



m49607

Food and Drug Administration  
Center for Biologics Evaluation  
and Research  
1401 Rockville Pike  
Rockville MD 20852-1448

DEC 15 2000

## WARNING LETTER

CBER-01-008 ...

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Mr. Glenn Carlisle  
Site Manager  
Murex Diagnostics, Inc.  
3075 Northwoods Circle  
Norcross, GA 30071-1542

Dear Mr. Carlisle:

The Food and Drug Administration (hereinafter FDA or the agency) conducted an inspection of Murex Diagnostics, Inc. (Murex), located at 3075 Northwoods Circle, Norcross, Georgia, between August 14 and August 24, 2000. During the inspection, the FDA investigators documented numerous significant deviations from section 501(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and deviations from the applicable standards and requirements of Subchapter H, Part 820, Title 21, Code of Federal Regulations (CFR), and the applicable standards in your license. The deviations noted on the Form FDA 483, Inspectional Observations, issued at the conclusion of the inspection include, but are not limited to, the following:

1. Failure to establish and maintain 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 nonconforming product and other quality problems; failure to document all activities and results required; and failure to employ appropriate statistical methodology to detect recurring quality problems [21 CFR 820.100(a) and (b)] in that:
  - a) Complaints of high background controls and leaking reagent bottles are not adequately investigated. For example, planned investigative testing is not performed, assignable causes are not identified, and investigations are not adequately documented.

- b) There was no investigation into high reflectance readings for the Center for Biologics Evaluation and Research (CBER) negative control panel members.
  - c) There was no documentation of an investigation into the presence of fibrin clots found in both bulk and filled bottles of negative control lots ~~\_\_\_\_\_~~
  - d) There was no documentation of reviewed and approved investigations into particle monitoring excursions on February 24, March 8, and March 20, 2000.
  - e) Appropriate statistical methodology for test failures for raw materials, in process, and finished products has not been established.
  - f) There are no procedures for establishing appropriate statistical methodology for initial out-of-specification results, retests, aborted, and invalid tests.
2. Failure to validate processes with a high degree of assurance and to approve the validation according to established procedures [21 CFR 820.75(a)] in that:
- a) The manufacturing processes for the finished Human Immunodeficiency Virus Type 1 Single Use Diagnostic System (SUDS) HIV-1 test have not been validated.
  - b) Critical processing steps used in the manufacture of the bulk materials used in the formulation of test kit reagents have not been validated.
  - c) The sterile filtration processes for in-process bulk products have not been adequately validated.
  - d) The deionized water system has not been validated.
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) Discrepancies exist between the stated storage temperature on the container label and in the package insert for stop solution, diluent, and wash reagent.
  - b) Container closure integrity testing studies have not been performed for kit reagents.
  - c) There are no data to support the re-use of chromatography columns used for purification of monoclonal antibodies.
  - d) There are no reference chromatograms for identification of extraneous peaks in column residue and products run on the columns.

Page 3 – Mr. Glenn Carlisle

- e) The standard operating procedure (SOP) entitled "SUDS HIV-1 Stability Testing" requires that stability testing on Master Kit lots be performed at \_\_\_\_\_ Stability testing for Master Kit lot \_\_\_\_\_ was not conducted between January 31 and April 27, 2000.
4. Failure to assure that all inspection, measuring, and test equipment is suitable for its intended purpose and is capable of producing valid results [21 CFR 820.72] in that malfunctions of the SUDS reader are not investigated.
  5. Failure to establish and maintain adequate acceptance procedures for in-process and finished devices which include inspections, tests, or other verification activities [21 CFR 820.80] in that:
    - a) Specifications for reflectance testing for CBER panel members are not defined.
    - b) Reflectance test results are accepted based on the mean +/- the standard deviation. The test passes if the mean of three results passes even if individual test results are out of specification.
    - c) Absorbance readings were not taken for Lot 0110 released April 20, 2000, due to a malfunction in the SUDS reader.
  6. Failure to establish and maintain procedures to ensure that sampling methods are adequate for their intended use and are based on a valid statistical rationale [21 CFR 820.250(b)] in that:
    - a) There are no data to support testing master kits in triplicate against the internal panels.
    - b) Acceptance criteria for the \_\_\_\_\_ plastic bottles used to store diluent require sampling of \_\_\_\_\_ bottles for visual identity. There are no data to support this sampling level.
    - c) There are no data to support the sampling frequency for bioburden testing during filling.
  7. Failure to establish and maintain procedures to control product that does not conform to specified requirements [21 CFR 820.90] in that:
    - a) There are no procedures for re-testing raw materials, components, and finished products that do not meet specifications.
    - b) Expired lot \_\_\_\_\_ was used to test QC reference panel member 12.

