April 28, 2003

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Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Delmont Laboratories, Inc.: Opportunity for Hearing on a Proposal To Revoke U.S. License No. 299 (Docket No. 00N-1219)

Dear Sir/Madam:

On February 26, 2003, FDA issued a notice of opportunity for hearing (NOOH) on the proposed revocation of License No. 299 in the above-referenced proceeding. *See* 68 Fed. Reg. 8908 (February 26, 2003). On March 27, 2003, Delmont Laboratories, Inc. (Delmont) submitted a written notice of participation and request for hearing in response to that notice. Delmont manufactures Staphage Lysate (SPL) (staphylococcus phage lysate) under License No. 299, although the product has not been marketed for human use since 1994.

In further response to FDA's NOOH, Delmont submits this letter in support of its request for hearing in accordance with 21 C.F.R. §§ 12.22(a) and 601.7(a). Delmont objects to the proposed revocation of License No. 299 and is entitled to a hearing on the agency's proposed action. This submission is accompanied by factual information in support of Delmont's objection.

Although Delmont is responding to FDA's February 26 NOOH, the company also disputes the validity of the NOOH on the following three grounds.

First, by issuing the NOOH based on a proposed (rather than a final) reclassification order, FDA has failed to adhere to its own regulatory requirements. Under the regulations governing the reclassification of biologics, issuance of a final reclassification order was required

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prior to the NOOH. A final reclassification order would have been subject to judicial review, as FDA's own regulations recognize. As a result of FDA's failure to issue a final order, Delmont has lost the opportunity to seek judicial review of FDA's reclassification decision.

Second, the February 26 NOOH does not address, indeed does not mention, FDA's acknowledgment in 1978 -- based on materials submitted by Delmont under the biologics review process -- that Delmont had demonstrated it was entitled to a hearing on the efficacy of SPL. While the NOOH contains no mention of FDA's 1978 commitment or of the studies that commitment was based on, the agency's determination has never been rescinded and its commitment is still valid. Delmont is therefore resubmitting the materials provided to FDA in 1978 in support of its request for hearing.

Third, while the February 26 notice critiques data previously submitted by Delmont as if the "adequate and well-controlled study" requirement of 21 C.F.R. § 314.200(d) were applicable to SPL, the agency's own statements acknowledge that biological drugs are not subject to that requirement -- and that SPL in particular should be accorded more flexibility in satisfying FDA standards for efficacy.

I. FDA Failed to Follow Its Own Regulatory Requirements In Issuing the NOOH of February 26, 2003

The agency's February 26 notice states that "[i]n accordance with 21 C.F.R. § 601.5(b) and 21 C.F.R. § 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 SPL. *See* 68 Fed. Reg. 8908, 8909 (February 26, 2003) (emphasis added) (Tab B). The "proposal" referred to is the proposed order published on May 15, 2000, in which the agency proposed to "reclassify SPL into Category II." *See* 65 Fed. Reg. 31,003, 31,009 (May 15, 2000). The May 15 proposed order was issued pursuant to 21 C.F.R. § 601.26(d).

In issuing the February 26 NOOH before rendering any final decision on reclassification, FDA has failed to complete its own procedures for the reclassification of products previously assigned to Category IIIA -- procedures that govern FDA's current efforts to reclassify SPL. Specifically, the agency has failed to issue the final reclassification order contemplated by 21 C.F.R. § 601.26(e), which provides that "[a]fter reviewing the comments on the proposed order, [FDA] shall publish in the Federal Register a final order on the matters covered in the proposed order." As a result, Delmont has lost its opportunity to seek judicial review of the agency's reclassification. *See id.* § 601.26(g) ("[t]he final order(s) published pursuant to [§ 601.26(e)] constitute final agency action from which appeal lies to the courts"). In addition, FDA's failure to issue a final order is inconsistent with FDA regulation governing the revocation of biologics licenses generally. *See id.* § 601.5(b)(2).

