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

One Montvale Avenue
Stoneham, Massachusetts 02180
(781) 596-7700
FAX: (781) 596-7896

WARNING LETTER

NWE-20-08W

VIA FEDERAL EXPRESS

September 23, 2008

Mr. Glenn Alto
President / CEO
Pharmalucence, Inc.
10 DeAngelo Drive
Bedford, MA 01730

Dear Mr. Alto:

An inspection of Pharmalucence, Inc. located at 10 DeAngelo Drive in Bedford, MA, was conducted from April 7 through April 30, 2008. FDA investigators documented significant deviations from current Good Manufacturing Practice (cGMP) Regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211, with regard to the production of pharmaceutical products at this facility. These cGMP deviations were listed on an Inspectional Observations form (Form FDA-483) issued to and discussed with Mr. Glenn Alto, President and CEO. A copy of the Form FDA-483 is enclosed. These cGMP deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 351 (a)(2)(B)]. The following are examples of some of the significant cGMP deviations that were found during our inspection of your firm:

1. Failure to establish and follow written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, including procedures to validate sterilization processes [21 CFR § 211.113(b)]. For example:

   a. Bacterial filtration retention validation has not been performed.

      i. You have not conducted bacterial filtration retention validation for your use of the [redacted] filter for the following aseptically filled product CIS-PYRO: Kit for the Preparation of Technetium Tc99m Pyrophosphate Injection.

      ii. You have not conducted bacterial filtration retention validation for your use of the

[redacted] filter for the following aseptically filled products: A) AN-DTPA: Kit for the Preparation of Technetium Tc99m Pentetate Injection and B) CIS-Sulfur Colloid: Kit for the Preparation of Technetium Tc99m Sulfur Colloid Injection, Reaction Vial.

Your response dated June 10, 2008 indicates your intention to perform this validation, but no timeframe has been submitted. The response also lacks a commitment to cease shipment of any product that has been manufactured without a validated sterilization process and to address any product which may be in distribution. Please indicate if you intend to ship any product that has been manufactured without a validated sterilization process. If so, then please identify the product and provide your justification for releasing such product.

b. Poor aseptic technique by operators in the aseptic core was observed during the inspection. On April 23, 2008, the investigator observed that forceps were used to remove fallen vials and vials for weight verification samples from the filling line in the aseptic core directly above open vials awaiting filling. This was observed approximately six times in one hour.

c. Steam sterilization cycles for the [redacted] lack adequate validation.

i. Steam penetration studies did not identify and appropriately challenge areas representing the greatest difficulty to sterilize for the PREVAC1 cycle that is used for sterilization of equipment loads used in the manufacture of aseptically filled drug products. For example, thermocouple probes were placed [redacted] foot into tubing which exceeded [redacted] feet in length. In addition, biological indicators have not been placed in the lumen of the tubing.

ii. There was no justification provided for selection of the worst case maximum load for the PREVAC1 used for sterilization of aseptic manufacturing equipment loads and terminally sterilized drug product equipment loads. Furthermore, a minimum load was not established.

iii. All load configurations have not been validated to demonstrate that the sterilization of aseptic manufacturing equipment loads and terminally sterilized drug product equipment loads is adequate. Your procedures allow for the random, even distribution of smaller aseptic manufacturing items anywhere in the load for the PREVAC1, AOP1, and AOP2 cycles. Furthermore, you have no documentation to demonstrate that operators are always following validated load patterns.

Your response to the Form FDA-483 citations indicates that you plan to continue the practice of having your operators evenly distribute smaller items throughout your sterilization loads. Please provide your justification to support this practice. Further, you discuss evaluating your maximum and minimum load configurations. The conclusion of such studies, including any changes made to existing practices, and the

justification to support these load patterns should be provided.

d. For environmental and personnel monitoring:

i. Your active air sampling unit in one aseptic filling room is not located in a critical area representative of exposure of open containers on the aseptic line. The active air sampling unit was observed positioned behind stoppered vials.

ii. Validation studies have not been performed for the testing of multiple locations with one contact plate. This practice is performed for monitoring personnel working within the aseptic core and during the monthly environmental monitoring survey.

e. You have not evaluated the microbiological burden generated from the manual aseptic connection from the source vessel to the filling vessel.

f. Air flow pattern testing studies conducted by your firm in filling rooms do not fully demonstrate air flow movement away from work surfaces during representative personnel activities and manual simulations of the aseptic filling processes. For example:

i. Your air flow studies did not include the practice of one aseptic core filling operator passing a sample for volume verification across the aseptic core area to another operator who was located adjacent to unfilled vials. This activity was observed to occur approximately every 10-15 minutes during aseptic filling.

ii. Your air flow studies did not include the operator pushing open, unfilled vials from the side toward the filling wheel. This activity is performed routinely.

iii. Your air flow studies did not include the placement and removal of the portable non-viable and viable air sampling probes.

iv. Your air flow studies did not include aseptic connections performed during aseptic manufacturing operations. This activity is performed routinely.

2. Failure of your quality control unit to investigate thoroughly any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications, and failure to ensure that written records of investigations are made and include conclusions and follow-up [21 CFR § 211.192]. For example:

a. Your investigations into environmental and personnel monitoring excursions do not address potential links between identified microorganisms and the root cause, or indicate whether these microbes had been observed in past monitoring. Five investigations were conducted when the action level was exceeded for personnel monitoring. Results for aseptic core operators ranged from [redacted] cfu since June of 2007. Each investigation lacked the identification of potential sources or previous

occurrence of the identified microorganisms. Additionally, three of the above mentioned investigations conducted since June 2007 were not initiated until 7-9 months after the excursion had occurred. Your response to the Form FDA-483 was inadequate in that the written records of the investigations were not included and the rationale to support release of associated product was not provided.

b. For the imaging diagnostic Iobenguane Sulfate I 131 (MIBG) Injection used in pediatric patients, sterility testing samples were discarded inadvertently before completion of the required 14-day incubation period for lot 010717. Subsequently, only one retain vial was tested for verification of product sterility. In your response, you indicate that the sterility assurance was not compromised for this lot. However, your associated investigation did not include a review of your terminal sterilization cycle or whether it met all parameters per the validated cycle. Therefore, your investigation and retesting conducted were not adequate to support the marketing for this lot.

