



Atlanta District Office
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July 8, 2004

VIA FEDERAL EXPRESS

Philippe Sans, President and CEO
bioMerieux, Inc.
100 Rodolphe Street
Durham, NC 27712-9402

Warning Letter
(04-ATL-14)

Dear Mr. Sans:

During an inspection of your firm located at 100 Rodolphe Street, Durham,, NC on 4/13-4/30/2004, our investigators determined that your firm manufactures in-vitro diagnostics (immunodiagnostic, hemostasis, and microbiology reagents/tests). These products are devices as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C §321(h).

The above stated inspection revealed that these devices are adulterated within the meaning of Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for their manufacturing, packing, storage, or installation are not in conformance with the Current Good Manufacturing Practice (CGMP) requirements of the Quality (QS) System Regulation for medical devices, as specified in Title 21 Code of Federal Regulations (21 CFR), Part 820. At the close of the inspection, you were issued a Form FDA 483 which delineated a number of significant QS inspectional observations, including, but not limited to, the following:

1. Complaints representing events that are MDR reportable were not promptly reviewed, evaluated, and investigated by a designated individual, as required by 21 CFR 820.198(d). Specifically, you failed to promptly and adequately investigate complaint #282829 which was received on 04. This complaint involved a old child who was treated in the emergency room after a febrile convulsion. The culture was positive with a gram negative bacteria (GNB) and the child was admitted and started on IV antibiotics. The customer had reported that the subculture revealed Bacillus and the BacT/ALERT culture media bottle was contaminated prior to inoculation. Your firm's investigation into this complaint was still outstanding as of the date of the inspection.
2. Failure of management with executive responsibility to ensure that an adequate and effective quality system has been implemented and maintained at all levels of the organization, as required by 21 CFR 820.20. Specifically, the Quality Assurance (QA) unit is not overseeing overall product quality. The QA unit does not have independence and authority over the release/rejection of manufactured lots which do not conform to quality standards. Also, the QA unit is not involved in the investigation of device failures after product release. Management with executive responsibility has not ensured that the firm has implemented all actions needed to correct problem areas and prevent the recurrence of the contamination of the BacT/ALERT media bottles.

- 7
3. Failure to adequately validate and approve according to established procedures a process whose results cannot be fully verified by subsequent inspection and test, as required by 21 CFR 820.75(a). Specifically, your firm has failed to adequately validate the autoclave cycle for the new plastic BacT/ALERT bottles.
 4. Failure to establish process control procedures that describe any process controls necessary to ensure conformance to specifications, as required by 21 CFR 820.70(a). For example, your firm does not have a master SOP detailing the requirements for conducting lethality studies, including, but not limited to: conducting appropriate microbiological challenges; determining and measuring bioburden resistance; designating an appropriate Sterility Assurance Level (SAL) for products exposed to a terminal sterilization cycle or establishing an adequate SAL for microbiologically controlled products; and having appropriate sampling method(s) for sterility testing and validation studies. Your firm has not provided any written and approved SOPs describing procedures, standards, requirement, or guidance for employees to use in establishing adequate autoclave cycles based on valid scientifically accepted methods and processes.
 5. Failure to establish and maintain procedures for implementing corrective and preventive action, as required by 21 CFR 820.100(a)(1). For example, the failure investigations into the contamination of the BacT/ALERT media bottles (FICA #02-370), which include customer complaints of contamination beginning in early 2001, are inadequate. Your firm has not yet implemented all of the corrective/preventive actions in response to the contamination investigations. As part of the overall corrective action for the contaminated media bottles, your firm indicated that a separate air handling system in the BacT/ALERT production area will not be installed until [REDACTED]

Also, your firm failed to identify all actions needed to correct and prevent the recurrence of nonconforming product and other quality problems. Your firm's failure investigation (FICA #03-405) initiated in response to numerous customer complaints of instability in Simplastin L, is inadequate in that your firm has not determined the root cause for the lot-to-lot variability. In response to customer complaints, Customer Service has incorrectly instructed customers to calibrate the Prothrombin Time (PT) test to rule out quality control bias prior to using. Your firm has recommended recalibration; however, your firm has not determined the root cause of the reagent's instability.

