Inspections, Compliance, Enforcement, and Criminal Investigations

Greer Laboratories Inc 4/21/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Office of Regulatory Affairs
12420 Parklawn Drive
ELEM-2152
Rockville, MD 20857

Telephone: (301) 796-2720
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WARNING LETTER

April 21, 2014

OO-WL-13-02

UPS EXPRESS MAIL

Mr. John Roby
President and Chief Executive Officer
Greer Laboratories, Inc.
639 Nuway Circle NE
Lenoir, NC 28645

Dear Mr. Roby:

The Food and Drug Administration (FDA) conducted an inspection of Greer Laboratories, Inc., located at 639 Nuway Circle NE, Lenoir, North Carolina, between November 5 – 15, 2013. During the inspection, FDA investigators documented deviations from current good manufacturing practice (CGMP) requirements in the manufacture of your licensed allergenic extracts, which are biological drug products. Deviations from CGMP include non-compliance with the applicable requirements of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (FD&C Act), and the requirements of your biologics license application (BLA) approved under Section 351(a) of the Public Health Service Act (PHS Act), and Title 21, Code of Federal Regulations (21 CFR) Parts 210, 211, and 600-680. At the close of the inspection, FDA issued a Form FDA 483, Inspectional Observations, which described a number of significant objectionable conditions relating to your facility's compliance with CGMP. Significant deviations observed during the inspection include, but were not limited to, the following:

1. You failed to manufacture drug products in the manner described in your approved BLA. You combine various types and amounts of your licensed allergenic extracts to produce allergenic "custom mixtures;" however, you have not obtained a license to manufacture and distribute these combined product mixtures, as required by 21 CFR 610.17.

2. You failed to establish and follow written procedures that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of

each batch, in order to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of the in-process material and the drug product [21 CFR 211.110(a)]. During filling operations, technicians routinely decant or pipette the clear portion of the bulk extract away from precipitated product on the bottom of the storage bottle prior to filling final product vials. No subsequent testing is performed on the clear portion of the bulk extract prior to filling to assure uniformity and homogeneity. Further, this practice does not require review or approval by the quality control unit.

3. You failed to assure an adequate system for monitoring environmental conditions [21 CFR 211.42(c)(10)(iv)]. For example, air is not monitored for viable organisms throughout the filling operations in your aseptic filling suite, **(b)(4)**. Only one active air sample per filling location is taken in the morning and one sample is taken in the afternoon. Further, there are no settling plates used to monitor the environment during filling operations.

4. You failed to perform the general safety test for the detection of extraneous toxic contaminants on biological products intended for administration to humans as required by 21 CFR 610.11(c). Specifically, there is no documentation of the observation of each test animal every working day following injection with the allergenic test material, including any animal response which is not specific for or expected from your product.

5. You failed to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications [21 CFR 211.192]. For example:

a. The bioburden result for **(b)(4)**, tested on November 9, 2012, was too numerous to count (TNTC). **(b)(4)** was released for use on December 6, 2012, although there was no assurance that the bioburden load of the lot had not exceeded the validated retention capability of the filter used in the sterile filtration step. Further, the Product Specification and Release form for **(b)(4)** erroneously recorded that there were no deviations associated with the lot. This lot of **(b)(4)** diluent was subsequently used to manufacture your allergenic products.

b. Out of specification test results are invalidated without determining a definitive laboratory error. For example, **(b)(4)** bulk lot #**(b)(4)** failed sterility testing on July 24, 2012. Subsequent investigation concluded that the positive test result was due to laboratory error, although test results for negative controls and other allergenic extracts tested on the same day were negative and further laboratory investigation did not identify a definitive laboratory error. Bulk lot #**(b)(4)** passed repeat sterility testing and the lot was released for use on October 1, 2012.

c. Investigations of lots that failed the general safety test were inadequate. Although the failed lots were rejected, failure investigations were not initiated in a timely manner and root cause for the test failures was not determined. Further, "Production Record Investigations" forms for the following lots are incomplete in that there is no documentation of investigation review by the QA Director.

- **(b)(4)** lot #**(b)(4)**; general safety test failure recorded on February 11, 2013
- **(b)(4)** bulk lot #**(b)(4)**; general safety test failure recorded on February 25, 2013
- **(b)(4)** bulk lot #**(b)(4)**; general safety test failure recorded on June 20, 2013

6. You failed to demonstrate that the drug product containers and closures used in the manufacture of your allergenic products are not reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements [21 CFR 211.94(a)]. Specifically, extractable and leachable studies have not been conducted on the **(b)(4)** stoppers used in the manufacture of your allergenic products.

7. You failed to establish the reliability of the supplier's certificate of testing through appropriate validation of the supplier's test results at appropriate intervals [21 CFR 211.84(d)(3)]. Specifically, you have not performed periodic endotoxin, bioburden, or particulate matter

testing on your stoppers to validate the supplier's Certificate of Analysis. Your SOP QCG021 entitled "**(b)(4)**" only requires visual inspection and dimension verification of the stoppers used in the manufacture of your allergenic products.

