

DELMONT LABORATORIES, INC.
IMMUNOTHERAPEUTICS

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

COMMENTS OF DELMONT LABORATORIES, INC., ON FDA'S PROPOSAL TO RECLASSIFY STAPHAGE LYSATE® (SPL) INTO CATEGORY II (DOCKET NO. 00N-1219)

These comments are being submitted on behalf of Delmont Laboratories, Inc. (Delmont) in response to FDA's proposal to reclassify Staphage Lysate® (SPL) (staphylococcus phage lysate) from Category IIIA (permitted to remain on the market pending the completion of effectiveness studies) to Category II under FDA's Biologics Review. 65 Fed. Reg. 31,003 (May 15, 2000). As we explain below, FDA should assign SPL to Category I because, taking into account all the relevant evidence, the product meets FDA's standard of "effectiveness" for pre-1972 biological products.

I. Background

SPL is indicated for the treatment of staphylococcal infections and polymicrobial infections with a staphylococcal component, such as furunculosis, acne, hidradenitis suppurativa (HS), and other skin disorders, eye infections, and gastrointestinal disorders. SPL was first licensed to Delmont by the Division of

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Biologics Standards in 1950.¹ The product was on the market in 1971 when FDA assumed responsibility for administering the Biologics Act and it was, therefore, among the many products included in the Biologics Review.

Assessment of the evidence for effectiveness of SPL has thus been underway for nearly thirty years. As part of the Biologics Review in 1973 FDA convened the Advisory Panel on Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency" to evaluate the effectiveness of dozens of previously licensed biological products, including SPL.² The Advisory Panel held working meetings between February 1973 and January 1976.³ In 1977, the full text of the Advisory Panel's report was published in the Federal Register.⁴

The Advisory Panel's report summarized the available data for each biological product within its purview. With regard to SPL, the Advisory Panel determined that the five previously completed clinical studies of the product provided equivocal evidence of effectiveness. Specifically, although the Advisory Panel found that "some degree of effect may be inferred" from a four-year study of SPL aerosol therapy in chronic asthma, it determined that four other studies were inconclusive.⁵ The Panel did not find that SPL was ineffective. Nevertheless, the Panel felt obligated to

¹ 42 Fed. Reg. 58,266, 58,267 (Nov. 8, 1977).

² Id.

³ Id. at 58,266.

⁴ Id.

⁵ Id. at 58,282-83.

recommend that SPL be assigned to Class IIIB (withdrawn from the market pending additional testing) and that its license be revoked.⁶

The Advisory Panel's report discussed the difficulties of evaluating the safety and effectiveness of many biological products. The Panel explained that under its reading of FDA's regulations governing the Biologics Review, it could not recommend that a biological product be allowed to remain on the market without evidence of effectiveness from controlled clinical studies, even though such studies were not practicable. The report stated that the Panel could not recommend that FDA "waive[]" the "standards for . . . effectiveness . . . specified in the regulations governing the review procedures under which its report was prepared (21 CFR 601.25(d)(1) through (5)),⁷ notwithstanding plausible arguments that controlled clinical trials were "not feasible because of lack of funding, lack of interest, or difficulty in obtaining a sufficient number of patients."⁷

In the same Federal Register document containing the Panel's report, FDA published an omnibus proposal to accept all of the Advisory Panel's Category IIIB recommendations.⁸ The document stated "[t]he Commissioner agrees with the Panel's findings and recommendations concerning these drugs and . . . intends to publish a notice of an opportunity for hearing to revoke the licenses for these products"⁹

⁶ Id. at 58,285, 58,317. The recommendation was also based on considerations unrelated to effectiveness. Id. at 58,282, 58,285.

⁷ Id. at 58,271.

⁸ Id. at 58,318.

⁹ Id.

However, it did not set forth any independent agency assessment of the studies relating to the effectiveness of SPL or any other product that the Panel recommended for Category IIIB.

As it had promised, on December 9, 1977, FDA published a global notice of opportunity for a hearing (NOOH), thereby initiating proceedings to revoke the licenses of all products that the Panel had placed in Category IIIB (as well as products it had assigned to Category II), including Delmont's license to manufacture SPL.¹⁰

In response to this NOOH, Delmont cited the evidence submitted to the Panel and submitted additional data supporting the effectiveness of SPL on February 7, 1978. Delmont's submission included the protocol for a controlled clinical trial of SPL and data from completed clinical and in vitro studies. Following its review of Delmont's submission and its own review of the evidence previously considered by the Panel, FDA on October 27, 1978 announced that the evidence now available justified the reassignment of SPL to Category IIIA.¹¹ This decision allowed SPL to remain on the market pending additional clinical study.

Significantly, in its 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.¹² With its

¹⁰ 42 Fed. Reg. 62,162, 62,162 (Dec. 9, 1977).

¹¹ 43 Fed. Reg. 50,247, 50,248 (Oct. 27, 1978) (Tab A).

¹² Id. (Tab A).

decision to reclassify the product, however, FDA recognized that a hearing was no longer necessary and withdrew its earlier proposal to revoke Delmont's license. On January 5, 1979, FDA published final regulations embodying the Category IIIA designation for SPL and stating that "the requirements concerning completion of testing and labeling apply to" all Category IIIA products, including SPL.¹³

Thus, the first time that FDA closely evaluated the evidence supporting the effectiveness of SPL, the agency determined that the product should be assigned to Category IIIA. Under FDA's own regulations, this represented a judgment that the product might well satisfy the effectiveness standard and that the benefits of its availability during the time required for continued study outweighed any possible adverse consequences.¹⁴

Delmont subsequently initiated additional clinical studies, as contemplated for products assigned to Category IIIA. These included a two-center, double-blind efficacy study in hidradenitis suppurativa (HS) and an active-control, open study on patients with staphylococcal diseases of various types in Czechoslovakia.¹⁵ The

¹³ 44 Fed. Reg. 1,544, 1,548 (Jan. 5, 1979). FDA requested that holders of licenses for Category IIIA products "submit, within 30 days following publication of this order, a written statement of those studies which the licensee proposes to undertake to resolve the questions raised about the products." Delmont submitted such a statement on February 5, 1979, and FDA acknowledged the submission by letter dated February 26, 1979.

¹⁴ Id.

¹⁵ Delmont also planned a double-blind, placebo-controlled, crossover study in furunculosis, but the study was discontinued in 1984 due to the inability to recruit a sufficient number of study subjects.

company also began an in-house laboratory study of SPL designed to elucidate the product's mechanism of action.

On January 16, 1981, FDA took steps to revise the ground rules for the Biologics Review by publishing proposed regulations establishing a procedure to reclassify biological products that it had assigned to Category IIIA.¹⁶ In the preamble to this proposal, FDA stated that it had previously published the Commissioner's final order on the report of the Panel on Review of Bacterial Vaccines and Bacterial Antigens with "No U.S. Standards of Potency."¹⁷ FDA further stated that the final order had assigned eight products to Category IIIA "because of questions about their effectiveness (not safety)."¹⁸ The agency also noted that "[t]he testing recommended by the panel is under way for those Category IIIA products being marketed."¹⁹

FDA issued its final procedural regulations for the reclassification review on October 5, 1982.²⁰ In the preamble, FDA stated that an existing advisory review panel or newly established advisory committee would reexamine the data relating to each Category IIIA product and then recommend, based on all the available evidence, assigning the product to either Category I or Category II.²¹ FDA emphasized that the

¹⁶ 46 Fed. Reg. 4,634 (Jan. 16, 1981).

¹⁷ Id.

¹⁸ Id.

¹⁹ Id.

²⁰ 47 Fed. Reg. 44,062 (Oct. 5, 1982).

²¹ Id. at 44,062.

safety of all Category IIIA products (including SPL) for their intended uses had already been established and thus would not be reexamined by any of the panels.²²

Shortly thereafter, FDA asked its Vaccines and Related Biological Products Advisory Committee (VRBPAC) to examine the evidence of effectiveness for the products that had previously been recommended for Category IIIA by the Advisory Panel on Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency" as part of the original Biologics Review. On December 9, 1982, Delmont took advantage of the agency's invitation and submitted additional evidence to the VRBPAC supporting the effectiveness of SPL. This included information relating to its recently initiated clinical studies.

The VRBPAC met to discuss SPL on September 19, 1983. At the meeting, Delmont representatives described in detail the clinical research program for SPL. They reported that studies had been undertaken, by Delmont and others, to assess the effectiveness of SPL in a variety of staphylococcal infections and diseases of unknown etiology with a staphylococcal component. The two most promising studies involved furunculosis and hidradenitis suppurativa (HS).²³

The furunculosis study was a 20-patient, double-blind crossover study of the effectiveness of SPL in preventing abscesses in patients with recurrent furunculosis.

²² Id. at 44,068.

²³ The Delmont representatives also described clinical studies in AIDS, multiple sclerosis, and Crohn's Disease, and a non-clinical study of the immunological and immune adjuvant properties of SPL, which Delmont was planning to conduct in house. Although SPL was indicated for the treatment of staphylococcal infections, for many years research had suggested the product might have clinical utility in immunocompromised patients.

One component of the study involved testing the cell-mediated immune response in each patient. The study was already underway at the University of Minnesota. Delmont advised the committee that the investigators projected that, because of the rarity of the disease and the need to identify patients whose disease was not responsive to antibiotics, it would take two years to enroll 20 patients.

The HS study was a double-blind, prospective study involving patients at Hershey Medical Center in Pennsylvania. This study, too, was already underway at the time of the VRBPAC meeting. The primary investigator described the protocol for the study at the meeting, noting that the progress of the study had been stalled by the refusal of many prospective subjects to enroll because SPL was licensed already and thus readily available outside the auspices of the trial.

The transcript of the September 19, 1983 meeting of the VRBPAC indicates that the committee members disagreed over the showing of effectiveness that Delmont should be required to make. One of the committee members, Dr. Kenneth McIntosh, asked

"whether the committee would be willing to accept the results of the study which we've seen designed today as adequate information to put the product in Category I, if they showed efficacy?

In other words, does a single study on each of two different diseases qualify a product for licensure?"²⁴

The chair of the committee, Dr. Theodore C. Eickhoff, responded:

"[J]udging by some of the decisions that the efficacy panel on Bacterial Vaccines and Toxoids made in the past, and

²⁴ Transcript of Meeting, Vaccines and Related Biological Products Advisory Committee Meeting, September 19, 1983, at 159.

reflecting just momentarily on what, indeed, we accepted as recently as last January, my guess would be that probably yes, we would."

The chair and another committee member then had the following exchange:

"Dr. OSBORN: Yes, you would accept a single, convincing study?"

Dr. EICKHOFF: Yes, we would accept a single, convincing study."

Because data from the ongoing studies were not available, the VRBPAC recommended (by a 5-2 vote) that SPL be reclassified from Category IIIA into Category II.²⁵

In light of this recommendation, the VRBPAC did not recommend specific further studies that Delmont should undertake to support SPL's effectiveness. Nevertheless, Delmont continued to collect evidence of the effectiveness of SPL. In 1984, Delmont extended the HS study to include a second center to address the concern expressed at the VRBPAC meeting relating to study size. In 1987, the HS study was completed. As we discuss below, the study results provided further support for the effectiveness of SPL.

Delmont also initiated new studies. In 1992, the company undertook a comparative trial of SPL. The company also conducted an in-house study to characterize the cytokines produced by human mononuclear cells in vitro in the presence of SPL.

²⁵ Some members of the VRBPAC expressed concern about the design of some of the studies. Many of their concerns reflected the inherent variability of the diseases in which SPL had been tested (MS, for example) and the difficulty in enrolling an adequate number and homogeneous group of study subjects. These were the same kinds of design concerns acknowledged by FDA and the original advisory review panel that recommended SPL for Category IIIB in 1977.

In June 1994, Delmont provided FDA with a summary of the data from the two completed clinical studies and the in-house laboratory research.²⁶ The summary was submitted in response to an October 12, 1993 letter to the company from the Center for Biologics and Research (Tab B). In addition to the written summary, Delmont representatives made an oral presentation to several FDA officials regarding the data already obtained on SPL and planned clinical research. This meeting occurred on June 28, 1994. To date, FDA has not provided any sort of detailed analysis of Delmont's 1994 submission. A copy of Delmont's June 1994 submission is attached hereto at Tab C.

Inexplicably, on May 15, 2000—nearly six years after Delmont's latest submission of data to FDA and 17 years after the VRBPAC arrived at its recommendation—FDA published the notice that is the subject of these comments, in which it proposes to assign SPL to Category II.²⁷ FDA's proposal relies exclusively on the 1983 recommendation of the VRBPAC, which obviously could not have considered—and accordingly the proposal does not mention—Delmont's 1994 submission.

These comments discuss the effectiveness data supporting the assignment of SPL to Category I. FDA itself must evaluate all of the data for SPL, rather than mechanistically relying on the 17-year-old VRBPAC recommendation. The VRBPAC recommendation was arrived at without consideration of data from studies

²⁶ A copy of the minutes and attendance list from the meeting at which Delmont provided the summary to FDA appears at Tab D.

²⁷ 65 Fed. Reg. 31,003 (May 15, 2000).

that were then underway but have since been completed. These studies have been augmented by data from yet additional studies. No advisory committee has examined all the available effectiveness information for SPL. Nor has the agency documented that it has considered all the data supporting SPL's effectiveness.

As we show below, evaluated according to the legal standard applicable to pre-1972 biological products, the evidence as a whole demonstrates that SPL is effective. FDA has already determined that there were sufficient data in the record as of 1978 to create a genuine issue of fact as to the effectiveness of SPL. This finding was reached before any of the clinical trials described in these comments were even begun. Further, FDA itself has reviewed the existing evidence supporting the effectiveness of SPL only once, and that review resulted in a determination (finalized in 1983) that the product was presumptively effective and should remain on the market. That finding predated the initiation of the clinical trials described in this document.

