



CBER - 99- 009

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

WARNING LETTER

• JAN 21 1999

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

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

Dear Dr. Lenhard:

An inspection of Biotest AG, Landerstreinerstrasse 5 , 63303 Dreieich, Germany, was conducted from October 19, 1998 through October 23, 1998. During the inspection, violations of Section 501(h) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations, Subchapter F, Parts 600-680, and Subchapter H, Part 820 were documented as follows:

1. Failure to establish procedures for quality audits and to conduct such audits to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system [21 CFR 820.22] in that SOP SV-TD: A-005-00/00, entitled "Quality Audits", does not include specific requirements for auditing training, documentation systems, complaint-handling, calibration, purchasing, facilities, packaging, labeling, product storage, and product release. In addition, two deficiencies which were identified on a June 1998 internal audit have no record of activity since June 1998 and have not been resolved.
2. Failure to establish, maintain, and follow procedures to adequately control environmental conditions that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(c), 660.20(a), and 660.50(a)] in that:
 - a. environmental monitoring is not performed during media fills.
 - b. there are no studies that demonstrate the filling area (room ~~and~~ filtration area (room ~~and~~ and laminar airflow benches meet the firm's requirements for Class ~~and~~ and Class ~~and~~ areas during dynamic conditions.

- c. there are no procedures for measuring air velocities for the filling area, filtration area, and laminar airflow benches
 - d. there is no surface monitoring of the filtration area (room [redacted] and the filling area (room [redacted])
 - e. Standard Operating Procedure (SOP) SV-DS-A-0095-00/01, entitled "Microbial Viable Particle Monitoring", does not instruct laboratory personnel to perform microbial identification when initial action limits are exceeded.
3. Failure to establish, maintain, and follow procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(e), 660.20(a), and 660.50(a)] in that:
 - a. SOP SV-NR:10110/00, entitled "Validation of the Aseptic Filling Machine-[redacted]", does not include established acceptance specifications for media fill results, does not include instructions to perform media fill runs for the lyophilized licensed products, and does not include planned interventions to simulate worst case conditions
 - b. the Water for Injection (WFI) system used in the manufacture of Blood Grouping Reagents has not been validated
 - c. there are no sanitizer efficacy studies for the use of [redacted] and [redacted] to clean the filtration area (room [redacted] and the filling area (room [redacted]) or for the use of [redacted] and [redacted] for the sterility test area (room [redacted])
4. 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. there are no written procedures for corrective and preventive action.
 - b. there is no evidence of an investigation of the cause or an identification of the action needed to correct and prevent a recurrence of [redacted] out-of-specification [redacted] WFI microbiology results which have occurred since December 1997.
 - c. there is no evidence of management review of the investigation and corrective actions taken for [redacted] rejected lots of [redacted] Anti-Jkb #2017 bulk in 1997

- d. there was no corrective and preventive action taken for ~~media~~ media fills (#170998, #031197, #210596, and #269796) that had contaminated vials.
- e. there was no corrective and preventive action taken for a sterility failure for final product lot # 11109698, Anti-s, dried.
- f. there was no corrective and preventive action taken when the filtration area (room ~~microbial~~ microbial viable particle counts exceeded the action limit on 7/11/97.
- g. SOP SV-DS: A-0095-00/01, entitled "Microbial Viable Particle Monitoring" allows for ~~_____~~

5 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 preservative effectiveness studies for Blood Grouping Reagents and Anti-Human Globulin have not been performed.
- b cleaning validation on the multi-use equipment used in the manufacture of licensed products has not been performed. In addition, there are no cleaning procedures when changing from licensed to unlicensed products.
- c there is no established shelf life for autoclaved in-house plastic and glass containers used for bulk storage of Blood Grouping Reagents.
- d there are no established storage hold times for Blood Grouping Reagent bulks.
- e there is no SOP for ~~_____~~ sterilization of containers and closures describing procedures for preparation of lots for shipping to the contract sterilizer and for receipt after sterilization.
- f stability testing is not performed for the reconstituted lyophilized products, Anti-S and Anti-s. The package insert claims that the reconstituted product has a storage time of 4 weeks when stored at 2-8°C.

6 Failure to establish and maintain procedures to control product that does not conform to specified requirements [21 CFR 820.90]

7 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 there is no established procedure for changing the vent filter on the lyophilizer ~~_____~~ and for performing a filter integrity test.