8. You failed to maintain buildings used in the manufacture, processing, packing, or holding of your allergenic products in a clean and sanitary condition and free of infestation by insects [21 CFR 211.56]. Investigations QAINV 12-015 and QAINV 13-010 were conducted in response to a continuing trend of live insects being observed in the aseptic filling suite, **(b)(4)**. Live insects were observed during and after filling operations. Further, your corrective actions implemented as a result of the investigations were inadequate in that live insects continued to be observed in these areas.

We acknowledge receipt of your written responses dated December 8, 2013, January 8, 2014, and February 7, 2014, which address the inspectional observations on the Form FDA 483 issued at the close of the FDA inspection. You may reference corrective actions explained in your letters in your response to this Warning Letter. We have reviewed your responses and have the following specific comments. The items are numbered to correspond to the observations listed on the Form FDA 483.

Form FDA 483 observation #1
Your response of December 8, 2013 explains that Greer has manufactured Custom Mixes for some time. Please note that the sale of these "custom mixes" violates 21 CFR 610.17, and should not continue without approval of each custom mixture manufactured under a BLA. You explain that FDA has long permitted the preparation of such mixes in response to a physician's order. Regardless of whether or not FDA has objected to the manufacture of prescription sets after receipt of a physician's prescription for a specific patient, the FDA investigator noted that Greer's current manufacture of these mixes is not linked to specific patients or a prescription.

Form FDA 483 observation #2.A
Your response states that your SOP QCM018 entitled "**(b)(4)**" has been revised to clarify that bioburden results must be reported as numerical counts and not as "TNTC," and to require identification and investigation of microbial isolates that are considered objectionable. However, your response did not address the establishment of bioburden specifications. Please comment on whether you intend to establish such specifications.

Form FDA 483 observation #2.B
Your response states that you have revised your SOP QCA008 entitled "**(b)(4)**" to clarify that all glycerinated extracts are to be safety tested using the **(b)(4)** dose and route of administration, i.e., a **(b)(4)**. However, our records indicate that the **(b)(4)** dose and route of administration for the general safety test have only been approved for products containing **(b)(4)**. The Center for Biologics Evaluation and Research (CBER) will contact you at a future date regarding general safety testing of products containing less than **(b)(4)**. We request that you do not initiate any studies prior to consultation with CBER.

Form FDA 483 observation #3.B
Your response states that you will revise SOP QCM059 entitled "**(b)(4)**" to state that for all sterility failures, regardless of the root cause and including laboratory error, the disposition will be "reject" and the lot will be destroyed. Please be reminded that all sterility failures should be thoroughly investigated. Information obtained from such investigations should subsequently be used to improve your manufacturing processes.

Form FDA 483 observation #5.A
Your response states that you have completed a new smoke study to confirm unencumbered air flow in the aseptic filling suite. Air pattern or "smoke" studies should demonstrate laminarity and a sweeping action over and away from the product under dynamic conditions; these studies should be well documented with written conclusions. Review of **(b)(4)** to your response dated January 8, 2014, found that your smoke study was limited to the airflow patterns surrounding the **(b)(4)** areas within rooms **(b)(4)** with a worse-case, full set-up condition and additional personnel in place. Documentation does not include the date the study was completed or indicate whether the study was conducted under dynamic or static conditions. Further, the

terms "worst-case, full set-up conditions" are not defined. Attachments to the final report were not included in your response. Please provide these attachments.

Form FDA 483 observation #5.B
Your response states that the **(b)(4)** fill process, including the use of **(b)(4)** dispensed during the vial volume check to fill final product vials, has been simulated during media fills 12 times since 2011. Your response included a table with a list of protocol numbers and dates of execution; however, there was no documentation provided to support this table. Please provide the supporting documentation.

Form FDA 483 observation #5.E
Your response states that a comprehensive review of the overall environmental monitoring program has been conducted and that the review included both viable and nonviable monitoring for all classified environments. Please provide a rationale to support the adequacy of the modifications you made to the environmental monitoring program, including the revised number of surface and air sampling sites, as well as the revised sampling frequency.

Neither this letter, nor the observations listed on the Form FDA 483 presented at the conclusion of the inspection is intended to be an all-inclusive list of deviations that may exist at your facility. We remind you that it is your responsibility to ensure that your establishment is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, all applicable federal laws and regulations, and the standards in your license. Federal agencies are advised of the issuance of all Warning Letters about biological products 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 promptly correct these deviations may result in regulatory action without further notice. Such actions may include license suspension and/or revocation.

Please notify this office in writing, within 15 working days of receipt of this letter, of any additional steps you have taken or will take to correct the noted violations and to prevent their recurrence. Include any documentation necessary to show that corrective action has been achieved. 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.

You may call Julie D. Bringger, Compliance Officer, at (904) 281-1924, extension 104, to discuss any questions regarding this letter and to schedule a meeting with FDA. Your reply to this letter should also be sent to Mrs. Bringger at the following address: U.S. Food and Drug Administration, 6800 Southpoint Parkway, Suite 100, Jacksonville, FL 32216.

Sincerely,
/S/
Alonza Cruse, Acting Director
Office of Medical Products and
Tobacco Operations

cc: David P. Burney, PhD
Chief Operating Officer
Greer Laboratories, Inc.
639 Nuway Circle NE
Lenoir, NC 28645

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