



CBER-98-020

Food and Drug Administration
Rockville MD 20857WARNING LETTER

JUN 22 1998

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. John W. Morgan
President and Chief Executive Officer
Epitope Inc.
8505 SW Creekside Place
Beaverton, OR 97008

Dear Mr. Morgan:

An inspection of Epitope Inc., located at 8505 SW Creekside Place, Beaverton, OR, was conducted from April 6 through 28, 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:

1. 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. your stability program for components and controls of the HIV-1 Western Blot Kit does not include bioburden analyses or periodic preservative effectiveness testing.
 - b. lot release panels have not been placed on a stability program, although Incident Report Forms #96-021301, dated February 13, 1996, and #98-020202, dated February 2, 1998, attribute failures of Western Blot kits to meet final release requirements to possible panel member degradation.
 - c. data are not available to support the established five year shelf life of processed serum/plasma or the HIV-1 bulk serum controls stored at [REDACTED]
2. 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. your Study [REDACTED] entitled “[REDACTED]” (related to the OraSure® HIV-1 Oral Specimen Collection Device) does not support the established mix time of [REDACTED] minutes after [REDACTED] addition. In the study, pad buffer lot # [REDACTED] was manufactured using a mix time of [REDACTED] after [REDACTED] addition.
 - b. cleaning validation has not been performed to demonstrate removal of residuals after cleaning of carboys with [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. growth promotion testing is not performed on media used for environmental monitoring.
 - b. your standard operating procedure (SOP) #EMS-061 entitled “Equipment Maintenance Specification: Manufacturing HVAC System” is not followed in that HEPA filter recertification was not performed in 1997; your SOP requires annual recertification.
 - c. your SOP #QA-045 entitled “Environmental Monitoring” is not followed. For example this SOP requires an “Environmental Monitoring Notification/Facility Change” notice to be issued to the QC Supervisory Team by Engineering, Facilities, and/or Validation personnel executing HVAC changes, addition of large equipment, or other construction changes. There is no indication that notices were issued for work on building hoods referenced in the July 10, 1997, “Microbiology Memo” attached to Incident Report Form (IRF) #97-061001 or HVAC system adjustments noted on IRF #97-102101.
4. 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)] in that the method for collecting deionized water samples for microbial monitoring described in your SOP #QA-050 entitled “Deionized Water Quality Maintenance” does not assure that water samples are representative of water used in production. Section IV.F.1.b of your procedure states “Prior to sampling each port, spray the interior and exterior of the port with [REDACTED]. Then turn on the water flow and allow the port to flush [REDACTED].” There are no written procedures which instruct operators to disinfect or flush ports during production.

5. Failure to establish, maintain, and follow procedures to control all documents including procedures providing for document approval, distribution and changes [21 CFR 820.40(b)] in that there is no documented approval to discontinue use of the *OraSure® HIV-1 Oral Specimen Collection Device Training Video Script, Quiz, and Quiz Answer Sheet* (approved February 1995) and institute use of the *Step-by-Step OraSure® HIV-1 Oral Specimen Collection Device Training Manual*.
6. Failure to establish and maintain an adequate quality system appropriate for the product manufactured and to provide adequate resources, including trained personnel, for assessment activities [21 CFR 820.20] in that:
 - a. the Manufacturing Work Order (MWO) for HIV-1 Western Blot Kit nitrocellulose strips master lot # [REDACTED] indicates the label accuracy review performed by QC personnel on June 18, 1997, failed to detect an error which led to half of the nitrocellulose strips being mislabeled.
 - b. the MWO for Powdered Milk lot # [REDACTED] indicates the label accuracy review performed by QC personnel on April 3, 1998, failed to detect an error which led to [REDACTED] labels being incorrectly printed with lot # [REDACTED]. The lot was subsequently redesignated as lot # [REDACTED] instead of lot # [REDACTED], as originally assigned.
 - c. your Deviation Report Worksheet dated February 4, 1998, documents that the MWO for OraSure® HIV-1 Western Blot high positive control Lot # [REDACTED] was reviewed and approved by QC personnel on January 20, 1998 although the Antimicrobial Activity Assay test results for the control were not reviewed and approved until February 4, 1998.
 - d. Complaint Database (Data Entry) CCR #97-041409 documents a reported problem with HIV-1 Western Blot Kit # [REDACTED]. This lot number was incorrectly transcribed from the Organon Teknika Supplier Corrective Action Request record; the correct lot number is # [REDACTED]. CCR #97-041409 was not signed as reviewed by the QA Manager. The incorrect lot number was also listed on the Semi-Annual Western Blot Kit and OraSure® Device Complaint Trend Analysis report dated November 20, 1997. This error was not detected by your review personnel but was detected by our investigator during review of complaint records.
 - e. there is no formal review mechanism for the Environmental Monitoring Quarterly Trend Analysis reports.