II. SPL Belongs In Category I

A. FDA's Effectiveness Standard For Pre-1972 Biological Products

Under Section 351 of the Public Health Service Act, a biological product must be safe, pure, and potent.²⁸ FDA regulations implementing Section 351 define "potency" to mean that "the specific ability or capacity . . . , as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result."²⁹ In

²⁸ 42 U.S.C. § 262.

²⁹ 21 C.F.R. § 600.3(s).

addition, a biologic must be "effective" for its labeled uses to avoid being misbranded under Section 502(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).³⁰

In contrast to new biologics, pre-1972 biologics had been marketed for significant periods, and enjoyed significant physician support, before they were examined by the advisory review panels under FDA's Biologics Review. The Category I or IIIA designation reflected this empirical clinical experience, as well as any additional data developed by the licensee to support an effectiveness finding in equivocal cases.

To account for such experience, FDA adopted an interpretation of the effectiveness requirement specifically for pre-1972 biological products. This standard is distinct from the standard of effectiveness imposed on new drugs under Section 505 of the FD&C Act. FDA issued regulations defining "effectiveness" for pre-1972 biological products to mean:

"a reasonable expectation that, in a significant proportion of the target population, the pharmacological or other effect of the biological product, when used under adequate directions for use and warnings against unsafe use, will serve a clinically significant function in the diagnosis, cure, mitigation, treatment, or prevention of disease in man."³¹

In 1981, FDA "reexamined this standard" and concluded that effectiveness for pre-1972 biological products must take account of the "special problems" presented by such

³⁰ 21 U.S.C. § 352(a).

³¹ 21 C.F.R. § 601.25(d)(2).

products.³² FDA has specifically recognized that "many biological products may not be readily amenable to controlled clinical trials."³³

Consequently, FDA has developed special procedures for evaluating the clinical effectiveness of allergenic extracts, whose effectiveness is difficult to determine because it may be masked by a subject's allergic reaction to another allergen, and because "it is not possible with existing technology to identify and quantitate all active ingredients."³⁴ Because of these difficulties, FDA stated in 1981 that it would accept "alternative methods . . . to substantiate effectiveness" of allergenic extracts and identified a number of potentially suitable alternative testing methods.³⁵ It expressly declined, however, to name other biological products that might not be amenable to well-controlled clinical trials, announcing that it would reach these decisions "in the course of the reclassification process."³⁶

In 1982, FDA explicitly recognized that SPL was one of the biological products for which well-controlled clinical trials would be difficult:

SPL will be reclassified with all other Category IIIA products. The 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

³² 46 Fed. Reg. at 4,637.

³³ 47 Fed. Reg. at 44,065.

³⁴ 46 Fed. Reg. at 4,637.

³⁵ Id. at 4,638.

³⁶ Id.

demonstrating SPL's effectiveness will be taken into account in reclassifying it.³⁷

Thus, under FDA's effectiveness standard for pre-1972 biologics, the effectiveness of SPL should be determined by examining all relevant scientific evidence, including evidence in addition to data from controlled clinical studies. SPL should be found effective if, given the state of the art for biologics testing, it has the specific ability or capacity to effect a given result—that is, to stimulate an immune response in individuals with staphylococcal infections or infections with a staphylococcal component.

B. SPL Meets FDA's Established Effectiveness Standard For Biologics

Since FDA or any advisory committee last considered the effectiveness of SPL, additional evidence has become available. This evidence is summarized below. In the aggregate, the evidence demonstrates that SPL is "effective" because it shows that SPL is superior to other agents in treating staphylococcal infection, and indicates that in hidradenitis suppurativa (HS), patients receiving SPL exhibited approximately two times greater reductions from baseline in total score relative to patients on placebo. Finally, a non-clinical study conducted by Delmont in-house showed that SPL may have important applications in treating immunocompromised patients.

1. Study in Staphylococcus Infections

From 1992 to 1993, Delmont sponsored an active-control, open study on patients with staphylococcal diseases of various types in the Czech Republic. The study was supervised by Dr. Frantisek Vymola, a well-known investigator with extensive experience in the research of staphylococcal disease. The study compared the

³⁷ 47 Fed. Reg. at 44,064.

effectiveness of SPL supplied by Delmont to two other staphylococcus vaccines in treating patients with various staphylococcal infections and who are resistant to other treatments or are chronically infected. The study was not placebo-controlled because use of placebo in such studies is ethically prohibited in the Czech Republic.

The study involved 130 patients diagnosed with skin infections, osteomyelitis, respiratory infection, or otitis. In the study, 68 were administered SPL, 47 patients were treated with one staphylococcus vaccine, and 15 received the second staphylococcus vaccine. The second vaccine was discontinued in most of the 15 patients due to excessive epidermal reactions following injection.

Although all three products were effective in treating staphylococcal infections, SPL exhibited the highest observed cure rates. The safety profile of SPL was also superior to the other agents used in the study. The results of this study were submitted to FDA in 1994 and are provided here at Tab E. This study alone has been accepted by the government of the Czech Republic to justify licensure of SPL for human use in that country.

2. Hidradenitis Suppurativa Study

From 1982 to 1987, Delmont sponsored a two-center, double-blind, placebo-controlled study of 41 patients with hidradenitis suppurativa (HS), a chronic suppurative skin disorder affecting the apocrine sweat gland bearing skin of the perianal, axillary, and genital areas and under the breasts. HS produces abscesses or sinuses with discharge that contains staphylococcus bacteria. Delmont presented the results of this study to FDA in its 1994 submission, which FDA has neither evaluated (to Delmont's knowledge) nor acknowledged.

As reported by the investigators, the results of this study did not provide definitive statistical evidence of the effectiveness of SPL in HS. However, an analysis of the data 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 . . ." The reanalysis also showed that while the observed treatment differences did not achieve statistical significance, there was a trend "among the more severely affected patients for the change from baseline to last visit." The results of this study, as reanalyzed for Delmont, were initially submitted to FDA in 1994 and are included in Tab C.

3. Characterizing Study

In 1994, Delmont completed an in-house non-clinical study to identify the cytokines produced when certain human cells were exposed to SPL in vitro. The researchers determined that different preparations of SPL stimulated the production of IFN-gamma, IL-1 beta, TNF-alpha, and IL-10 from human monocytic cell line (THP-1) and human mononuclear cells (HuMNC). The results of the study suggest that in vivo, SPL may stimulate the production of immunocompetent cells, triggering immune responses that might have clinical significance in certain diseases.

The results of this study were presented at the 12th European Immunology Meeting in Barcelona, Spain, in June 1994, and were included in Delmont's submission to FDA of the same month. They are also attached to this submission at Tab F.

III. Conclusion

The clinical effectiveness of SPL has been difficult to evaluate because of the inherent variability of the diseases in which it has clinical utility. Moreover, availability of licensed SPL has made clinical trial enrollment difficult. The comparative

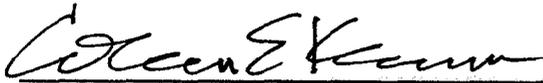
rarity of certain staphylococcal diseases has contributed to this difficulty. Thus, SPL is not easily studied in conventional clinical trials.

Judged by the standard of effectiveness it has applied to pre-1972 biologics, FDA should assign SPL to Category I. The in-house research conducted by Delmont indicates that SPL has the capacity to stimulate the production of immunocompetent cells, thereby triggering immune responses that might be useful in treating certain diseases. In addition, two clinical studies of SPL, completed since the VRBPAC deliberated and since Delmont's June 1994 submission to FDA, support the effectiveness of SPL in treating a variety of staphylococcal infections, including HS.

In 1994, Delmont supplied FDA with a summary of clinical trial data generated for SPL since the last time any advisory committee considered the product. As noted above, FDA has not responded to these data and has provided Delmont no other information concerning its reactions. Before FDA makes any final decision regarding the classification of SPL, it must carefully consider the data in this submission, as well as the summary of evidence submitted to the agency in 1994. Until FDA completes a thorough evaluation of both submissions, FDA can have no scientific or legal basis for determining whether a license revocation proceeding is warranted.³⁸

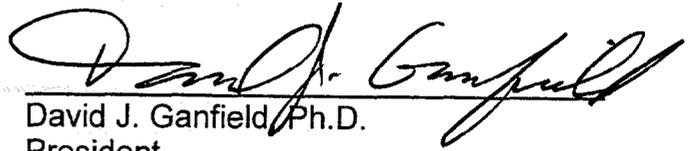
³⁸ Statements in the preamble accompanying the proposed order suggest FDA might decide to initiate license revocation proceedings by publishing an NOOH before it issues the final order reclassifying SPL and other Category IIIA products into Category II, and perhaps even concurrently with publication of the final order. Because FDA is required to consider the data and information submitted by Delmont before reaching a decision on the final classification of SPL, it is premature for the agency to signal its intention to revoke Delmont's license. 5 U.S.C. § 553(c); 21 C.F.R. § 10.40(c).

Respectfully submitted,



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National Archives and Records Service
ARCHIVES ADVISORY COUNCIL
 Meeting

Notice is hereby given that the National Archives Advisory Council will meet at the time and place indicated below. Anyone interested in attending, or who wishes additional information, should contact the person shown below.

NATIONAL ARCHIVES ADVISORY COUNCIL

Meeting Dates: November 30-December 2, 1978; November 30: 7 p.m. to 10 p.m.; December 1: 9 a.m. to 5 p.m.; December 2: 9 a.m. to adjournment.

Place: Room 410, National Archives and Records Service, 8th and Pennsylvania Avenue NW., Washington, D.C. 20408.

Agenda: Implementation of Preservation Report, Accessioning and Processing Priorities, and the National Historical Publications and Records Commission.

For further information contact: Robert Brookhart, General Services Administration (NS), Washington, D.C. 20408, 202-523-3013.

Issued in Washington, D.C., on October 17, 1978.

JAMES E. O'NEILL,
*Deputy Archivist
 of the United States.*

[FR Doc. 78-30364 Filed 10-26-78; 8:45 am]

[4110-86-M]

**DEPARTMENT OF HEALTH,
 EDUCATION, AND WELFARE**

Center for Disease Control

**TUBERCULOSIS THERAPY AND GONOCOCCAL
 INFECTIONS**

Open Meetings

The following meetings will be convened by the Center for Disease Control and will be open to the public for observation and participation, limited only by the space available:

Meeting on Tuberculosis Therapy

Dates: November 7-8, 1978.
 Time: 9 a.m.

Place: Room 165, Building 6, Center for Disease Control, 1600 Clifton Road NE., Atlanta, Ga. 30333.

Purpose: To review tuberculosis short-course therapy study data and discuss the need for and nature of additional data to be gathered.

Additional information may be obtained from: Dr. Dixie E. Snider, Jr., Chief, Research and Development Branch, Tuberculosis Control Division, Bureau of State Services, Center for Disease Control, Room 222, Building 6, 1600 Clifton Road NE., Atlanta, Ga. 30333, telephones: FTS: 236-3956; commercial: 404-329-3956.

Meeting on Gonococcal Infections

Dates: November 9-10, 1978.

Time: 8:10 a.m.

Place: Room 207, Building 1, Center for Disease Control, 1600 Clifton Road NE., Atlanta, Ga. 30333.

Purpose: To discuss Public Health Service-recommended treatment regimens for gonococcal infections.

Additional information may be obtained from: Dr. Ronald K. St. John, Deputy Director, Venereal Disease Control Division, Bureau of State Services, Center for Disease Control, Room 3043, Building 1, 1600 Clifton Road NE., Atlanta, Ga. 30333, telephones: FTS: 236-3935; commercial: 404-329-3935.

Dated: October 20, 1978.

WILLIAM C. WATSON, Jr.,
*Acting Director,
 Center for Disease Control.*

[FR Doc. 78-30430 Filed 10-26-78; 8:45 am]

[4110-03-M]

Food and Drug Administration

[Docket No. 77N-0091]

**BACTERIAL VACCINES AND BACTERIAL
 ANTIGENS WITH NO U.S. STANDARD OF
 POTENCY**

Revocation of Licenses and Reclassification

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Commissioner of Food and Drugs is announcing revocations of licenses and a reclassification concerning bacterial vaccines and bacterial antigens with "No U.S. Standard of Potency" manufactured by six licensees. These actions result from manufacturers' response or failure to respond to an earlier notice of opportunity for a hearing.

EFFECTIVE DATE: October 27, 1978.

FOR FURTHER INFORMATION CONTACT:

Joe Holloway, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, Md. 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION:

In a proposal published in the FEDERAL REGISTER of November 8, 1977 (42 FR 58266), the Commissioner announced his intention to revoke the license(s) for certain bacterial vaccines and bacterial antigens with "No U.S. Standard of Potency" classified as categories II and IIIB, under §§ 601.5(b) and 601.25(f) (21 CFR 601.5(b) and 601.25(f)), based on the recommendations of the panel on review of bacte-

rial vaccines and bacterial antigens with "No U.S. Standard of Potency." The Commissioner agreed with the panel's recommendations and adopted them as the grounds for revocation.

THE PRODUCTS

After publication of the panel's report, a notice of opportunity for a hearing was published in the FEDERAL REGISTER of December 9, 1977 (42 FR 62162) on a proposal by the Commissioner to revoke categories II and IIIB product licenses as follows:

(1) Category II. Biological products determined to be unsafe or ineffective or to be misbranded and which should not continue in interstate commerce. Bacterial Vaccine Diagnostics and Bacterial Vaccine T-50 made from *Streptococcus pyogenes* type L-8 or by prescription (Hollister-Stier, Division of Cutter Laboratories, License No. 8).

