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

CBER-99-004

NOV 13 1998
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WARNING LETTER

CERTIFIED - RETURN RECEIPT REQUESTED

William Boeger
Chairman, President, and CEO
Calypse Biomedical Corporation
1440 Fourth Street
Berkeley, California 94710

Dear Mr. Boeger:

The Food and Drug Administration (FDA) conducted an inspection of Calypse Biomedical Corporation, 1440 Fourth Street, Berkeley, California, from August 17, 1998, to August 28, 1998. During the inspection, our FDA investigators documented significant deviations from the applicable standards and requirements of Subchapter H, Part 820, Title 21, Code of Federal Regulations as follows:

1. Failure to establish and maintain an adequate complaint handling system, 21 CFR 820.198. For example:
 - a. Customer Complaint Record (CCR) 802 was issued based on a user report of multiple failed runs due to out of specification positive control results. Documentation of the failed runs was not available during the inspection. In addition, the user was advised to: 1) maintain the conjugate concentrate at refrigerated temperatures until just prior to dilution; and 2) limit the substrate incubation step to _____ These instructions were not in accordance with the package insert requirements, in that the package insert states that kit reagents are to come to room temperature prior to use, and that the substrate incubation can be between twenty-eight and thirty-two minutes.
 - b. CCR 709 was issued based on a user report of an abnormally high rate of initial reactive samples. While the documentation associated with this complaint indicates that your firm tested a retained sample of the implicated lot, documentation of the results of the testing was not available. In addition, during a visit to the user site by your technical service representative, abnormally colored

substrate tablets were observed. While the complaint record notes that the manufacturer of the substrate tablet was contacted about the issue, there is no documentation of the conclusion or follow-up based on the discussion.

- c. Two complaints were received concerning failures of the negative and positive controls to meet specifications, however, there is no documentation of investigations into these complaints nor is there documentation of the reason not to initiate an investigation.
 - d. CCR 701, concerning a February 28, 1997, report of an increased initial reactive sample rate, remains open. The last activity concerning this complaint was in November 1997, when a summary report was written.
2. Failure to document training designed to assure that personnel can adequately perform their assigned functions, 21 CFR 820.25(b), in that there is no training documentation for the designated individual responsible for handling complaints.
 3. Failure to establish and maintain procedures for implementing corrective and preventative actions, 21 CFR 820.100, in that:
 - a. The SOP for finished test kit inspection does not address the corrective actions to be performed if any failures are found.
 - b. SOPs do not address the need for corrective and preventative actions when microbial limits are exceeded during testing of the deionized water system.
 - c. Investigations have not been performed of environmental monitoring excursions documented as "no ID" or "insufficient growth."
 - d. Numerous deviation reports noted the cause of the deviation as operator error, however, there is no documentation that operators were retrained to prevent future occurrences of the error.
 - e. The SOP for bioburden testing does not address the investigation of bioburden excursions.
 4. Failure to adequately develop, conduct, control, and monitor product processes to ensure that a device conforms to its specifications, 21 CFR 820.70. For example:
 - a. There is no procedure that defines specifications to include dating periods and limits for the pooling of purified gp160 HIV Antigen lots.

- b. The procedures for collection of water from the deionized water system do not ensure that the methods of water collection for microbial sampling and use are consistent.
 - c. There is no documentation to support the assignment of _____ expiration period to quality control chemicals when the vendor does not provide an expiration period.
 - d. The SOP that allows the expiration dates of raw materials to be extended does not specify the maximum number of times the material's expiration date can be extended. In addition, the SOP does not state how long the material's expiration date will be extended.
5. Failure to establish and maintain contamination control procedures, 21 CFR 820.70(e).
For example:
- a. Antimicrobial preservative effectiveness studies failed for the Microwell Strip Assembly, Stop Solution, Conjugate Concentrate, and Sample Buffer.
 - b. Cleaning validation studies did not include an evaluation of:
 - (i) the effectiveness of cleaning agents against spore forming organisms, even though such organisms have been isolated from the manufacturing environment.
 - (ii) the effectiveness of the _____ alcohol that is commonly used in various manufacturing areas.
 - c. There is no assurance that the current method of bioburden testing is adequate to ensure that preservative is effectively neutralized.
6. Failure to establish and maintain procedures for the use and removal of manufacturing material, 21 CFR 820.70(h), in that for the cleaning validation for process equipment:
- a. The multi-use _____ large and small syringes were challenged with water and not actual test kit components.
 - b. Evaluation of the microplate washer used to dispense conjugate did not include an analysis of the removal of the gp160 HIV Antigen.

