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CBER-99-014

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

MAR 18 1999

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. David Schwartz
President
Bio-Rad Laboratories, Inc.
1000 Alfred Nobel Drive
Hercules, California 94547

Dear Mr. Schwartz:

An inspection of Bio-Rad Laboratories, Inc., located at 4000 Alfred Nobel Drive, Hercules, California, was conducted from September 29 through October 8, 1998. During the inspection, violations of Section 501(h) of the Federal Food, Drug, and Cosmetic Act (the Act) and Title 21, Code of Federal Regulations, Subchapter H, Part 820 were documented as follows:

- I. Failure to establish and maintain 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)] in that:
 - a. the DI/RO water system, used in production of your licensed product, has not been validated.
 - b. the method for collecting DI/RO water samples for microbial monitoring described in your standard operating procedure (SOP) 206 entitled "Microbial Monitoring of Deionized Water System" does not assure that water samples are representative of water used in production. The written procedure requires longer flushing of the water system prior to collecting microbial monitoring samples than prior to use for production or cleaning. Sampling ports are sanitized with _____ prior to collecting microbial monitoring samples but not prior to use for production or cleaning.

- c. your SOP 206 entitled "Microbial Monitoring of Deionized Water System" states that microbial testing and sampling of the DI/RO water system is performed [redacted] Most of the records of microbial monitoring for 1997 and 1998 could not be located.
 - d. the DI/RO water system drop used for equipment rinsing is not sampled during microbial monitoring.
 - e. hoses connected directly to the DI/RO water system drops were observed lying in drains without any means of preventing backflow.
 - f. multi-use equipment including bulk storage containers, filling machines, hoses, and accessories were observed stored in room [redacted] there was no designation to indicate whether the equipment was clean or dirty. An operator in room [redacted] when questioned by our investigators regarding the status of reusable carboy containers, was uncertain whether the carboys were clean or dirty.
 - g. there is no SOP describing the proper technique to be employed for handling stoppers used for lyophilized products during weighing procedures. Stoppers used for lyophilized products were observed being weighed in an open warehouse on a dirty cart; the operator weighing the stoppers was observed handling the stoppers with bare hands. Stoppers are not washed prior to use.
2. Failure to ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed; failure to establish and maintain schedules for the adjustment, cleaning, and other maintenance of equipment [21 CFR 820.70(g)] in that:
- a. there was no documentation of preventative maintenance performed on equipment used for production of your licensed product.
 - b. qualification of the [redacted] autoclave in room [redacted] has not been performed since 1988; insulation on the autoclave was observed to be damaged; the autoclave alarm was not operational.
3. 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. no load pattern has been established for the [redacted] autoclave in room [redacted]
 - b. the time/temperature charts for the [redacted] autoclave in room [redacted] are discarded [redacted]

- c. there are no records maintained identifying the contents of autoclave loads. During the inspection, our investigators observed filters being autoclaved with biohazardous waste (trash). There was no record or identification maintained to indicate whether the filters were to be used for production or discarded. The autoclave operator, when questioned by our investigators, was uncertain as to the status of the filters.
4. Failure to establish and maintain 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. preservative effectiveness studies have not been performed for all components of the *Novapath™ HIV-1 Immunoblot* kit.
 - b. cleaning validation has not been performed to demonstrate the effectiveness of cleaning multi-use equipment or the removal of cleaning agent residue from equipment.
5. Failure to identify by suitable means the acceptance status of product [21 CFR 820.86] in that product was observed being stored in the walk-in freezer without designation as to the acceptance status of the product.
6. 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 [21 CFR 820.150(a)] in that:
 - a. product with specific temperature requirements was observed being stored in the warehouse; the temperature in the warehouse is not monitored.
 - b. _____ used in the manufacture of your licensed product, was observed being stored in an area accessible to rodents; boxes containing the _____ had been gnawed.
7. Failure to evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specific requirements, including quality requirements, and to document the evaluation [21 CFR 820.50(a)] in that your contract laboratories, _____ have not been evaluated.
8. Failure to establish and maintain procedures to control all documents including procedures to remove obsolete documents so as to prevent unintended use

[21 CFR 820.40(a)] in that an obsolete version (version 1, effective March 18, 1994) of your SOP 206 entitled "Microbiological Monitoring of Deionized Water System" was still in use and was initially provided to our investigators as the current version.

We acknowledge receipt of your written response, dated October 20, 1998, to the FD-483 issued on October 8, 1998. Your written response will be made part of the inspectional file. Corrective actions will be verified on reinspection of your firm. We have the following comments regarding your response:

We note that the failure of employees to follow written procedures contributed to the deficiencies identified by FD-483 observations 2J, 4, 7, 14, 22B, 22C, 22D, and 26. Failure of employees to follow procedures should have been detected during your firm's internal audits and corrected prior to the FDA inspection. We recommend that you conduct an internal audit of the device manufacturing operations that were not covered during the inspection to ensure written procedures are being followed and to identify training needs.

Your response to FD-483 observations 2B, 2C, 2D, 3E, 6, 16, 17, 22B, and 23 indicates that SOP's will be revised. Incomplete revisions of the SOP's were submitted so we were not able to evaluate the adequacy of the proposed corrective actions. The subject SOP's will be reviewed during reinspection of your firm.

Regarding FD-483 observation 2K, our investigators' report indicates that records of the _____ microbial testing of water performed by your firm as well as records of _____ monitoring by the contract firm were missing.

Regarding FD-483 observation 3C, your response lacks a commitment to label items being autoclaved as to status (trash, production equipment, etc).

Regarding FD-483 observation 3G, please comment on the studies conducted to determine whether the missing and damaged insulation on the _____ autoclave has affected the empty chamber temperature distribution by allowing heat to escape from the autoclave. The record of autoclave inspection conducted by _____ was not submitted for review but it appears that no empty chamber temperature distribution study was performed.

Your response to FD-483 observations 22B and 22C indicates that references to SOP 096 were erroneously added when procedure 971.04.03 was updated. Your document control procedures should include review and approval protocols designed to prevent incorporation of erroneous information into newly established or revised procedures.

The above violations are not intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility to assure that your establishment is in compliance with all requirements of the federal regulations.

You should take prompt action 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 and/or injunction, and/or civil penalties.

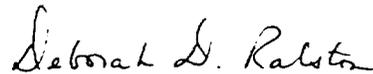
During the inspection it was noted that corrective action for some of the noted violations which were brought to your firm's attention during an inspection in February 1997 had not been effected up until the time of our September-October 1998 inspection. It is your responsibility as management to exercise control of Bio-Rad Laboratories, Inc., in all matters relating to compliance and to implement effective corrective action whenever necessary.

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.

You should notify the Food and Drug Administration 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. All corrective actions will be verified during reinspection 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 Anna Flynn at (301) 827-6201.

Sincerely,

A handwritten signature in cursive script that reads "Deborah D. Ralston".

Deborah D. Ralston
Acting Director
Office of Regional Operations

cc: Mr. John P. Goetz
Group Operations Manager
Clinical Diagnostics Group
Bio-Rad Laboratories, Inc.
4000 Alfred Nobel Drive
Hercules, California 94547

Mr. Bill Link
Authorized Official
Bio-Rad Laboratories, Inc.
4000 Alfred Nobel Drive
Hercules, California 94547