The deviations identified above are not intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility as management to assure compliance with all requirements of the federal regulations and the standards in your license.

We acknowledge receipt of your written responses dated September 9, 2000, October 9, 2000, November 9, 2000, and those provided at the October 24, 2000, meeting between representatives of FDA, Murex Diagnostics, and Abbott Laboratories to the Form FDA 483 issued at the close of the inspection. We have reviewed your responses and find that they are inadequate. For example, while there are numerous inspectional observations pertaining to the lack of thorough investigations into complaints, out of specification test results, and equipment failures, your responses fail to discuss implementation of adequate quality assurance oversight to ensure prompt identification, documentation, correction, and follow-up for all problems associated with the manufacture of your product. We have the following specific comments to your response, which are numbered to correspond to the observations listed on the Form FDA 483:

Item 1. Reports of the complete investigations should be provided to FDA.

Items 1a and 1b. General Comments:

- A. Although you have agreed to perform Level III investigations in some instances, your response fails to state how it will be assured that Level III investigations are performed when necessary in the future.
- B. The steps that will be taken to investigate the elevated negative control and leaking bottle problems are not clear. The document entitled "Minutes of 09/19/00 \_\_\_\_\_ meeting" addresses both problems and does not delineate the steps to be taken in each investigation. Please explain item 5 in this document that states "Noticing more surface Irregularities."
- C. The response does not include protocols for conducting the investigations.
- D. Please provide a justification for the August 23, 2001, closure date for both investigations.
- E. We disagree with your statements on the Murex \_\_\_\_\_ and the October 6, 2000, document signed by \_\_\_\_\_ that parts of item 1 are complete. These investigations should not be viewed as complete based on the initiation of the investigations and should continue to be tracked until the investigations are closed and any necessary corrective actions have been taken.
- F. The response did not provide information as to the contents of the proposed Quality Directives and when they would be submitted to customers.

Item 1a. High background and false positive complaints:

- A. At the October 24, 2000, meeting, FDA requested data regarding the number of tests affected by the high background/false positive problem rather than the number of complaints received since some complaints involve several test cassettes. Please submit this information.
- B. It is our view that your health hazard evaluation should have identified a risk of false negative results associated with the high background problem. The labeling for the test kit does not clearly state that a run in which the negative control result shows some color (i.e., high background) is invalid. A user may simply compare patient results with the negative control results and assume that any patient result which has color that is not more than the negative control color is negative. Per our request during the October 24, 2000, meeting, please advise all customers that results of all runs with any color appearing in the negative control should be invalidated. Please provide documentation of this notification.
- C. Because of the risk identified in item B above, SOPs should set specifications and action levels for fibrin or any other problem that is known to cause high background.
- D. The September 27, 2000, document entitled ~~\_\_\_\_\_~~ "Elevated Negative Control Initial Investigation Plan" indicates that it is an "initial" (rather than final) plan, and it is not clear that this plan is complete. The document does not provide time frames for completion of the steps in the investigation.

Item 1b. Please explain whether the ~~—~~ leak rate in reagent bottles is for the recently (Spring 2000) approved containers as well as previously approved containers. In addition, your investigation should include protocols for stress testing that check for worst case leak rates in a thorough manner.

Item 1c. Your responses do not state whether any corrective action was taken to prevent future particulate monitoring excursions, especially during construction.

Item 1f. Your response fails to address specifications for acceptable amounts of contaminating materials (e.g., fibrin) that have been associated with high background.

