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DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
New England District

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WARNING LETTER

NWE-02-08W

VIA FEDERAL EXPRESS

October 30, 2007

Mr. Ronald Lewis
President
Cytosol Laboratories, Inc.
55 Messina Drive
Braintree, MA 02184-6783

Dear Mr. Lewis:

The Food and Drug Administration (FDA) conducted an inspection of Cytosol Laboratories, Inc., located at 55 Messina Drive, Braintree, Massachusetts, between May 23 and June 20, 2007. During the inspection, FDA investigators documented significant deviations from current good manufacturing practice (CGMP) in the manufacture of your human drug products. These deviations from CGMP include deviations from the applicable requirements 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), Part 211.

During the inspection, FDA investigators observed that you manufacture and distribute Anticoagulant Citrate Phosphate Dextrose Adenine Solution (CPDA-1). CPDA-1 is a drug within the meaning of section 201(g)(1) [21 U.S.C. 321 (g)(1)] of the Act because it is intended to diagnose, cure, mitigate, treat, or prevent disease in animals or to affect the structure or function of the body of animals. Further, your drug is not generally recognized as safe and effective for the recommended use, and is a new animal drug within the meaning of section 201(v) [21 U.S.C. 321 (v)] of the Act. Moreover, your product is not the subject of an approved new animal drug application filed under section 512(b) [21 U.S.C. 360b(b)] of the Act. Therefore, your product is unsafe within the meaning of section 512(a) [21 U.S.C. 360b(a)] of the Act, and adulterated within the meaning of section 501(a)(5) [21 U.S.C. 351(a)] of the Act. As such, this drug may not be introduced or delivered for introduction into interstate commerce under section 301(a) [21 U.S.C. 331(a)] of the Act.

At the close of the inspection, FDA issued a Form FDA 483, Inspectional Observations, which described a number of significant deviations in the manufacture of your human and animal drug products. Specific areas of concern include, but are not limited to:

1. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of human drug products purporting to be sterile, including the validation of any sterilization process [21 CFR 211.113(b)]. For example:

   a. The validation/revalidations of your steam sterilization cycles are inadequate.

      i. Your validation/revalidations do not calculate accumulated heat exposure contributed during heat-up/cool-down of the steam sterilization cycles to demonstrate it is equivalent to exposure at [redacted]C; therefore, there is no assurance that required temperatures are achieved during routine steam sterilization cycles.

      ii. Your validation/re-validations do not include the thermocouple locations monitored during routine use when a minimum load is placed into the steam sterilizers.

      iii. Your validation/revalidations do not document an evaluation of the average total accumulated heat exposure to product at the coldest location for a maximum load in your steam sterilizer. Further, there is no evidence that the total accumulated heat exposure to product at the coldest location for a maximum load was compared to the total accumulated heat exposure to product at the coldest location for a minimum load.

      iv. Your validation/revalidations do not determine the distribution of steam within your empty sterilizers; heat distribution studies were conducted by placing thermocouples into water-filled bottles and the temperature of the water within the bottles was determined. Heat distribution studies did not evaluate minimum/maximum load configurations.

   b. Biological indicators (BIs) are used in biological challenges during validation/revalidations. They are prepared by [redacted]

      There is no documentation supporting the use of the spore strips in this manner or confirming the D-value of BIs prepared in this manner.

c. Your validation supplement PCR-101-Misc-Supp#1, Rev. A, dated December 18, 2006, is inadequate. The purpose of the validation supplement was to determine the maximum amount of time a vacuum could be pulled after sample filtration without adversely affecting sample bioburden levels, thereby potentially altering the outcome of further testing. Initial bioburden levels of control samples used in the validation were not determined; therefore, bioburden recovery in the test samples could not be accurately demonstrated. Furthermore, results from [redacted] of [redacted] validation test runs were excluded from evaluation since recovery after initial filtration was less than [redacted]/100mL. This supplement was intended to validate the "hold time" of the filtration method used in your SOP E100 entitled "Sterility Testing;" SOP E103 entitled "Microbiological Testing of Water;" and SOP E111 entitled "Microbiological Testing of Final Product Before Autoclaving."