7. Failure to ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, adjusted, cleaned, and maintained, 21 CFR 820.70(g). For example:
 - a. Concerning the _____ Aspirator:
 - (i) Determination that the aspirator cannula are at least _____ from the bottom of the microplate, required by the manufacturer's instructions, is not performed.
 - (ii) Documentation of cleaning of the filling unit and aspirator head is not available as required by SOP
 - (iii) High purity water is not used to clean the aspirator head and hose as required by SOP.
 - b. Concerning the Nitrogen System:
 - (i) A point of use filter is not installed in the purification room as required in the _____ diagram.
 - (ii) The in-line filters are not changed at the manufacturer's required _____ interval.
 - c. The power setting and sonication time settings currently used for the _____ are not in accordance with the settings used during validation of the equipment.
 - d. Concerning the _____ plate coating machine:
 - (i) The dispense volumes have not been verified since 1995.
 - (ii) The dispense head is not attached and removed before and after use as required by SOP.
 - (iii) Cleaning with _____ cleaning agent during the shutdown procedure is not performed as required by SOP.
 - e. SOPs state that HEPA filter leaks may be patched as long as the surface area of the patch is _____ however, records do not always document the location of the leak and size of the repair patch area.

- f. Qualification studies have not been performed for the _____ filters used during ultrafiltration.
 - g. There is no qualification study for the _____ microbial identification system.
8. Failure to document the disposition of nonconforming product, 21 CFR 820.90(b)(1), in that there was no documentation of the date, quantity, and method of destruction of products associated with CCR 707, issued due to questionable product storage conditions.
9. Failure to validate with a high degree of assurance and approved by established procedures those processes that cannot be fully verified by inspection and test, 21 CFR 820.75. For example:
- a. There is no data to support the use of the _____ column for up to _____ runs and the storage of the column in storage buffer between uses.
 - b. There is no data to support the expiration periods of purification and cell culture buffers.
10. Failure to establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements, 21 CFR 820.50, in that:
- a. No growth promotion testing, supplier audit, or other periodic verification of the Certificate of Analysis is performed for media used for environmental monitoring, water system microbial testing, and bioburden testing.
 - b. No verification, through either testing or supplier audit, is performed of the bacteriological purity noted on the Certificate of Analysis of the purchased water used for manufacturing.
 - c. Since 1995, there has been no Certificate of Analysis or testing to ensure that nitrogen gas meets its purity specification of _____

We acknowledge receipt of your written response dated September 4, 1998, and signed by Ms. Karen Long, which responded to the inspectional observations. We have reviewed your response, and find that it is inadequate to address our concerns. We have the following comments on your response, which are numbered to correspond to the observations listed on the Form FDA 483:

- 1 We question the rationale for your statement in the response "Calypte did not need to test retains and/or complainant sample of this lot as this was the exception not the norm for this lot at this account." Based on the statement in the Complaint Report "Account runs _____" we estimate that as many as _____ plates would have been run by

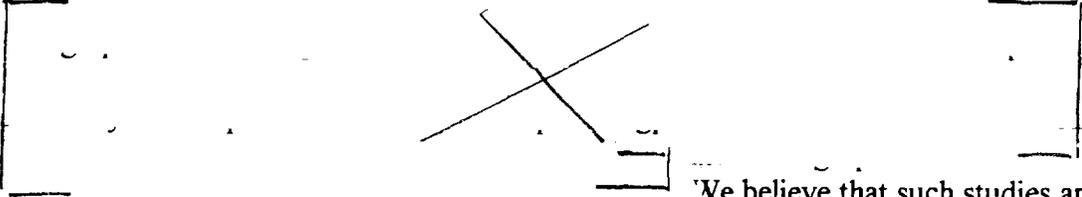
the user during the time period that failures were occurring. As — plates failed, this results in a failure rate of at least — This appears to be an excessive failure rate.