(2) Category IIIB. Biological products for which available data are insufficient to classify their safety and effectiveness and which should not continue in interstate commerce. Mixed Respiratory Bacteria (Center Laboratories, Inc., License No. 193); Staphage Lysate (SPL), type I, and types I and III combined, for Staphylococcal Disease (Delmont Laboratories, Inc., License No. 299); Pooled Stock B.A.C. No. 1, Pooled Stock B.A.C. No. 2, Gram-Negative B.A.C. and Pooled Skin B.A.C. (Hoffmann Laboratories, Inc., License No. 283); Bacterial Vaccines for Treatment (Special Mixtures) (Hollister-Stier, Division of Cutter Laboratories, License No. 8); PIROMEN (*Pseudomonas polysaccharide*) (Travenol Laboratories, Inc., License No. 140); V-677 *Streptococcus Vaccines* (Intravenous) (Eli Lilly and Co., License No. 56).

ACTION

The manufacturers' responses to the notice of opportunity for a hearing concerning the above products and the Commissioner's action concerning their responses are as follows:

The following firms did not request a hearing concerning their products:

(1) Hollister-Stier, Division of Cutter Laboratories, Inc., for Bacterial Vaccine Diagnostics, Bacterial Vaccine T-50, and Bacterial Vaccines for Treatment (Special Mixtures);

(2) Center Laboratories, Inc., for Mixed Respiratory Bacteria;

(3) Travenol Laboratories, Inc., for PIROMEN (*Pseudomonas polysaccharide*); and

(4) Eli Lilly and Co., for V-677 *Streptococcus Vaccines* (Intravenous).

The Commissioner has received numerous letters from patients and doctors expressing concern over the recommendation to revoke the license for the manufacture of V-677, *Streptococcus Vaccines* (Intravenous). Most let-

ters provided testimonials in support of the effectiveness of the V-677 product for the treatment of arthritis. Some letters requested a formal hearing.

The Commissioner recognizes the concern and the sense of frustration some patients must feel regarding the proposed revocation. However, the law provides that the safety and effectiveness of biological drugs must be established by scientifically sound evidence. The expert panel evaluated all the bacterial vaccines, using the same criteria to establish safety and effectiveness. These standards are set forth in the regulation that established the biological review (see 21 CFR 601.25(d)). The data submitted by Eli Lilly and Co. did not satisfy the criteria, and the panel and the Commissioner concluded that V-677 should be removed from the market pending the results of scientific studies to establish its safety and effectiveness. In addition, the testimonials submitted by individuals do not satisfy the statutory standard and do not support approval of a biological drug (see *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973)).

Several persons who commented expressed a willingness to volunteer for testing of V-677. Persons who wish to participate in investigational new drug (IND) clinical trials of V-677 or who are otherwise interested in the availability of this product should contact manufacturers or other organizations concerning the possible submission of an IND for V-677 or similar products.

The Commissioner advises that a hearing may be requested only by a manufacturer whose license is the subject of the proposed revocation. If a hearing is requested by the manufacturer and granted, any person desiring to participate in the hearing may do so (see § 12.45 (21 CFR 12.45)). However, if a licensee is given the opportunity to request a hearing but fails to demonstrate an interest in continuing to market the product by not requesting a hearing or submitting data, there is no hearing in which to participate. The December notice provides that the failure of a licensee to request a hearing constitutes an election not to avail itself of the opportunity. Under the biologics law, section 351 of the Public Health Service Act (42 U.S.C. 262), no product can be lawfully marketed except by a person holding an unrevoked license. Although anyone can apply for licensure, patients and/or doctors cannot compel a licensee to continue to produce or to take any particular action to protect its license. For this reason, the Commissioner is obliged to deny requests for a hearing from patients.

Further response to comments concerning V-677 and other products re-

viewed by the panel on Review of Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency" will be included in the final order soon to be published, respecting the November 8, 1977 proposal.

The following firms requested hearings:

(1) Hoffmann Laboratories requested a hearing and presented data concerning its Bacterial Antigen Complexes, License No. 283. However, Hoffmann Laboratories subsequently requested that its establishment license and product licenses to manufacture the six Bacterial Antigen Complexes reviewed by the panel and four other products not reviewed by the panel be revoked. The request for license revocation constitutes a withdrawal of the request for a hearing, and consideration of the data is unnecessary.

(2) Delmont Laboratories, Inc., requested a hearing and submitted data and information in support of its Staphage Lysate (SPL) type I, and types I and III combined, License No. 299. The Commissioner concludes that these data would not only justify a hearing but are adequate to justify reclassification at this time. The Commissioner finds that the potential benefits outweigh the potential risk in use of the product. Therefore, Staphage Lysate (SPL) type I, and types I and III combined, for Staphylococcal Disease (bacterial antigen made from staphylococcus) are reclassified from category IIIB to category IIIA (biological products for which available data are insufficient to classify their safety and effectiveness but which may remain in interstate commerce pending completion of testing). Because no hearing is necessary for a category IIIA product, the December notice is withdrawn for the product.

Accordingly, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)); §§ 314.200, 601.5(b), and 601.25(f) and (g) (21 CFR 314.200, 601.5(b), and 601.25(f) and (g)); the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), the following product licenses are revoked:

(a) Hollister-Stier, Division of Cutter Laboratories, for the manufacture of Bacterial Vaccine Diagnostics (bacterial vaccines for diagnostic use containing (1) *Aerobacter aerogenes*, (2) *Corynebacterium pseudodiphtheriticum*, (3) *Diplococcus pneumoniae*, mixed, (4) *Escherichia coli*, (5) *Gaffkya tetragena*, (6) *Hemophilus influenzae*, (7) *Hemophilus pertussis*, (8) *Klebsiella pneumoniae*, (9) *Neisseria ca-*

tarrhalis, (10) *Proteus vulgaris*, (11) *Pseudomonas aeruginosa*, (12) *Salmonella enteritidis*, (13) *Salmonella paratyphi*, (14) *Salmonella schottmulleri*, (15) *Salmonella typhosa*, (16) *Shigella dysenteriae*, (17) *Shigella flexneri*, (18) *Streptococcus fecalis*, *pyogenese*, *viridans*, and *nonhemolyticus*, (19) *Staphylococcus albus*, and (20) *Staphylococcus aureus*), License No. 8; Bacterial Vaccines for Treatment (Special Mixtures containing one or more of the following organisms: (1) *Aerobacter aerogenes*, (2) *Corynebacterium pseudodiphtheriticum*, (3) *Corynebacterium (propionibacterium) acnes*, (4) *Corynebacterium xerosis*, (5) *Escherichia coli*, (6) *Gaffkya tetragena*, (7) *Hemophilus pertussis*, (8) *Proteus vulgaris*, (9) *Pseudomonas aeruginosa*, (10) *Salmonella enteritidis* (this organism was inadvertently omitted when the notice of opportunity for a hearing was published), (11) *Shigella paradysenteriae* (Type Y), (12) *Salmonella paratyphi*, (13) *Salmonella schottmulleri*, (14) *Salmonella typhosa*, (15) *Shigella dysenteriae*, (16) *Shigella flexneri*, and (17) *Streptococcus fecalis* (*Staphylococcus albus* and *aureus* were incorrectly listed for this product when the proposal and the notice of opportunity for a hearing were published)), License No. 8; Bacterial Vaccine T-50 (made from *Streptococcus pyogenes* type L-8 or by prescription), License No. 8;

(b) Center Laboratories, Inc., for the manufacture of Mixed Respiratory Bacteria (made from (1) *Staphylococcus aureus* and *albus*, (2) *Streptococcus mitis* and *salivarius*, (3) *Streptococcus pyogenes*, Group A, (4) *Diplococcus pneumoniae*, I, II, and III, (5) *Klebsiella pneumoniae*, two strains, (6) *Neisseria catarrhalis*) License No. 193;

(c) Eli Lilly and Co., for the manufacture of V-677 Streptococcus Vaccines (Intravenous), License No. 56;

(d) Travenol Laboratories, Inc., for the manufacture of PIROMEN (*Pseudomonas polysaccharide*), License No. 140; and

(e) Hoffmann Laboratories, Inc., for the manufacture of Pooled Stock B.A.C. No. 1 (bacterial antigens made from (1) *Diplococcus pneumoniae*, (2) *Streptococcus species*, (3) *Staphylococcus species*, (4) *Neisseria catarrhalis*, (5) *Escherichia coli*, (6) *Hemophilus influenzae*), Pooled Stock B.A.C. No. 2 (bacterial antigens made from (1) *Diplococcus pneumoniae*, (2) *Klebsiella pneumoniae*, (3) *Streptococcus species*, (4) *Pseudomonas aeruginosa*, (5) *Escherichia coli*, and (6) *Aerobacter aerogenes*) and Gram-negative B.A.C. (bacterial antigens made from (1) *Pseudomonas aeruginosa*, (2) *Escherichia coli*, (3) *Aerobacter aerogenes*), Pooled Skin B.A.C. (bacterial antigens made from (1) *Staphylococcus species* and (2) *Proteus vulgaris*), License No. 283.

Shipment in interstate commerce by the manufacturer of a product after the effective date of revocation constitutes a violation of the Public Health Service Act. The Commissioner advises that those products for which licenses are herein revoked do not constitute a danger to public health and those lots that have already been sold and delivered may be resold through their expiration dates.

All data and information not prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, that have been used by the Commissioner in reaching this decision, may be seen in the office of the Hearing Clerk between 9 a.m. and 4 p.m., Monday through Friday.

Effective date. These actions are effective October 27, 1978.

Dated: October 19, 1978.

DONALD KENNEDY,

Commissioner of Food and Drugs.

[FR Doc. 78-30350 Filed 10-26-78; 8:45 am]

[4110-03-M]

[Docket No. 78N-0378]

GRAS SAFETY REVIEW OF MANGANESE SALTS

Public Hearing

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: In response to several requests, the Food and Drug Administration (FDA) announces a public hearing concerning the safety of manganese salts. The hearing will enable those parties who have so requested to present data, information, and views as part of the agency's review to determine whether the salts are generally recognized as safe (GRAS) or subject to a prior sanction.

DATE: The hearing will be held November 6, 1978.

ADDRESS: The hearing will be held in the Lee Building, Federation of American Societies for Experimental Biology, 9650 Rockville Pike, Bethesda, Md. 20014.

FOR FURTHER INFORMATION CONTACT:

Corbin I. Miles, Bureau of Foods (HFF-335), Food and Drug Administration, Department of Health, Education, and Welfare, 200 C Street SW., Washington, D.C. 20204, 202-472-4750; or

George W. Irving, Jr., Life Sciences Research Office, Federation of American Societies for Experimental Biology, 9650 Rockville Pike, Bethesda, Md. 20014, 301-530-7033.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of April 21,

1978 (43 FR 17055), the Commissioner of Food and Drugs issued a notice advising the public that an opportunity would be provided for the oral presentation of data, information, and views at public hearings to be conducted by the Select Committee on GRAS Substances of the Life Sciences Research Office, Federation of American Societies for Experimental Biology (hereafter referred to as the Select Committee), concerning the safety of manganese salts and silicates and the Select Committee's tentative determination of whether or not they are GRAS or subject to a prior sanction.

A written statement on silicates was submitted by the PQ Corp., P.O. Box 258, Lafayette Hill, Pa. 19444, in lieu of an oral presentation at a public hearing. No requests for a public hearing were received. Accordingly, no hearing will be held on silicates.

The Select Committee received requests for a public hearing on manganese salts from the American Feed Manufacturers Association, Inc., 1701 North Fort Myer Drive, Arlington, Va. 22209; Southeastern Minerals, Inc., Bainbridge, Ga. 31717; and Chemetals Corp., 711 Pittman Road, Baltimore, Md. 21226 (formerly a division of Diamond Shamrock Corp., 1110 Superior Avenue, Cleveland, Ohio 44114). No other requests were received for a hearing on manganese salts.

Under the procedures set forth in the April 21, 1978, notice, announcement is hereby made that a hearing on manganese salts will be held at 9 a.m., on November 6, 1978, in the Lee Building, Federation of American Societies for Experimental Biology, 9650 Rockville Pike, Bethesda, Md. 20014. Those who have requested to make oral presentations will be expected to complete their presentations within the period indicated and in accordance with the following schedule:

1. American Feed Manufacturers Association, Inc., and Southeastern Minerals, Inc.: Mr. L. H. Boyd and/or A. Poitevint will make a joint presentation for both corporations—30 minutes.

2. Chemetals Corp.: Dr. Dennis De-Craene—15 minutes.

The hearing will be chaired by a member of the Select Committee and will be transcribed by a reporting service. A transcript of the hearing will be placed on public display in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

Dated: October 23, 1978.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner
for Regulatory Affairs.

[FR Doc. 78-30353 Filed 10-26-78; 8:45 am]

[4110-03-M]

[Docket No. 78M-0260]

LOMBART LENSES LTD.

Premarket Approval of Amsof Soft Contact Lens

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) announces approval of the application for premarket approval under the Medical Device Amendments of 1976 of the Amsof (deltafillicon A) Soft Contact Lens sponsored by Lombart Lenses Ltd. After reviewing the Ophthalmology Device Classification Panel's recommendation, FDA notified the sponsor that the application was approved because the device had been shown to be safe and effective for use as recommended in the submitted labeling.

DATE: Petitions for administrative review by November 27, 1978.

ADDRESS: Requests for copies of the summary of safety and effectiveness data and petitions for administrative review may be addressed to the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

Keith Lusted, Bureau of Medical Devices (HFK-402), Food and Drug Administration, Department of Health, Education, and Welfare, 8757 Georgia Avenue, Silver Spring, Md. 20910, 301-427-7550.

SUPPLEMENTARY INFORMATION: The sponsor, Lombart Lenses Ltd., Norfolk, Va. 23501, submitted an application for premarket approval of the Amsof (deltafillicon A) Soft Contact Lens to FDA on April 6, 1977. The application was reviewed by the Ophthalmology Device Classification Panel, an FDA advisory committee, which recommended approval of the application. On June 30, 1978, FDA approved the application by a letter to the sponsor from the Director of the Bureau of Medical Devices.