2. Failure to establish written procedures for production and process control designed to assure that the human drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100(a)]. For example:

a. Your standard operating procedure SOP F103 entitled "Operation of the AMSCO Sterilizers" specifies minimum/maximum heat exposure times during steam sterilization of your drug products. However, there is no assurance that the required temperatures are achieved for the specified periods of time during routine use, since you do not calculate accumulated heat exposure during routine steam sterilization cycles. Further, there is no assurance that your products are not over exposed to heat during your steam sterilization cycles.

b. The thermocouple locations monitored during your routine steam sterilization cycle and specified in SOP F103 are not the thermocouple locations monitored during the validation/re-validation of your sterilizers. There is no assurance that adequate temperatures are achieved during the steam sterilization cycles.

c. SOP F103 does not accurately describe the thermocouple locations monitored during routine use when a minimum load is placed into the steam sterilizers.

3. Failure to establish and follow written standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties for human drug product containers and closures [21 CFR 211.94(d)]. More specifically, cleaning procedures for the removal of endotoxin from product-contact rubber stoppers have not been adequately validated.

4. Failure to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, human drug product containers, closures, in-process materials, labeling, and human drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)]. For example:

   a. Your SOP E112 entitled "Determination of Spore, Bacteria, Yeast and Mold Viability" is inadequate.

      i. The testing protocol for biological spore strips outlined in your SOP does not conform to the testing instructions provided by the spore strip provider [redacted]. The product warranty for the spore strips clearly states "D-value reproducible only when exposed and cultured under the exact conditions used to obtain results reported here." Biological spore strips are used to prepare biological indicators (BIs) for validation/revalidations of your steam sterilization cycles. There is no assurance of the validity of biological challenges during validation/revalidations since you do not confirm the D-value and/or assayed microorganism population of biological spore strips according to supplier instructions.

      ii. Your SOP does not specify upper limit acceptance criteria for microorganism recovery when confirming the assayed microorganism population of biological spore strips. Testing performed by you on July 5, 2006, reported an average recovery of [redacted]% of the assayed microorganism population reported by the spore strip supplier [redacted]. There was no investigation into this recovery result since your SOP does not define an upper limit acceptance criteria.

      iii. Your SOP allows testing to be repeated [redacted] for a total of [redacted] before a lot must be rejected for failure to meet the lower limit acceptance criteria for microorganism recovery when confirming the assayed microorganism population of biological spore strips. Further, there is no requirement to investigate test failures.

   b. Your SOP E130 entitled "Out-Of-Specification Investigation" is inadequate. The SOP does not clearly specify the documented evidence required to provide scientific justification for invalidating out of specification (OOS) results when no obvious evidence of laboratory error has been identified. Your SOP does not define the maximum number of retests to be performed on a sample. Further, the procedure fails to clearly specify when the use of outlier testing is appropriate, the specific outlier test to be applied, and how test results should be assessed. Additionally,

your SOP does not require an evaluation of the impact of the OOS result on other batches/other products.

5. Failure to routinely calibrate, inspect, or check automatic, mechanical, or electronic equipment, or other types of equipment, used in the manufacture, processing, packing, and holding of a human drug product according to a written program designed to assure the equipment's proper performance, and to maintain written records of calibration checks and inspections [21 CFR 211.68(a)]. For example:

   a. Your SOP A134 entitled "Calibration of Thermocouples, RTD and Load Probes" is inadequate, as the SOP does not require equipment that failed calibration to be taken out of service.

6. Failure to establish and follow written procedures describing the handling of all written and oral complaints regarding a human drug product, including provisions for review by the quality control unit of any complaint involving the possible failure of a human drug product to meet any of its specifications, and a determination as to the need for an investigation in accordance with 21 CFR 211.192 [21 CFR 211.198(a)]. Your SOP A122 entitled "Customer Complaint Procedure" is inadequate.

   a. The SOP does not describe the responsibilities of your distributors in handling customer complaints, including the need for distributors to obtain complete complaint information. Further, the SOP does not specify the method by which complaint information is provided to you by your distributors for investigation and followup. As a result, there is no assurance that all product complaints are received, reviewed, and/or investigated.

   b. The SOP does not define the criteria for determining when an investigation is to be conducted and/or the steps to be followed in the conduct of the investigation.

   c. The SOP does not provide for review of complaints by the quality control unit.