A. The Final Order Requirement Under The Reclassification Procedures Is Well Established and Embodies Important Notice and Comment Principles

The requirement that a final reclassification order be issued before publication of an NOOH originated with the procedures FDA promulgated to govern the review of all biological products licensed before 1972. *See* 21 C.F.R. § 601.25 (originally promulgated at Subchapter F, § 273.245 (*see* 38 Fed. Reg. 4319 (February 13, 1973)). In the "biologics review," FDA undertook to classify all pre-1972 biologics into one of four categories: Category I (safe, effective, and not misbranded), Category II (unsafe, ineffective, or misbranded), Category IIIA (continued licensing, manufacturing, and marketing permitted pending further study), and Category IIIB (marketing discontinued pending further study). *See* 37 Fed. Reg. 16,679, 16,681 (August 18, 1972); 38 Fed. Reg. 4319, 4323 (February 13, 1973); *see also* 46 Fed. Reg. 4634 (January 16, 1981).

In rulemaking under the biologics review process, FDA bound itself to follow a notice and comment procedure whereby an advisory panel would review the product and report its recommendation to the agency. Having reviewed that recommendation, FDA would first issue a proposed order stating the category for reclassification, and then -- after reviewing comments received from the public on the proposed order -- publish a final order formally reclassifying the product and providing an effective date for the agency's action. *See* 37 Fed. Reg. 16,679, 16,682 (August 18, 1972) (proposed rule); 38 Fed. Reg. 4319, 4323 (February 13, 1973) (final rule). This notice and comment procedure, culminating in a final order, was adopted out of concern that products of potential benefit to patients not be summarily removed from the market with insufficient notice or justification. As the agency stated in promulgating the biologics review procedures, "[l]icenses for [products subject to the biologics review] will not be revoked until such time as [FDA] has published the final order establishing standards for the safety, effectiveness, and labeling of the particular category of biological products . . . This approach has been adopted so as to ensure that no person currently receiving a licensed biological product in a medical context will be deprived of any of the possible benefits of the product until an expert advisory panel has made a thorough evaluation of all available safety and effectiveness data concerning the product." *See* 38 Fed. Reg. at 4320. Under the biologics review procedures, the final order was designated a final agency action giving rise to a right of judicial review. *See id.* at 4323.

In 1981, FDA determined to eliminate Category IIIA, and promulgated new procedures to reclassify the products formerly placed in that category. *See* 21 C.F.R. § 601.26. These reclassification procedures, which govern FDA's current efforts to reclassify SPL, were designed to be "analogous to the procedures established in § 601.25 for the 1972 biologics review." *See*

46 Fed. Reg. 4634, 4635 (January 16, 1981) (proposing § 601.26). In particular, "[t]he procedure for [FDA's] consideration of panel recommendations and the issuance of proposed and final orders would be the same as the procedures currently followed as part of the biologics review" -- that is, a final reclassification order would have to be issued prior to the initiation of license revocation proceedings. *See id.* (*citing* § 601.25(f) and (g)). Again, final reclassification orders under 21 C.F.R. § 601.26(e) were designated final agency actions from which appeal could be taken in court. *See* 47 Fed. Reg. 44,062, 44,073-73 (October 5, 1982).

B. The Final Order Requirement At 21 C.F.R. § 601.26(e) Cannot Be Consolidated With Other Procedural Steps In Delmont's Case

The importance of the final order requirement at § 601.26(e) of the reclassification procedures is illustrated by FDA's treatment, in the implementation of those procedures, of products that had not yet been the subject of a final order formally classifying them in Category IIIA. Such products included those that, at the time of the reclassification rulemaking, were subject only to an advisory committee recommendation for classification in Category IIIA, or for which FDA had proposed Category IIIA classification and invited public comment but had not yet issued a final order under the biologics review procedures.

In proposing the reclassification procedures, FDA announced its intention to "reclassify all Category IIIA products upon issuance of [the reclassification procedures], even if those products are not the subject of final orders." *See* 46 Fed. Reg. 4634, 4638 (January 16, 1981). In order to effectuate this purpose, FDA specifically provided that all Category IIIA products, whether classified by "advisory review panel reports, proposed orders, or final orders," would be "immediately submitted to the advisory review panels responsible for reclassification of Category IIIA biological products." *Id.* Under this system, reclassification prior to the issuance of a final order under 21 C.F.R. § 601.25(g) would be justified because the reclassification

process had its own "notice and comment procedures," which would ensure that "the public will have an adequate opportunity to comment upon the reclassification of those biological products that have not been subject to notice and comment procedures under the existing biologics review procedures." *See id.*