Before enactment of the Medical Device Amendments of 1976 (the amendments), soft contact lenses were regulated as new drugs. Because the amendments broadened the definition of the term "device" in section 201(h) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(h)), soft contact lenses are now regulated as class III devices (premarket approval). As FDA explained in a notice published in the FEDERAL REGISTER of December 16, 1977 (42 FR 63472), the amendments provide transitional provisions to assure continuation of premarket

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Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

OCT 12 1993

OCT 18 1993

David J. Ganfield, Ph.D.
Responsible Head
Delmont Laboratories, Inc.
P.O. Box 269
Swarthmore, PA 19091

Dear Dr. Ganfield:

We have reviewed your August 12, 1993, letter which was in response to the FDA-483, List of Observations, dated July 13, 1993, which outlined deficiencies noted during the July 12-13, 1993, inspection of your establishment.

Our review indicates that your corrective action is not adequate. Please provide the following additional information so that we may complete our review of your corrective action.

1. Please provide a Curriculum Vitae and documentation of training and continuing education which qualifies persons in supervisory positions, including yourself. Specifically, what training and certification in Quality Control (QC), Quality Assurance (QA) and Current Good Manufacturing Practices (CGMPs) has Dr. Wang completed, who is responsible for production and QA/QC of the Staphage Lysate (SPL) product?
2. Please provide the SOPs for the proper filling-out and time table for completion of form 210, batch record summary sheet. We request that a person of equal or greater authority, e.g., head of QA, countersign the documents at the appropriate time to ensure complete and accurate record keeping. Please comment.
3. Please provide SOPs for all QC water analysis tests, including the methods for standardization and the upper and lower limits of detection for each test performed.
4. Please provide the SOPs for the following release tests: purity (including rabbit pyrogen test), potency, identity, and general safety.
5. Please provide the SOPs for the bulk and final container sterility tests, including how and when samples are taken. We believe that the bulk sterility sample should be obtained from the combined types 1 and 3 lysates after mixing but prior to instituting filling procedures. Please note that we do not consider samples taken during the filling operation as bulk samples; however, they are

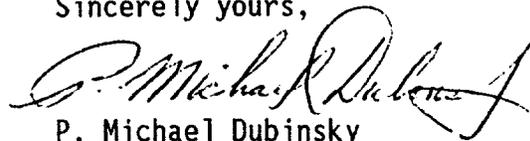
final fill samples. Also, are any changes made to the filling machine during filling of ampules to accommodate taking of the "bulk" samples or are the "bulk" samples filled into ampules or vials?

6. You state in your answer to observation 5 b that "Manufacturing research samples will be labeled and kept in the Q.C. lab." We recommend that samples taken for research purposes be kept in the research facilities and not in the Q.C. lab. Please comment.
7. You state in your answer to observation 6 that "If temperature exceeds range the person observing the deviation will report it to the responsible head so it can be promptly corrected." Please provide the SOPs for the corrective action to be taken. Please note that the use of "cold packs" is not an acceptable method of maintaining incubator temperature. Please comment.
8. Please provide SOPs for the avidity testing using old phage cultures to test the avidity of new cultures, as stated in your answer to observation 7. Also, please include a detailed explanation of the rationale for using this procedure. Furthermore, please explain how the cultures are maintained during storage and culturing to prevent mixing up the old and new cultures during production.
9. Your answer to observation 15 only addresses corrective action for determining a dating period for testing media and not for production media. Please provide the SOPs and results of the growth promotion quality tests performed on all media, including 2X and 4X HIB, for the time intervals used to establish the dating periods.
10. Please provide stability data demonstrating the potency of the SPL at time intervals during and at the end of the 15 month dating period of the bulk product.
11. Please provide the protocol and data from your proposed validation studies that will demonstrate the adequacy of mixing before, during and at the end of the filling procedure from a representative size fill.
12. Please provide SOPs for the reconciliation of vials or ampules used during filling operations, rejected filled vials including reason for rejection, and printed labels.
13. Please provide SOPs for the determination of the theoretical yield as compared to the actual yield for the growth of staphylococcus types I and III cells and for the amount of SPL produced from the staphylococcal cultures as required by Title 21, Code of Federal Regulations (21 CFR), parts 211.186 (b)(6) and 211.188 (b)(7). This information should be maintained as part of the batch production and control records.

14. Please provide data from stability tests performed on the final container product at specified intervals, e.g., every 6 months, during the time interval specified by the dating period.
15. Please provide a clinical plan that includes human trials that demonstrate efficacy for each indication and route of administration of SPL. The plan should include the proposed relevant clinical endpoint as well as the statistical methods used for trial size determination and analysis of efficacy. Also, please include all data from previous human and animal trials which support your clinical plan.
16. Please provide a copy of the proposed validation master plan to include the process descriptions of systems at your firm. Also, provide a proposed time table for implementation of the plan.

Please advise us, in writing, of your actions to correct the deviations noted, within 30 days of receipt of this letter, in sufficient detail to permit us to determine compliance with the regulatory standards. Should you have any questions, please contact Louis Mocca, HFM-475, at 301-594-2090.

Sincerely yours,



P. Michael Dubinsky
Acting Director
Office of Compliance
Center for Biologics Evaluation
and Research

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**An Overview of the Human and Animal Experience with Bacterial
Antigen Made from Staphylococcus Aureus (Staphage Lysate)
in the Treatment of Staphylococcal Infections**

February 28, 1994

Prepared by:

**Bio-Pharm Clinical Services
4 Valley Square
Blue Bell, PA 19433**

For submission by:

**Delmont Laboratories
P.O. Box 269
Swarthmore, PA 19081-0269**

Contact: Dr. David Ganfield

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0. Synopsis

Staphage Lysate (SPL) is a biologically derived product indicated for treatment of staphylococcal and polymicrobial infections with a staphylococcal component.

Since the early 1980s Delmont Laboratories, the sponsor and manufacturer of SPL, has undertaken three clinical studies and one double-blind efficacy animal study with SPL. The results of the double blind human clinical study did not provide definitive statistical evidence of the effectiveness of SPL due to failure to enroll a sufficient number of evaluable patients. This study was for hidradenitis suppurativa a difficult condition for which to recruit patients. However, the animal efficacy study resulted in the granting of a veterinary biological product license by the US Department of Agriculture in 1988.

At present, Delmont Laboratories plans two additional studies to demonstrate the efficacy of SPL. These studies are for the indications of atopic dermatitis and of nasal staphylococcus carriers - both conditions in which it should be possible to recruit evaluable patients in a relatively short period of time.

1. Background

Staphage lysate (SPL) is a biologically derived product prepared by lysing parent cultures of *Staphylococcus Aureus*, Serologic Types I and III, with a polyvalent staphylococcal bacteriophage. After ultrafiltration, the lysate contains active bacteriophage and heat labile and heat stable antigenic fractions

plus the extracellular enzymes of *S. Aureus* and culture medium ingredients (sodium chloride and Bacto Heart Infusion Broth). No preservatives are added to SPL, in order to maintain maximum immunogenic potency.

SPL is standardized on the basis of bacterial cell content before phage lysis. Each milliliter contains 120-180 million colony-forming units of *S. aureus* and 100 to 1000 million staphylococcus bacterial plaque-forming units.

In its labeling, SPL is indicated for treatment of staphylococcal infections and polymicrobial infections with a staphylococcal component. It has been used in a variety of such conditions, including bronchial asthma and staphylococcal pneumonia; furunculosis, acne, hidradenitis suppurativa and other dermatological conditions; conjunctivitis, sty, blepharitis and other infections of the eye; and Crohn's disease and other gastrointestinal disorders.

SPL is supplied in 1-ml ampules and 10-ml vials and it is administered by subcutaneous injection, intranasal aerosol inhalation or nasal drop instillation, oral administration, topical application or irrigation, or combinations of these routes, as appropriate to the condition being treated. Because of evidence that SPL acts as an immunopotentiator of nonspecific cell immunity this product has also been used in the treatment of conditions which do not appear to have a staphylococcal component including viral warts, herpes simplex (types 1 and 2) and other viral conditions. The use of SPL in the various conditions listed above is documented in the Submission to the Food and Drug Administration Vaccines and Related Biological Products Advisory Committee, filed by

Delmont Laboratories in December, 1982, and in additional data submitted in September 1983.

2. Regulatory History

The National Institutes of Health (NIH) issued a biological product license in 1957 that provided for marketing of SPL for intranasal, topical, and oral therapy. This license was amended in 1962 to provide for administration of SPL by injection.

Following the institution of the FDA Biologics Review, Delmont submitted data on the safety and effectiveness of SPL which was later reviewed by the FDA's Advisory Panel on Bacterial Vaccines and Bacterial Antigens with no U.S. Standard of Potency. The recommendation of the Advisory Panel was to classify SPL as Class III-B (i.e. a product for which further studies were required to establish safety or effectiveness and which the Panel did not recommend be permitted to remain on the market while the studies were being conducted). FDA initially concurred with the recommendation of the Advisory Panel, but, upon review of data submitted by Delmont, the Agency withdrew its proposal. A final rule classifying SPL in Category III-A (44 Fed. Reg. 1544) that is, a product which may remain on the market while further studies are conducted, was subsequently issued by the FDA.

Thereafter, Delmont initiated the studies that are required for products in Category III-A, including a two-center, double-blind, efficacy and safety study on hidradenitis suppurative patients in the U.S, as well as an active-controlled,

open, study on patients with staph sickness of various types in Czechoslovakia. An additional double-blind, placebo-controlled, crossover study for patients with furunculosis was planned, but this study was discontinued due to a failure to recruit eligible patients. Animal data were obtained from a double-blind, efficacy study on dogs with recurrent canine pyoderma.

3. Efficacy Studies in Humans and Animals

An overview of the studies mentioned above is presented in this Section.

3.1 " A Prospective, Two-Center, Double-Blind, Placebo-Controlled, Parallel Group Study of the Efficacy and Safety of Staphage Lysate in the Treatment of Hidradenitis Suppurativa"

This double-blind, placebo-controlled study consisted of two clinical trials that employed the same protocol: one was conducted at the Hershey Medical Center, Division of Plastic Surgery, in Hershey, PA from November 18, 1982 through May 10, 1985 with Dr. Ernest K. Manders as principal investigator; the other was conducted at the Pittsburgh Medical Center, Division of Plastic Surgery from December 15, 1984 through September 29, 1987, with Dr. Sai S. Ramasastry as principal investigator.

Hidradenitis suppurativa (HS) is a chronic suppurative and cicatricial disease of the apocrine gland-bearing skin areas of the body and it is associated with pain, drainage, limitation of activity and frequently offensive odor. The earliest stages of this disease are treated with antibiotic therapy, however, incision and

drainage of abscesses must be kept to a minimum in order to avoid fistula formation. Untreated HS will progress eventually to the chronic cicatricial form. The only accepted therapy for the chronic form is excision of affected areas of the skin, which are subsequently healed by flaps, grafts or secondary intention.

The rationale for using SPL in this indication was based on the fact that evidence of efficacy of SPL appears to be associated with its role as an immunoadjuvant in the induction-elicitation immune reaction, and the fact that the predominant organisms found in cultures of HS are *S. aureus* and *Streptococcus viridans*. The only FDA licensed immunologic agent, specific for one of these bacterial species, at the time of study initiation, was SPL.

Objective and Design

The objective of this study was to assess whether SPL was a valid therapeutic modality in patients with HS for whom conventional forms of therapy (surgery or antibiotics) are not indicated.

The study was designed as a prospective, double blind, placebo controlled, parallel group study involving 20 subjects, to be conducted at the Hershey site. Due to slow recruitment at this site from 1982 to 1984, the Pittsburgh site was opened to enroll twenty additional patients. The patient population was to include adults, ages 18 to 65, of either sex, with advanced HS.

At both centers, patients entering the study were randomized to receive either SPL or placebo in a double blind fashion. For the first four weeks patients were to receive 0.1 ml subcutaneously and by intranasal aerosol instillation of 0.3 ml of SPL or matching placebo; thereafter, patients were to receive 0.2 ml subcutaneously and by 0.6 ml intranasally for an additional 12 weeks (Hershey, Dr. Manders) or an additional 16 weeks (Pittsburgh, Dr. Ramasastry).

Assessments

Efficacy and safety assessments were made by examination and questioning of the patients prior to treatment and biweekly thereafter.

The effectiveness of treatment with SPL was to be assessed by comparing the change in the lesions and disability status of SPL treated patients with placebo treated patients before and during the course of treatment. The skin lesions were graded before each treatment with respect to:

- 1) amount of odor;
- 2) consistency of drainage;
- 3) amount of drainage;
- 4) presence of spontaneous drainage;
- 5) duration of inflammation;
- 6) number of flareups;
- 7) amount of pain;

A similar scale was used to grade the extent of the patient's physical disability.

The safety of SPL was assessed by clinical observation, physical examination and questioning the patients about their general health. In addition, the patients were specifically asked about the presence of rash, light-headedness, malaise, nausea, headache, and changes in stamina.

Although the protocol indicated 16 weeks of treatment at Hershey and 20 weeks of treatment at Pittsburgh, patients were treated for shorter or longer periods of time.

The Pittsburgh center has continued to treat patients with SPL through February of 1994. A total of 18 patients are currently being treated and three of these are from the original study group.

Analyses

Upon completion of the study, the data were analyzed by Dr. Emil R. Smith, a statistical consultant, in behalf of Delmont Laboratories. This report is available upon request. The methods and results of these analyses are summarized below.

