DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Dr. Leslie Steven Aufseeser
1700 Madison Avenue
Lakewood, New Jersey 08701

JUL 22 2003

Re: Docket No. 76N-0482
Comments No. CP7, LET10, EMC1

Dear Dr. Aufseeser:

This letter is in response to your citizen petition dated October 26, 2001, your letter dated July 11, 2002 concerning the status of the petition, and your fax dated February 24, 2003 regarding results of a small clinical trial. These submissions were filed under Docket No. 76N-0482 in the FDA's Dockets Management Branch as Comments No. CP7, LET10, and EMC1, respectively. The petition was received by the Division of Over-the-Counter Drug Products on November 4, 2002. The petition requested that FDA amend the proposed monograph for over-the-counter (OTC) topical antibiotic drug products (published in the FEDERAL REGISTER (FR) of April 1, 1977, 42 FR 17642-17681) to lower the proposed amounts of bacitracin zinc and polymyxin B sulfate in an ointment dosage form.

I. PETITIONER'S REQUEST AND FDA'S DECISION

In January 2001 the agency received a letter dated January 22, 2001, from the Honorable Christopher H. Smith, Member of the U.S. House of Representatives, in which you asked for his assistance in obtaining FDA approval for your Regenicel Healing Ointment through the OTC drug monograph process. On April 26, 2001, the agency issued a letter (copy enclosed) to Mr. Smith on your behalf stating that the indication for your product (the treatment of diabetic ulcers) is not an approved indication under the "Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Final Monograph for OTC First Aid Antibiotic Drug Products". The monograph indication for these products is "First aid to help prevent infection in minor cuts, scrapes, and burns."

Specifically, your petition requested a change of the bacitracin topical ointment dosage proposed in the monograph (42 FR 17654), which states: "Topical ointment dosage, for both adults and children, should be not less than 500 units of bacitracin per gram (gm) of finished ointment dosage form." You requested that the bacitracin dosage be lowered to 44 units of bacitracin per gm. Your petition also requested a change in the polymyxin B sulfate proposed monograph dosage at 42 FR 17655, which states: "Topical ointment dosage, for both adults and children, should be 4,000 to 5,000 units of polymyxin B per gm of finished ointment dosage form when used in combination." You requested that the dosage be lowered to 892 units of polymyxin B sulfate per gm.

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The final monograph was published in the FEDERAL REGISTER of December 11, 1987 (52 FR 47312-47324) and is included in Title 21 of the Code of Federal Regulations (CFR), Subpart B of Part 333, "First Aid Antibiotic Drug Products". The applicable section, 333.120(a)(6), for permitted combinations of active ingredients states: "Bacitracin zinc-polymyxin B sulfate oinment containing, in each gram, 500 units of bacitracin and 10,000 units of polymyxin B in a suitable ointment base."

Your petition included two study reports involving a product that was a mixture containing A & D Ointment, Vitamin E Oil, and Polysporin Powder (bacitracin zinc and polymyxin B sulfate powder). You stated that your test product contained the following amounts per gram of finished product: 141 I.U. of vitamin E, 892 units of polymyxin B sulfate, and 44.05 units of bacitracin zinc. The petition also provided the formulation of the A & D Ointment that was used in the test product. However, the ratio of the three components (A & D Ointment, vitamin E, and Polysporin Powder) in the test product was not provided.

The agency has reviewed your petition and denies your requests. The basis for these decisions is set forth below.

II. DISCUSSION

1. Data Submitted for Review.

The objective of your two studies was to evaluate the effectiveness of the product in healing a variety of lower extemity lesions in subjects who presented themselves to a private podiatry practice for treatment. Both of the studies were nonrandomized, uncontrolled, unblinded, open-ended, single center studies. One study included 67 subjects, the other study included 94 subjects. The petition also included four testimonials.

Your February 24, 2003 fax transmission included an uncontrolled open-label, pilot study in which only five patients completed the trial. The data generated from this trial are of limited value. The lack of a study protocol and the small number of patients enrolled (associated case reports) preclude a meaningful evaluation of data from this study. Because of these limitations, this study will not be considered further.

