



OCT 13 2000

CBER-01-002

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Dr. Volker Lenhard
Head/Development & Production Diagnostics
Biotest AG
Landerstreinerstrasse 5
63303 Dreiech
Germany

Dear Dr. Lenhard:

An inspection of Biotest AG, Landerstreinerstrasse 5, 63303 Dreiech, Germany, was conducted from June 26 through July 3, 2000. During the inspection violations of Section 501 (h) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations (CFR), Subchapter H, Part 820 were documented as follows:

1. Failure to establish, maintain, and follow procedures for implementing corrective and preventive action, including requirements for investigating the cause of nonconforming product and identifying the action(s) needed to correct and prevent recurrence of nonconformities and other quality problems [21 CFR 820.100] in that:
 - a. the investigation of media fill, PA-NR:150786, March 3, 2000, which exceeded the acceptable contamination limits, did not include a complete investigation to assess employee training or the vial capping process. This media fill failure was not reported to management or Quality Assurance.
 - b. there was no investigation and no corrective and preventive action taken when documented container closure problems, including loose caps and discarded vials, were identified in media fills PA-NR:149621, January 28, 2000, and PA-NR:154069, May 25, 2000.

- c. there was no investigation and no corrective or preventive action taken to include re-validation or procedural changes following the failure of autoclave [REDACTED] to meet the required temperatures during validation procedures on March 3, 1999.
 - d. there were no investigations and no corrective and preventive actions taken for the microbial contamination of the [REDACTED] water system used to produce the steam supply to the autoclave and for rinsing equipment and surfaces. Since January 1999, microbiological test results of too-numerous-to-count have been documented in the [REDACTED]
 - e. there was no investigation and no corrective and preventive actions taken regarding missing vials for Media fill PA-NR:149621. Records indicated that [REDACTED] vials were filled and [REDACTED] vials were issued to Quality Control (QC). However, the records indicated that [REDACTED] vials were incubated instead of [REDACTED] vials.
2. Failure to establish, maintain, and follow procedures for process validation in order to ensure that processes have been adequately validated and that specifications continue to be met [21 CFR 820.75] in that:
- a. during the February 1999 validation of the [REDACTED] sterilizer [REDACTED], six positive biological indicators (BI) were identified in the first three runs at sensors [REDACTED] and [REDACTED]. In a subsequent validation attempt, placement of BIs was limited to areas that failed during the initial validation. A complete re-validation has not been conducted.
 - b. the manufacturing process for [REDACTED] has not been validated and expiration dates have not been established. Additionally, [REDACTED] concentration in products is not tested during production or at release.
3. Failure to ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use [21 CFR 820.70(g)] in that:
- a. [REDACTED] filters in the [REDACTED] water system at points-of-use [REDACTED] and [REDACTED] have not been changed or tested since installation of the distribution loop in [REDACTED] and there are no procedures to do so. Since January 1999, numerous microbiological test results of too-numerous-to-count were documented at points-of-use, [REDACTED], and [REDACTED]
 - b. incubator [REDACTED], located in room [REDACTED], has not been qualified for the intended use of incubating media fill vials. The incubator has been in use since [REDACTED]

- c. the [REDACTED] water system and the disinfection procedure for the [REDACTED] building water system have not been validated. Water specifications, including alert and action limits, have not been established. Although routine disinfection of the system occurs every six weeks, microbial contamination has been identified during water bioburden testing after disinfection.
4. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications [21 CFR 820.70(a)] in that:
 - a. during media fills, culture media contact with the container closures and swirling of filled media vials is not performed until seven days after incubation is initiated.
 - b. during media fill PA-NR:154069, 25 vials were removed from the total number of vials that were filled and submitted to QC for testing. The removed vials were not incubated and examined for contamination by production or QC. In addition, the calculation for the rate of contamination did not include the removed vials.
5. Failure to establish and maintain an adequate organizational structure to ensure that devices are designed and produced as required [21 CFR 820.20(b)] in that Quality Assurance does not perform a routine review of product manufacturing and product release records.
6. Failure to validate computer software for its intended use [21 CFR 820.70(i)] in that software used in the quality system has not been fully validated. To date, only 20% of the system elements in the [REDACTED] system used for inventory control, including [REDACTED] have been fully validated. Additional systems included in and ancillary to the quality system have not been validated. A formal computer validation program was initiated in January 1999 and completion dates are not projected until at least 2001.
7. Failure to establish and maintain the requirements, including quality requirements, that must be met by suppliers, contractors, and consultants [21 CFR 820.50(a)] in that contractors supplying service for maintenance and calibration of water systems, HVAC systems, sterilization, and laboratory equipment have not been formally qualified.

We received your response dated July 7, 2000, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection. Your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. Our evaluation of your response and requests for further information are detailed below. Please note that our comments are numbered to correspond to the items listed on the Form FDA 483.

1. We acknowledge the corrective program you are instituting, including hiring water experts to investigate the [REDACTED] water system to determine effective and preventive action. Any corrections implemented must address the manufacturing uses of the [REDACTED]

water system. Route of contamination studies and evaluation of your procedures should be conducted to ensure that the [REDACTED] water system will not contaminate products.

2. The response to the above item indicates you will hire a validation consultant to investigate the [REDACTED] water system to determine effective corrective and preventive action. Please provide details on the completion date or timeframes for re-validating the [REDACTED] water system.
3. The response indicates that it is a routine procedure for the manufacturing staff to [REDACTED] filter after each out-of-specification result. However, during the inspection, the production manager stated that the [REDACTED] filters have not been changed since installation. Please clarify the specific filters you are referencing and which procedure(s) will be updated.
4. The response states that an “FDA task force” will be established to assure full compliance with Quality System Regulation (QSR) requirements. Please assure the task force assesses the adequacy of the resources that are provided to meet the QSR requirements.
9. Please provide the details regarding the purpose of all the software systems, the validation priority, or the date the validation will be completed.
17. Please review the calibration program to ensure that all of the equipment used in production is included and will be calibrated as required.

Neither the above deviations nor the observations listed on the Form FDA 483 presented to your firm at the conclusion of the inspection are intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility to ensure adherence to each requirement of the Federal Food, Drug, and Cosmetic Act and the applicable regulations and standards. The specific violations noted in this letter and the Form FDA 483 may be symptomatic of serious underlying problems in your establishment’s manufacturing and quality systems.

You should take prompt measures to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes license suspension and/or revocation, seizure, civil penalties, and/or import alert, which would prevent your product from entering the United States. 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. In addition, no license applications or supplements for devices to which the deficiencies are reasonably related will be approved until the violations have been corrected.

In order to help FDA make the determination that adequate corrections have been made, we request that you provide certification by an outside expert consultant that he/she has conducted an audit of your firm’s manufacturing and quality assurance systems. Please

submit a copy of the consultant's report, and your personal certification that you have reviewed the report, showing that your firm has initiated or completed all corrections called for in the report. Also provide information regarding the qualifications of your consultant, and verification that his/her services have undergone the vendor qualification process required under 21 CFR 820.50. The enclosed guidance may be helpful in selecting an appropriate consultant.

Please notify this office in writing, within 15 working days of receipt of this letter, of the specific 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.

Your reply should be directed to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike; Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-624. If you have any questions regarding this letter, please contact, Janet Claggett, Consumer Safety Officer, at 301-827-6201.

Sincerely,



 Deborah D. Ralston
Director
Office of Regional Operations

Enclosure:

Selecting A Consultant