



**WARNING LETTER**

MAY 3 1999

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**

Charles Don Evans  
Director RA/QA  
Calypte Biomedical Corporation  
1500 East Gude Drive  
Rockville, MD 20850-5307

Dear Mr. Evans:

An inspection of Calypte Biomedical Corporation, located at 1500 East Gude Drive, Rockville, MD, was conducted by the Food and Drug Administration (FDA) from November 30 - December 11, 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 investigate the cause of nonconformities relating to product, processes, and the quality system [21 CFR 820.100(a)(2)]. For example:
  - a. Standard Operating Procedures (SOP) QC007, entitled, \_\_\_\_\_ and QC-087-1, entitled, "Infectivity Assay for HIV-1 or HIV-2 Antigen", require as a release specification a positive result for the \_\_\_\_\_ dilution of the HIV-1 viral lysate. Non-Conforming Material Reports (NCMR) 3502 and 3504 indicate that the \_\_\_\_\_ dilution has tested negative on multiple occasions. The corrective actions outlined in the NCMR reports have not been implemented.
  - b. Western Blot functional assay results for strip lot 72621, dated 9/22-23/97, noted that the intensity of the p17 band was weaker than the p17 band on the strong positive reference strip, which is considered a failure according to SOP \_\_\_\_\_ entitled, "Western Blot Strip Scoring Procedure". The lot was approved for use in kit assembly without investigation into the cause.
  - c. Stability testing was performed on 2/16-17/98 for the \_\_\_\_\_ timepoint for lot C8126, with test results of unexpected bands on the \_\_\_\_\_ and the negative

control strips. The test was repeated multiple times with the same results. There is no documented investigation into the cause of these failures.

- d. NCMR 3534, dated 1/7/98, regarding a pseudomonas contamination of HIV-1 Antigen, lot 1829P, authorized a retest without investigation into the cause of the contamination.
  - e. \_\_\_\_\_ Panel testing for lot D8126 was repeatedly conducted from 11/24-12/4/97, resulting in two out-of-specification (OOS) results and one valid result. There were no documented investigations of the OOS results.
2. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications [21 CFR 820.70(a)]. For example:
- a. Cannulas were stored in a plastic container with clear liquid in the Purification Room. The container was not identified as to its contents or status.
  - b. Water monitoring records, dated 9/8/98, indicate that the system was OOS for room 201A. The records show that a System Notification of Discontinuation was issued but was not signed by Quality Assurance and, when the system was cleared for use, a Notification of Resumption was not issued as required by SOP \_\_\_\_\_ entitled, "Monitoring the Purified Water System(s)".
  - c. SOP \_\_\_\_\_ entitled "Western Blot Function Assay - In-Vitro Kit Testing," does not include all steps necessary to assure proper interpretation of results in that there is no section covering the interpretation of results, the SOP does not address the Calypse requirement that the CBER Panel be scored by three technicians, and the SOP does not indicate the actions to be taken when OOS results occur.
  - d. SOP \_\_\_\_\_ entitled, "Western Blot Strip Scoring Procedure," does not contain clear specifications for intensity nor does it contain criteria for failures.
3. 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)]. For example:
- a. In the separation room of the Virus Production area, the concentration tank tubing and connector were noted to be laying on the floor and the status (i.e., clean, dirty, in-use) of the tank was not identified.
  - b. Empty used carboys were stored on top of a workbench in the separation room of the Virus Production area without identification as to their status.

- c. A cart, located under an airblower in the ceiling of the Purification Room, was noted to be covered with dirt and grit.
4. Failure to validate computer software for its intended use according to an established protocol when computer software is used as part of production or the quality system [21 CFR 820.70(i)] in that the \_\_\_\_\_ computer system is not validated for the purpose of shipment of finished goods.
5. Failure to establish and maintain procedures for acceptance activities which include inspections, tests, or other verification activities [21 CFR 820.80] in that NCMRs 3511 (lot NC396), 3512 (lot SP228), 3515 (lot AH224), 3516 (lot BB241), 3517 (lot RC9888), 3518 (lot RC9887), 3520 (lot RC9886), and 3521 (lot RC9818), indicate that vials used for finished components had failed the requirements for the Biological Indicator Sterility Test after being \_\_\_\_\_ by a contracted vendor. The vials were accepted for use in production.
6. Failure to document the monitoring and control methods and data, the date performed, the individual performing the process, and the major equipment used for validated processes [21 CFR 820.75(b)(2)] in that there is no validation protocol or study summary for the 1997 revalidation performed by an outside contractor of the autoclave units located in the buffer preparation laboratory, the glassware laboratory, and the virus plant laboratory.
7. Failure to validate a process that cannot be fully verified by subsequent inspection and test [21 CFR 820.75(a)] in that the alarm system used to monitor refrigerators, coldrooms, and freezers is not validated. In addition, not all refrigerators, coldrooms, and freezers are connected to the system.
8. Failure to document training to ensure that all personnel are trained to adequately perform their assigned responsibilities [21 CFR 820.25(b)]. For example:
  - a. Training files for laboratory technicians \_\_\_\_\_ contain no documentation that they were trained in Western Blot strip scoring.
  - b. There is no documentation to show that technician \_\_\_\_\_ was retrained after making multiple errors in QC testing.
  - c. Required supervisory signatures were missing in the training records of \_\_\_\_\_ the current, recently promoted, QC supervisor.

Your written responses, dated December 21, 1998, January 21, 1999, and February 3, 1999, are currently under review. You will receive our assessment of your responses upon completion of our review. Corrective actions addressed in your previous letters may be referenced in your

response to this letter, as appropriate.

Neither the above violations nor the observations noted on the Form FDA 483 presented to your firm at the conclusion of the inspection are intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility to ensure adherence to each requirement of the Act and the applicable regulations and standards. The specific violations noted in this letter and the Form FDA 483 may be symptomatic of serious underlying problems in your establishment's manufacturing and quality systems. You are responsible for investigating and determining the causes of the violations identified by FDA.

You should take prompt action to correct these deviations. Failure to do so may result in regulatory action without further notice. Such action includes license suspension and/or revocation, seizure, 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. In addition, no license applications or supplements for devices to which the deficiencies are reasonably related will be approved until the violations have been corrected.

You should respond to FDA 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. Corrective actions addressed in your previous letter may be referenced in response to this letter, as appropriate. 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. FDA will verify your implementation of promised corrective action during the next inspection 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 Annette Ragosta at (301) 827-6322.

Sincerely,



Deborah D. Ralston  
Acting Director  
Office of Regional Operations