3. Failure to ensure that drug product containers are clean, sterilized, and processed to remove pyrogenic properties to assure that they are suitable for their intended use [21 CFR § 211.94(c)].

Your unfilled vial depyrogenation process has not been demonstrated to provide a 3-log reduction in bacterial endotoxins for 3cc and 10cc vials, which represent all vial sizes that are aseptically filled at your facility. You have never performed quantitative recovery studies from 3 cc and 10 cc vials. Additionally, you did not document that the applied endotoxin solution was allowed to air dry. Therefore, you have not demonstrated that the worst-case conditions were challenged to validate depyrogenation of all vial sizes that are aseptically filled at your facility.

4. Failure to ensure that protective apparel of personnel engaged in the manufacturing and processing of drug products is appropriate to protect drug products from contamination [21 CFR § 211.28(a))].

Protective eye goggles worn by operators who enter and work in the aseptic core, including those who enter the critical areas of the aseptic filling lines, are not rendered free of microorganisms before use and are not of suitable design. Goggles are re-used multiple times and are not sterilized; they are only sanitized by spraying with [redacted] IPA between uses. As it is not effective against bacterial and fungal spores [redacted] IPA does not protect drug products from contamination by operators who enter and work in the aseptic core. Further, the investigator observed that each pair of goggles had four holes that were open to the environment for ventilation, and that the holes were circular and approximately 25mm in diameter. In your response, you state that goggles with holes have been removed from use, however, the sealed goggles that your firm uses are also not suitable for use because they cannot be sterilized and they prevent operators from being able to see due to fogging.

5. Failure to maintain buildings used in the manufacture, processing, packing, or holding of a drug product in a good state of repair [21 CFR § 211.58]. For example:

a. The Formica walls in one aseptic filling room were degrading, resulting in surfaces which were not easily cleanable.

b. All three HVAC return vents in one aseptic filling room were observed to have chipping paint. One of the vents is located approximately two feet from where empty vials are loaded onto the line.

In your response, you indicate that your environmental monitoring program includes these two specific surfaces and that your testing confirms the effectiveness of your cleaning. Your response is inadequate: (1) environmental monitoring and testing are not a substitute for adequate maintenance of the facility and (2) your timeframe to correct this deficiency by August 2008 included over three months of possible manufacturing while the building was in a state of disrepair.

6. Each batch of drug product required to be free of objectionable microorganisms is not tested through appropriate laboratory testing [21 CFR § 211.165(b)]. For example:

a. Iobenguane Sulfate I 131 (MIBG) Injection sterility testing is conducted on [redacted] units per [redacted] batch. The current USP requires testing [redacted] for a batch size of [redacted].

b. There is no documentation in the Quality Control testing records which demonstrates that the [redacted] hour incubation duration required by SOP 1-02-001 "Quality Control Test Procedures Microbiological Sterility" was met before conditional release of Iobenguane Sulfate I 131 (MIBG).

c. There is no documentation in the batch history record for the number of sterility samples tested for Sulfur Colloid Reaction Vial or the Solution B vial.

Your response to the Form FDA-483 observations indicated that immediate corrective actions were taken. Please provide updated procedures and related training records.

7. Failure to establish and document the accuracy, sensitivity, specificity, and reproducibility of test methods [21 CFR § 211.165(e)].

At the time of the inspection, you did not have a qualification program for inspectors performing the 100% visual inspection of parenteral products to ensure that inspectors can consistently and effectively remove non-conforming vials during typical production operations. Furthermore, the procedure, "Visual Inspections-Intermediate and Final Products," SOP 06-8-001, Version 7 does not provide a maximum allowable duration for inspectors to perform visual inspection of parenteral drug product vials. In addition, we noted during the inspection that your firm has received complaints of damaged vials and that your inspection of retain samples found damaged vials which were not removed during the 100% visual inspection. In your response to the Form FDA-483, you indicated that you would have your qualification program completed for all visual inspection personnel by June

30, 2008. Please provide the results of your qualification program, including any changes to your existing practices, and supporting procedures and documentation.

8. Failure to maintain equipment at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements. [21 CFR § 211.67(a)].

   Your firm has not performed in-line integrity testing of [redacted] filters. These filters are used for the air intake for the [redacted] used for steam sterilization of equipment.

We acknowledge receipt of your June 10, 2008 letter in response to the Form FDA-483, Inspectional Observations. For the violations identified above, please provide supporting documentation for your promised corrective actions, such as updated procedures and training records. Additionally, please provide supporting justification and documentation for corrective actions to your media fill procedures.

The violations identified above are not intended to be an all-inclusive list of deficiencies at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction. Other federal agencies may take this warning letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of new drug applications listing your facility as a manufacturer until the above violations are corrected. A re-inspection may be necessary.

You should notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct all the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If you cannot complete corrective action within 15 working days, state the reason for the delay and the time within which you will complete the correction.

Your reply should be directed to the Food and Drug Administration, One Montvale Avenue, 4th floor, Stoneham, MA 02180, Attention Amber G. Wardwell, Compliance Officer.

John R. Marzilli
Acting District Director
New England District

Attachment: FDA 483 dated April 30, 2008