



WARNING LETTER

APR 27 1999

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Foster T. Jordan
General Manager
Charles River Endosafe, Inc.
1023 Wapoo Rd., Suite # 43-B
Charleston, South Carolina 29407

Dear Mr. Jordan:

An inspection of Charles River Endosafe, Inc., located at 1023 Wapoo Road, Charleston, South Carolina, was conducted from January 19 through January 29, 1999. 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, Parts 600-680 and Part 820, were documented as follows:

1. Failure to investigate the cause of nonconformities related to product, processes, and the quality system, [21 CFR 820.100(a)(2)], in that:
 - a. No investigations have been conducted into test kits which failed the initial moisture test and passed a retest. The specification is less than -- % moisture. For example:
 - i. The moisture results dated April 11, 1997, for Lot L4921X were — % and — %.
 - ii. The moisture results dated February 2, 1998, for Lot M4291CT were — % and — %.
 - iii. The moisture results for the twelve month stability sample for lot L2892X were — % and — %.
 - iv. The moisture results for the twelve month stability sample for lot L3462X were — % and — %.

- b. The refusal of a customer to accept _____ lot L2792S manufactured October 6, 1997, because of negative control problems was not investigated.
2. Failure to implement and record changes in methods and procedures needed to correct and prevent identified quality problems [21 CFR 820.100(a)(5)]. The corrective actions that were proposed on Deviation Reports 97-068, approved August 19, 1997; 98-045, approved April 15, 1998; and 98-046, approved April 15, 1998 in response to product failures caused by bacterial contamination were not implemented.
3. Failure to validate processes which can not be verified by subsequent inspection [21 CFR 820.75(a)]. For example:
 - a. The lyophilization cycle for _____ vial configuration has not been validated.
 - b. The _____ method for testing moisture has not been validated. In addition, there is no data to support _____ changes that were made in the methodology between March 17, 1997 and September 30, 1998.
 - c. Bacteriostasis and fungistasis studies have not been performed.
 - d. The effectiveness of the disinfectants used to sanitize surfaces in the aseptic processing area has not been validated.
 - e. The _____ holding time for glassware and metal equipment after depyrogenation has not been validated. In addition, there is no established storage time for rubber stoppers used for the product vials.
 - f. There are no validation data to support mixing times for LAL product formulation which can range from _____
4. Failure to identify valid statistical techniques for verifying the acceptability of product characteristics [21 CFR 820.250] in that the _____ limit for visual examination rejects is not based on historical data.
5. Failure to inform FDA about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling, established in the approved license application [21 CFR 601.12] for the product Coatest LAL (Chromogenic), lot K4121CT, in that the lot release protocol method was submitted to FDA on March 7, 1996, and included _____ test data obtained by the _____ test. The moisture test method listed in the license is the _____ method.

6. Failure to notify the Director, Office of Compliance, Center for Biologics Evaluation and Research (CBER), of the failures of the following stability samples to meet specifications [21 CFR 600.14 (a)]. Stability test failures are considered to be errors or accidents within the meaning of this regulation.
 - a. Lot L1891X, manufactured July 8, 1997, had — % moisture at the — test point. The limit is — %.
 - b. Lot L2892X, manufactured October 16, 1997, had — % moisture at the — test point. The limit is — %.
 - c. Lot M4611X, manufactured March 2, 1998, had — % moisture at the test point. The limit is — %.

Your written responses, dated February 16, 1999, March 10, 1999, and April 14, 1999 to the FDA-483 issued on January 29, 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 Federal Food, Drug, and Cosmetic 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. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

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,

A handwritten signature in cursive script that reads "Deborah D. Ralston".

Deborah D. Ralston
Acting Director
Office of Regional Operations