DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00N–1219]

Delmont Laboratories, Inc.; Opportunity for Hearing on a Proposal to Revoke U.S. License No. 299

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing an opportunity for hearing on a proposal to revoke the biologics license (U.S. License No. 299) issued to Delmont Laboratories, Inc. (Delmont), for Polyvalent Bacterial Antigens with ‘‘no U.S. Standard of Potency’’ (Staphage Lysate). The proposed revocation is based on FDA’s proposed reclassification of this product in Category II (unsafe, ineffective, or misbranded), based on the recommendations of the Vaccines and Related Biological Products Advisory Committee (VRBPAC).

DATES: Delmont Laboratories, Inc., may submit written or electronic requests for a hearing by [*insert date 30 days after date of publication in the* **Federal Register**], and any data and information justifying a hearing by [*insert date 60 days after date of publication in the* **Federal Register**]. Other interested persons may submit written or electronic comments on the proposed revocation by [*insert date 60 days after date of publication in the* **Federal Register**].

ADDRESSES: Submit written requests for a hearing, any data and information justifying a hearing, and any written comments on the proposed revocation

to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic requests or comments to http://www.fda.gov/dockets/ecomments.

FOR FURTHER INFORMATION CONTACT: Astrid L. Szeto, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–6210.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of May 15, 2000 (65 FR 31003), FDA issued a proposed order to reclassify certain Category IIIA (remaining on the market pending further studies in support of effectiveness) bacterial vaccines and related biological products into Category I (safe, effective, and not misbranded) or Category II (unsafe, ineffective, or misbranded). This action was taken under the reclassification review procedures in § 601.26 (21 CFR 601.26), and was based on the findings and recommendations of the VRBPAC and the Panel on Review of Allergenic Extracts (the Allergenics Panel). The proposed order also announced our intent to revoke the biologics licenses for those bacterial vaccines and related products proposed for reclassification in Category II.

Based on VRBPAC's recommendations, FDA 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. FDA further proposed that bacterial vaccines and related biological products with ''no U.S. standards of potency'' be classified into Category II for their labeled indications based on either the VRBPAC's or the Allergenics Panel's recommendations. Five manufacturers of Category IIIA products were subject to the proposed order, as listed in the following table:

TABLE 1—CATEGORY IIIA PRODUCTS PROPOSED BY FDA FOR RECLASSIFICATION INTO CATEGORY II AS A PRIMARY IMMUNOGEN OR FOR ALL LABELED INDICATIONS

Manufacturer/License Number	Product(s)	Proposed Category II Indication
Aventis Pasteur, Inc., No. 1277	Tetanus Toxoid (fluid)	Primary Immunogen
BioPort Corporation, No. 1260	Diphtheria and Tetanus Toxoids Adsorbed	Primary Immunogen
Wyeth Laboratories, Inc., No. 3	Tetanus and Diphtheria Toxoids Adsorbed (Adult Use).	Primary Immunogen
Delmont Laboratories, Inc., No. 299	Polyvalent Bacterial Antigens with ''No U.S. Standard of Potency'' (Staphage Lysate).	All Labeled Indications
Hollister-Stier Laboratories LLC, No. 1272 (1)	Polyvalent Bacterial Vaccines with ''No U.S. Standard of Potency'' (Bacterial Vaccines Mixed Respiratory (MRV or MRVI, Bacterial Vaccines for Treatment, Special Mixtures).	All Labeled Indications

[1]As described in the proposed order, this product was reviewed by the Allergenics Panel. The remaining products in this table were reviewed by the VRBPAC.

FDA also proposed that the bacterial vaccines with U.S. standards of potency recommended for classification into Category II as a primary immunogen be placed into Category I for use as a booster immunogen. Manufacturers who intended to market their products for use as a booster immunogen needed to submit supplements for changes to the container and package labels and the package insert, to include the statement, ''For Booster Use Only''.

Three of the five manufacturers submitted requests to voluntarily revoke their licenses. Accordingly, FDA revoked the licenses for: (1) Polyvalent Bacterial Vaccines with ''no U.S. Standard of Potency'' (Bacterial Vaccines Mixed Respiratory), Hollister-Stier Laboratories, U.S. license No. 1272, effective August 3, 2000 (66 FR 29148, May 29, 2001); (2) Diphtheria and Tetanus Toxoids Adsorbed and Tetanus Toxoids Adsorbed, BioPort Corporation, U.S. license No. 1260, effective November 20, 2000 (66 FR 29148, May 29, 2001); and (3) Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use), Wyeth Laboratories, Inc., U.S. license No. 3, effective May 30, 2002.

On January 18, 2002, we approved a license supplement for Aventis Pasteur, Inc.'s, Tetanus Toxoid fluid. In this supplement, Aventis Pasteur, Inc., requested that their license for Tetanus Toxoid fluid be amended to revoke the primary immunization indication and maintain the booster use only indication. In addition, the supplement included updated labeling for the

Tetanus Toxoid fluid product stating that the product was for ‘‘Booster Use Only’’, as specified in the proposed order.

Comments on Proposed Reclassification

Polyvalent Bacterial Antigens with ‘‘No U.S. Standard of Potency’’ [Staphage Lysate (SPL)], Delmont Laboratories, Inc., U.S. License No. 299

On August 9, 2000, Delmont submitted a written comment on the proposed order opposing the proposed Category II reclassification of its product. Delmont proposed, instead, reclassification into Category I and submitted information in support of its proposal, including an SPL clinical trial summary dated February 28, 1994, an English translation of a clinical study report for a study performed in the Czech Republic, and an abstract of a 1994 in vitro study performed by Delmont. We have carefully considered the information provided by Delmont, and find that it does not support a reclassification of SPL into Category I. A discussion of the studies included in Delmont’s submission follows.

