



M3174M

CBER 99- 022

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

AUG 2 1999

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Leif E. Olsen
Vice President
Biowhittaker, Inc.
8830 Biggs Ford Rd.
Walkersville, MD 21793-0127

Dear Mr. Olsen:

An inspection of Biowhittaker, Inc., located at 8830 Biggs Ford Road, Walkersville, Maryland, was conducted from April 6 - 27, 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 F, Parts 600-680 and Subchapter H, Part 820, were documented as follows:

1. Failure to validate corrective and preventive actions to ensure that such actions are effective and do not adversely affect the finished device, [21 CFR 820.100(a)(4)], in that the corrective action for PIR # BL98TP0016, which included changing the package insert with the recommendation that the 36 minute test should be performed in glass, was based on limited testing and insufficient information from the microplate contractor.
2. Failure to investigate the cause of nonconformities related to product, processes, and the quality system, [21 CFR 820.100(a)(2)], in that:
 - a. the investigation into Product Incident Report (PIR) BL98TP0016, which involved chromogenic LAL test kit, QCL-1000, lot number 7L3410, did not include an evaluation of other kit lots and related components to determine the scope of the failure and there was no record to indicate that a review of the device history record was performed during the investigation.
 - b. stability test results for Chromogenic Lysate, #6L3810, failed at 18 months. A failure investigation was not conducted.
 - c. stability test results for Chromogenic Lysate, #7L0910, failed at 12 months. The product was retested and passed. There was no investigation into the initial test result failure.

- d. the final Quality Control test for the Kinetic-QCL test kit, #8L0380, failed on initial testing. The test was repeated and passed, and the kit was released for distribution. There was no investigation into the initial test result failure.
3. Failure to employ appropriate statistical methodology to detect recurring quality problems, [21 CFR 820.100 (a)(1)], in that the trending of in-process failures is not performed.
4. Failure to validate processes which can not be verified by subsequent inspection [21 CFR 820.75(a)], in that the lyophilization process has not been validated.
5. Failure to establish and maintain the requirements, including quality requirements, that must be met by suppliers and contractors [21 CFR 820.50(a)], in that specifications have not been developed for the plastic microplates, recommended in the package inserts for the QCL-1000, Kinetic-QCL, and the Pyrogen-5000 test kits and used for in-house testing in Quality Control and Production.
6. 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], in that the package insert for the chromogenic LAL test kit, QCL-1000, was changed as a result of a complaint investigation without submission of a supplement to CBER. The change included the recommendation that glass microplates and tubes be used for the 36 minute test.
7. Failure to complete tests for conformity with standards prior to lot release [21 CFR 610.1], in that the final release testing for the Chromogenic QCL-1000 test kit does not reflect the two methods (test tube and microplate) described in the package insert.

We acknowledge receipt of your written responses dated May 14, 1999, May 19, 1999, June 15, 1999, and June 28, 1999, to the Form FDA 483 issued at the close of the inspection. We have reviewed your responses and find that they are inadequate to address our concerns and have the following specific comments to your responses, which are numbered to correspond to the observations listed on the Form FDA 483:

1. In your May 14, 1999 response you indicated that CBER's Office of Compliance was consulted in reference to Biowhittaker's obligation to notify FDA of an Error and Accident which resulted in the issuance of a customer alert letter and the revision of the package insert. Based on the information you provided in your telephone call, you were given guidance that submission of an Error and Accident report was not necessary. However, after a thorough review of the facts, FDA has decided that an Error and Accident report is required to be submitted.
2. The data and information provided in your May 14, 1999 response does not support the conclusion that the plastic composition of the microplate affected the 36 minute chromogenic QCL-1000 test. We have the following comments relating to Attachments A, B, and D of your response:

- a. page 5 of Attachment A, Product Improvement Report (PIR), indicates that complaint #BL98TP0015 was received on May 8, 1998. Page 6, Quality Control Test Report, has PIR #BL98TP0011 and BL98TP0015 handwritten on the form and indicates a test completion date of April 20, 1998. Please clarify the date that testing was performed for BL98TP0015 since the test date was approximately two weeks before the sample was received.
 - b. the data provided in Attachment A is unacceptable. On pages 9 and 10, the blank values of [REDACTED] are above the specification of [REDACTED] for the final product. On pages 15 and 16, the variance, as measured by C.V., for the first and last standard ([REDACTED]) is [REDACTED], which is above the reproducibility claim of 10% in the package insert.
 - c. please provide the testing dates, the investigation dates, and the production dates for the lots listed in the chart provided in Attachment B. In addition, please indicate whether the 36 minute tests were performed in plastic or glass microplates.
 - d. the data provided on page 2 of Attachment D is unacceptable in that the Optical Density (OD) readings of the unused wells [REDACTED] have higher OD readings than wells with LAL and endotoxin standards. Also, please resubmit page 3 which is unreadable.
3. On page 4 of the May 14, 1999 response it is indicated that the package insert will be revised and will be submitted to CBER by October 15, 1999. Please explain how these revisions differ from those made for the QCL-1000 test in June 1998.

Corrective actions addressed in your previous letters may be referenced in your response to this letter, as appropriate.

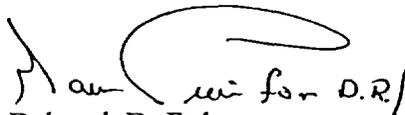
Neither the above violations nor the observations noted on the Form FDA 483 presented to your firm at the conclusion of the inspection are intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility to ensure adherence to each requirement of the Federal Food, 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 letters 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-616. 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