After publishing its proposed rule on the reclassification procedures, FDA received a comment asserting that each Category IIIA biologic should be reclassified "only after it is definitively placed in Category IIIA as a result of a final rule issued under § 601.25(g)." *See* 47 Fed. Reg. 44,062, 44,067 (October 5, 1982) (comment 17). Again, FDA's response to this comment highlights the importance of the final order requirement contained in § 601.26(e) of the reclassification procedures. FDA stated that information concerning each product recommended for Category IIIA would be forwarded to the appropriate advisory panel for reclassification, and that during the reclassification process all interested persons "will be offered the same opportunity for participation in the decisionmaking process as would be offered by the existing [biologics review] procedures under § 601.25." 47 Fed. Reg. at *id.*

Specifically, in addition to the opportunity for interested parties to appear before the advisory panels, "notice will be provided through publication of the advisory review panel's report and FDA's responding proposed rule; and opportunity for comment and submission of additional information will be offered by the proposed rule; *the final rule will provide notice of the agency's decision; and finally, for those products reclassified into Category II, a notice of opportunity for hearing will be published on the agency's intent to revoke the product license.*" *Id.* (emphasis added). As FDA's response clearly indicates, therefore, the final order required by § 601.25(g) could be waived for certain of these Category IIIA products only because those products were passing directly into a reclassification process in which full notice and comment

would be provided, including a final order issued under § 601.26(e) prior to the publication of an NOOH.

In a second and more recent scenario under the reclassification regulations, where FDA has proposed to reclassify a Category IIIA product into Category II and the manufacturer has not objected to that proposal, the issuance of a final order could be superfluous. FDA anticipated this possibility when it issued its May 2000 proposed order accepting the advisory panel recommendations on Category IIIA products, stating in the preamble that "[a]fter reviewing the comments on the proposed order, FDA will issue a final order on the matters covered in the proposed order," but that "[d]epending upon whether a manufacturer requests a hearing on the revocation of its biologics license, FDA may consolidate the final order with license revocations." *See* 65 Fed. Reg. 31,003, 31,005 (May 15, 2000). FDA took this consolidated approach with several products that advisory panels had recommended for reclassification into Category II -- a recommendation adopted by FDA in the May 2000 proposed order -- and whose manufacturers responded to the proposed order by voluntarily requesting revocation of the product licenses. *See* 66 Fed. Reg. 29,148, 29,149 (May 29, 2001) (discussing manufacturers' requests that licenses be revoked for Polyvalent Bacterial Vaccines With "No U.S. Standard of Potency" (Hollister-Stier Laboratories, LLC) and Diphtheria & Tetanus Toxoids Adsorbed and Tetanus Toxoid Adsorbed (BioPort Corp.)). In announcing the revocation of these licenses in 2001, the agency noted that while the proposed order of May 15, 2000 had announced that FDA "would publish a notice of opportunity for hearing on the revocation of the license of each product classified in Category II," these two manufacturers "waived their opportunity for a hearing when they voluntarily requested license revocation for their reclassified Category II products" based on FDA's proposed order. *See* 66 Fed. Reg. 29,148, 29,149. Because of the

manufacturers' voluntary request for revocation, the need for further notice and comment was eliminated and the final order could be consolidated with the actual revocation of the license. *Id.*

In the two situations above, the requirement for a final reclassification order -- while applicable under FDA regulation -- could arguably be waived or consolidated with other agency action without violating the principles of public participation and judicial review that underpin FDA procedures. In Delmont's case, by contrast, there is no justification for FDA's failure to complete the process of formally reclassifying Delmont's product into Category II before proceeding to initiate license revocation. In failing to issue a final order on the SPL reclassification as required by 21 C.F.R. § 601.26(e), FDA has simply failed to follow its own requirements for the reclassification of Category IIIA products, and as a result Delmont -- which consistently opposed the revocation of SPL's license -- has lost its opportunity to challenge the agency's action in court. FDA has also ignored the more general regulatory provisions requiring notice from the agency prior to revocation of a biologics license. *See id.* § 601.5(b)(2). Under those provisions, unless the case involves license suspension or "willfulness" on the part of the license holder, FDA is required to "provide a reasonable period for the licensed manufacturer to demonstrate or achieve compliance" with licensing requirements, "before proceedings will be instituted for the revocation of the license." *Id.*

Having adopted the regulatory requirements contained in 21 C.F.R. Part 601, FDA is bound by them. As the U.S. Supreme Court has recognized, an agency is bound by the regulations it issues, which have "the force of law." United States v. Nixon, 418 U.S. 683, 696 (1974) (*citing* United States *ex rel.* Accardi v. Shaughnessy, 347 U.S. 260, 268 (1954); Service v. Dulles, 354 U.S. 363, 388 (1957)); *see also* 1 Richard J. Pierce, Jr., *Administrative Law Treatise* § 6.1 (4th ed. 2002) ("A legislative rule is . . . binding on the agency that issues it.").

