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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 24 2005

CBER-05-023

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. John G. Roby
President and CEO
Greer Laboratories, Inc.
639 Nuway Circle NE
Lenoir, North Carolina 28645-0800

Dear Mr. Roby:

The Food and Administration (FDA) conducted an inspection of Greer Laboratories, Inc., 639 Nuway Circle NE, Lenoir, North Carolina, between February 14 and March 3, 2005. During the inspection, FDA investigators documented violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), Section 351 of the Public Health Service Act (PHS Act), 42 U.S.C. Section 262, and deviations from the applicable standards and requirements of Subchapter C Parts 210 and 211, and Subchapter F Parts 600-680,Title 21, Code of Federal Regulations (21 CFR). At the close of the inspection, FDA issued a Form FDA 483, Inspectional Observations, that described a number of significant objectionable conditions relating to the facility's compliance with current good manufacturing practice (CGMP). Significant deviations in the manufacture of allergenic extracts observed during the inspection include, but are not limited to, the following:

1. You failed to assure that your drug product meets the applicable standards of identity, strength, quality, purity, and potency at the time of use by appropriate stability testing [21 CFR 211.137(a), 211.166, 680.3(e), and 610.10]. The standardized Aqueous Short Ragweed Pollen Extracts Diluted Using Coca's Buffer were given an 18 month expiration date which is not supported in that three lots of product failed to meet the 12-month potency test requirements, and one of those lots failed the 9-month potency test. You continued to release Aqueous Short Ragweed Pollen Extracts Diluted Using Coca's Buffer lots with expiration dates exceeding 12 months. In addition, you failed to report the potency stability failures to the Center for Biologics Evaluation and Research (CBER) [21 CFR 600.14].

2. Your firm failed to establish and follow appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile and to assure

that such procedures include validation of sterilization processes, [21 CFR 211.113(b)] in that final product vials were subjected to the following manipulations during and subsequent to the aseptic fill operations.

a. Sterility test samples were collected from stoppered final product vials by removing product from the vials with syringes. The vials from which samples were withdrawn were then subsequently released and distributed.

b. Personnel were observed adding product from a graduated cylinder to under-filled final product vials and removing product with a syringe from over-filled final product vials.

3. Your quality control unit failed to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated; the quality control unit also failed to investigate thoroughly any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications [21CFR 211.22 and 211.192 respectively]. For example:

a. The quality control unit's written record of its investigation of complaint 05-017, dated 8/19/04, of mold growing around the cap of a vial did not include examination of reserve samples, of other units of the lot that were still in inventory at the time the complaint was received, or of batches of other drug products manufactured at the same time or under the same conditions as the lot, or that may otherwise have been associated with that lot. Similarly, the quality control unit's written record of its investigation of complaint 05-027, dated 12/27/04, regarding a dented metal cap, did not reveal any examination of reserve samples or of any other drug products that may have been associated with the failure. The quality control unit's duty is to determine what batches of products may have been associated with failures or discrepancies that it is investigating, and to include the basis for that determination among its conclusions in its written investigation record.

b. The quality control unit's investigation in June 2004 of the failure of liquid phenol [redacted] raw material lot [redacted] to meet incoming specifications did not consider that a previous shipment of this raw material lot had been used in formulating final product that was distributed.

c. The quality control unit did not thoroughly investigate the potency stability failures for the final product lots of standardized Aqueous Short Ragweed Pollen Extracts Diluted Using Coca's Buffer. The final product lots failed to meet the 12-month minimum potency requirements yet lots continued to be released with expiration dates exceeding 12 months.

4. Your firm failed to establish written procedures applicable to the function of the quality control unit [21 CFR 211. 22(d)]. For example, there is only one procedure intended to describe the functions and responsibilities of your firm's quality control unit which is in draft, with no implementation date or signatures of review and approval.

5. Your firm failed to establish written procedures for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in the drug product specifications or manufacturing and control procedures, including provisions for

the review of complaints, recalls, and investigations conducted for each product [21 CFR 211.180(e)].

6. Your firm failed to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions [21 CFR 211.42(c)(10)(v) and 600.11(a)]. For example your firm's cleaning validation studies demonstrate the selected cleaning agent is not effective on spore forming microorganisms. However, spore forming microorganisms have been detected in the environmental monitoring samples, personnel monitoring samples, and sterility test samples of final product.

7. Your firm failed to establish an adequate system for monitoring environmental conditions of aseptic processing areas [21 CFR 211.42(c)(10)(iv)]. For example:

    a. There is no documentation that monitoring covers all production shifts and is performed during active operations.

    b. There is no assurance that monitoring is at the locations where critical operations are performed.