- 2 Your response states that "...at no time did this facility have an IR rate of — for lot G10805 or — for lot G16805." However, this information was obtained directly from the written complaint report. Specifically in #CCR709, absorbance data is presented on — repeatedly reactive samples which were retested on 12/8/97 at the complainant site in the presence of a Calypte Technical representative. Data shows that using Lot #G10805 and Lot #G16805, positive reactivities were (—), respectively. We note that you have revised SOP 920043, Complaint Files, to address the noted deviation. However, review of the SOP by CBER's Office of Blood Research and Review has comments on other sections of the SOP unrelated to the Form FDA 483 observation. Please contact that Office to discuss these additional comments.
- 5 We note that you have revised your SOP to address the need for — numbers and complete data in the file. However, the SOP does not address how you will achieve compliance with 21 CFR 820.198(b) concerning documentation when an investigation is not initiated.
- 7 We note that you have revised your SOP to ensure that on a monthly basis affiliates are to provide a copy of closed complaints, or documentation that no complaints were received. We recommend that distributors also provide a summary of all pending complaints to assist in monitoring the progress of these ongoing complaints and generate a complete monthly summary.
- 11 We acknowledge your commitment to follow your SOP for ongoing kit stability. In addition, we recommend that you: 1) evaluate your current ongoing stability program to determine whether your current monitoring frequency is adequate to identify a trend in instability; and 2) incorporate methods to determine that preservative levels remain adequate throughout the dating period. Moreover, it was related to our investigators that test results for FDA panel members 3, 7, and 10 can be either positive or negative during stability testing. This information is not consistent with your SOP for ongoing stability testing, which indicates that the acceptance criteria for the FDA panel is the same as found in part number 600000, Final Product Packaging. This document requires panel members 3, 7, and 10 to be positive.
- 13 Please describe the methods you will use to ensure that kit components that are changed are placed on stability. We note that documentation collected during the inspection indicates that a number of component manufacturing changes may have been made.

16 We note that an investigation into the contaminated _____ was performed, however, the contents of the contaminated roller bottles were never investigated nor identified. In addition, regarding Lot G13505, the cell maintenance forms indicate that roller bottles were discarded. It was related to the investigators that operators can discard the roller bottles if they do not achieve cell density and if found contaminated. Therefore, it is not clear in the cell maintenance form if the roller bottles were discarded for low viability and/or contamination.

17 While your response states that identification of the contaminate in the roller bottles was attempted for _____ of the bottles, you did not address why the other contaminated roller bottles were not also tested.

19 During the inspection, it was related to the investigators that recently Calypte began


_____ We believe that such studies are needed.

21 While DHR 200026 states to dispose the contaminated roller bottles as outlined in Growth and Maintenance of _____ cells, document 910008, it does not state in document number 910008 to conduct an investigation of the contents of the roller bottle contamination.

25 We believe that you must incorporate some additional level of control into your purchase of the water other than a review of a Certificate of Analysis.

26e It is not clear whether you intend to calibrate the pressure gauges.

41a The acceptance criteria for the _____ included the requirement for dispensing of between _____ and between _____ solution. Please explain that even though this requirement was not met for every well used to evaluate the validation protocol, the equipment was considered valid for this purpose.

44 Quality assurance methods for microwell coating have evolved so that a periodic visual check of plate filling or random sampling is no longer considered industry standard. We believe that a more comprehensive verification that each well has been filled properly to assure proper coating is appropriate.

- 46 Your response states that two engineers have certified that the placement of the HEPA supply vents adjacent to the exhaust vents are acceptable. Please submit the documentation of the certifications.
- 51b Your response does not address whether Calypte has demonstrated that the storage hold time of the column in the buffer does not effect the quality of the column when it is used.
- 52 Please identify the source of the antigen reference standard referenced in your response.
- 62 While your response indicates that the SOP will be changed, it does not address your planned course of action (investigation) for initial and/or secondary testing if bioburden failures occur.

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 promptly correct these deviations may result in regulatory action without further notice. Such action includes license suspension, revocation, and/or denial, 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. 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. Moreover, no requests for Certificates to Foreign Governments will be approved until the violations related to the subject devices have been corrected.

You should notify FDA in writing, within 15 working days of receipt of this letter, of specific 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. In addition, we note that your response to the Form FDA 483 contained numerous SOP and DHR revisions that were in draft. Please include as part of your response to this letter the current status of these documents.

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Your reply should be sent to Dr. Jerome A. Donlon, Acting Director, Office of Compliance and Biologics Quality, Food and Drug Administration, Center for Biologics Evaluation and Research, Suite 200N, 1401 Rockville Pike, Rockville, Maryland 20852-1448, ATTN: Division of Case Management, HFM-610.

Sincerely,

A handwritten signature in black ink, appearing to read "Michels", written in a cursive style.

Daniel L. Michels
Acting Director
Office of Regional Operations