



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

447

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Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448WARNING LETTERCertified-Return Receipt Requested

Gerald L. Friesen, Pharm.D.
Responsible Head
Greer Laboratories
639 Nuway Circle, NE
Lenoir, NC 28645-0800

Dear Mr. Friesen:

During an inspection of Greer Laboratories, 639 Nuway Circle, NE, Lenoir, NC, conducted on August 11-15, 1997, FDA investigators documented significant deviations from Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations (21 CFR), Parts 600 and 211 with respect to the manufacture of your product, Plague Vaccine. The deviations documented by the FDA investigators include the following:

1. Failure to report to the Director, Center for Biologics Evaluation and Research, important proposed changes in manufacturing methods for Plague Vaccine as required by 21 CFR 601.12 in that inoculation of ██████████ was performed from an ampule of the Master Seed lot under investigation and not approved in the product license.
2. Failure to perform thorough investigations when batches or components fail to meet the specifications for Plague Vaccine [21 CFR 211.192]. For example:
 - a. There was no investigation into the loss of potency of lot F0829Y1; and
 - b. Some of the deviation reports lacked a resolution of the deviation and evaluation of the affected product.

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3. Failure to establish and/or follow written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess and to assure that such procedures, including any changes, are drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by quality control [21 CFR 211.100]. For example:
 - a. There are no Standard Operating Procedures (SOP's) governing the interpretation of results from the [REDACTED]
 - b. There are no SOP's for disposing expired bulk; [REDACTED]
 - c. SOP's are lacking for the control of changes in production processes, the facility, and documentation; and [REDACTED]
 - d. Sterilized equipment and gowning are not identified as having been sterilized in accordance with SOP [REDACTED]
4. Failure 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)]. For example:
 - a. The steam supply for the autoclaves in Building [REDACTED] and [REDACTED] is not monitored;
 - b. Reuse of disk air filters on the compressed air system used for product transfer has not been validated; [REDACTED]
 - c. The cleaning process for reuse of [REDACTED] bottles has not been validated to demonstrate that no significant residuals of detergents remain after cleaning; and
 - d. The potential for contamination of [REDACTED] discrete harvest lot of *Yersinia pestis* prior to pooling) by microorganisms through contact of the "agar trap" with the neck of the bottle has not been evaluated.
5. Failure to separate or define areas or such other control systems for the firm's operations as necessary to prevent contamination or mixups [21 CFR 211.42 (c)]. For example:
 - a. There are no requirements to separate operations and equipment for live and inactivated bacterial processes in Room [REDACTED]
 - b. Bulk vaccines stored in Cold Room [REDACTED] are not identified as quarantined or released; and

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- c. The impact of concurrent activities in the east side of the aseptic processing suite (Room [REDACTED]) on the filling operations in the west side has not been evaluated.
6. Failure to establish a system for monitoring environmental conditions [21 CFR 211.42(c)(10)(iv)] For example:
 - a. The aseptic processing of product in Building [REDACTED] has not been evaluated via media fills since 1994; [REDACTED]
 - b. Documentation of the results of the February, 1997 media fill in Room [REDACTED] (specified by the SOP) were not available; and [REDACTED]
 - c. The gowning rooms in Building [REDACTED] are not included in the routine environmental monitoring program. The media prep/wash room, Room [REDACTED] is not monitored for viable particulates.
7. Failure to establish written quality control unit procedures for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product [21 CFR 211.22(d)] in that internal QC product release does not document the review of environmental monitoring data.
8. Failure to establish scientifically sound and appropriate specifications, standards, sampling plans and test procedures to assure that components, drug products conform to appropriate standards of identify strength, quality and purity [21 CFR 211.160(b)] in that SOP [REDACTED] specifies that, in testing potency, the antigenic value of the test vaccine expressed as the relative potency must be .5 or greater in relation to the reference vaccine. It is your practice to "round up" all fractional values in hundreths to the next higher tenths place. Thus, relative potency values from .41 through .49 are rounded up to .5 and are deemed to be acceptable even though they are less than the .5 value specified in your own SOP. No rationale or validation documentation has been provided to show the appropriateness or validity of the rounding up procedure. The recalled lot of plague vaccine (lot F0829Y1) had to reach a value of less than .4 (it tested at .35) before it was considered out of specifications.

The above identified deviations are not intended to be an all inclusive list of deficiencies at your facility. It is your responsibility as Responsible Head to assure that your operations are in compliance with all the provisions of the Federal Food, Drug and Cosmetic Act and all applicable regulations.

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You should take prompt action to correct these deviations. Please notify this office, in writing, within 15 working days of receipt of this letter of any steps you have taken to correct the noted violations and to prevent their recurrence. If corrective action 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 promptly correct these deviations may result in regulatory action without further notice. These actions include license suspension and/or revocation, seizure, and/or injunction.

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.

Your reply should be sent to me at the Food and Drug Administration, Center for Biologics Evaluation and Research, Attention: Division of Case Management, HFM-610, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448.

Sincerely,



for.

James C. Simmons
Director
Office of Compliance
Center for Biologics Evaluation and Research