



CBER-98-026

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

WARNING LETTER

SEP 18 1998

CERTIFIED MAIL - RETURN RECEIPT REQUESTED

Noel L. Buterbaugh
President and Chief Executive Officer
BioWhittaker, Inc.
8830 Biggs Ford Road
Walkersville, MD 21793

Dear Mr. Buterbaugh:

During an inspection of BioWhittaker, Inc., Walkersville, Maryland, on July 14 through August 3, 1998, FDA investigators documented violations of Sections 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and significant deviations from current good manufacturing practices for drug components. The deviations were presented to you on a 29-item list of inspectional observations (Form FDA 483) at the close of the inspection. Specific areas of concern include, but are not limited to, the following:

1. The serum of _____ donors is tested for antibody to the human immunodeficiency virus types 1&2, and the hepatitis C virus encoded antigen using test kits that are not FDA-approved. There are no assurances that the testing is performed correctly by adequately trained and experienced personnel.
2. There is no evidence that the _____ are adequately screened for risk factors for infectious diseases such as HIV and hepatitis.
3. Standard operating procedure number 1300.1040, "Investigation of Quality Control Initial Test Failures" is not followed in that, for at least — lots of _____ that initially failed sterility testing, there was no investigation into the cause of the contamination and form 1165, "Quality Control Initial Test Failure Inter-Department Investigation" was not completed.
4. The containers used to ship _____ from _____ to BioWhittaker have not been validated.
5. The storage temperature of _____ is not monitored or documented.

6. _____ intended for use in the production of _____ are not stored in a manner to prevent contamination, in that this material is stored in the same _____ tank as potentially infectious material of human and animal origin.

In addition, the Food and Drug Administration has determined that your firm's _____ are misbranded within the meaning of Section 502(a) of the FD&C Act in that:

1. The warning labeling for _____ shipments states in part, "Each serum/plasma donor unit used in the preparation of this product has been tested by an FDA approved method and found non-reactive for the presence of HBsAg and antibody to HIV-1, HIV-2, and hepatitis C," when in fact, the test kits used for the antibody to HIV-1 (anti-HIV-1), HIV-2 (anti-HIV-2), and the hepatitis C virus (HCV) are not U.S.-licensed products.
2. The labeling for shipments of _____ states, "These cells are NON-HAZARDOUS - NON-INFECTIOUS, and NON-RESTRICTED," when in fact, this material is potentially infectious.
3. The labeling for shipments of _____ states, "...ampules containing _____ for medical research purposes," and "Non infectious biological material for medical research," when in fact, this material is intended for use in the production of a drug product, _____

Neither this letter nor the list of inspectional observations is meant to be an all-inclusive list of deviations at your facility. It is your responsibility as management to ensure that your facility is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act and all applicable regulations and standards. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

We acknowledge receipt of your response dated August 13, 1998, to the Form FDA 483 issued at the close of the inspection. We have made an initial review of the contents of your response and we have a number of comments addressing the adequacy of your corrective actions which are, in part, detailed below. The items correspond to the observations listed on the Form FDA 483.

Observation 12

Your response is inadequate in that it does not explain the time frame or mechanism by which the technology for anti-HIV-1 and HCV testing will be changed back to correspond with the test kits listed in the current Drug Master File. You provide no assurances that this transition from use of unapproved viral marker test kits to U.S. licensed kits by the supplier in _____ will be implemented in a controlled manner and verified by BioWhittaker. Additionally, the current Drug Master File does not contain any information relative to testing _____ donors or _____ serum samples for anti-HIV-2.

Observation 19

In your response, you state that BioWhittaker has implemented the use of a form to record the temperature of the _____ shipping container upon receipt from your supplier. You intend to collect the recorded data over the next year to "validate this process." It is our view that merely recording the temperature of the shipping container upon receipt for one year does not constitute an appropriate validation plan. Your response is also inadequate in that it does not address the wide variation in ambient temperature possible during shipment or the extended duration of time between shipment and receipt of _____ which may be up to six days.

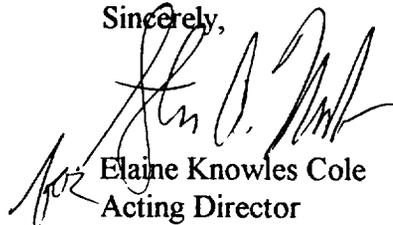
Observation 22

You state that shipping containers for _____ will be labeled with the same shipping label as described in your response to observation 18, however, you do not address the remainder of the labeling which routinely accompanies shipments of _____ from your supplier and was found by the agency to contain false and misleading statements.

We acknowledge receipt of your letter dated September 11, 1998, the contents of which you will present during the meeting with the FDA on September 22, 1998. Please submit in writing, within 15 working days of receipt of this letter, your responses to the violations identified in this letter. Failure to promptly correct these deficiencies may result in regulatory action, such as seizure or injunction, without further notice. In addition, failure to promptly correct these deficiencies may result in FDA denying entry into the U.S. of _____ manufactured for your firm. Such drug components could be subject to refusal of admission pursuant to Section 801(a)(3) of the FD&C Act in that the methods and controls used in their manufacture do not appear to conform to current good manufacturing practices within the meaning of Section 501(a)(2)(B) of the FD&C Act.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, please contact Anita Richardson at (301) 827-6201.

Sincerely,



Elaine Knowles Cole
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research