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Food and Drug Administration  
Rockville MD 20857

CBER-01-001

WARNING LETTER

OCT 13 2000

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Mr. David Schwartz  
President  
Bio-Rad Laboratories, Inc.  
4000 Alfred Nobel Drive  
Hercules, CA 94547

Dear Mr. Schwartz:

The Food and Drug Administration (FDA) conducted an inspection January 24 through February 9, 2000, of Bio-Rad Laboratories, Inc., located at 4000 Alfred Nobel Drive, Hercules, California. During the inspection, FDA investigators documented violations of Section 501(h) of the Federal Food, Drug, and Cosmetic Act (the Act) and deviations from the applicable standards and requirements of Title 21, Code of Federal Regulations (CFR), Subpart H, Part 820, as follows:

1. Failure to investigate the causes of nonconformities relating to product, processes, and the quality system [21 CFR 820.100(a)(2)] in that:
  - a. there were numerous complaints regarding erratic/inconsistent test results and drifting controls. Investigation determined that products were contaminated with microorganisms. These complaints were not fully investigated in that the firm did not attempt to determine the source of the contamination.
  - b. there were numerous complaints regarding positive control band p18 intensity. No investigation was conducted to determine that the Novapath™ HIV-1 Immunoblot test kit functioned as intended, and no corrective action was taken to prevent recurrence of the problem.

2. 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 out of specification initial and retest results occurred during microbiological monitoring of deionized water. The root cause of the problem was not determined and the identification of the organism was not documented as required by SOP 206 entitled [REDACTED] "
3. 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)] in that:
  - a. filling operations for Novapath™ HIV-1 Immunoblot test kit components were observed during which items were placed in the laminar airflow hood in such a way as to divert the flow of air away from the filling area.
  - b. routine environmental monitoring is not performed in areas where manufacturing and filling take place.
4. 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. out of specification results for water microbial sampling are not always investigated.
  - b. there was no documented investigation or corrective action taken regarding out of specification results for sampling test location [REDACTED]
  - c. there is no assurance that cleaning validation for equipment used in the manufacture of the Novapath™ HIV-1 Immunoblot test kit is sufficient in that your validation studies did not include all equipment that directly contacts product components.
5. Failure to establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished device meets acceptance criteria [21 CFR 820.80(d)] in that:
  - a. retention samples are not always retained as stated in the written procedures for the retention samples and [REDACTED] Review of production records revealed that retention samples are used to retest [REDACTED] that failed initial release testing.

- b. [REDACTED] initially failing the functionality test for release were retested using the retention sample, and released. SOP 971.06.19 entitled "[REDACTED] Testing and Release" states that if any parameter does not meet specifications, the material must be rejected.

We acknowledge receipt of your written initial response, dated February 15, 2000, to the Form FDA-483 issued on February 9, 2000. For each Form FDA-483 item, the response indicates that your firm has initiated a corrective action request to evaluate and/or take various steps to correct certain aspects of each observation. This response is not sufficient because it lacks the detail necessary to determine that the violations have or will be adequately corrected. Contrary to the claim on page 1 of the attachment to your response letter, we do not agree that your firm was able to successfully address and close out each of the findings from our 1998 inspection. In fact, our review finds that some of the same or similar violations brought to your firm's attention as a result of the 1998 inspection had still not been corrected by the time of our January-February, 2000 inspection. These include, for example, inadequate control of the microbiological quality of the deionized water, inadequate cleaning validation for equipment, and several instances involving failure to follow established written procedures. 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.

The above violations are not intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility to assure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the Form FDA-483 issued at the closeout of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket submissions for devices to which the deviations from the Quality System (QS) regulation are reasonably related will be cleared until the violations have been corrected. Also, no requests for export certificates will be approved until the violations related to the subject devices have been corrected.

In order to facilitate FDA's the determination that such corrections have been made and thereby enabling FDA to withdraw its advisory to other federal agencies concerning the award of government contracts, and to resume marketing clearance and export clearance for products manufactured at your facility, we are requesting that you submit to the

Center for Biologics Evaluation and Research (CBER) on the schedule below, certification by an outside expert consultant that it has conducted an audit of your firm's manufacturing and quality assurance systems relative to the requirements of the device to the QS regulation (21 CFR, Part 820). You should also submit a copy of the consultant's report, and certification by your firm's CEO (if other than yourself) that he or she has reviewed the consultant's report and that your firm has initiated or completed all corrections called for in the report. The attached guidance may be helpful in selecting an appropriate consultant.

The initial certifications of audit and corrections (if required) should be submitted to CBER by March 20, 2001. If all corrections called for in the consultant's report have not been completed by the time of the initial submission to CBER on March 20, 2001, the initial submission should also include an estimated time frame when each remaining correction is expected to be completed. Further reports on the status of all incomplete corrections should be submitted to CBER at not more than three-month intervals following the initial submission, until all corrections recommended by the consultant have been completed.

One year after certifying the completion of all recommended corrections, your firm should submit certification by an expert outside consultant that it has conducted an update audit relative to compliance with 21 CFR, Part 820 requirements. You should also submit a copy of the consultant's report and certification by your CEO that the update report was reviewed and that your firm has made all required corrections.

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 include, but are not limited to, seizure, injunction, and/or civil penalties.

Please notify this office within 15 days of receipt of this letter, of the specific steps you will take to comply with our request.

Your response 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 Janet Claggett at (301) 827-6201.

Sincerely,



 Deborah D. Ralston  
Director  
Office of Regional Operations