Item 2 Process Validation:

- A. Your response discusses the development of a Master Validation Plan as part of the Murex Diagnostics, Inc., Norcross, Quality Compliance Plan dated March 24, 2000. We are concerned by the number and type of deviations noted during the August 2000 inspection despite the Compliance Plan in place for the previous five months.
- B. The Summary of SUDS HIV-1 Process Validations and November 8, 2000, Initial Master Validation Schedule cover only items on the 483. Please clarify whether the

entire manufacturing process will be evaluated using your decision tree and whether any additional processes will be validated. Please provide a complete and final timeline when all validations have been identified.

- C. Process validation should be based on results from at least three consecutive production runs (using final process SOPs).
- D. The Equipment Qualification Decision Tree on Page 20 of 23 of the Validation Master Plan has an incomplete box in the upper left side which states " \_\_\_\_\_"  
\_\_\_\_\_
- Please complete this statement.
- E. We note that the schedule for validation extends through December 2001. Please describe the resources that are allotted to addressing the 483 deficiencies, and explain the reasons for the prolonged schedule. Please address your projections regarding the availability of product since the SUDS reader validation will not be complete until June 2001.

Item 2cIII. The SOP 09-41-3 entitled " \_\_\_\_\_ Sterilization of Components" does not include the \_\_\_\_\_ documenting that the current cycle parameters have been added to the SOP.

Items 2e, 2g. We have reviewed your document entitled "Study/Validation Protocol for Sanitization of a Deionized Water System" dated October 13, 2000. Item 4 in the section entitled "Acceptance Criteria" is not clear. The protocol indicates that mean microbial counts are to be \_\_\_\_\_. Please explain in detail how the mean microbial result is calculated and clarify whether the terms "value" and "result" are data points or calculated means. Please also explain whether data points that fall outside of the acceptance criteria will be included in the mean calculation. In addition, it is not clear whether the acceptance criteria is \_\_\_\_\_. The protocol states that an investigation will be conducted if the result is between \_\_\_\_\_. Please address the action to be taken if a result is greater than \_\_\_\_\_.

Item 3. Method Validation. SOP 12-57-0 entitled "Test Method Validation" should be revised to include specific identification of the method protocol proposed for use, a study designed with sufficient power to provide statistically valid results, and acceptance specifications based on defined/qualified standards and/or variability tolerances relevant to the analyte/component being tested.

Item 3a. As we have discussed, we disagree with your proposal to discontinue the use of the reflectance test at this time. Your response should include a complete report on the investigation of the SUDS reader variability. Any corrective actions should be identified and qualified.

Item 3f. The protocol for "Suitability of Use Test Method Validation of the \_\_\_\_\_" is not adequate in that it does not have sufficient power to

determine repeatability or intermediate precision in a statistically significant manner (e.g., operator-to-operator variability cannot be sufficiently determined with two operators performing two runs). Please explain how the two lots of viral lysate were qualified as the standard and explain how the specifications for acceptance (concentration and %CV ranges) were determined. The study does not clearly identify details of the method proposed (e.g., is the ~~method~~ followed exactly, is the test lysate lot always tested ~~times~~ times, do values have to fall between the ~~range~~ range for which accuracy was tested)? Please refer to these questions as well as comments above in item 3 above regarding Method Validation to write a new protocol. Please submit the protocol for our review.

Item 4a. Your response should clearly identify and include appropriate specifications in SOPs (e.g., pH of negative control material). Please submit your proposal, including your justification, for elimination of any "For Information Only" testing. It is our view that reflectance testing should not be eliminated at this time.

4b. We disagree with the elimination from your batch production records of absorbance and reflectance evaluations for the CBER test panel at this time. Please reevaluate this plan.

Item 10. The revision of SOP 12-13-3 entitled "Assigning/Extending Expiration Dates" is not sufficient to allow the use of expired components. Components past current expiration date can be used only if sufficient data (based on stability program protocol) to extend their expiration date are available. SOP 12-13-3 should state this requirement or state that components may not be used past established expiration dates.

