports on 50 patients that Dr. Arthur Baker had treated with SPL. Delmont submitted those individual case reports to "show that no allergic reactions or adverse effects were observed in any of the patients who received SPL over extended periods of

time." Delmont did not include a study result report analyzing the data for effectiveness.

The second set of documents consists of protocols for two clinical studies of SPL that Dr. John Silva was conducting. One was then underway at the Department of Veterans Affairs hospital in Biloxi, MS and the second had not begun. Delmont did not submit any effectiveness data from the ongoing study. Instead, it submitted a letter from Dr. Silva stating that no allergic reactions or other adverse effects had been observed. Therefore, the information related to safety rather than efficacy.

## iii. FDA's 1979 Final Order on SPL

On January 5, 1979 (44 FR 1544), FDA published a final order formally classifying into Category IIIA those products, including Delmont's SPL, for which the data were insufficient to determine their safety and effectiveness, but which FDA would allow to remain on the market pending completion of testing. That final order confirmed that the Commissioner agreed with the Original Antigen Panel's conclusions and recommendations about all the deficiencies in the Category IIIA data (44 FR 1544 at 1546, comment 5). It further confirmed that the manufacturers of those products had to submit data from controlled clinical investigations, and that their products could not remain in category IIIA indefinitely (44 FR 1544 at 1545 to 1548).

That final order also expressly confirmed that SPL was subject to the same requirement. The order stated as follows: "Because data submitted by Delmont Laboratories, Inc., have been found to be adequate to reclassify its staphage lysate types I and [III] combined, License No. 299, from Category IIIB to IIIA, the requirements concerning *completion of testing* and labeling *apply to these products*" (44 FR 1544 at 1548) (emphasis added). The order also made clear that those testing requirements were the ones that the Original Antigen Panel had recommended; after listing all of the Category IIIA products, including SPL, the order stated that "[l]icenses remain in effect for these products *pending conformance with the Panel's recommendations and completion of testing*" (44 FR 1544 at 1548) (emphasis added). As discussed above, the Original Antigen Panel was clear that all Category IIIA products reviewed by that Panel needed further clinical investigations to establish their effectiveness.

## c. 1983 Data

In December 1982, FDA assigned the VRBPAC to follow the reclassification procedures in § 601.26 (65 FR 31003 at 31004) to reclassify the bacterial vaccines and antigens with “no U.S. standards of potency” that had been previously classified into Category IIIA, including SPL into either Category I or Category II. Under these procedures, Delmont submitted to the VRBPAC additional data on SPL. The VRBPAC held reclassification meetings in January, June, and September 1983 (65 FR 31003 at 31006).

After reviewing all of the data, VRBPAC voted to recommend placing SPL into Category II and to revoke Delmont’s license. VRBPAC’s Final Report provides VRBPAC’s detailed critique of all the data that Delmont submitted (*see* Ref. 1, at pages 47 to 54). The Final Report confirmed that the VRBPAC members voted unanimously to recommend placing SPL into Category II because the evidence was insufficient to prove effectiveness. (*See* Ref. 1, at page 55). We continue to agree with the VRBPAC’s analysis as described in that portion of the Final Report at page 55.

## d. 1994 Data

On February 28, 1994, Delmont submitted to FDA results from a study on hidradenitis suppurativa (HS) that had just begun in 1983, along with the results from some other studies. (A copy of Delmont’s February 28, 1994, submission is attached as Tab C to comments that Delmont submitted to the Docket No. 2000N–1219, Item C1 on August 9, 2000). In FDA’s February 26, 2003, NOOH, FDA published a detailed critique of Delmont’s 1994 data (68 FR 8908 at 8909). Of all the study results that Delmont submitted, only the HS study, a prospective, double-blind, placebo controlled trial, constituted a controlled clinical investigation (68 FR 8908 at 8909). The investigators in that study, however, found “[n]o significant differences between treatment groups or between the two centers” after performing efficacy analyses, and concluded that “[u]nder the conditions of the study, SPL was not demonstrated to be effective in the treatment of HS” (Delmont’s February 28, 1994, submission, at page 9). A third party that Delmont contracted with to perform a reanalysis of the data reached a more optimistic conclusion (Delmont’s February 28, 1994, submission, pages 9 to 11, and 68 FR 8908 at 8909). But it reached that conclusion only after first unblinding the patient data and performing a subset analysis on a