II. As FDA Has Recognized, Delmont Has Already Demonstrated Its Entitlement to a Hearing

A. FDA Acknowledged In 1978 That Delmont Merited a Hearing Based On Materials Submitted At That Time

Under the biologics review process, SPL was initially recommended by an advisory panel for classification into Category IIIB. FDA ultimately classified the product in Category IIIA after Delmont made substantial submissions on the safety and efficacy of the product. In arriving at that final classification, FDA acknowledged that Delmont had shown it was entitled to a hearing based on the materials submitted to the agency at that time. Since 1978, FDA has not rescinded or qualified this conclusion or provided any reasons why the agency's 1978 commitment should not still be valid. Therefore, Delmont is resubmitting its 1978 materials (discussed in more detail below), which the agency has already concluded entitle Delmont to a hearing.[1]

The previous section discussed FDA's failure to issue a final order prior to the issuance of its February 26, 2003 NOOH on the SPL license. In FDA's earlier review of SPL under the biologics review process, the agency likewise attempted to finalize the initial Category IIIB recommendation without first issuing a final order as required by 21 C.F.R. § 601.25(g). Since 1978, FDA has offered no explanation of its authority to ignore that final order requirement, in apparent violation of applicable FDA regulations.

1. FDA's Treatment of SPL And The Materials Submitted By Delmont Under The Biologics Review Process

In 1977, the advisory panel that had been convened as part of the biologics review process to consider Bacterial Vaccines and Bacterial Antigens With "No U.S. Standard of

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[1] A table of attachments is provided at Tab A.

Potency" completed its review and submitted a report to FDA. *See* 42 Fed. Reg. 58,266, 58,269 (November 8, 1977). The panel recommended that a series of products, including SPL, be classified in Category IIIB, and on November 8, 1977 FDA issued a proposed order pursuant to 21 C.F.R. § 601.25(f) reflecting the agency's acceptance of that recommendation. *See* 42 Fed. Reg. at 58,285, 58,318. Shortly thereafter, on December 9, 1977, FDA issued an NOOH on its proposal to revoke these licenses that had been recommended for classification in Category IIIB, soliciting any interested licensee to submit a written request for hearing under 21 C.F.R. § 12.21(b). *See* 42 Fed. Reg. 62,162-163 (December 9, 1977).

On January 8, 1978, Delmont submitted comments in response to the proposed order, requesting classification under Category IIIA, and attaching substantial new data in support of classification into Category IIIA. *See* Delmont Comments of January 8, 1978 (Docket No. 77N-0091) ("Delmont January 1978 Comments") (Tab C). Specifically, Delmont submitted "[a]cute, subacute, and chronic toxicity studies of SPL in rats conducted by the Fujizoki Pharmaceutical Co., Ltd., of Japan"; a teratogenicity study of SPL in rats, also conducted by the Fujizoki Pharmaceutical Co.; "[n]ew evidence of the effectiveness and mode of action of SPL, contained in a report from Dr. Kenji Takeya, Professor of Bacteriology and President of Kyushu University in Fukuoka, Japan"; and "[a] series of reports sent to Delmont by Fujizoki Pharmaceutical Co. on December 28, 1977, dealing with specifications for SPL and assessment of its effectiveness as an immunopotentiator." *See id.* at 2.

Following submission of these comments, Delmont sought a meeting with the Bureau of Biologics to discuss the new studies submitted in support of classification in Category IIIA. *See* Letter From Richard F. Kingham, Covington & Burling to John J. Singleton, FDA Bureau of Biologics (January 24, 1998), at 1. This meeting took place on February 2, 1978. At the

meeting, Delmont also raised a "procedural issue [that is] at least irregular, and perhaps even a violation of FDA regulations," namely "for the notice of hearing to have issued prior to the completion of a rulemaking procedure" in the form of a final order as required by 21 C.F.R. § 601.25(g). *See* Transcript of Meeting Re: Comments on Report of the Panel on Bacterial Vaccines and Antigens With "No U.S. Standard of Potency" (February 2, 1978), at 3. FDA representatives present at the meeting did not address this procedural irregularity, and did not explain whether the issues raised by Delmont's January comments and submission would be resolved before the agency proceeded with the NOOH process.