Item 12. Your November 9, 2000, response under the tab marked "2, 12," states, "The validation of column life would still continue to assure we have data to support the number of times a column may be used." Please confirm that data are on file to support the number of times columns can be used in production. These data should be available for review during future inspections. Please also submit your procedure(s) for column cleaning and state whether there are data demonstrating the removal of residual detergent(s) after cleaning.

Item 16. SOP 12-50-0 entitled "Murex-Norcross Site Document Hierarchy, Including the SUDS-HIV-1 Device Master Record (DMR)" is not clear with regard to the following:

- A. Identification of the documents related to lot release testing.
- B. Identification of the department(s) responsible for all aspects of lot release. If the manufacturing group is responsible for lot release, please explain your rationale.
- C. Identification of the documents related to testing and acceptance of raw materials.
- D. Identification of the department(s) with authority for testing and acceptance of raw materials.
- E. Identification of SOPs NS-0127, -0128, and -0135 as Quality Control documents.
- F. Identification of some documents related to labels as Quality Control documents and others as manufacturing documents.

Items 17a and 17b. Your response fails to include a commitment to perform a trend analysis on in-process failures for the time period leading up to the current manufacturing problems. SOP 12-39-1 entitled "Nonconformance Control System" is not adequate for tracking and trending of failures. Murex should submit an SOP that includes a mechanism for capturing and maintaining testing information for all raw materials, in-process components, and test kits.

We also note that your firm promised corrective action in response to the Form FDA 483, Inspectional Observations, issued at the conclusion of FDA's September 14-30, 1999, inspection of Murex; however, the most recent inspection and the recent manufacturing problems at Murex related to the failure of microparticles to pass reflectance testing has shown that adequate and effective corrective actions have not been implemented. Therefore, in addition to the responses requested above, your response to this letter should include Murex's plan for the following:

- a. ensuring that the Quality System Regulations (QSR) requirements are effectively established and effectively maintained;
- b. conducting a thorough review of all SOPs to achieve compliance with the QSR requirements, as specified in 21 CFR 820, and with the applicable regulations for biological products specified in 21 CFR 600-680;
- c. establishing a system of training and evaluation to ensure that personnel have capabilities commensurate with their assigned functions, a thorough understanding of the manufacturing operations they perform, and knowledge of the QSR requirements;
- d. conducting thorough complaint and failure investigations which include an assessment of whether other products, lots, systems, or processes may have been similarly affected or have similar deviations; and
- e. developing a process that ensures a thorough review of all appropriate records and process deviations prior to release of product to ensure that its quality specifications have been met.

Please also advise FDA in writing of the status of the investigation into manufacturing problems at Murex related to the failure of microparticles to pass reflectance testing.

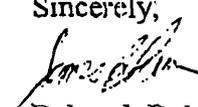
Neither this letter nor the list of inspectional observations is meant to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure that your facility is in compliance with all the provisions of the FD&C Act, all applicable regulations, and the applicable standards in your license. 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.

Page 9 – Mr. Glenn Carlisle

Please notify this office in writing, within 15 working days of receipt of this letter, of any steps you have taken or will take 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. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include seizure, injunction, license suspension, and/or revocation.

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.

Sincerely,



Deborah Ralston  
Director  
Office of Regional Operations

cc: Mr. Thomas D. Brown, President  
Abbott Diagnostics Division  
Abbott Laboratories  
100 Abbott Park Road, AP6C  
Abbott Park, Illinois 60064-6092

Mr. Miles D. White  
Chairman and Chief Executive Officer  
Abbott Laboratories  
One Abbott Park Road  
Abbott Park, Illinois 60064-3500

Ms. Marcia A. Thomas  
Corporate Vice President  
ADD Quality Assurance, Regulatory Affairs and Compliance  
Abbott Laboratories  
One Abbott Park Road  
Dept. 9Y6, BLDG AP6C  
Abbott Park, Illinois 60064-6092

Cecilia Kimberlin, Division Vice President  
Abbott Diagnostics Division Regulatory Affairs , Compliance and Audits  
Abbott Laboratories  
Department 9Y6, Building AP6C  
100 Abbott Park Road, AP6C  
Abbott Park, Illinois 60064-6092