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March 10, 2000  
CBER-00-016

**WARNING LETTER**

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

Peter R. Hauck  
Head of Operations  
Center Laboratories Inc.  
35 Channel Drive  
Port Washington, New York 11050

Dear Mr. Hauck:

During an inspection of your facility located at 35 Channel Drive, Port Washington, New York, between November 1 and 18, 1999, our investigators identified the following violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and Title 21, Code of Federal Regulations (21 CFR), Parts 211 and 600-680:

1. Failure to maintain adequate procedures for handling all written and oral complaints regarding drug products [21 CFR 211.198] in that investigations were not conducted for complaints received from January 1998 to August 1999 of precipitation in both standardized and non-standardized allergenic extract products.
2. Failure to establish procedures to visually examine reserve samples of drug products at least once a year for evidence of deterioration, and investigate any evidence of deterioration [21 CFR 211.170(b)] in that in 1998 and 1999, visual examinations were not conducted on reserve samples.
3. Failure to establish written procedures to ensure that reprocessed batches of product will conform with all standards, specifications, and characteristics [21 CFR 211.115(a)] in that the [REDACTED] process described in the standard operating procedure (SOP) entitled "Procedure for [REDACTED]" has not been demonstrated to be effective.

4. Failure to establish procedures to validate the performance of those manufacturing processes that may be responsible for causing variability in characteristics of in-process material and finished product [21 CFR 211.110(a)(3)] in that the mixing operation [REDACTED] has not been validated.
5. Failure to promptly notify the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research (CBER), of errors and accidents in the manufacture of products that may affect the safety, purity, or potency of any product [21 CFR 600.14(a)]. For example:
  - a) The following products were distributed with missing or incorrect expiration dates on the labeling: Mixed Ragweed lot #s 8D00341 and 7J00521, Western Weed lot # 7M00743, Standardized Cat Pelt lot #8M00372.
  - b) At least three lots of non-standardized extracts that were the subject of customer complaints contained precipitation. Examination of retention samples of these lots confirmed the presence of heavy precipitation.
6. Failure to clean, maintain, and sanitize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67] in that the effectiveness of the cleaning and rinsing procedures of product residues on non-dedicated manufacturing equipment has not been established.
7. Failure to assure that container closure systems provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product [21 CFR 211.94(b)] in that studies were not performed to demonstrate compatibility of stoppers used in container closure systems of non-standardized allergenic extracts.

We acknowledge receipt of your written response dated December 9, 1999, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate. However, your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. Our evaluation of your response follows, and is numbered to correspond to the items listed on the Form FDA 483:

4. The response states that a formal validation protocol will be established and studies regarding [REDACTED] product will follow. Please provide the completion date for the studies.
5. Although the response states that all tests remain within specification, Attachment 3 indicates that during visual examination of the vials placed on stability,

precipitation was observed at 24 months for Standardized Timothy Grass Extract. Please comment. In addition, we note that data are missing from each of the parameters tested, including visual examination. Please comment.

The study that you provided to address container closure compatibility included only standardized grass extracts. Container closure compatibility studies should be conducted with several additional standardized extracts such as [REDACTED], [REDACTED]. In addition, the response does not address container closure compatibility with respect to non-standardized allergenic extracts.

9. The response states that bioburden will be monitored beginning March 2000 and that the interim in-process bioburden limit, which is supported by the bacterial retention studies, will not be greater than [REDACTED] CFU/ml. The bacterial retention studies were not submitted; therefore, we cannot determine whether [REDACTED] CFU/ml is the typical bacterial load of your product or the worst case bioburden load used in the bacterial retention studies. However, please note that the in-process bioburden limit should be based on historical data and an understanding of your manufacturing process and the bioburden load rather than the worst case load used to assess the ability of a filter to reduce bioburden.
- 10a. The SOP entitled "Quality Assurance Chemistry Department Retest" states that if a retest agrees with the original assay within [REDACTED] then the results will be averaged. Please provide the rationale for using a range of [REDACTED] when averaging an original assay with a retest.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deficiencies that may exist at your facility. It is your responsibility as management to assure that your establishment is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act and applicable regulations.

You should take prompt action to correct these deviations. Failure to correct these deviations may result in regulatory action without further notice. Such action includes seizure and/or injunction, license suspension and/or revocation.

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. Your reply should be sent to Mr. Steven A. Masiello at the U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Compliance and Biologics Quality, HFM-610, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448.

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If you have any questions regarding this letter, please contact Cathy Conn, Director, Division of Case Management, at (301) 827-6201.

Sincerely,

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

Deborah D. Ralston  
Director  
Office of Regional Operations