A. Methods

For the efficacy analyses, data obtained from days -8 through 148 relative to the start of study medication, were included. This period of time was divided into five periods:

Period 0:	Days -8 to 0
Period 1:	Days 1 to 35
Period 2:	Days 36 to 70
Period 3:	Days 71 to 105, and
Period 4:	Days 106 to 148.

For each of the eight efficacy parameters, the mean score of the evaluations carried made on each patient during clinic visits in each period was calculated, yielding five mean scores per patient. These scores were used in three analyses:

1) A comparison of treatments for changes in the severity of symptoms from period 0 to period 4; 2) ANOVA comparisons of the slope of the regression lines for each efficacy parameter vs time (period); 3) three-way ANOVA analyses of the mean scores with factors for center, treatment, time, and all two-way interactions.

The analyses of safety were based on all the available data for all patients. These analyses examined the absence or presence on each clinic day of rash, light-headedness, malaise, nausea, fever, headache or decrease in stamina. Three safety analyses were carried out:

1) For each parameter, the proportion of patients who did or did not report the occurrence of an event in that category; 2) for each parameter, the average proportion of visits during which patients reported an event in that category; and 3) a life-table analysis of distribution of time to experience of each event.

B. Findings

A total of 41 patients were enrolled in this study, 16 at Hershey and 25 at Pittsburgh. Two patients (4.9%), both treated with SPL, were discontinued prematurely due to treatment failures.

The treatment groups and the centers were well balanced with respect to patient demographic characteristics and pre-treatment severity of the lesions.

No significant differences between treatment groups or between the two centers were found in any of the efficacy analyses for any of the parameters analyzed.

The statistical analyses of safety did not reveal any treatment differences in the presence/absence of adverse conditions. However, in all cases a higher incidence of adverse events were reported by the patients treated at Hershey (Dr. Manders) than by the patients treated at Pittsburgh (Dr. Ramasastry).

Under the conditions of this study, SPL was not demonstrated to be effective in the treatment of HS. Treatment with SPL was not associated with adverse effects in this study.

Additional Efficacy Analyses

In January, 1994 the efficacy data from this study were re-analyzed by Bio-Pharm Clinical Services at the request of Delmont Laboratories. For this re-

analysis, the data files created by Dr. Smith in preparation for his report were transferred to Bio-Pharm; no additional data entry was carried out.

A. Methods

For consistency with Dr. Smith's report all data collected more than 148 days post the start of study medication were excluded from the analysis. After exclusion of these data, the sum of the eight efficacy scores (seven skin lesion scores plus the disability score) was calculated for the baseline visit and for the last four visits no more than 148 days after the start of medication.

Efficacy assessments were based on the change from baseline to the last visit and the change from baseline to the average of the last four visits in the sum of efficacy scores. Treatment comparisons were made with a two-sample t-test. In addition, the two treatments were compared with respect to the incidence rate of patients who reported improvement, that is a decrease from baseline in the summed symptom score.

A review of the data revealed that the patients enrolled at Hershey had substantially lower lesion scores at baseline than those enrolled at Pittsburgh. Furthermore, at both centers, some patients were enrolled who had baseline scores too low to measure improvement. For this reason, two sets of treatment comparisons were carried out, one on the entire set of patients and the other on the subset of patients with baseline sum of scores greater than or equal to 7.

B. Findings

The analyses showed approximately two times greater reductions from baseline in total score for SPL treated patients than for placebo treated patients, both in the set of all patients and in the subset of patients with baseline scores greater than equal to 7. The observed treatment differences were not statistically significant in either set of patients, however a trend ($p < 0.15$) was found among the more severely affected patients for the change from baseline to last visit. These results are summarized in the table below.

A total of nineteen out of 39 (49%) patients showed a decrease in symptom scores from baseline to last visit, 10/18 (56%) treated with SPL and 9/21 (43%) treated with placebo. All of the patients who showed improvement had baseline total symptom score ≥ 7 . For the 30 patients with baseline symptom scores ≥ 7 at baseline, 19 (63%) showed improvement : 10/14 (71%) treated with SPL and 9/16 (56%) treated with placebo.

Descriptive Statistics - Sum of Lesion and Disability Scores		
	Last Visit	Average Last 4 Visits
	N	N
	Mean	Mean
	(SD)	(SD)
	p-value	p-value
Entire Set of Patients (n=39)		
SPL	18 -0.64 6.04 0.2865	18 -1.26 4.86 0.3181
Placebo	21 0.33 4.62	21 -0.48 5.29
Patients with Baseline Sum of Scores ≥ 7 (n=30)		
SPL	14 -2.54 4.58 0.1422	14 -2.93 4.15 0.2271
Placebo	16 -0.75 4.38	16 -1.72 4.58

3.2 "Staphage Lysate for the Treatment of Recurrent Furunculosis"

In May, 1983, a protocol was finalized for a double-blind, crossover trial of SPL vs placebo in the treatment of recurrent furunculosis. This long-term study (2 years course) was to be conducted at the University of Minnesota under the supervision of Dr. Mark V. Dahl, Associate Professor of Dermatology. However, in May 1984 only one patient had been enrolled into the study and the study was discontinued. The failure to recruit more patients may have been due to the stringency of the inclusion criteria, a lower referral rate than had been anticipated, and/or the length of the study.

3.3 A Comparison of the Effectiveness of STAVA, SPL, and POLYSTAFANA vaccines

Staphylococcal infection, particularly that accompanied by chronic process and repeated relapses, presents a serious medical, ethical, and social problem. Management of this disease presents a financial burden.

This comparative trial was conducted from August 1992 to August 1993 at the Budejovicka Health Clinic, Prague 4, Association of Out-Patient Wards, Prague 8, Czech Republic, under the supervision of Dr. Frantisek Vymola, a well known investigator in the field of staphylococcal infections. Between August 1993 and February 1994 an additional 67 patients with staphylococcal infections of the skin have been treated with SPL at this site.

The objective of the study was to verify and compare the effectiveness of staphylococcus vaccine STAVBU CSAV, SPL-Delmont, and POLYSTAVA-USOL in the treatment of patients with various staph infections who manifest a chronic process or are resistant to other treatments, mainly antibiotic cures. A placebo arm was not included because, in the Czech republic, placebo treatment is not considered ethically acceptable in this indication.

One hundred thirty patients suffering from staphylococcal infections were treated in the study. All patients had received previous treatment in which they were predominantly given antibiotics. Of the 130 patients, 47 received STAVA, 68 received SPL, and 15 received POLYSTAFANA.

The use of POLYSTAFANA resulted in excessive epidermal reactions (swelling, pain, erythema) after injections in certain patients. Therefore, most of the clinics refused to continue administering POLYSTAFANA.

The results have been accepted for presentation at the 5th Biennial Conference on Chemotherapy of Infectious Diseases and Malignancies in Salzburg, Austria, March 20-22, 1994 and also at the 6th International Congress for Infectious Diseases in Prague, April 26-30, 1994.

The diagnoses for each treatment group is summarized in the following table:

Diagnosis	SPL	STAVA	POLYSTAFANA
Skin Infections	32	19	5
Osteomyelitis	6	5	0
Respiratory Infection	19	13	6
Otitis	11	10	4

The clinical results of the immunotherapy for staphylococcal infections are summarized in the following table:

Diagnosis	SPL		STAVA		POLYSTAFANA		
	Cured	Improved	Cured	Improved	Cured	Improved	No effect
Skin Infections	30 (94%)	2	12 (63%)	7	2 (40%)	1	2
Osteomyelitis	3 (50%) stabilized	3	2 (40%) stabilized	3			
Respiratory Infection	10 (53%)	9	6 (46%)	7	4 (67%)		2
Otitis	6 (55%)	5	3 (30%)	7	1 (25%)		3

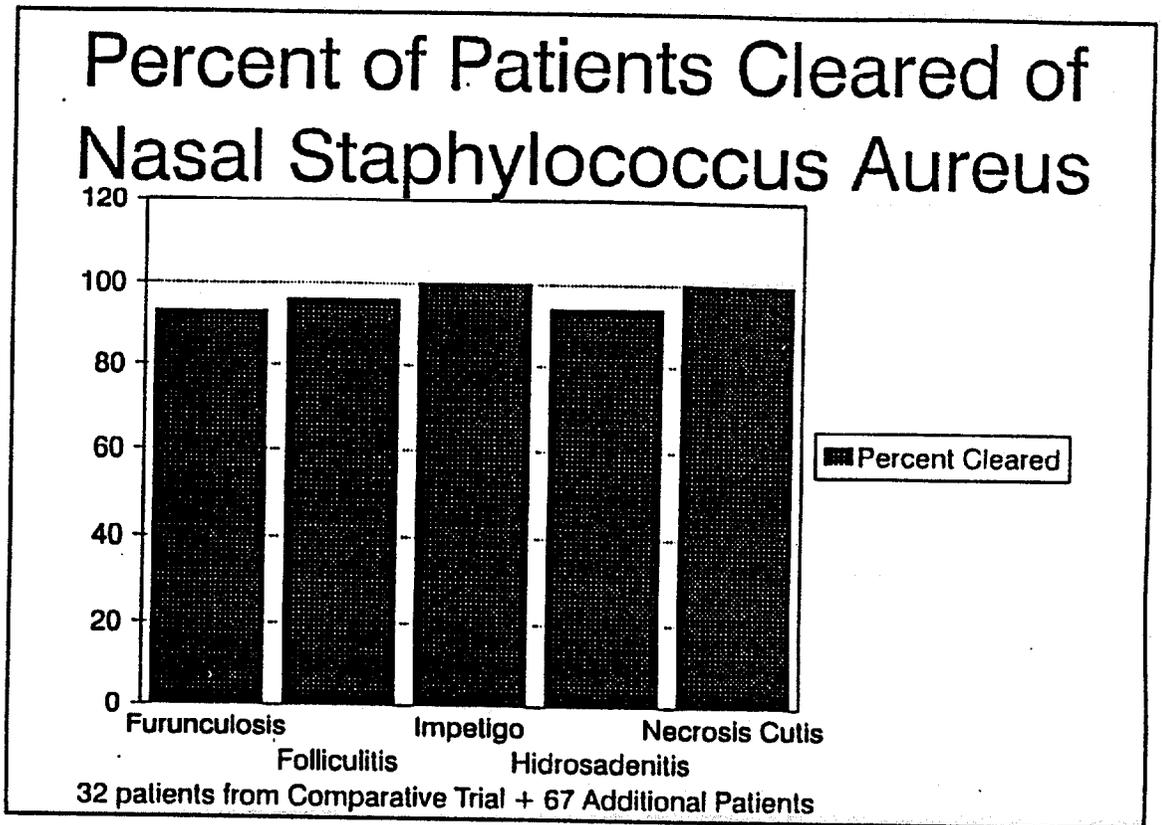
All the products tested were efficacious in the treatment of staphylococcal infections. In all indications, the observed cure rates were highest for SPL treatment. The SPL and STAVA patients has a progressive increase in the phagocytic function of their monocytes during the time of treatment.

The safety profile of SPL was superior to that of the comparators, since none of the SPL patients had severe adverse reactions to the injections whereas three STAVA patients who experienced reactions of induration, erythema larger than 6 cm, local pain, headache, and tiredness , usually in combination.

The data has been submitted and accepted by the Czech Republic Health Officials and Staphage Lysate in now registered for human use in the Czech Republic.

The 32 patients with skin infections treated with SPL in the comparative trial and the additional 67 patients with skin infections treated with SPL since August 1993 were followed with bacterial cultures of the nasal cavity. Ninety four of these patients showed clearing of staphylococcal organisms. A breakdown of these results by type of skin infections is presented in the following table and figure.

Diagnosis	Treated	Cleared of Staph	Average Months of SPL Treatment
Furunculosis	44	41 (93%)	5.5
Folliculitis	24	23 (96%)	4.5
Impetigo	8	8 (100%)	3.5
Hidrosadenitis	17	16 (94%)	6.5
Necrosis Cutis	6	6 (100%)	4.0



3.4 Evaluation of Staphage Lysate for the management of idiopathic recurrent superficial pyoderma in dogs

Delmont sponsored this double-blind, placebo controlled efficacy study which was conducted between February and December 1987. The purpose of the study was to document the efficacy of a commercial staphylococcal bacterin in the management of idiopathic recurrent superficial pyoderma in dogs, a disease that is seen frequently in veterinary practice. In addition, this canine disease is a useful model for atopic dermatitis and impetigo in humans due to similarities in the type of staphylococcal skin infections (Dr. Douglass DeBoar, veterinary dermatologist personal communication)

Staphylococcal bacterin preparations are reported to be efficacious as adjunct treatment in the management of some canine pyogenic skin infections, although other products have not been proven with similar double blind studies.

Treatment spanned an 18-week period, with reevaluation performed at weeks 6, 10, 14, and 18. All dogs were administered sodium oxacillin for the initial 6 weeks of the study. During the entire study, benzoyl peroxide shampoo was used on all dogs once to twice weekly to kill staphylococci topically. Dogs were randomized to either the commercial staphylococcal bacterin (SPL) or placebo treatment group in blinded fashion. The dosage regimen for SPL or placebo injections was as follows: starting the first week of the study, each dog was given 0.5 ml of SPL or placebo twice weekly, at 3 to 4 day intervals. The SPL or placebo was administered at home by the owner. Injections were

continued during the initial 6-week course of antibiotic treatment and for 3 months after cessation of antibiotics (18 weeks).

Examinations were conducted at the end of antibiotic administration (6 weeks after the start of the study) and at weeks 10, 14, and 18. At each visit, the examiner assigned a clinical score to the dog based on the predetermined criteria detailed in the following table:

Grade	Recurrence seen	Control evident	Antibiotics needed
1	None	Yes	No
2	Mild	Yes	No
3	Mild	Yes	Yes
4	Mild to moderate	No	Yes
5	Severe	No	Yes
6	Worse than ever	No	Yes

Differences in treatment effects between the two groups were determined at weeks 10, 14, and 18 using the nonparametric Kruskal-Wallis test modified for analysis of ordinal categorical data. A treatment response was considered statistically significant if the p value < 0.05.

