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

CBER-98-

WARNING LETTER

. MAR 9 1998

CERTIFIED -- RETURN RECEIPT REQUESTED

Rebecca Leaper
Vice President Operations
Cambridge Biotech Corporation
1500 East Gude Drive
Rockville, MD 20850

Dear Ms. Leaper:

The Food and Drug Administration (FDA) conducted an inspection of Cambridge Biotech Corporation (CBC), 1500 East Gude Drive, Rockville, MD, from October 6-17 and November 7, 1997. During the inspection, FDA investigators documented significant deviations from the applicable standards and requirements of the Quality System Regulations, as specified in Title 21, Code of Federal Regulations, (21 CFR) Part 820¹ as follows:

1. Failure to assure that all production and quality assurance measurement equipment, such as mechanical, automated, or electronic equipment, are suitable for its intended purposes and are capable of producing valid results [21 CFR 820.72(a)], in that:
 - a. the _____ plate reader, which is used in quality control testing of ELISA kits, kit components, and antigen for manufacturing, was not validated to determine the precision, reproducibility, and repeatability of the instrument; and
 - b. the alarm systems for the cold rooms, refrigerators, and freezers have not been validated.
2. Failure to establish and maintain procedures for control and distribution of finished devices to ensure that only those devices approved for release are distributed, in that HTLV-1 (rp21e Enhanced) ELISA kits, lot 123E8025, which were labeled with an unapproved expiration date, were distributed [21 CFR 820.160(a)].
3. Failure to establish and maintain procedures for implementing corrective and preventive actions, including implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems, in that

¹ The deviations described in this Warning Letter would also be violations of the Good Manufacturing Practice Regulations established in 1978.

entitled "Western Blot Kit Assembly," did not reflect the procedural steps which are currently being performed during assembly of the Western Blot test kits [21 CFR 820.100(a)(5)]. The current practice employed by your firm involves _____ to assure that tray tops properly fit or seal to the tray bottoms; however this step in manufacturing was not established in the above referenced SOP. The modification of the procedure was attributed to an investigation of complaint #97-00098 which involved HIV-1 Western Blot assay kit, lot A7062. The complaint stated that there was inadequate sealing of the tray tops to the tray bottoms which were packaged in the assay kit.

4. Failure to assure that a process is validated with a high degree of assurance and approved according to established procedures in that, there is no documented stability data for the dating period of the _____ which is used in the manufacture of the HTLV-1 (rp21e) ELISA test kits [21 CFR 820.75(a)].
5. Failure to establish and maintain procedures for the control of storage areas and stockrooms for product to prevent mix-ups, damage, deterioration, contamination, or other adverse effects pending use or distribution and to ensure that no obsolete, rejected, or deteriorated product is used or distributed in that, there are no procedures established to assure that out-of-date materials are quarantined and/or discarded. For example, it was observed during the inspection that two bottles of _____, lot RC7641, with an expiration date of September 30, 1997, were stored in Cage SCG9 next to in-date _____. [21 CFR 820.150(a)].

The above violations are not intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility to assure that your establishment is in full compliance with all requirements of the federal regulations.

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 and/or 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.

We acknowledge receipt of your October 23 and November 10, 1997, responses to the Form FDA-483(s) that were issued at the conclusion of the most recent inspections of your firm. We have determined that your response is inadequate to address all the violations that FDA documented at your firm. Our evaluation of your response follows and is numbered or labeled to correspond to the items as they appeared on the Form FDA-483 and in your response.

- 3b. The installation qualification (IQ) performed on the _____ plate reader for use in quality control testing of ELISA test kits, kit components, and antigen for manufacturing was necessary but not sufficient to fully validate the instrument for CBC's purposes. IQ demonstrated that the instrument can measure optical density (OD) with a precision of _____ however performance qualification data was not produced. Such data is utilized to define quality limits for

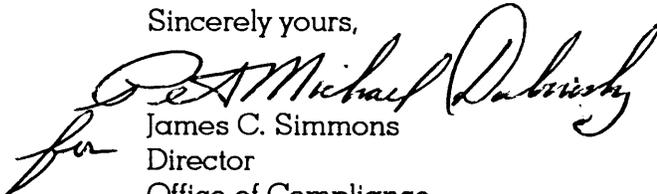
the instrument. In addition, you stated that, historically, CV's for the Reactive Control have ranged between _____ however historical data is not a sufficient substitute for validation.

Furthermore, the linearity study referenced in your response is not sufficient to demonstrate IQ. The study was performed at _____ neither of which is used in the analysis with the HTLV-1 ELISA test kit. Your study demonstrated _____ however the labeling for the HTLV-1 ELISA test kit indicates that the positive control can have an OD as high as 2.0. There is no assurance that the product can produce an OD as high as 2.0 and can continue to demonstrate accurate results. Considering this information, assurance that the instrument is capable of properly performing during the quality control testing has not been established.

You should notify this Office in writing, within 15 working days of receipt of this letter, of additional steps you have taken to correct the noted violations and to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Additionally, please include, as part of the response, your plan to address the status of any extant product that was labeled with the unapproved storage temperature and expiration period and was subsequently distributed. You may reference your October 23 and November 10, 1997, letters in responding to this Warning Letter.

Your reply should be sent to my attention at the following address: Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, Suite 200N, 1401 Rockville Pike, Rockville, Maryland 20852-1448.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "James C. Simmons". The signature is written in dark ink and is positioned above the typed name and title.

James C. Simmons
Director
Office of Compliance
Center for Biologics
Evaluation and Research