The following week, therefore, on February 7, 1978, Delmont responded to FDA's NOOH of December 9, 1977 by filing a written request for hearing. *See* Delmont Submission of February 7, 1978 (Docket No. 77N-0091) ("Delmont February 1978 Submission") (Tab D). Delmont's submission included data, information and analysis to support its request for hearing. These materials included not only extensive additional preclinical and clinical safety data, but also several new studies presenting data on effectiveness. *See* Delmont February 1978 Submission (*attaching* George G. Salmon, Jr., M.D. and Margaret Symonds, M.B., B.S., *Staphage Lysate Therapy in Chronic Staphylococcal Infections*, The Journal of The Medical Society of New Jersey, Vol. 60, 180-193 (May 1963); Azuma, C. et al., *Immunopotentiator Activity of Staphage Lysate*, 25th General Assembly of the Japanese Society of Chemotherapy (June 1977); Tsuda et al., *Immunotherapy for Infections -- With Particular Reference to Staphage Lysate*, Dep't of Dermatology, Kurume University School of Medicine, Kurume, Japan; Dale C. Rank, M.D., F.A.C.S., *Immune Stimulation Therapy for Inflammatory Disease of the Gut* (December 1977)).

Delmont's written request for a hearing also reiterated the important procedural issue raised and unresolved at the February 2 meeting: while the agency had issued a proposed classification order on November 8, 1977 under 21 C.F.R. § 601.25(f), the agency had issued no final order as required by § 601.25(g) prior to issuing the NOOH. *See* Delmont February 1978 Submission at 2. Delmont pointed out that it had submitted comments in response to the proposed order, requesting classification under Category IIIA, along with "substantial new data concerning the safety and effectiveness of the [Delmont] products that supported a favorable risk-benefit assessment for inclusion in Category IIIA." *Id.* In addition to failing to comply with § 601.25(g), Delmont argued, FDA appeared to be in violation of § 601.5(b)(2), which provided that absent certain narrowly defined circumstances, FDA must allow "a reasonable period for the licensed manufacturer to demonstrate or achieve compliance" with the biologics licensing requirements before issuing an NOOH. *See id.* at 2-4.

On March 31, 1978, Delmont supplemented its January 8 comments by submitting to FDA further information on the Fujizoki animal studies, which had been requested by FDA representatives at the February 2 meeting. *See* Letter From Charles E. Lincoln, President, Delmont Laboratories to Jennie C. Peterson, Hearing Clerk, FDA (March 31, 1978), at 1 (Tab E). In addition, Delmont attached further safety and efficacy data that had been unavailable when the January 8 comments were filed. *Id.* at 2. On May 26, 1978 Delmont submitted additional clinical safety and effectiveness data to FDA in support of "Delmont's position, set out in its January 8 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." *See* Letter From Charles E. Lincoln, President, Delmont Laboratories to Jennie C. Peterson, Hearing Clerk, FDA (May 26, 1978), at 2 (Tab F).

On October 27, 1978, FDA published a notice acknowledging that Delmont had "requested a hearing" and "submitted data and information" in support of SPL's classification in Category IIIA. *See* 43 Fed. Reg. 50,247, 50,248 (October 27, 1978) (Tab G). The agency concluded that "these data would not only justify a hearing but are adequate to justify reclassification at this time." *Id.* Finding that "the potential benefits outweigh the potential risk in use of the product," FDA reclassified SPL from Category IIIB to Category IIIA. The agency further noted that "[b]ecause no hearing is necessary for a Category IIIA product, the December notice [of opportunity for hearing] is withdrawn for the [SPL] product." *See id.*

2. There Is No Basis To Conclude That The Hearing Merited By Delmont In 1978 Is Not Still Merited Now

The standard FDA applies to requests for hearing under 21 C.F.R. Part 12 was the same in 1978 as it is today. The principal requirements are that the person requesting a hearing must demonstrate "a genuine and substantial issue of fact"; the factual issue must be subject to resolution "by available and specifically identified reliable evidence"; the data submitted, if established at a hearing, must be "adequate to justify resolution of the factual issue in the way sought by the person"; and the factual issue must be determinative with respect to the action requested. *See* 21 C.F.R. § 12.24(b); 21 C.F.R. § 12.24(b) (revision of April 1, 1978). FDA determined under this standard in 1978 that Delmont merited a hearing on the efficacy of SPL, and that commitment should still be valid. The hearing would still be addressed to the same issue -- the continued licensure of SPL.