In addition, a dog with a mean score < 3.0 was termed to have achieved a good clinical response, while a mean score \geq 3.0 was termed a poor response.

Twenty-one dogs completed the study, 8 in the placebo group and 13 in the SPL group. At the end of week 6, no dog had evidence of superficial pyoderma and, therefore, all received a score of 1. The mean scores for each treatment group at weeks 10, 14, 18, and overall are presented in the following table:

Treatment	Week 10	Week 14	Week 18	Overall
Placebo	2.62	3.25	3.38	3.08
SPL	1.92	2.31	2.46	2.23

A statistically significant treatment response was observed at weeks 10, 14, and 18 with $p < 0.02$ at week 10, $p < 0.05$ at week 14, and $p < 0.01$ at week 18.

In the SPL group, 10 of 13 dogs (77%) had a good clinical response and 3 of 13 (23%) had a poor clinical response. In the placebo group, 3 of 8 (38%) had a good clinical response and 5 of 8 (63%) had a poor clinical response.

Twenty-two months after conclusion of the study, participants were telephoned to determine how many dogs were still benefitting from SPL injections. Of the 10 dogs that had a beneficial response to SPL, 5 (50%) were still receiving injections, with continued remission of disease; 4 were not being given the injections; and the owner of 1 dog could not be contacted. These results showed that SPL treatment was an efficacious alternative to repeated use of

antibiotics. SPL treatment is less expensive and does not contribute to establishing resistant strains of Staphylococcal organisms.

The clinical efficacy study was designed to satisfy the requirements for a USDA veterinary biologics division. The results were submitted to USDA and a veterinary biological product license was granted in 1988.

A report entitled "Evaluation of a Commercial Staphylococcal Bacterin for the Management of Idiopathic Recurrent Superficial Pyoderma in Dogs" was published in the American Journal of Veterinary Research. The raw data and a reprint of this report are attached.

4. Clinical Development Plan

Two studies are currently being considered: one in atopic dermatitis patients and the other in otherwise healthy nasal carriers of staphylococcus - both conditions in which eligible patients may be recruited readily.

The results of the canine pyoderma study indicate that SPL should provide efficacious treatment for atopic dermatitis in humans and merits study in this indication. The eradication rates of Staphylococcus aureus that were observed with SPL treatment in the Comparative Czech study suggest that SPL may be efficacious in clearing Staphylococcus organisms from the nasal passages of otherwise healthy carriers - a serious problem in many health care institutions today.

Outlines of the two planned protocols under consideration are attached. Statistical input is being secured to determine the appropriate sample size and efficacy measures to be analyzed.

4.1 "A Study of the Effectiveness of SPL in the Treatment of Atopic Dermatitis"

Current therapy for severe staphylococcal infections associated with atopic dermatitis consists of antibiotic treatment. Recurrences of the infection and flare-up of the underlying condition soon after the cessation of antibiotic treatment demonstrate the need for a therapy which will prevent the recurrence of staphylococcal infections.

Staphage Lysate is a bacteriologically sterile staphylococcal vaccine which has been used in the treatment of staphylococcal infections. There is evidence in clinical studies to suggest that Staphage Lysate would be a useful treatment modality in the prevention of staphylococcal infections in patients with dermatologic conditions, including atopic dermatitis. The use of Staphage Lysate for this indication can provide a cost effective treatment with the potential to reduce the need for hospitalization and reduce the need for repeated courses of antibiotics, improving the quality of life for these patients. Another positive impact would be to eliminate the pressure of the antibiotics which would result in the development of more resistant strains of staphylococci.

In order to prove the value of Staphage Lysate for this use, the following study has been proposed.

- o at least 2 or more health care centers would participate.
- o enrolled patients will have atopic dermatitis with staphylococcal infection which will meet a minimum severity score.
- o patients will have a documented history of their disease and incidence of staphylococcal infections for a minimum of one year prior to entry into the study.
- o patients will be treated for up to two weeks with an appropriate antibacterial agent and with Staphage Lysate or placebo.
- o patients will be followed for a period of 3 to 4 months.
- o the primary efficacy endpoints will be:
 - o clinical response determined by a disease severity score.
 - o microbiologic response determined by obtaining cultures at appropriate intervals.
 - o time to recurrence of staphylococcal infection.
 - o safety will be evaluated through weekly clinical assessments and laboratory assessments at appropriate intervals.

Discussions are now underway with the principal investigator to determine whether a pilot study should be conducted to refine the protocol for the multi-center efficacy study.

4.2 "A Study of the Effectiveness of SPL in the Elimination of the Staphylococcus aureus nasal carrier state"

Staphylococcus aureus is the number one cause of nosocomial infections. These infections result in morbidity and mortality in patients and adds a tremendous amount to the overall cost of healthcare in the United States. One of the most likely causes for such infections is the contamination of patients with organisms carried in the nares of healthcare providers. At the current time, carriers of nasal staphylococcus aureus are treated with either topical or systemic antibiotics in order to eliminate the carrier state. In a significant percentage of cases, the carrier state becomes a chronic problem, not responding adequately to therapy with antibiotics. The use of antibiotics to eliminate the carrier state also carries with it the additional problem of selecting for more resistant strains of staphylococcus aureus. The spread of these organisms into the hospital environment can result in serious infections which may be extremely difficult to treat.

Staphage Lysate is a bacteriologically sterile staphylococcal vaccine which has been used in the treatment of staphylococcal infections. There is evidence to suggest that Staphage Lysate may be useful in the elimination of the Staphylococcus aureus nasal carrier state. The use of Staphage Lysate for this indication would be an important tool for the hospital infection control unit to have in reducing or eliminating the spread of nosocomial infections from the nares of employees. The impact on patient care and the economics of healthcare could be quite significant if the use of Staphage Lysate for this indication is proven to be effective.

In order to prove the value of Staphage Lysate for this use, the following study will be conducted.

- o 2 or more large hospitals, or other health care facilities will be considered. These centers will have active infection control units and ongoing screening programs to identify employees with nasal carriage of staphylococcus aureus.
- o participants will be treated for a period of 3 to 4 months agent and with either Staphage Lysate or placebo.
- o participants will be followed for a period of 6 months, with nasal cultures obtained every two weeks.
- o the primary efficacy endpoint will be to compare the difference between placebo and Staphage Lysate groups in the length of time that the participants remain free of staphylococcus aureus in the nares.
- o other endpoints will include:
 - o development of resistant staphylococcus aureus strains in the two groups.
 - o number of recurrences of the carrier state which occur in the two groups.
 - o differences in treatment necessary to treat recurrences in the two groups.

- o safety will be evaluated through clinical and laboratory assessments at 2 weeks, 1 month, 2 months, 4 months and 6 months.

D

MEETING ATTENDANCE LIST

Meeting between Delmont Labs and the
Center for Biologics Evaluation and Research.

DATE: 6/28/94 Time: 9:00 Room: 300N

<u>NAME</u> Please Print	<u>AFFILIATION</u>
<u>Lou Mocco</u>	<u>FDA/CBER/DVRPA</u>
<u>William Murphy</u>	<u>Delmont (Bio-Pharm - Biostatistics)</u>
<u>JOHN E. ENDERS</u>	<u>Consultant to Delmont</u>
<u>Catherine Burns</u>	<u>Delmont Laboratories Inc</u>
<u>Abbe Brautman</u>	<u>CRA consultant to Delmont</u>
<u>My Ch...</u>	<u>Delmont Labs Inc</u>
<u>Marshall Phillips</u>	<u>Delmont Labs</u>
<u>Lois Simmons</u>	<u>Lois Simmons FDA/CBER/OC/DIS</u>
<u>B.F. ANTHONY</u>	<u>FDA/CBER/DBP</u>
<u>Charles F. Lennow</u>	<u>BIOPHARM CLINICAL SERVICES</u>
<u>David J. Gimpel</u>	<u>Delmont Labs.</u>
<u>Lay & White</u>	<u>TULANE UNIVERSITY NO LA</u>
<u>PAUL RICHMAN</u>	<u>FDA/CBER/DVRPA</u>
<u>Julie Hannah</u>	<u>FDA/CBER/DBP</u>

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JAN 12 1981

Minutes of Meeting Between Representatives of Delmont
Laboratories and Bureau of Biologics

Bureau of Biologics
Bethesda, MD
December 10, 1980

Purpose of meeting: To discuss the protocol for clinical testing of Staphage Lysate (SPL) products (a study of SPL in the treatment of hidradenitis suppurativa) and to consider additional studies of SPL.

PARTICIPANTS: Carolyn Hardegree, BoB
William P. Graham, Penn State, Hershey, PA
Donald W. Kress, Penn State, Hershey, PA
Charles E. Lincoln, Delmont Laboratories
Sarah F. Lincoln, Delmont Laboratories
Samuel J. DeCourcy, Jr., Delmont Laboratories
John B. Robbins, BoB
Elaine Esber, BoB
Jack Gertzog, BoB
Morris Schaeffer, BoB
Sam Gibson, BoB
Richard F. Kingham, Covington & Burling

1. Dr. Hardegree asked if the results of the Mason Research Institute studies to determine the antigenic effect of SPL on bovine serum sensitized animals were available. She was advised that the study had been completed and the report submitted to BoB. Mr. Gertzog said he would send her a copy of the Mason study.
2. Mr. Kingham noted Delmont's proposed clinical study is being implemented ahead of the schedule recommended by the advisory committee in its report.
3. Dr. Schaeffer gave a short background report on the status of the efficacy review and follow-up studies, pointing out the factors which require that the studies be completed as expeditiously as possible.
4. Dr. Robbins asked Drs. Graham and Kress to describe in more detail the blinding mechanisms discussed in the study protocol. These procedures appear acceptable with the exception that both Dr. Hardegree and Dr. Robbins believe that bandages should not be applied over the injection sites.
5. Dr. Robbins asked what response could be measured in the patient that could be correlated with the potency of the product. Could there be, in effect, some sort of measurable serological response or test analogous to what is possible with such standardized products as DTP? Dr. Robbins noted that this sort of quantifiable response would be useful in assuring product lot-to-lot standardized potency.

6. Dr. Schaeffer noted that while he agrees with Dr. Robbins about the importance of measuring some quantifiable or serologic response in the patients, he believes that it is best to proceed with the clinical trial as soon as possible, and then address this issue.
7. Dr. Graham observed that as the clinical study progresses it might be appropriate to obtain blood/serum samples from the patients and then enlist the aid of immunologists/hematologists to see if they could identify some useful measurable parameters.
8. Dr. Robbins recommended that Dr. W. J. Karakawa of Penn. State University be considered as one of the immunology consultants because of his experience with staph organisms.
9. Dr. Esber asked if the administration of 0.1 mL SPL to all patients prior to initiation of treatment - to determine immunologic status - might alter the response of the control group in some way. Both Drs. Graham and DeCourcy did not believe that this would be a problem.
10. Dr. Esber asked if the results from the initial skin test would cause the investigators to alter the patient randomization process. Dr. Graham stated that all patients would be entered into the study as planned.
11. Dr. Esber wanted to know the purpose of the initial skin test. What is its value? Dr. Graham replied that its purpose was to show that the control and study groups were comparable in terms of staph sensitivity in addition to anergy. However, if a patient was negative to all four test antigens, Dr. Graham proposed excluding such patients from the study. Dr. Robbins disagreed and recommended that such patients not be excluded from the study.
12. Dr. Esber asked what would be measured that would be clearly ascribable to the treatment rather than to spontaneous remission and when such measurement might be made, e.g., during or at the end of treatment. Dr. Kress noted that patients admitted into the study are at the stage when the disease is chronic and extensive with generally continuing increase and that spontaneous remission is not significant. Dr. Graham said that approximately 80 percent of the patients at this stage of disease are at sub-performance levels. Changes in patients' status would be expected to be seen within 6 weeks of beginning treatment.
13. In a discussion between Drs. Esber and Graham about the possibility of quantifying the clinical parameters to be monitored rather than relying on general observations and photos, it was agreed that attempts would be made such as noting the number of dressing pads used per day for drainage, and measurement of range of joint motion.

14. There was a question regarding the cultures discussed in the protocol. Dr. Graham explained that the cultures will be made from drainage material and that previous studies have shown staph organisms to be the predominant group in such cultures.

15. Dr. Esber asked about aerosol administration of SPL - control of dosage, hypersensitivity, why the method is used. Dr. Graham stated that the nebulizer procedures used assured that dosage administration is well-controlled. It was noted that the aerosol method of administration is indicated in the labeling and that more hypersensitivity was seen after aerosol administration.

16. Dr. Esber asked about follow-up of patients in previous studies; and in the proposed study e.g., was the allergic status of any patients changed or did any of the negatives become skin test positive. Dr. Graham did not recall how many of the skin test negatives he had treated subsequently become skin test positive. He has used booster injections in the pilot study.

17. Dr. Graham noted that patients are kept in the hospital for about one to one and one-half hours after treatment.

18. Dr. Esber expressed concern about the complication of "vertigo" reported with the use of SPL. Dr. Kress answered that it was not true vertigo, but simply "light-headedness" or dizziness associated with fever and malaise. It was agreed that, the term "vertigo" be corrected in the listed complications.

19. Mr. Gertzog asked how long it would take to find 20 patients for inclusion in the study. Dr. Graham said it would take eight to 12 months for him to get 20 patients.

20. Dr. Hardegree asked for a copy of the manuscript of Dr. Graham's previous study. She determined that pregnant women would be excluded from the study. A question was also raised about whether people with asthma should also be excluded. This question was not resolved.