7. Failure to establish and follow written procedures applicable to the responsibilities of the quality control unit [21 CFR 211.22(d)]. Your SOP A138 entitled "Procedure for Process and Product Validations" addresses review and approval of validation protocols/reports and states that Team Quality is responsible for assuring the SOP is followed. However, during the inspection the investigators documented numerous and significant discrepancies in your Process Validation Report PCR-099-Strlztn, Rev.A., which was approved by Team Quality on December 12, 2006. For example:

a. Section 5.4.5 of the report documents results that conflict with sterilization cycle descriptions outlined in Section 5.2 of the report.

i. Section 5.2 of the report describes Validation Cycle A with a heat exposure " . . . not to exceed [redacted] minutes and [redacted] seconds . . ." The results reported in Section 5.4.5 of the report state " . . . minimum exposure of [redacted] minutes."

ii. Section 5.2 of the report describes Validation Cycle C with a heat exposure " . . . not to exceed [redacted] minutes and [redacted] seconds . . ." The results reported in Section 5.4.5 of the report state " . . . minimum exposure of [redacted] minutes."

iii. Section 5.2 of the report describes Validation Cycle D with a heat exposure " . . . not to exceed [redacted] minutes and [redacted] seconds . . ." The results reported in Section 5.4.5 of the report state " . . . minimum exposure of [redacted] minutes."

iv. Section 5.2 of the report describes Validation Cycle A as a ". . . [redacted] mL Type [redacted] Glass Bottle, [redacted] mL fill," and "[redacted] type." The results reported in Section 5.4.5 of the report state "50 mL S.C. bottle, 40 mL fill: a closed crimp . . ."

b. Table 2 entitled "Executed Sterilization Cycle Parameters" reports heat exposure time as "[redacted]" Heat exposure time for Validation Cycle C on November 9, 2006, is recorded as "16:24:10." Section 5.2 of the report describes Validation Cycle C with a heat exposure ". . . not to exceed [redacted] minutes and [redacted] seconds . . ." Similar discrepancies were noted in Table 2 for Validation Cycles D, E, and F.

8. Failure to determine actual yields and percentages of theoretical yields at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the human drug product [21 CFR 211.103]. Percentages of theoretical yields are not determined using theoretical yields established in master production records. For example:

a. Batch production and control records for ACD-A, 30 mL, batch D71 indicates that the theoretical yield is [redacted] units and that [redacted] units were filled. The discrepancy in formulated versus filled volume is not explained in the batch production records.

b. Batch production and control records for ACD-A, 40 mL, batch J67 indicates that the theoretical yield is [redacted] units and that [redacted] units were filled. The discrepancy in formulated versus filled volume is not explained in the batch production records.

c. Batch production and control records for ACD-A, 50 mL, batch C73 indicates that the theoretical yield is [redacted] units and that [redacted] units were filled. The discrepancy in formulated versus filled volume is not explained in the batch production records.

d. Batch production and control records for triCitrasol®, 30 mL, batch K611 indicates that the theoretical yield is [redacted] units and that [redacted] units were filled. The discrepancy in formulated versus filled volume is not explained in the batch production records.

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 FD&C Act and applicable FDA regulations.

While these deviations were documented during the most recent inspection of your facility, we note that similar significant deviations were documented during previous FDA inspections. We also note that your firm has repeatedly promised corrective actions but the recent inspection has shown that adequate and effective corrective actions have not been implemented.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in FDA initiating regulatory action without further notice. Such action may include seizure and/or injunction.

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 written responses dated July 13, 2007, and August 31, 2007, which address the inspectional observations on the Form FDA 483, issued at the close of the inspection. Corrective actions addressed in your responses may be referenced in your reply to this letter, as appropriate. However, these two responses do not provide sufficient information to fully assess the adequacy of your corrective actions. Further, your comments relating to many of the inspectional observations merely indicate that the observations will be corrected, without providing details or timeframes for implementing your proposed corrective actions.

Please notify this office 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. Your response should include documentation supporting the corrective actions you have taken. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time frame within which all corrections will be completed.

Your reply should be sent to Karen Archdeacon, Compliance Officer, Food and Drug Administration, One Montvale Avenue, 4th Floor, Stoneham, Massachusetts 01280. If you have any questions regarding this letter, please contact Ms. Archdeacon at (781) 596-7707.

In addition, we request a meeting with you, at your earliest convenience, to discuss the issues cited in this letter together with your proposed corrective actions. Please contact Ms. Archdeacon at the above address to schedule the meeting, to be held at FDA's Office of Enforcement, Rockville, MD, with representatives from the Center for Biologics Evaluation and Research, the Center for Veterinary Medicine, the Office of Enforcement, and the New England District.

Sincerely,

Gail T. Costello
District Director
New England District

cc: Mr. Alan Gray
Vice President
Cytosol Laboratories, Inc.
55 Messina Drive
Braintree, MA 02184-6783