8. Your firm failed to establish the control systems necessary for aseptic processing operations to prevent contamination [21 CFR 211.42(c)(10) and 600.11(a)]. For example, studies to determine airflow patterns have not been conducted in the sterile filtration room where aseptic connections are made.

9. Failure to inform FDA about each change in the production process [21 CFR 601.12] in that supplements were not submitted for products that were reprocessed due to precipitates and filter integrity test failures.

We acknowledge receipt of your letters dated March 31, 2005, and April 29, 2005, which respond to the inspectional observations listed on the Form FDA 483. Corrective actions addressed in your responses may be referenced in your reply to this letter, as appropriate. We have reviewed your responses and the accompanying attachments. Our evaluation of your responses follows, and is numbered to correspond to the items listed on the Form FDA 483:

Observations 1- 16:

Generally, your responses included commitments to correct the specific deviations on the Form FDA 483 in a narrow sense, however, there was no evidence of an evaluation as to whether any of the deviations reflect a problem with your systems that may require a more comprehensive corrective and or preventive action. Please be advised that an FDA inspection is not intended to uncover each deviation present at your facility. You are responsible for evaluating whether each observation on the Form FDA 483 represents an isolated incident or a systemic problem. Please address this issue in your response to the Warning Letter.

Observations 1, 5, 6, 8, 10 and 12:

We note that your responses to observations 1, 5, 6, 8, 10 and 12 included commitments to revise written standard operating procedures (SOPs). The implementation of revised SOPs should include employee training. However, your response did not mention training. Please comment.

Observation 1:

While we agree with your decision to recall the product that failed stability testing, we request, in addition, that you document a review of the raw stability data for all products on the market to assure there are no other stability problems.

Observation 4:

We acknowledge your response that you will no longer adjust fill volumes by adding or removing product from already sterilized vials and you will no longer distribute vials from which sterility samples were collected. These interventions into vials of already sterilized products pose a risk of contamination. We are concerned about the products remaining on the market that were manufactured under these conditions. To verify the safety of the product that remains on the market, we request that you conduct a product risk assessment for those lots. In addition, your response failed to address the issue of employees performing aseptic operations, collecting sterility samples and adjusting fill volumes in a manner that is not covered by your written standard operating procedures. Please conduct a formal comparison of employee aseptic filling practices and the corresponding written standard operating procedures. Additionally, please address in your response whether retraining is needed for employees in aseptic operations and whether written standard operating procedures for aseptic filling and for collection of sterility samples are adequate.

Observation 9:

Your response consisted of an organization chart with bullet points listing the responsibilities of the quality units. This organization chart is not dated and bears no documentation that it has been reviewed and approved by management. The document describing the duties of the quality units should be developed according to your firm's formal change control system.

Observation 11:

You admit in your response that you learned from the December 1999 inspection that you must submit a supplement to the license, and receive FDA approval, for each product for which you intend to make a major production change (as described in 21 CFR 601.12(b)), such as reprocessing a product. Nevertheless, you continued to implement major production changes without submitting supplements and receiving FDA approval. We remind you that it is your responsibility to identify the need for filing supplements when major process changes are made. Please review all of your products to make sure that you have submitted all necessary license supplements for major process changes.

Observation 14:

During the inspection, investigators observed that some of the plastic gaskets and plastic containers had turned yellow. Please address leachables in both normal and discolored containers in the study promised in your response.

Neither this letter nor the observations noted on the Form FDA 483, which were discussed with you at the conclusion of the inspection, are intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure that your establishment is in compliance with the provisions of the FD&C Act, PHS Act, and all applicable federal laws and regulations. Federal

agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

Please notify this office in writing within 15 working days of receipt of this letter, of the steps you have taken or will take to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Failure to correct these deviations promptly may result in regulatory action without further notice. Such actions may include license suspension and/or revocation, seizure or injunction without further notice. Your response should be sent to the Ms. Mary Malarkey, Director, Office of Compliance and Biologics Quality, U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200 North, Rockville, Maryland 20852-1448. If you have any questions regarding this letter, please contact Ms. Diane Alexander in the Division of Case Management at (301) 827-6201.

Sincerely,

Carl E. Draper
Acting Director
Office of Enforcement

cc: Mr. Mark J. Hites
Director
Regulatory Affairs
Greer Laboratories, Inc.
639 Nuway Circle NE
Lenoir, NC 28645-0800