21. There was general agreement that Delmont should proceed with the clinical trial, but that the Bureau of Biologics would like to see the protocol and consent forms revised in accordance with this meeting before the study gets underway. Mr. Kingham also requested that the agency put its approval in writing after the revisions are submitted. Dr. Robbins also asked that an interim report be submitted to BoB some three or four months after the study is underway.

22. Delmont has identified a number of other possible studies using SPL, and investigators who appear willing to participate in controlled studies. Other diseases which Delmont is considering for investigation are eczema, chronic furunculosis, pustular acne, post operative infections and folliculitis. Four physicians have expressed interest in participating in these studies.

23. Delmont asked about cooperative studies in multiple locations to assure sufficient study populations. Dr. Robbins noted that this is an acceptable procedure which is frequently followed.

24. Delmont noted that some of the physicians they have talked to have reservations about the use of placebo in controls and would prefer to use either historical or other effective products as controls. Dr. Robbins stressed the importance of assuring that the only difference in treatment between control and test groups is the substance (SPL in this case) under investigation. It was noted that study designs are possible that would meet both Dr. Robbins' stipulation and the concern of the investigators who prefer not to use a placebo, e.g. the test group could receive both standard therapy and vaccine while the control group could receive standard therapy plus placebo. This issue will be considered when protocols for additional studies are submitted.

E

**English Translation of the Report on the Study
A Comparison of the Effectiveness of STAVA,
Staphage Lysate (SPL)[®] and Polystafana**

Study conducted 1992-1994 in the Czech Republic
Study coordinator – Frantisek Vymola, MD, PhD

TITLE OF THE PILOT STUDY

A Comparison of the Effectiveness of STAVA, SPL, and Polystafana Vaccines

NAME AND ADDRESS OF ORGANIZATION

Budejovicka' Health Clinic, Prague 4, Association of Out-Patient Wards (SAZZ), Prague 8, Czech Republic

STUDY COORDINATOR

MUDr. Frantisek Vymola, Health Clinic-Budejovicka', Prague 4, Czech Republic, Immunology Dept. - Staphylococcus Disease Center

ALSO COOPERATING ON THE STUDY

MUDr. Eva Vrbova, Director of Microbiology and Immunology, Institute for Mother and Child Care, Prague 4, Podoli' Immunology Dept., Health Clinic Budejovicka', Prague 4/Czech Republic, Center for Staphylococcus Disease

MUDr. Dagmar Jakoubkova', ORL Dept. Hazurska' (SAZZ), Prague 8

MUDr. Dory Maturova', Dept. Mazurska' Health Clinic (SAZZ), Prague 8

MUDr. Jirina Zabloudilova', Dermatology Dept., (SAZZ), Prague 8

MUDr. Marta Hajasova', Dermatology Dept., Medical Equipment, Prague 4,

MUDr. Lubos Tamele, Medical Laboratory, Immunology Dept., (SAZZ),

LAB WORK CARRIED OUT BY:

SAZZ Medical Laboratories, Prague 8, Czech Republic; Immunization Laboratory, Budejovicka Health Clinic, Prague 4, Czech Republic

MAIN PRINCIPLE OF THE STUDY

The basic principle of the study was to verify and compare the effectiveness of staphylococcus vaccine STAVBU CSAV, SPL-Delmont, POLYSTAVA-USOL in patients with staph. infections, mainly those having chronic process and resisting other treatments, mostly antibiotic cures.

DESCRIPTION OF CURRENT PROBLEM STATUS

Staph. sickness, particularly that accompanied by chronic process and repeated relapses, presents a serious medical, ethical, and social problem both here and abroad. In the Czech Republic several thousand citizens are afflicted by staph. infections and the number of new cases is constantly on the rise. Financial outlays for care and worker disability thereby rise, and the amount reaching in some cases over 150,000Kcs per person per year. To cite one statistic: the financial outlays for care of the 1000 sickest patients results in an annual loss of roughly 150,000 million KC.

Basic Idea

Economic reasons as well as medical, ethical, and social, led several experts to work out a multiple recovery regimen whose basis is immunotherapy aided by vaccines. Wherever staph. vaccines were used in the framework of the multiple recovery regimen, treatment was more rational and successful. Costs were also markedly lower. Results of previous treatment with STAVA vaccine confirm this, esp. among those with chronic staph. diseases; skin and epidermal adnex such as folliculitis, furunculosis, carbunculosis, phlegmona, cheilitis, panaritium, hidrosadenitis, impetigo, necrosis, cutis et subcutis, skin ulcers, etc., as well as mastitis, chronic inflammation of glandulae

vestibularis maioris bartholini, chronic fistulae in surgical wounds, otitis media in externa, pharyngitis, laryngitis, otitis et osteomyelitis, post-op complication, multiple trauma, states of oversensitivity to *S. aureus*, etc. Doctors are turning more and more to immunotherapy when treating patients suffering repeated relapses with staph. etiology. Most of the ailments have become chronic as a result of unsuccessful antibiotic treatment.

JUSTIFICATION OF THE STUDY AND A BRIEF DESCRIPTION:

Above all the study was made with purpose of comparing the therapeutic effect of the two vaccines mentioned below during out-patient treatment. They were chosen because both preparations are prepared by lysing bacterial culture of *S. aureus* with specific polyvalent phage. Concurrently, any undesirable side effects during treatment with the two above mentioned vaccines were monitored. Finally, the dynamic of changes among the leading indicators of the immunological profile was determined and the sensitivity of an isolated etiological agent to antibiotics, lysatic characteristics, and the production of hemolysates was determined (see below)

Vaccines Used for Injections

1. Registered Product Name
STAVA//CK SUKL 94026-1 form of usage injection: 10 x 2 ml prod. SIU, cntry CS reg. R, IS 59, reg. no 59/101/89-C.
2. International Medicine Title:
SPL/Staphage Lysate-Delmont Lab. Inc./Bacterial Antigen made from *S. aureus* Serol. Types I & III. Food and Drug Admin. US License No. 299 IP-108 A, Nov. 1952.
3. Registered Product Name:
POLYSTAFANA/CK-SUKL 94269-6/ form of usage injection of 10 x 0.5 ml product SIU, cntry CS reg. R, IS 59.
This vaccine was used only in a few cases because doctors in charge refused to continue applying the preparation to the majority of the patients. While some results were obtained from this treatment they were not evaluated because of the small number of patients involved.

Fundamental Characteristics of Phagelysate Vaccine

-STAVA injection-product of the Biophysical Institute of CSAV (Czechoslovak Academy of Sciences). For detailed designation see above

Composition:

STAVA injection is a complex of antigen components with a potent immunization effect, particularly against staph. infections. Antigens liberated by lysing of two *S. aureus* strains/No. 6409, Knycl ILF/ by a polyvalent phage have a ribosomal, cytoplasmic origin. This comes from surface walls of bacteria, as well as their extracellular products. For further data see introductory note.

SPL/Staphage Lysate/ - producer, Delmont Laboratories, Inc. For detailed designation see above.

Composition:

SPL/Staphage Lysate/ is a complex of bacterial antigens prepared by lysing of two *S. aureus* strains having a serologic type I and III by means of a polyvalent bacteriophage. The vaccine includes no preservatives. Sterilization is attained through ultrafiltration. SPL is standardized on the basis of the content of staph. cells before a lysing by a phage. One ml contains 120-180 million colonies of *S. aureus* and 100-1000 million staph. plaques of a bacteriophage. A more detailed description is found in the original English instructions

Important Note

The same procedure was maintained with both preparations concerning dosage and application. The application of both preparations for injectable administration always began with an intracutaneous form (dose) of 0.02-0.05 ml into the forearm. The size of the dose was always dictated by the patient's age, medical history, overall clinical progress, and immune status. The dosage during intracutaneous application was not increased if the host reaction (erythema) at the spot of the injection exceeded 2-3 cm. Most patients were given the vaccine bilaterally-subcutaneously by the second visit (i.c.) If the erythema from the application was less than 2 cm and there was no swelling in the area of infection, the application of the vaccine was as follows: a 0.02-0.05 ml dose was injected (i.c) into the inner side of one forearm, and subcutaneously into the medial deltoid of the other arm. At each further visit (intervals were usually 3-5 days) the application procedure was reversed, i.e., the arm which received the deltoid injection was injected in the forearm, and vice versa. During the subcutaneous application the dosage reached 0.3 ml, in exceptional cases 0.5 ml. The duration of the vaccine treatment was guided by the general clinical picture and lab findings. Following the dual means of vaccination the host (patient) usually showed a reaction (swelling, pain, and erythema), on occasion fatigue syndrome appears. The reaction can be timely (within 5-30 min.), distant (within 5-6 hours), or late (within 16-48 hrs.) If a patient's reaction lasted 72 hours, the interval between visits was extended to 5-6 days, and the next dosage was increased. The dosage was cut in half for persons under 10 years of age. Otherwise it was recommended to maintain an individual approach to treatment.

The injection procedures used with POLYSTAFANA will not be described because it was used on a very small number of staph. patients. Nevertheless, the attached character of the POLYSTAFANA vaccine as introduced by the producer enables one to glance at the composition of the vaccine with a description of indicators, and eventually contraindicators and instructions on its dosage scheme.

Lysates for Local Use

Since it has long been proved that *S. aureus* lingers in the nasal cavity mainly in the mucous membranes of staph patients, and is usually identical with the etiological agent, the staph. lysate STAFAL Sevac was used during local applications into the nasal passages as well as SPL-Staphage Lysate- Delmont in an amount proportionate to the SPL injection preparation. The dosage scheme was the same in both cases: the vaccine was administered in the form of nose drops. First nasal passages were cleaned thoroughly! Adults were given 2-3 drops and children 1-2, 2x daily at 12 hour intervals.

The goal of this procedure was to eliminate residual staph. from the main potential infection reservoirs in the framework of the multiple care regimen.

Selection of Patients

In all, 130 patients suffering from chronic staph. infections were treated in the study. All of the patients had received previous treatment, often following a different regimen in which they were given predominately antibiotics. Specifics are introduced in the individual treatment histories.

The original aim of dividing patients into three groups of approx. equal size which would correspond to the three vaccines was scrapped. Most of the clinics refused to continue administering POLYSTAFANA to certain patient because of excessive epidermal reactions (swelling, pain, erythema) after injections. This in no way influenced the basic idea, which was to compare the effectiveness of the two most used vaccines (STAVA produced in the CR and SPL in the USA by Delmont). Further, these two vaccination materials are prepared by a lysate of staph. production strains through a polyvalent viral specific phage.

Of the 130 patients
47 received STAVA
68 received SPL
15 received POLYSTAFANA

Table 1 shows the total number of those treated by diagnosis and sex. It does not introduce average age or relative duration of illness because reliable statistics were not available.

Monitoring the Immunological Background

The amounts of immunoglobulins G, A, and M, a further complement of C₃ and C₄, phage activity, and sedimentation of erythrocytes (FW) were traced in all patients.

Other indicators: the dynamics of antitoxic titres against individual staph. toxins after administration of the appropriate vaccines was not monitored. The reason was that previous studies did not succeed in proving their significance. The antitoxin response to phage particles was not determined because it did not show up in earlier studies.

Note:

Both of the laboratories which took part in ascertaining the immunoglobulin serum values used methods routinely practiced in the CR. There was one difference: the Prague 8 lab expressed the measurements by weight, whereas the Prague 4 lab expressed them in units (ml) of tested blood serum.

Determination and Characterization of the Cause of Illness

Production of the toxin hemolysin was discovered in isolated strains of S. aureus along with susceptibilities to a specific polyvalent viral phage, and antibiotics used most often in out-patient practice (penicillin, oxacillin, erythromycin, spiramycin, tetracycline, chloramphenicol, and in exceptional cases even lincomycin.)

EVALUATION OF RESULTS:

Detailed results and their analysis will be presented at congresses in Saltzburg March 1994 and Prague April 1994 as well as published in three independent memoranda. In view of this we will only mention conclusions from clinical results and laboratory findings. They are as follows:

CLINICAL RESULTS:

Among those suffering from dermal illness (A) 30 out of 32 patients who received SPL injections were completely cured. The condition of the other two improved.

Nineteen of the patients were administered the STAVA preparation. Twelve were cured and the condition of the remaining seven improved. After administering POLYSTAFANA to 5 patients, 2 were cured, 1 improved. The remaining 2 are under constant observation. Their treatment is being continued in the surgery ward.

Conclusion:

Based on the above results we can state that the SPL injections achieved outstanding results in patients with epidermal disturbances. Its results were a shade better than those achieved by the STAVA injections. The results of the STAVA injections were however very good, especially considering that most of the patients had been treated unsuccessfully before with antibiotics, autovaccines, and surgery (their improvement was only temporary). For illustration purposes we note that the POLYSTAFANA injections resulted in 2 complete recoveries, 1 improved condition. The treatment did not master the illness in the other two cases.

The following results were recorded with patients diagnosed with osteomyelitis B: SPL injections resulted in a cure (or rather, in a currently lasting stabilization of the process) in three cases; and improvement in three. STAVA injections resulted in a cure (lasting stabilization) in 2 cases and improvement in 3. The total number of patients treated for osteomyelitis was 11. In group C those with respiratory infections were treated (otitis are introduced under a separate heading). The following results were achieved: Of the 39 patients treated, 19 were injected with SPL. 10 were cured and the other 9 experienced a subjective improvement. Among patients treated with STAVA injections (13) good effectiveness was recorded in 6, and significant clinical improvement was the result in 7 cases (patients were able to work.) POLYSTAFANA was used on only 6 patients in a limited succession of time. Four patients showed improvement, two showed a clinical effect. In group D 25 patients with Otitis were treated. There were 11 treated by SPL injections. A clinical effect was the result in 6 cases, and significant improvement gotten in 5 cases. Ten patients received STAVA injections. After treatment 3 showed a clinical effect, 7 showed significant improvement in the course of monitoring period. POLYSTAFANA was used with only four patients, usually for only a short time (see log). Treatment was continued with either SPL or STAVA injections. For an overview see tables 2 and 3.