7. Failure to establish, maintain and follow procedures for implementing corrective and preventative 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. Incident Report Form (IRF) #96-021301, dated February 13, 1996, documents test results for HIV-1 Western Blot Kit master lots # [REDACTED] and # [REDACTED] did not meet your specified final release requirements in that p31 band intensity of lot release panel member [REDACTED] was interpreted as indeterminate; your minimum requirements specify that band intensity of p31 bands must be interpreted as present for this panel member. The Material Review Committee (MRC) meeting record of March 5, 1996, indicates the committee reviewed this IRF and decided to replace lot release panel member [REDACTED]; however, there is no indication that this corrective action has been taken.
 - b. your SOP #QA-031 entitled “Deviation Reporting” stipulates that the QA Manager documents the reason for not presenting the deviation report to the (MRC) within the description of action/final disposition on all Deviation Report Worksheets. Review of Deviation Report Worksheets by our investigator reveals that this SOP is not followed. For example, Deviation Report Worksheets reviewed by the QA Manager on January 8, 1997, January 8, 1998, and February 5, 1998, do not document the reason for not presenting the deviation reports to the MRC.
 - c. there is no written procedure addressing the trending of data from Incident Report Forms, Deviation Report Worksheets, complaint records, and other quality data to identify existing and potential quality problems.
8. Failure to establish and maintain data that clearly describe or reference the specified requirements, including quality requirements, for purchased product/services and to maintain purchasing documents including, where possible, an agreement that the supplier will notify the manufacturer of changes in the product/service [21 CFR 820.50(b)] in that there is no supplier agreement with [REDACTED], your conjugate supplier.

9. Failure to establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit [21 CFR 820.198] in that:
 - a. there is no written procedure addressing reconciliation of complaints received at Organon Teknika, distributor of your HIV-1 Western Blot Kit and OraSure® Western Blot Kit, with those forwarded by Organon Teknika to Epitope Inc. During the period June 1996 to April 1998, six complaints received at Organon Teknika relating to the HIV-1 Western Blot Kit were not forwarded to your firm. These complaints include reports of weak or no banding.
 - b. your SOP #QA-014 entitled “Field Complaints and Failures” stipulates that each complaint record is reviewed and signed by the QA Manager. Review of complaint records by our investigator revealed that this SOP is not followed in that 25 of 26 complaint records received in 1997 were not signed as reviewed by the QA Manager.

10. Failure to establish procedures for identifying training needs and ensuring that all personnel are trained to adequately perform their assigned responsibilities [21 CFR 820.25(b)] in that there is no formal training program which outlines and tracks training requirements for specific job functions.

We note your failure to comply with the requirements applicable to the device as outlined in the letter approving the OraSure® HIV-1 Oral Specimen Collection Device in that not all adverse events required to be reported by the December 23, 1994, approval letter and reported to your firm were included as part of the 1997 annual report.. For example:

- a. Complaint Database (Data Entry) record CCR #97-052211 documents a report of blisters appearing where the OraSure® collection device was placed.
- b. Complaint Database (Data Entry) record CCR #97-062420 documents a report of small blood blisters on the inside of the mouth after sample collection.

We interpret the letter of approval to require all adverse events to be reported as part of the annual report regardless of the manner in which reports are received by your firm.

Your response of May 21, 1998, to the Form FDA 483 issued at the close of the inspection is currently under review. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate. Based upon your response to FDA 483 item #1 and further review of the conditions of export described in the inspection report, it has been determined that unlabeled Oral Specimen Collection Devices

may be exported as unapproved products provided they comply with the export requirements in Sections 801(e)(1) or 802 of the Act. To be considered an unapproved device, the manufacturing records for the Oral Specimen Collection Device must demonstrate that a specific lot of the device is intended for export to a specific foreign purchaser within a specific country and meets the specifications of this foreign purchaser, i.e., no labeling, prior to the manufacturing of the device.

In addition to the Quality System Regulation deficiencies addressed above, we are aware of ongoing review/discussion regarding changes which have been made to the originally approved labeling for your OraSure® HIV-1 Oral Specimen Collection Device. The Office of Blood Research and Review (OBRR) has assumed the lead for review of these labeling issues which will continue to be addressed by OBRR under separate cover.

The above violations are not intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility as management 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.

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.

Sincerely,

A handwritten signature in cursive script, appearing to read "Gerald Vince".

Gerald Vince
Director, Office of Regional Operations

cc: Dr. J. Richard George
Authorized Official
Epitope Inc.
8505 SW Creekside Place
Beaverton, OR 97008