FDA has never advanced any reason why its 1978 determination that Delmont merited a hearing should be discounted. In fact, FDA has never since mentioned its 1978 commitment, or commented on the materials submitted by Delmont under the biologics review process. *See* 65 Fed. Reg. 31,003, 31,009 (May 15, 2000) (citing information submitted by Delmont in 1978 that

"result[ed] in reclassification of SPL from Category IIIB to Category IIIA," but discussing only "additional information" submitted by Delmont "[f]ollowing this reclassification").

Delmont has raised this point previously with FDA, in its August 2000 comments on FDA's proposal to reclassify SPL into Category II. *See* Delmont Comments of August 9, 2000 (Docket No. 00N-1219) ("Delmont August 2000 Comments"), at 4-5 ("Significantly, in its [October 27, 1978] notice reclassifying SPL, FDA acknowledged that the aggregate scientific evidence submitted by Delmont presented a genuine and substantial issue of material fact with respect to the effectiveness of SPL, a finding that under the law would have entitled Delmont to a formal evidentiary hearing."). FDA, however, has never responded, including in its May 2000 proposed order or in the current NOOH. Because the agency's 1978 acknowledgment that Delmont merited a hearing on efficacy is still valid,[2] Delmont is resubmitting its 1978 materials with the present submission.

In the October 1978 notice, FDA's failure to issue a final order on its proposal to classify SPL in Category IIIB -- as required by the agency's own regulations -- was mooted by FDA's

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[2] This is particularly the case because FDA's effectiveness standard for biological drugs (and SPL in particular) has become, if anything, more flexible since FDA first acknowledged Delmont merited a hearing in 1978. At that time, the effectiveness standard for pre-1972 biological products was defined as a "reasonable expectation" that "the pharmacological or other effect of the biological product . . . will serve a clinically significant function in the diagnosis, cure, mitigation, treatment, or prevention of disease in man." *See* 38 Fed. Reg. 4319, 4322 (February 13, 1973) (promulgating Subchapter F, Part 273.245(d) (subsequently recodified at 21 C.F.R. § 601.25(d)(2)). In 1981, FDA acknowledged that certain biological products "cannot be feasibly tested in an adequate and well-controlled study," and indicated that decisions regarding the standard of effectiveness for specific products would be made "in the course of the reclassification process." *See* 46 Fed. Reg. 4634, 4638 (January 16, 1981). One year later, FDA further acknowledged that well-controlled clinical trials would be difficult to conduct for SPL in particular, and that therefore "[t]he standard of effectiveness of SPL will be consistent with the current state-of-the-art for biologics testing. Thus, the difficulty of selecting the appropriate population for demonstrating SPL's effectiveness will be taken into account in reclassifying it." *See* 47 Fed. Reg. 44,062, 44,064 (October 5, 1982).

subsequent decision to classify the product in Category IIIA. It is worth noting, however, that FDA has never explained how it could legally issue an NOOH directly following a proposal to revoke a license, without completing the intervening requirement for a final classification order under 21 C.F.R. § 601.25(g). Delmont asserts that this action violated FDA's biologics review procedures, just as the agency's failure to issue a final order in the current revocation proceeding is a violation of the rules governing reclassification.

B. The "Adequate and Well-Controlled Study" Requirement of 21 C.F.R. § 314.200(d) Is Not Applicable to Delmont's Response to the Current NOOH

FDA's elimination of Category IIIA from the biologics review process, and the promulgation of regulations to govern the reclassification of Category IIIA products, were largely precipitated by a citizen's petition filed by the Public Citizen Health Research Group (HRG). *See* 46 Fed. Reg. 4634, 4635 (January 16, 1981). In addition to seeking the elimination of Category IIIA, HRG also contended that "biological products are subject to the new drug provisions of the [Federal Food, Drug, and Cosmetic Act (FDCA)] and that the standard for determining their effectiveness was that prescribed for new drugs, namely, 'substantial evidence' consisting of 'adequate and well-controlled clinical investigations.'" *See id.* (*quoting* 21 U.S.C. § 355(e)).