selected subgroup of patients based on a different method of assessing effectiveness (68 FR 8908 at 8909). Even then, the third party found no statistically significant difference between the patients treated with placebo and with SPL (68 FR 8908 at 8909).

The rest of Delmont’s 1994 data fails to satisfy the controlled clinical investigations standard, as FDA explained in its February 26, 2003, NOOH (68 FR 8908 at 8909). We continue to support the analysis described in the **Federal Register** document of February 26, 2003 (68 FR 8908).

Significantly, Delmont’s April 28, 2003, hearing request does not attempt to argue that any of the data it submitted to FDA during the reclassification process in 1983 and 1994 satisfies the controlled clinical investigations standard or otherwise is adequate to demonstrate effectiveness. Instead, Delmont’s hearing request argues that the data that it submitted to FDA in 1978 sufficiently demonstrates that SPL is effective. Delmont does not, however, discuss the specific data that it submitted in 1978 or explain why it is sufficient to prove that SPL is effective. Rather, Delmont argues that in 1978, FDA stated that Delmont’s data were sufficient to justify a hearing. What FDA actually stated, however, is that the data justified a hearing only on whether FDA should classify SPL into Category IIIA or IIIB—not Category I. In other words, FDA did not find that the data justified a hearing on whether SPL was effective—only on whether SPL was safe enough to allow Delmont to keep marketing it while Delmont conducted further effectiveness studies. Indeed, even Delmont admitted that further effectiveness studies were necessary.

Therefore, Delmont has not raised a genuine and substantial issue of fact justifying a hearing as to whether SPL is effective.

## 3. Delmont’s Procedural Objection

Delmont also argues that FDA did not follow correct procedures during the effectiveness reclassification process and that, therefore, Delmont deserves a hearing on SPL’s effectiveness. Delmont’s specific objection is that because FDA issued a NOOH before finally reclassifying SPL into Category II, FDA has violated its own procedures and has deprived Delmont of fair notice and opportunity for judicial review.

Delmont is incorrect that FDA violated its own procedures. The reclassification procedures, set forth in § 601.26, are silent as to when FDA should issue an NOOH. However, the

preamble to § 601.26 provides that the procedures for review and reclassification of the Category IIIA products were designed to be “analogous to the procedures in § 601.25 for the 1972 biologics review,” as Delmont itself admits (Delmont’s April 28, 2003, hearing request, at page 4) (46 FR 4634, January 16, 1981). Section 601.25 required FDA to issue an NOOH before issuing its final classification order. Specifically, § 601.25(g) required FDA’s final classification order to address all matters in the proposed order, and § 601.25(f)(2) required that for products that FDA proposed to classify into Category II, FDA also include a license revocation proposal in the proposed order. However, before revoking a license, FDA first had to issue an NOOH (§ 601.5(b)(1) (21 CFR 601.5(b)(1))). Therefore, under § 601.25, FDA had to issue an NOOH before issuing a final classification order because that final classification order had to include the license revocation.

Although § 601.26 is silent on this issue, as stated in the preamble, the agency did follow the process analogous to § 601.25 for this license revocation. In the proposed order issued at 65 FR 31003, May 15, 2000, FDA stated that the proposed order contained the agency’s intent to revoke the licenses of certain products that the agency proposed to reclassify into Category II. The agency further stated that, after the end of the comment period on the proposed order, if it decided to proceed with the license revocation proceeding, it would publish a NOOH on the revocation of the license of each Category II product. The agency also stated it would issue a final order on all matters covered by the proposed order (65 FR at 31005). In fact, § 601.26(e) provides for the final order to cover all matters in the proposed order. As with the procedures under § 601.25, FDA included notice of its intent to revoke certain licenses in the proposed order. In order to finalize all matters in the proposed order in the final order, it was necessary for FDA to issue the NOOH prior to the final order. Therefore, contrary to Delmont’s arguments, FDA has not violated its procedures.

