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CBER-01-003

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

WARNING LETTER

NOV 17 1 2000

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Thomas J. Novitsky, Ph.D.
President and CEO
Associates of Cape Cod, Inc.
704 Main Street
Falmouth, MA 02540

Dear Dr. Novitsky:

The Food and Drug Administration (FDA) conducted an inspection August 1 through August 17, 2000, of Associates of Cape Cod, Inc., located at 704 Main Street, Falmouth, Massachusetts. During the inspection the FDA investigator documented violations of Section 501(h) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations, (CFR), Subchapter H, Part 820, as follows:

1. Failure to investigate and identify actions needed to correct and prevent the cause of nonconformities relating to products, processes, and the quality system [21 CFR 820.100(a)(2) and (3)]. For example:
 - a. serum vials, lot # 1127063, received on April 13, 2000, failed to meet the optical density specifications. The vials were released and the failure was not investigated.
 - b. during shipping and packaging operations of Limulus Amebocyte Lysate (LAL) Gel Clot, 5-mL multi-test vials, lot # 599-12-130, 133 cracked vials (including 15 broken vials) were identified. The cause of the defects was not identified. No investigation or corrective and preventive action was implemented.

- c. no corrective and preventive actions were implemented when finished product inventories did not match production amounts on finished product release notices as per Non-Conformance Report (NCR) 00-104, dated January 28, 2000; NCR 00-0275, dated May 15, 2000; NCR 00-0261, dated May 11, 2000; NCR 00-0283, dated May 24, 2000; and NCR 00-295 dated June 26, 2000.
 - d. no corrective and preventive actions were implemented when visible black smudges were observed on 5-mL glass vials in lot # 1013410011 (25,410 vials). Procedures were implemented to discard 5-mL glass vials that are received with visible black smudges, but no preventive actions have been established.
 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(a)]. For example:
 - a. there is no documentation to demonstrate that the autoclaving of the LAL product stoppers _____ during the wash and depyrogenation process at _____ will not affect the stopper's performance.
 - b. stability studies have not been conducted to support the dating period assigned to buffers and manufacturing components used to manufacture LAL products.
 3. Failure to ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use [21 CFR 820.70(g)]. For example:
 - a. validation studies are incomplete and/or have not been conducted for the _____ used for endotoxin removal for numerous LAL products and components.
 - b. validation of the _____ used in the endotoxin removal of the 0.6 M Tris buffer, has not been completed.
 - c. the _____, the _____ and the _____, have not been validated for product compatibility and extractable substances.
 - d. the cleaning processes for the re-usable _____ and the _____ have not been validated, and there is no approved procedure for the cleaning of the _____
 - e. there is no documentation to demonstrate filter integrity testing has been performed for filters used in manufacturing processes.

4. 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. the cleaning processes for Class 100 filling rooms #1 and #2, the Class 100,000 Lysate Processing clean area #1, and the Class 100,000 Amebocyte Process clean area #3 have not been validated.
 - b. operators loading the lyophilizers in filling room #2 were noted going back and forth between Class 100 and Class 10,000 areas.
 - c. there is no assurance that the improperly functioning door in filling room #2 does not adversely affect product quality. The door remains open two to four inches during filling operations.
5. 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 there is no microbial validation to support the Class 100 classification and sampling sites for filling room #2.
6. Failure to establish and maintain requirements for the health, cleanliness, personal practices, and clothing of personnel in contact with products or environments which could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(d)] in that environmental monitoring of personnel is not routinely monitored during LAL vial filling operations in filling rooms #1 and #2. Unidentified microbial contaminants have been isolated from the gloves of employees working in these areas and there are no procedures to address the status of the employees associated with positive environmental samples.
7. Failure to establish and maintain procedures for the control of storage areas and stock rooms to prevent mix-ups, damage, deterioration, contamination, or other adverse effects of products pending use or distribution [21 CFR 820.150] in that products with no status labels were observed stored in the receiving area. For example:
 - a. unreleased Albumin 25%, (50 boxes, 10 vials/box), received on June 30, 2000, did not have a label designating its unreleased status. These boxes of Albumin 25% were co-mingled in the new basement storage area (NB-A) with released products. Depyrogenated and rinsed — bottles were also co-mingled in the same area.
 - b. in-process and released water and buffer vials were co-mingled on shelves in storage areas NB-C and NB-B.

- c. released and unreleased components were observed stored in the new basement lock-up storage area and there were no labels identifying the processing status of the components.
 - d. quarantined products were co-mingled with finished products inside finished products storage area #I RT.
8. Failure to establish and maintain procedures to ensure that sampling methods are adequate and that sampling plans are based on valid statistical rationale [21 CFR 820.250(b)]. For example:
- a. quality assurance testing of _____ is not based on a documented valid statistical sampling plan.
 - b. the sampling method used for the 10 mL serum vials is not based on a valid statistical rationale.
9. Failure to establish and maintain procedures to ensure all products conform to specified requirements. For example:
- a. there is no documentation that the supplier of serum vials was notified when multiple lots of serum vials failed to meet product specifications. These failures have occurred from 1996 to the present. [21 CFR 820.50(a)(1)].
 - b. the extent of control to be exercised over suppliers, contractors and services is not included in SOP #513, entitled "Vendor Evaluation." [21 CFR 820.50(a)(2)].

We acknowledge receipt of your written response dated September 13, 2000, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection. We have reviewed your responses and find that they are inadequate. We have the following specific comments to your responses, which are numbered to correspond to the observations listed on the Form FDA 483:

- 1. Please review your original product and establishment license applications and update your biologics license application file to ensure the procedures represent current processes at your firm. The Office of Vaccines Research and Review, Division of Bacterial Parasitic and Allergenic Products should be contacted if changes have been made to the original applications.
- 2. Your response indicates that you are collecting data in uncontrolled areas to allow trending of the data in order to reduce risk and support targeted cleaning practices. Please indicate whether you will be establishing specifications for these areas.
- 10. Your response indicates that the validation study will be drafted by December 15, 2000. Please indicate the projected date for completion of the validation study.

13. The disinfectant effectiveness studies for : _____, demonstrated that they are ineffective for certain organisms found in your facility for the _____ that is specified in your cleaning procedures, however, the disinfectants are effective if the _____ Please indicate what immediate actions will be taken to resolve this discrepancy.

26. The existing old-model lyophilizers may be sanitized, not sterilized. An adequate cleaning validation study, use of the "Petri Dish" approach, and successful media fill results may be sufficient to demonstrate microbiological control during lyophilization.

Neither the above violations nor the observations noted on the Form FDA 483, presented to you 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 on 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 the 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 promptly correct these deviations 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 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.

In order to help FDA make the determination that corrections have been made, we are requesting that you submit certification by an outside expert consultant that he/she has conducted an audit of your firm's manufacturing and quality assurance systems. Please submit a copy of the consultant's report, and your personal certification that you have reviewed the report, showing that your firm has initiated or completed all corrections called for in the report. Also provide information regarding the qualifications of your consultant, and verification that his/her services have undergone the vendor qualification process required under 21 CFR 820.50. The enclosed guidance may be helpful in selecting an appropriate consultant.

Please notify this office in writing within 15 working days of receipt of this letter, of the steps you have taken to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 days, state the reason for the delay and the time within which the corrections will be completed.

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 Diane Alexander at (301) 827-6201.

Sincerely,



Deborah Ralston
Director
Office of Regional Operations

Enclosure:

Selecting A Consultant