The February 28, 1994, clinical trial summary contained data from two human clinical studies. The first study in the submission was a prospective, double blind, placebo controlled study of the efficacy of SPL for the treatment of Hidradenitis Suppurativa (HS). The clinical trial summary stated that, ‘‘under the conditions of the study, SPL was not demonstrated to be effective in the treatment of HS,’’ and that no significant differences between treatment groups (SPL, placebo) or between clinical centers ‘‘were found in any of the efficacy analyses for any of the parameters analyzed.’’ Delmont stated in its written comment on the proposed order that a data reanalysis provided by an independent third party engaged by Delmont demonstrated ‘‘approximately two times greater reductions from baseline in total score for SPL treated

patients than for placebo treated patients'' and that SPL showed a ''trend among the more severely affected patients for the change from baseline to last visit.'' However, the reanalysis of the data was performed after the patient data were unblinded. In addition, the method of efficacy assessment was changed from the initial blinded and controlled study, and a subset analysis of a selected subgroup of patients was performed in order to reach these conclusions. There was no statistically significant difference between the SPL and placebo treatment groups after the reanalysis was performed. The data are inadequate to support a reclassification of SPL from Category II to Category I.

The second study included in the 1994 clinical trial summary was an open label (unblinded) comparative study between SPL and 2 similar products, STAVA and POLYSTAFANA, not licensed in the United States. The study was performed in the Czech Republic and included patients with staphylococcal diseases of various types. An English translation of the study report was included in Delmont's submission. The study report contained several deficiencies, such as: No patient recruitment details with respect to the diagnoses of various staphylococcal infections, no detailed explanations of patient inclusion or exclusion criteria, no adequate control group, no description of patient randomization procedures (if performed), no explanation of how patients were reassigned to treatment groups after clinics refused to continue administering the POLYSTAFANA, no information on treatment compliance or individual dose regimens, no clinical descriptions or associated clinical measurements for the endpoints of ''cured,'' ''lasting stabilization,'' ''improved,'' or ''no effect,'' no statistical analysis performed (only observed cure rates were reported), and no reporting of individual adverse events. These

deficiencies are inconsistent with generally accepted standards of clinical trial design and performance. Therefore, this clinical study is also inadequate to support reclassification of SPL from Category II to Category I.

Delmont also included an abstract of an in vitro study performed in two human cell lines. The study authors found that human cell cultures secreted gamma interferon, interleukin 1, interleukin 2, and tumor necrosis factor when exposed to SPL. Delmont interprets the study to suggest that SPL ‘‘may stimulate the production of immunocompetent cells, triggering immune responses that might have clinical significance in certain diseases.’’ However, the data provided in the abstract are limited, and deficiencies in the data exist (e.g., lack of information on some positive and negative control results). While in vitro studies are frequently used to study the biological mechanisms of a product, they are not supportive of human efficacy in the absence of adequate and well-controlled clinical trials. Therefore, the limited data contained in Delmont’s abstract are not adequate to support a reclassification of SPL from Category II to Category I.

Delmont submitted no other data or information to support a reclassification of SPL to Category I or to preclude FDA’s reclassification of this product to Category II.

Notice of Opportunity for Hearing

In accordance with 21 CFR 601.5(b) and 21 CFR 12.21(b), FDA is offering an opportunity for hearing on its proposal to revoke the biologics license, U.S. License No. 299, issued to Delmont Laboratories, Inc., for Polyvalent Bacterial Antigens with ‘‘no U.S. Standard of Potency’’ (Staphage Lysate). A copy of the August 9, 2000, written comment is on file with the Dockets Management Branch (see **ADDRESSES**) under the docket number found in brackets in the

heading of this notice. The document is available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. Delmont may submit a written or electronic request for a hearing to the Dockets Management Branch by [*insert date 30 days after date of publication in the* **Federal Register**], and any data and information justifying a hearing must be submitted by [*insert date 60 days after date of publication in the* **Federal Register**] (21 CFR 12.22(b)(1)). Other interested persons may submit comments on the proposed revocation by [*insert date 60 days after date of publication in the* **Federal Register**].

FDA procedures and requirements governing a notice of opportunity for a hearing, notice of appearance and request for hearing, grant or denial of hearing, and submission of data and information to justify a hearing on a proposed revocation of a license are contained in part 12 (21 CFR part 12) and 21 CFR part 601. In requesting a hearing, a person must submit to FDA's Dockets Management Branch objections and a request for a hearing on each objection, along with a detailed description and analysis of the factual information to be presented in support of each objection, as provided in § 12.22. A deficient request or objection will be returned; however, the deficient submission may be supplemented and subsequently filed if submitted within the 30-day time period (§ 12.22(c)). The objections should identify the specific fact or facts that are genuine, substantial, and in dispute (§ 12.24(b)(1)). Mere allegations or denials are not enough to obtain a hearing (§ 12.24(b)(2)). The Commissioner of Food and Drugs (the Commissioner) will deny the hearing request if the Commissioner concludes that the data and information submitted are insufficient to justify the factual determination urged, even if accurate (§ 12.24(b)(3)).

Two copies of any submissions are to be provided to FDA except that individuals may submit one copy. Submissions are to be identified with the docket number found in brackets in the heading of this document. Submissions, except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be examined in the Dockets Management Branch (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under section 351 of the Public Health Service Act (42 U.S.C. 262) and sections 201, 501, 502, 505, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 355, and 371), and under authority delegated to the Commissioner (21 CFR 5.10) and redelegated to the Director, Center for Biologics Evaluation and Research (21 CFR 5.202).

Dated: February 4, 2003.

Mark Elengold,

Deputy Director for Operations, Center for Biologics Evaluation and Research.

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