FDA rejected this contention. In its January 1981 proposal to eliminate Category IIIA from the biologics review process, the agency stated: "FDA regulations make clear that biological products have never been subject to the new drug provisions of the [FDCA]." *See* 46 Fed. Reg. 4634 at *id.*[3] In support of this position, FDA specifically cited 21 C.F.R. § 310.4,

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[3] The agency further clarified that "'[w]hile it is clear that as drugs biological products are misbranded if they are not effective for their labeled uses, and that the applicable statutory requirement for potency in the Public Health Service Act has been interpreted as requiring that a (continued...)

which at that time provided that "[e]xcept for radioactive biological products intended for human use, a new drug shall not be deemed to be subject to section 505 of the [FDCA] if it is a drug licensed under the Public Health Service Act . . . or under the animal virus, serum, and toxin law." *See* 21 C.F.R. § 310.4(a) (revision of April 1, 1980). Radioactive biologicals as a group were at that time subject to Section 505 of the FDCA. *See id.* § 310.4(b).[4]

FDA's 1981 statement that the FDCA's new drug provisions are inapplicable to biologics has never been withdrawn, and remains consistent with the regulations cited in FDA's current NOOH to govern Delmont's request for hearing. Specifically, the NOOH of February 26, 2003 indicates that the request for hearing is governed by "part 12 (21 C.F.R. part 12) and 21 C.F.R. part 601." 68 Fed. Reg. 8908, 8909. Part 12 contains generally applicable requirements for formal hearings. The relevant provision in Part 601 is Section 601.7(a), which was issued as a "conforming change" to accompany what is now Subpart B of 21 C.F.R. Part 12 (originally codified at Subpart B of 21 C.F.R. Part 2). *See* 40 Fed. Reg. 40,682, 40,716 (September 3, 1975). Section 601.7(a) provides:

> A notice of opportunity for hearing, notice of appearance and request for hearing, and grant or denial of hearing for a biological drug pursuant to [21 C.F.R. Part 601], for which the exemption from the [FDCA] in § 310.4 of this chapter has been revoked, shall be subject to the provisions of § 314.200 of this chapter except to the extent that the notice of opportunity for hearing on the matter issued pursuant to § 12.21(b) of this chapter specifically provides otherwise.

21 C.F.R. § 601.7(a).

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product be effective, the specific statutory criteria governing new drugs, "adequate and well-controlled studies," have not been applied to biological drugs.'" *See* 46 Fed. Reg. at 4635 (*quoting* Letter From FDA Commissioner to HRG (September 18, 1980)).

[4] Section 310.4 has since been amended. While licensed biologicals generally remain exempt from Section 505 of the FDCA, the approval requirements for radioactive biologicals vary depending on the nature of the product, and are governed by 21 C.F.R. § 601.2(b). *See* 21 C.F.R. § 310.4(a), (b); 64 Fed. Reg. 56,411 (October 20, 1999).

The plain language of Section 601.7(a) indicates that Section 314.200 -- which sets forth the requirements for requests for hearing on new drugs, including the submission of adequate and well-controlled studies, *see* 21 C.F.R. § 314.200(d) -- applies to biologics only where the "exemption" from FDCA requirements contained in 21 C.F.R. § 310.4 "has been revoked." In 1981, FDA cited Section 310.4 for the proposition that biological products "have never been subject to the new drug provisions of the [FDCA]." *See* 46 Fed. Reg. 4634, 4635.

Taken together, therefore, FDA's 1981 interpretation of Section 310.4 and the plain language of Section 601.7(a) -- which was the same in 1981 as it is today[5] -- indicate that Section 314.200 is not applicable to biological products as a class, but only to those biological products for which the exemption from the FDCA has been "revoked" by FDA.[6] Because the FDCA exemption has not been "revoked" for SPL, Delmont submits that the requirements of Section 314.200(d) are not applicable to its request for hearing. Rather, as FDA indicated in proposing amendments to Part 601 to conform to its proposed agency-wide hearing requirements, "[h]earings on denial, revocation, or suspension of a biologics license would be governed by [21

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[5] The text of Section 601.7(a) has not changed since it was promulgated in 1977, except that the reference to the section on hearing procedures -- "§ 12.21(b) of this chapter" -- originally referred to 21 C.F.R. § 2.111(b), where the hearing procedures were then codified. *See* 21 C.F.R. § 601.7(a); 42 Fed. Reg. 4680, 4718 (January 25, 1977).