- b. there is no established procedure for maintaining the integrity of vent filters for the ~~autoclave~~ autoclave. There is no evidence that filters have been integrity tested since installation of the autoclave in 1989.
 - c. there is no data to support placement of ~~biological indicators~~ biological indicators during validation for ~~sterilizers~~ sterilizers.
 - d. the SOP SV-DS.P-0020-00/00 for validation of ~~sterilizers~~ sterilizers does not specify loading patterns or load sizes
 - e. Cooler ~~and Freezer~~ and Freezer ~~in the central receiving area~~ in the central receiving area are not calibrated or monitored for temperature control.
8. Failure to establish, maintain, and follow procedures for process validation in order to ensure that processes have been adequately validated and that the specified requirements continue to be met [21 CFR 820.75] in that:
- a. container closure integrity tests for Blood Grouping Reagents and Anti-Human Globulin have not been performed
 - b. the in-line sterilization filter for Blood Grouping Reagents has not been validated to assure bacterial retention or for compatibility with the product.
 - c. the manual ~~Test~~ Test used for integrity testing of the in-line sterilization filter for Blood Grouping Reagents has not been validated.
 - d. the 1989 validation campaign for the ~~Autoclave in Room~~ Autoclave in Room ~~used to sterilize bulk containers for Blood Grouping Reagents~~ used to sterilize bulk containers for Blood Grouping Reagents, did not include loaded chamber temperature distribution studies, determination of cold spots, evaluation of hardest to heat materials, and an evaluation of the equipment's ability to inactivate microorganisms throughout the chamber.
 - e. there are no established specifications for mixing speeds for Blood Grouping Reagent bulks. In addition, there are no validation data to support the mixing times which can range from ~~for bulk lot sizes of~~ for bulk lot sizes of ~~ml~~ ml
 - f. the quarterly autoclave revalidation campaign is only conducted on program ~~however, the autoclave is used on~~ however, the autoclave is used on ~~programs~~ programs. There is no data to support the use of only one program ~~for revalidation~~ for revalidation
9. Failure to establish and maintain requirements for the health, cleanliness, personal practices, and clothing of personnel if contact between such personnel and the product or environment could reasonably be expected to have an adverse effect on product quality

[21 CFR 820.70(d)] in that there is no personnel monitoring of filling operators in the filling room (room ~~XXXX~~). Operators are allowed in the filling area without gloves.

10. Failure to identify and maintain the acceptance status of product throughout manufacturing, packaging, labeling, installation, and servicing to ensure that only product which has passed the required acceptance activities is distributed, used, or installed [21 CFR 820.86] in that ~~XXXX~~ bottles of AB serum were in the QC receiving area (room ~~XXXX~~) without documentation of acceptance status and date of receipt, packaging material was stored without designated status in the production warehouse (room ~~XXXX~~), and bottles of Anti-D without designated status were in the production cooler (room ~~XXXX~~).
11. Failure to establish and maintain procedures for the control of storage areas and stock rooms for product to prevent mixups, damage, deterioration, contamination, or other adverse effects pending use or distribution [21 CFR 820.150] in that raw material, in-process material, and finished product which has temperature storage specifications of 2-8°C are stored in several coolers (~~XXXXXX~~) that are set at 2-10°C. In addition, the alarms for these coolers are set at 10°C.
12. Failure to evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements, and to document the evaluation [21 CFR 820.50(a)] in that there is no SOP for qualifying suppliers of components and services.
13. Failure to ensure that all inspection, measuring, and test equipment is suitable for its intended purposes and is capable of producing valid results [21 CFR 820.72] in that:
 - a. refrigeration units (~~XXXXXXXXXX~~) in the QC lab (room ~~XXXX~~) do not have calibration status and are not included in the routine calibration program. The units are used to store reagents, and reference, retention, stability, and product samples.
 - b. there are no acceptance specifications for the verification of the centrifuge timer for all centrifuges used in manufacturing.

Your written response of December 17, 1998, to the Form FDA-483 issued at the close of the inspection is currently under review. You will receive our assessment of your responses upon completion of our review. Corrective actions addressed in your previous letter may be referenced in your response to this letter, as appropriate.

Neither the above violations nor the observations noted 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 are responsible for

investigating and determining the causes of the violations identified by FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

You should take prompt action to correct these deviations. Failure to do so 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 U.S. 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.

You should respond to FDA 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 actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. FDA will verify your implementation of promised corrective action during the next inspection of your facility. Your reply should be sent 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-610. If you have any questions regarding this letter, please contact Annette Ragosta at (301) 827-6322.

Sincerely,



Deborah D. Ralston
Acting Director
Office of Regional Operations