In the two studies provided in the petition, the subjects' diagnoses included delayed wound healing, diabetic ulcerations, venous stasis ulcerations, gouty ulcerations, trauma, wound dehiscence, abscess, thermal burn, vascular ulcers, and decubitus ulcers. Although the majority of subjects entered in the 67 subject study were treated with biweekly applications of ointment to their wounds, some subjects used the study ointment four times a day. Subjects took systemic antibiotics concurrently as needed. A jar of ointment was dispensed to each subject. If a wound was draining heavily, additional polysporin powder was added to the ointment. If an ulcer was recalcitrant or cultured positive for methicillin resistant *Staphylococcus aureus*, vancomycin powder was sprinkled onto the ointment prior to its application.

The 94 subject study used a similar protocol. In addition to being treated with the study ointment, subjects with venous stasis ulcers also received concomitant treatment with 1 percent hydrocortisone cream to the skin surrounding the wound and treatment with Unna boots. Subjects were seen on a weekly basis, except for subjects with venous stasis ulcers who were seen twice a week. The study does not report which subjects used an antibiotically enriched study ointment, and it fails to state how many subjects were treated with concurrent systemic antibiotics.

2. Agency's Comments on the Submitted Data

The agency finds the data inadequate to support the effectiveness of 44 units of bacitracin and 892 units of polymyxin B sulfate per gram of finished ointment as an OTC first aid antibiotic, which is the monograph applicable to this product. The studies provided were designed to assess effectiveness of the product for wound healing in wounds requiring treatment by a physician instead of the monograph first aid indication for the prevention of infection "in minor cuts, scrapes, and burns".

The agency finds major deficiencies in the data from the two studies for a number of reasons:

1) The data were generated from nonrandomized, uncontrolled, unblinded, open-ended, single-center studies, which are not consistent with the usual conduct of wound studies.
2) Because of the unblinded nature of the studies, investigator bias cannot be ruled out.
3) The studies failed to characterize wounds to exclude neoplastic, immune mediated, or infectious etiologies.
4) The studies did not have adequate methods to assess wound infections or to differentiate between colonized or infected wounds.
5) The studies lacked quantitative measurements, a grading system for wound severity, or a modality of wound imaging that could document wound healing for the study subjects.
6) The studies failed to capture pertinent demographic characteristics, the use of concurrent background medications, the subjects' smoking habits, and the duration of healing and recurrence of previously treated study wounds, which are important in a wound study.
7) Only descriptive statistics and not comparative statistical analysis could be used to analyze the studies' results due to the uncontrolled study design and lack of designated treatment endpoints.

Further, the study results were confounded by the use of "antibiotically enriched" study ointment, which contained additional Polysporin powder or powdered vancomycin in some cases, as well as concurrent treatment with systemic or topical antibiotics/antimicrobials or other wound healing modalities such as Unna boots. Due to the poorly designed nature of the studies and the lack of a clearly defined standard of wound care, there was extreme variability in the scheduling of follow-up visits, the frequency of application of the study ointment, and the type of dressing applied, which may have also confounded study results. In addition, pertinent

information was missing in the petition, such as the protocol, subject consent and adverse event forms, and the raw data for the studies. Therefore, from these studies, it is impossible to conclude that 44 units of bacitracin and 892 units of polymixin B sulfate per gm of finished ointment are truly effective.

III. CONCLUSION

The agency mentioned in our April 26, 2001, letter to Mr. Smith that the 1951 Durham-Humphrey amendment to the Federal Food, Drug, and Cosmetic Act stated that U.S. drugs that cannot be used safely without professional supervision are to be dispensed only by prescription [of a licensed practitioner]. Such drugs may be deemed unsafe for nonprescription use because they are habit-forming or toxic, have too great a potential for harmful effects, or are for medical conditions that can not be readily self-diagnosed. The use of your ointment mixture for the treatment of diabetic ulcers, venous ulcers, gouty ulcers, decubitus ulcers, vascular ulcers, wound dehiscences, abscesses, and thermal burns would require a physician's diagnosis and medical supervision. The agency concludes that your product should be developed as a prescription product, which requires prior agency approval through the New Drug Application (NDA) process. The agency recommends that you refer to current agency guidances on developing products for the treatment of chronic cutaneous ulcer and burn wounds (copy enclosed).

Based on the above, your petition is denied.

Any comments you wish to make on the above information should be identified with the appropriate docket and comment numbers (76N-0482/CP7) and submitted in three copies to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.

Sincerely yours,

John M. Taylor, III
Associate Commissioner
for Regulatory Affairs

Enclosures