[6] As previously discussed, various classes of radioactive biologicals have at different times been made subject to Section 505 of the FDCA. Thus in 1981, the exemption from FDCA requirements at Section 310.4 was "revoked" for all radioactive biological products. Currently, the exemption is "revoked" for most radioactive biologicals, but not for "radioactive coupled antibodies," provided there are no "significant scientific issues associated with the radionuclide or other chemically synthesized component." *Compare* 21 C.F.R. 310.4(b) (revision of April 1, 1980) *with* 21 C.F.R. §§ 310.4(b), 601.2(b).

C.F.R.] Part 2 [now Part 12]." *See* 40 Fed. Reg. 40,682, 40,716 (September 3, 1975).[7] Specifically, the relevant provision governing the content of Delmont's submission is 21 C.F.R. § 12.22(a).

Notwithstanding all of the above, the February 26 NOOH appears to apply the "adequate and well-controlled study" standard to clinical data previously submitted by Delmont. *See* 68 Fed. Reg. 8908, 8909. This is inconsistent with FDA's 1981 statement that the "adequate and well-controlled study" standard does not apply to biological drugs such as SPL. The discussion of SPL in the February 26 notice also fails to take account of subsequent FDA statements, made in 1982 at the time the reclassification procedures were issued, in which the agency acknowledged the difficulty of conducting controlled studies on the efficacy of SPL due to "the difficulty of selecting the appropriate population for demonstrating SPL's effectiveness." *See* 47 Fed. Reg. 44,062, 44,064 (October 5, 1982).[8] FDA further indicated that "the difficulty of selecting the appropriate population for demonstrating SPL's effectiveness will be taken into account in reclassifying it." *See id.*

III. Current Posture of Delmont's SPL Product

In response to FDA's concerns regarding the compliance of Delmont's production facility with current Good Manufacturing Practices (cGMPs), Delmont voluntarily halted

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[7] FDA received no comments on the proposed changes to Part 601, including the addition of Section 601.7(a), and these changes were promulgated in the same form in which they were proposed. *See* 42 Fed. Reg. 4680, 4696, 4718 (January 25, 1977).

[8] These statements were made in response to comments received on the proposed reclassification procedures, which asserted that "because of the small number of patients for whom SPL therapy is successfully undertaken," there is a special difficulty associated with "demonstrating the product's effectiveness through controlled clinical studies." *See* 47 Fed. Reg. 44,062, 44,064.

shipments of SPL for human use in 1994, and since that time has been working to address FDA's cGMP concerns.[9]

The company continues, however, to develop further evidence of SPL's efficacy. Delmont is currently engaged in launching several proposed studies, including a double-blind, placebo-controlled crossover study led by Dr. Ritchie Shoemaker of Pocomoke, Maryland. This study will investigate the use of SPL in 30 patients with chronic fatigue syndrome (CFS). Delmont is also assisting Professor Carl-Gerhard Gottfries of the University of Göteborg, Sweden, who is undertaking a pilot study involving 30 patients with CFS. Delmont expects these studies to be followed by a more extensive round of research conducted by Dr. Shoemaker, along with a 50-patient replacement study by Dr. Gottfries in which SPL will be compared to a European product known as Staphypan Berna. This product, a staphylococcus preparation similar to SPL, is being withdrawn from the market because it contains the mercury-based preservative thimerosol. Following completion of this replacement study, Dr. Gottfries has proposed to undertake a placebo-controlled study of SPL. Dr. Gottfries previously published the results of his controlled investigations using Staphypan Berna on CFS patients in the European Journal of Pain.

Delmont would welcome the opportunity to discuss the procedural posture of its hearing request with FDA in light of these proposed studies, and particularly in light of the fact that SPL is not currently being marketed for human use.

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[9] SPL is also licensed for veterinary use in an identical formulation, and continues to be marketed for that use.

Respectfully submitted,

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Attachments

Delmont Laboratories, Inc.:
Opportunity for Hearing on a Proposal to Revoke
U.S. License No. 299 (Docket No. 00N-1219)

April 28, 2003

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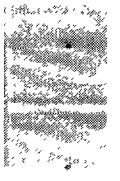

Tab A:

TABLE OF ATTACHMENTS