In addition, Delmont is mistaken that FDA has deprived Delmont of fair notice and an opportunity for judicial review. This final order, which contains all of FDA’s reasons for denying Delmont a hearing and for revoking Delmont’s license, is final agency action that is reviewable in the courts (§ 12.28(d) (21 CFR 12.28(d))). Moreover, Delmont has had years of notice that FDA intends to reclassify SPL into Category II and to revoke its license based on that



reclassification, and has availed itself of two opportunities to comment on and object to FDA's proposal: (1) On August 9, 2000, in response to FDA's May 2000 proposal, and (2) on April 28, 2003, in response to FDA's NOOH (68 FR 8908). FDA has not deprived Delmont of fair notice, nor has FDA precluded Delmont from seeking judicial review.

#### D. Denial of Hearing Request

For the reasons stated previously in this document, the Commissioner of Food and Drugs (Commissioner) determines that Delmont has failed to raise a genuine and substantial issue of fact to justify a hearing on the proposed revocation of U.S. License No. 299 issued to Delmont Laboratories, Inc. for Polyvalent Bacterial Antigens with "no U.S. Standard of Potency" (Staphage Lysate), and, therefore, denies Delmont's request for a hearing. The Commissioner also determines that Delmont's procedural arguments do not provide a basis for a hearing.

#### IV. Categorization of Products—Final Order

The Commissioner has considered all relevant information regarding the four Category IIIA bacterial vaccines and bacterial antigens subject to reclassification and concludes that FDA's proposal for the reclassification of Category IIIA products into Category I or Category II is adopted as set forth in this section of this document and hereby formally classifies:

Category I—Biological products determined to be safe, effective, and not misbranded, and which may continue to be introduced into interstate commerce. Sanofi Pasteur Inc., U.S. License No.

1725:  
Tetanus Toxoid Adsorbed (primary and booster use), and  
Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (DECAVAC™) (primary and booster use).

Category II—Biological products determined to be unsafe, ineffective, or misbranded, and which may not continue to be introduced into interstate commerce.

Delmont Laboratories Inc., U.S. License No. 299:  
Polyvalent Bacterial Antigens with "No U.S. Standard of Potency" Staphage Lysate® (SPL)

#### V. License Revocation—Final Order

For the reasons set forth in this document, under section 351 of the Public Health Service Act (42 U.S.C. 262) and 21 CFR 601.5(b)(1)(vi), the Commissioner revokes the license (U.S.

License No. 299) issued to Delmont Laboratories, Inc., for Polyvalent Bacterial Antigens with "No U.S. Standard of Potency" Staphage Lysate® (SPL).