6. Failure to investigate where necessary complaints involving the possible failure of a device to meet any of its specifications, as required by 21 CFR 820.198(c). For example, your firm received at least eight (8) complaints concerning the high and erratic control results of Fibriquik. An investigation into these complaints has not been performed. Also, your firm received a complaint dated 4/17/03 in which a customer indicated receiving a false negative result from an FA BacT/ALERT media bottle. Your firm did not investigate this complaint.
7. Failure to have complete procedures for monitoring and control of process parameters for validated processes, as required by 21 CFR 820.75(b). For example, your firm has no procedures for the routine sanitization of the USP water system to include evaluation/cleaning of the system after exceeding the action limits.
8. Failure to investigate indicators of nonconformities to determine the cause of the nonconformity, as required by 21 CFR 820.100(a)(2). Specifically, out-of-specification USP water was not evaluated in the investigation of Simplastin L finished Lot # 161719. The bulk lot (132146B)

was found to contain 9.5 cfu/ml of mold. This finished lot has exhibited vial-to-vial variability and four customer complaints related to this lot were received on 8/3-10/03.

9. Failure to establish procedures for quality audits and to conduct such audits to assure that your firm's quality system is in compliance with the established quality system requirements and to determine the effectiveness of your firm's quality system, as required by 21 CFR 820.22. Specifically, the internal audits conducted in 2002 and 2003 did not cover significant quality systems such as CAPA, Complaints, Non-conforming products, Training, Purchasing, Labeling and Packaging, Identification and Traceability, Acceptance Activities, Statistical Techniques, and Records.
10. Failure to establish and maintain procedures for acceptance activities, as required by 21 CFR 820.80(a). Specifically, your firm incorrectly excluded data points in the [redacted] determination for Simplastin EXCEL for the following lot #s 161761, 161783 and 161763. Also, your written procedure, TR 50.152, Investigating Out-of-Control Results, is not adequate in that the procedure allows for the acceptance of products that fall outside of the control limits.

Additionally, the above stated inspection revealed that your devices are misbranded within the meaning of section 502(t)(2) of the Act in that your firm failed or refused to furnish material or information required by or under section 519 respecting the devices, and 21 CFR Part 803 (Medical Device Regulation Reporting regulation). Your firm failed to file an adverse event report as required by 21 CFR 803.50(a)(1). Specifically, your firm failed to promptly report to the FDA one MDR-reportable complaint that was received by your firm on or about [redacted]/03 concerning the instability of MDA Simplastin. The facility reported to your firm that it had been experiencing erratic INR (International Normalized Ratio) and that a patient on therapeutic [redacted] had a stroke.

Review of the submitted Medical Device Reports (MDRs) revealed that seven MDRs were not submitted within the 30 day timeframe. Some of the MDRs were submitted anywhere from 3 months up to seven months after becoming aware of the MDR reportable incidents.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA 483 issued at the close 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 causes of the violations identified by the FDA. You also must promptly initiate permanent corrective and preventative action on your quality system.

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, FDA will not approve any applications for premarket approval (PMAs) for Class III devices to which the Quality System regulation deficiencies are reasonably related until the violations have been corrected. Also, no request for Certificates For Export will be approved until the violations related to the subject devices have been corrected.

You should take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action being initiated by FDA without further notice. These action include, but are not limited to, actions for seizure, injunction, and/or civil money penalties.

Please provide this office in writing within fifteen (15) working days of receipt of this letter a report of the specific steps you have taken, or will take, to identify and correct the noted violations, including an explanation of each step being taken to ensure that similar violations will not recur. If corrective actions cannot be completed within fifteen (15) working days, state the reason for the delay and time within which the corrections will be completed.

We acknowledge receipt of your letter dated May 20, 2004 which was in response to the FDA 483. We are currently reviewing your response letter. You may refer to your May 20, 2004 response in your answer to this Warning Letter. Please send your response to the attention of Serene N. Ackall, Compliance Officer at the address noted in the letterhead. If you have any questions about this letter, you can contact Serene Ackall at 404-253-1296.

Sincerely,



Mary Woleske, Director
Atlanta District