Note:

The healing effects of the aforementioned immunological substances were monitored at most by four consecutive laboratory examinations.

This brief report introduces only the results found in the logs at the end of the pilot study. The final results of the treatment, which continued after the study, are not included. It is thus necessary to state that all patients with the exception of 5 having dg osteomyelitis were cured in the course of 6 months further treatment by the multiple treatment regimen without antibiotics. The immunization-substance preparations STAVA and SPL created the regimen basis in the form of injections and local instillation. This report does not include either the average age of the patients due to their wide range, or the average length of previous treatment due to the heterogeneity of the regimens.

Lab Evaluation:

Microbiological Findings

Microbiological findings showed that *S. aureus*, often isolated from nasopharynges (but above all from nasal mucous membranes!), was the instigator of illness in a large majority of cases with a clinical diagnosis. Preparations of STAVA and SPL were thus applied by means

of drops to the nasal passages of patients in whom *S. aureus* was isolated as a potential reserve (nasal cavity.) Either an amount of SPL injection preparation (conformable to SPL injection preparation) was used during the application of SPL injection prep., or STAFAL-Sevac during application of the STAVA injection preparation. *S. aureus* was eliminated from the nasal cavity in all cured persons; in cases of improvement *S. aureus* was never eliminated from the nasal cavity. We understand this to be the reason for the incomplete cure, and therefore continued treatment. In our opinion the antibiotic treatment also failed because the staphylococcus cannot be eradicated by antibiotics from the surface of mucous membranes in the nasal cavity. If the antibiotics were eliminated, it was only for a short time and there was a risk of resistance to antibiotics applied locally.

Immunological Findings

Certain immunological parameters were measured in blood serum at approximately the same time intervals as in the bacteriological investigations. One could hardly show more emphatically the defects of serum immunoglobulins and the compositions C_3 and C_4 , even though with vaccination they measured slightly higher. In patients with lowered measurements of IgM, the values were slowly and gradually restored. Concerning FA values, it was possible to state phage activity gradually increased to the highest level in the group suffering from dermal forms of staph. infection. High levels were also noted in patients with dg osteomyelitis, otitis, and less significantly in those with classic infections of the upper respiratory tract. FW data (ER sedimentation) from lab findings classed with immunological parameters tended to provide the most reliable information on the clinical course of a staph. infection. The original values of FW (at the beginning of the treatment) gradually fell in a predominant majority of cases to normal.* It follows from this that in cases of staph. infections it is sufficient to monitor only the fluctuations in FW and FA values. The antitoxic response (as earlier studies showed) did not give reliable information on the clinical course of staph. sickness.

OVERALL EVALUATION:

The Pilot Study showed:

- the outstanding healing properties of SPL inj. as an immunopreparation. STAVA injections proved somewhat less effective, but still provided good results.
- the excellent tolerance of host tissue for SPL and STAVA injections after subcutaneous and intradermal applications. Only two patients were observed to have more violent local reactions - swelling, pain, erythema exceeding 6cm, and fatigue lasting two days.
- the STAFAL-Sevac and SPL injections used in the pilot study were applied locally in the framework of multiple-patient care. These preparations notably eliminated *S. aureus* from the nasal cavity, the most frequent reservoir of infection.
- it was determined that costs for treatment of the studied illnesses were 5 times lower in comparison with previous treatment. The most important result was that, with only three exceptions, none of the patients suffered a relapse. The patients were monitored for 6 months after completion of treatment.
- it was determined by lab tests following each specific vaccination that:
 - FW values gradually decreased, and
 - phagocytic activity increased.
 - IgM, C_3 and C_4 values reverted to normal, if these defects were present at the beginning of treatment.

* This concerns patients who were eventually cured.

It is possible to consider the most important signal of a successful staph. infection cure to be the elimination of the instigator of the S. aureus infection from a potential reservoir usually the nasal cavity. The local application of staph. phage lysates is a necessary part of the overall treatment regimen.

RECOMMENDATION:

The pilot study clearly showed the superiority of immunomodulation by SPL in chronic staph. diseases, especially those which resist other cures. The best treatment is a regimen of SPL preparation in an injectable form combined with local application. We also recommend that the cost of this medicine be paid for by the appropriate health insurance companies in a manner commensurate with other such medicines.

Table 1

Chronic Staph. Infections.
 Total of 130 Total patients treated - Categorized by product

<u>Diagnosis</u>	<u>SPL</u>	<u>STAVA</u>	<u>POLYSTAFANA</u>
Skin/Dermal. inf., Osteomyelitis, Respiratory Inf., Otitis	68	47	15

Table 2

Chronic Staph. Infections
 Total of 130 patients treated - categorized by type of staph infection
 and sexual distribution

<u>Diagnosis</u>	<u>SPL</u>		<u>STAVA</u>		<u>POLYSTAFANA</u>	
	M	F	M	F	M	F
Skin Infections 56	13	19	8	11	2	3
Osteomyelitis 11	4	2	3	2	-	-
Respiratory Inf. 38	11	8	6	7	2	4
Otitis 25	3	8	3	7	2	2
Total 130	31	37	20	27	6	9

Table 3

Chronic Staph. Infections - Clinical Results of Immunotherapy

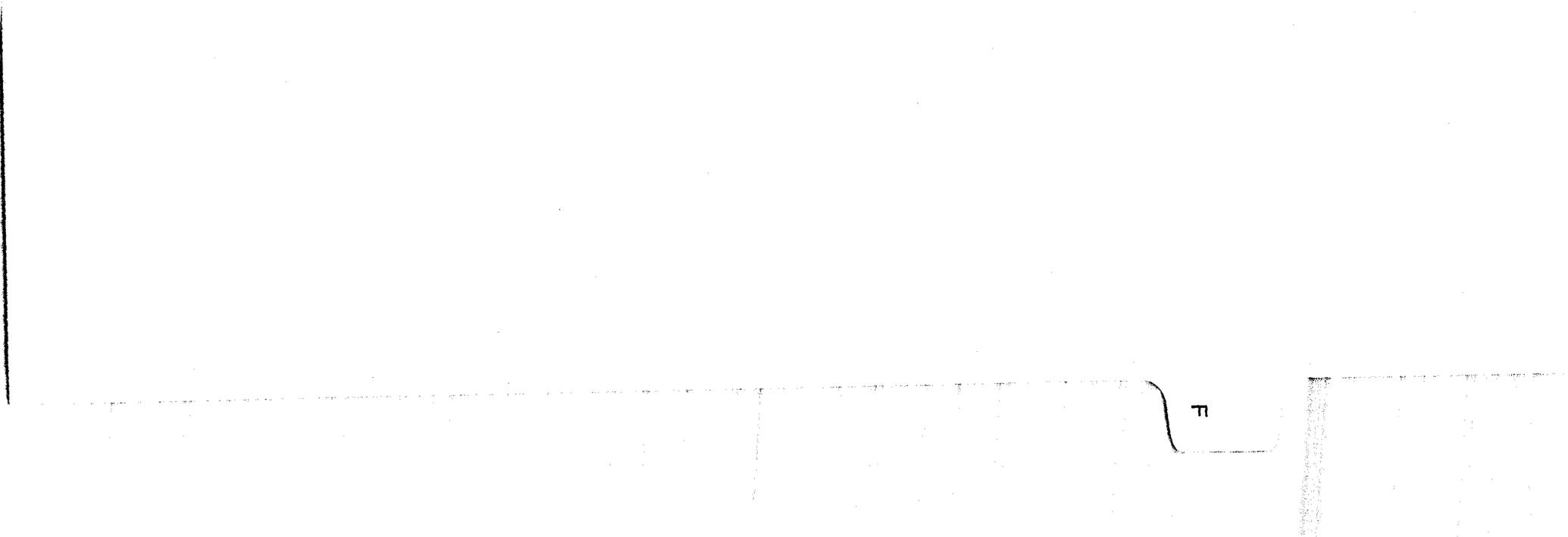
DIAGNOSIS		SPL		STAVA		POLYSTAFANA		
		C	I	C	I	C	I	N
Skin Infections*	56	30	2	12	7	2	1	2
Osteomyelitis	11	3	3	2	3			
		stabilized		stabilized				
Respiratory Infection	38	10	9	6	7	4		2
Otitis	25	6	5	3	7	1	-	3
Total		49	19	23	24	7	1	7

C = cured

I = improved

N = no effect

* impetigo, furunculosis, folliculitis, pyoderma, hidradenitis, pyoderma



CYTOKINES PRODUCED BY HUMAN MONONUCLEAR CELLS UPON STIMULATION BY STAPHAGE LYSATE (SPL)^{R*}

G.KRISHNAN **AND D.J.GANFIELD

Delmont Laboratories Inc, Swarthmore, PA-19081, USA.

SUMMARY

Staphage lysate, a complex mixture obtained by bacteriophage lysis of Staphylococcal Aureus, stimulated the production of various regulatory cytokines from human mononuclear cells (HuMNC) and THP-1 cell lines *in vitro*. These cytokines (TNF-alpha, IL-1 beta, IFN-gamma and IL-10) were quantitatively assayed by using ELISA technique. Since TH1, TH2 and monocytes are known to produce these cytokines, our study showed that Staphage Lysate contained both immunoenhancing and immunosuppressive factors that may have clinical relevance.

INTRODUCTION

Delmont's proprietary product, Staphage Lysate (SPL)^R has been earlier shown by several investigators to be effective against canine pyoderma and human staph infections (1-3). The ability of SPL^R to produce lymphotoxins and interferon has been documented as early as the 1970s (4). Other early investigators demonstrated the ability of SPL^R to elicit cell mediated immunity (5-7). Our early work (8) showed that SPL^R by itself or in combination with IL-2 restored the function of NK cells in cancer patients as assayed by *in vitro* 51Cr release method and by *in vivo* GVH method using immunosuppressed rats. Esber et al (9) showed that SPL^R was not only an immunomodulator of cell mediated immunity but also an effective potentiator of humoral antibody response. Our interest lies in understanding the mechanism of action of SPL^R and its biologically active products as anti-infective and anti-cancer agents. While TH1 cells provide cell mediated immune resistance to infection, TH2 cells provide humoral immune response and suppress cell mediated immune responses. While TH1 cells produce cytokines like IL-2, IFN-gamma etc, TH2 cells produce IL-4, IL-5, and IL-10. Since cytokines produced by the immunocompetent cells are known to regulate the immune responses, a systematic study of the cytokines produced by human mononuclear cells and cell lines upon stimulation by SPL^R - was undertaken by us.

*Part of this work was presented at 12th European Immunology meeting at Barcelona, Spain in June, 1994.

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Human monocytic cell line (THP-1) was purchased from American Type Culture Collection, USA and propagated in the laboratory using RPMI 1640-5%FBS-1%PS.

Activation of THP-1 cells /HuMNC by SPL^R was carried out using 6×10^5 cells /ml, 10% v/v of SPL^R in case of THP-1 cells and 1:1000 of SPL^R (final concentration) in case of HuMNC. The mixtures were incubated at 37°C for 2 days in case of THP-1 cells, and 6 days when HuMNC were used.

Assay for Cytokines

The levels of TNF-alpha, IL-1 beta, IFN-gamma and IL-10 present in the cultured supernatants were determined by using Medgenix cytokine kits. The vendor's procedure was essentially followed except in IL-10 assay. 50-200 microliters of culture supernatants were incubated with 50 microliters of anti-cytokine HRP conjugate for 2 hours at room temperature in microtiter wells, washed (3X, buffer-tween), incubated with 200 microliters of TMB substrate (1:100) at room temperature for 15 minutes, washed (3X), 50 microliters of 1.8 N sulfuric acid added and the yellow color that developed was read at 450 nm in an ELISA reader.

RESULTS

Production of cytokines from THP-1 cell line and HuMNC depends upon experimental conditions like the concentration of cells, and SPL^R, incubation time and temperature. Tables I-III describe the results obtained when the experimental conditions as described under "Materials and methods" were employed. In IL-10 assay, correction for background OD was made.

TABLE-I:

IL-1 beta levels in the culture supernatants of THP-1 cells activated by SPL^R or controls

Samples	IL-1 beta (pg/ml)
Medium-5% FBS	21.4
SPL ^R #1	229
SPL ^R #2	136
SPL ^R #3	142
LPS* (1ug/ml)	374

*List Biologics, USA

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TABLE-II

IL-1 beta, TNF-alpha, IFN-gamma levels in the culture supernatants of HuMNC stimulated by SPL^R

Samples	IL-1beta(pg/ml)	TNF-alpha(pg/ml)	IFN-gamma(IU/ml)
SPL ^R #4	680	1100	7.0
SPL ^R #5	160	1400	7.5

TABLE-III

IL-10 in the culture supernatants of HuMNC activated by SPL^R

Samples	OD(450 nm)
Standard IL-10(12pg/ml)	0.48
SPL ^R #4	0.64
SPL ^R #5	0.46

CONCLUSIONS

This preliminary study showed that different preparations of SPL^R stimulated the production of cytokines like IFN-gamma, IL-1 beta, TNF-alpha and IL-10 from human monocytic cell line(THP-1) and human mononuclear cells(HuMNC) in varying amounts depending upon the experimental conditions. Since regulatory cytokines are known to be produced by different subsets of T, B lymphocytes and monocytes, SPL^R should also be expected to stimulate various immunocompetent cells *in vivo*, providing positive or negative signals in immune responses that may have clinical relevance. A study of the different cytokines produced by purified factors from SPL^R would in future help us understand the mechanism of action of SPL^R as an anti-infective and anti-cancer agent.

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