#### VI. References

The following references have been placed on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Final Report: Addendum to Previous Panel Reports for the Reclassification of Category IIIA Biologics, VRBPAC, 1984.
2. Fujino, Ryuichi; Yuji Sugisaki; Junko Nakagawa; Masana Komatsu; and Hachihiko Hirayama, "Chronic Toxicity Test of SPL in Rats," Fujizoki Pharmaceutical Co., Ltd., Shinjuku-ku, Tokyo.
3. Fujino, Ryuichi; Yuji Sugisaki; Junko Nakagawa; Masana Komatsu; "Acute and Subacute Toxicity Tests of SPL," Fujizoki Pharmaceutical Co., Ltd., Shinjuku-ku, Tokyo.
4. Hirayama, Hachihiko, "Teratogenicity Study of SPL in Rats and Rabbits," Fujizoki Pharmaceutical Co., Ltd., Nerima-ku, Tokyo.
5. "Effect of SPL on the Development of Skin Lesion in Mice after Inoculation with Herpes Simplex Virus," Department of Microbiology, School of Medicine, Kyushu University, Fukuoka, Japan.
6. "Chemotactic Accumulation of Macrophages in the Peritoneal Cavity after Inoculation of SPL and their Antitumor Activity," Department of Microbiology, School of Medicine, Kyushu University, Fukuoka, Japan.
7. "S-27: Summary of Results of Tests Conducted at Fuji-Zoki Pharmaceutical Research Division," Fujizoki Pharmaceutical Co., Ltd., Tokyo.
8. Shigeno, N.; T. Mitsuma; and K. Kojima, "Susceptibility of Staphylococcus aureus Clinical Isolates to Gratia Bacteriophage," Junior College of Medical Technology and Nursing affiliated with Niigata University.
9. Mitsuma, T.; N. Shigeno; K. Kojima; and M. Tanaka, "Influence of Staphage Lysate (SPL) on Immune Responses In Vitro," Junior College of Medical Technology and Nursing affiliated with Niigata University and Santo Hospital.
10. Azuma, C.; Y. Tokuda; and T. Shibata, "Immunopotiator Activity of Staphage Lysate (Mudd)," Department of Dermatology, Tokyo College of Medicine, Tokyo.
11. Tsuda, Shingo and Kikuo Minami, "Immunochemotherapy for Infections—With Particular Reference to Staphage Lysate," Department of Dermatology, Kurume University, School of Medicine, Kurume, Fukuoka Prefecture.
12. Salmon, G.G. and M. Symonds, "Staphage Lysate Therapy in Chronic Staphylococcal Infections," *Journal of*

*the Medical Society of New Jersey*, 60:180-193 (1963).

13. Rank, Dale, "Immune Stimulation Therapy for Inflammatory Disease of the Gut," and "Immune Stimulation for Aphthous (Herpetic) Stomatitis & Rhinitis," (Study Nov. 1975 to Dec. 1977).
14. Rank, Dale, "Immune Stimulation for Aphthous (Herpetic) Stomatitis & Rhinitis," (Jan. 1976 to Jan. 1978).

Dated: November 24, 2010.

**Leslie Kux,**

*Acting Assistant Commissioner for Policy.*

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**BILLING CODE 4160-01-P**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Health Resources and Services Administration

#### National Advisory Council on Nurse Education and Practice; Notice for Request for Nominations

**SUMMARY:** The Health Resources and Services Administration (HRSA) is requesting nominations to fill eight vacancies on the National Advisory Council on Nurse Education and Practice (NACNEP).

**Authority:** 42 U.S.C. 297t, section 851 of the Public Health Service (PHS) Act, as amended by the Affordable Care Act. The NACNEP is governed by the Federal Advisory Committee Act, Public Law (Pub. L.) 92-463, as amended (5 U.S.C. Appendix 2), which sets forth standards for the formation and use of advisory committees.

**DATES:** The Agency must receive nominations on or before December 22, 2010. Addresses: All nominations are to be submitted either by mail to Lakisha Smith, MPH, Designated Federal Official, NACNEP, Division of Nursing, Bureau of Health Professions (BHPr), Health Resources and Services Administration (HRSA), Parklawn Building, Room 9B-45, 5600 Fishers Lane, Rockville, MD 20857 or e-mail at [Lsmith2@hrsa.gov](mailto:Lsmith2@hrsa.gov).

**FOR FURTHER INFORMATION CONTACT:** For additional information contact, Lakisha Smith, Executive Secretary, National Advisory Council on Nurse Education and Practice, by e-mail at [Lsmith2@hrsa.gov](mailto:Lsmith2@hrsa.gov) or telephone at (301) 443-5688. A copy of the current committee membership, charter and reports can be obtained by accessing the NACNEP Web site at <http://bhpr.hrsa.gov/nursing/nacnep.htm>.

**SUPPLEMENTARY INFORMATION:** Under the authorities that established the NACNEP and the Federal Advisory Committee Act, HRSA is requesting nominations