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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

19900 MacArthur Blvd., Ste 300
Irvine, California 92612-2445
Telephone (714) 798-7600

WARNING LETTER

March 11, 1998 WL-21-8

Mr. George F. Dembo II
Chairman and CEO
Arizona Natural Resources
2525 Beardsley Road
Phoenix, Arizona 85024

Dear Mr. Dembo:

During an inspection of your Phoenix drug manufacturing facility, conducted between July 29 and August 12, 1997, our investigator documented serious deviations from the Current Good Manufacturing Practice Regulations [Title 21, Code of Federal Regulations (CFR), Parts 210 & 211). These deviations cause your drug products to be adulterated within the meaning of Section 501 (a) (2) (B) of the Federal Food, Drug, and Cosmetic Act. For example:

1. Your firm failed to clean, maintain, and sanitize manufacturing equipment at appropriate intervals to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements. Specifically, filling equipment used to fill bottles wit[redacted] brand[redacted] Waterproof Sunscreen had a leaking valve temporarily repaired using tape. The equipment, broken valve and tape, and sinks used in the manufacture and filling of this product were found to be contaminated with various microbial organisms, including Pseudomonas putida, Pseudomonas auruginosa, and Pseudomonas pickettii. These sites and contaminants were the most likely source of microbial contamination subsequently found in lots of the sunscreen product. [CFR 211.67(a)]

2. Your firm failed to establish and follow written procedures for cleaning and maintenance of equipment. Specifically, the cleaning procedure established prior to the contamination was not followed and/or not validated. There was no validation study determining whether the cleaning and sanitization methods and chemicals used on manufacturing equipment was effective against microbial contaminants commonly found in your environment. [CFR 211.67 (b)]

3. Your firm failed to establish and follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality and purity they purport or are represented to possess. These procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit. Specifically, your firm's existing Standard Operating Procedures (SOP's) were outdated or had several different versions. There was no Change Control Procedure in place to assure that all SOP's used in manufacturing, testing, etc. were current and approved by appropriate management and quality unit. In addition, existing SOP's were written solely in English, despite numerous employees at your firm being unable to read or write in the English language. [CFR 211.100]

4. Your firm failed to maintain manufacturing records so that data was evaluated, at least annually, for quality standards of each drug to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures must be established and followed for such evaluations. Specifically, your firm failed to establish written procedures to perform this annual product evaluation and had never performed the review [CFR 211.180 (e)]

In addition to the above, our review of the batch records for the [redacted] Sunscreen Product and your firm's investigation into product failure due to bacterial contamination shows that the formula's amount of preservative may have been inadequate. The USP test for Preservative Effectiveness <51> should be performed on this product as well as all other products that contain preservatives that are manufactured by your firm. In addition to the five organisms specified by the USP method, you should test the products using the same contaminating organisms found in your manufacturing environment. Please include a corrective action plan that addresses this issue in your written response.

It also appears that many of the deviations uncovered during our inspection may be due to a quality unit that is inadequately staffed. Your own organization charts indicate that the quality control department consists of [redacted]. The cGMP regulations require that the quality unit be responsible for oversight of numerous activities including raw material and component testing and release, maintaining written procedures and change control, manufacturing activities and deviations, analytical testing and release of finished products. It was apparent during the inspection that [redacted] cannot handle all of the required cGMP QA/QC activities at your firm. Please submit an action plan on how your company is addressing these requirements..

We regret FDA's delay in sending this letter informing you of FDA's concern with your deficiencies due to delays in our review process. You should be aware that the list of

violations identified above is not intended to be an all-inclusive list of deficiencies at your facility. A list of observations (FDA 483) was issued and discussed with you at the conclusion of the inspection. It is also noted that your firm has a continuing history of failure to comply with cGMP regulations. Your firm received an extensive (FDA 483) list of deviations and Notice of Adverse Findings Letter following an inspection in 1988. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice regulation and other applicable regulations. Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to do so may result in regulatory action without further notice, including seizure and/or injunction.

You should notify this office in writing, within fifteen (15) working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step taken to prevent the recurrence of similar violations. If corrective action cannot be completed within fifteen (15) working days, state the reason for the delay and the time within which the corrections will be completed.
Your reply should be addressed to:

Patricia A. Gupta, Compliance Officer/Investigator
U.S. Food and Drug Administration
4615 East Elwood Street, Ste. 200
Phoenix, AZ 85040

Sincerely,

Elaine C. Messa

Elaine C. Messa
District Director