Inspections, Compliance, Enforcement, and Criminal Investigations

Promed Exports Private Limited 8/9/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-13-24

August 9, 2013

Mr. Deepak Bahri
President
Sentiss Pharma Pvt. Ltd.(formerly Promed Exports Private Limited)
Khera Nihla Village, Tehsil Nalagarh,
Solan District, Himachal Pradesh 174101
India

Dear Mr. Bahri:

During our March 25, 2013 through April 3, 2013 inspection of your pharmaceutical manufacturing facility, Promed Exports Private Limited located at Promed Exports Private Limited, Khera Nihla Village, Tehsil Nalagarh, Solan District, Himachal Pradesh, 174101, India, investigator(s) from the U.S. Food and Drug Administration (FDA) identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug product 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), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have conducted a detailed review of your firm's response dated April 21, 2013, and note that it lacks sufficient corrective actions. We acknowledge receipt of your firm's additional correspondence dated April 30, 2013, your updated 483 response dated June 18, 2013, and your Quality Progress Report dated July 5, 2013. We also acknowledge your correspondence of July 5, 9, 17, 23 and 26. We will provide a separate response to your Type C meeting request sent by email on July 19, 2013.

Our investigator(s) observed specific violations during the inspection, including, but not limited to, the following:

1. Your firm failed to establish adequate systems for monitoring environmental conditions and for cleaning and disinfecting the room and equipment in aseptic processing areas (21 CFR 211.42(c)(10)(iv)and (v)).

   a. The aseptic processing environment is not adequately monitored. For example, there is no viable air monitoring inside of the Class 100 (ISO 5) filling barrier on the "**(b)(4)** Line **(b)(4)**." This is the critical area where drug product and pre-sterilized components are exposed and it is important that your firm collect air samples that adequately represent filling conditions.

Moreover, outside of the line **(b)(4)** filling area, the three air samples taken in the Class 100 (ISO 5) area were not taken under dynamic conditions. These active samples were instead taken after line set-up and before any filling.

We are concerned that the environmental monitoring (EM) program is not adequate to ensure the environment is suitable for aseptic processing of sterile product. The data generated does not sufficiently demonstrate that an ISO 5 environment is maintained.

In your response, you commit to improving sampling in your aseptic operation lines. Specifically, you commit to revising the environmental monitoring procedures for aseptic processing lines (N/QC/066 and N/QC/180) to add the requirement of the performance of extensive EM. Additionally, you commit to re-establish the sampling locations of the EM program, to provide a scientific rationale for the selection of appropriate EM sampling, and to routinely review the EM trend data from a holistic, risk-based perspective. In response to this letter, provide a copy of the summary report identifying the critical active air sampling locations and their frequency.

   b. Your firm did not use a sporicidal disinfectant for cleaning inside of the Class 100 (ISO 5) filling areas. The inspection documented that your firm uses **(b)(4)** (**(b)(4)**) alone, which is not effective against spore-forming organisms such as *Bacillus* spp. The September 2011 media fill failure investigation for the **(b)(4)** Line **(b)(4)** identified the contaminating organism as *Bacillus pumilus.* Additionally, you did not sufficiently evaluate the disinfectant **(b)(4)** on surfaces inside the Class 100 (ISO 5) area including **(b)(4)**.

Your response indicates that the disinfectant procedure will be revised to include using a sporicidal disinfectant agent on a **(b)(4)** along with **(b)(4)** to clean and disinfect the machine parts in the Class 100 (ISO 5) filling area and that you scheduled qualification completion for May 2013. Please note that it is essential that the sporicidal agent be used regularly to ensure a suitable ISO 5 (Class 100) environment. Additionally, you indicate that **(b)(4)** will be evaluated on the other surfaces in the Class 100 (ISO 5) filling area. In response to this letter, provide a copy of the disinfectant program qualification reports for the **(b)(4)** and the sporicidal agent to adequately address all surface types in the Class 100 (ISO 5) filling area.

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

a. Your firm did not determine a root cause for the clogging of the **(b)(4)** experienced during the transfer of product from the **(b)(4)** tank to the **(b)(4)** tank for batches **(b)(4)**, and **(b)(4)** of **(b)(4)** ((**b)(4)**) **(b)(4)** between **(b)(4)** and March 2012. The **(b)(4)** clogging was not observed prior to these batches and your corrective action was to permit an in-process change of the **(b)(4)** if it becomes clogged. We note that you continued to manufacture and release these **(b)(4)** products without determining the most probable root cause of the **(b)(4)** clogging.

Your response states that the **(b)(4)** clogging would be investigated further to determine a root cause. You also state that you would not release the commercial batches of product currently in inventory until after the investigation is completed. In your response to this letter, provide a copy of the summary investigation report with corrective actions, which should include all follow-up actions.

b. The investigations for two media fill (process simulation) failures between September and December 2011 were not adequate Specifically, the investigation report for the "Process Simulation Failure of the **(b)(4)** Process" concluded that the probable root causes were inadequate cleaning of the pressure gauge and inadequate sampling technique. However, your firm did not provide sufficient basis or perform any studies to confirm these conclusions. Similarly, the investigation for the "Process Simulation failure of **(b)(4)** Process" concluded that the probable root cause was the handling and use of returned sterile primary packaging material, but the investigation had insufficient basis or studies to support the conclusion.

We understand that after you implemented your corrective actions, no media failures have occurred up to the time of the inspection. Your response indicated that you revised the SOPs for media fills *N/QA/070, 073 and 078* to include the performance of three consecutive successful media fills after a media fill failure, formal documentation of all planned and unplanned aseptic operations and specific interventions, and inspection of media fill vials on Day One prior to incubation as well as documentation of the results. Additionally, the procedure for media fill investigations (N/QC/159) will be revised to require a detailed description of the failure, identification of details of the contaminated units, identification of all isolates, and confirmation of identified root cause. In response to this letter, provide the data and information to support the root cause conclusions, and the revised SOP.

c. In November 2011 you did not initiate an investigation when filling was stopped for batch **(b)(4)** of **(b)(4)**, **(b)(4)**% **(b)(4)** because the filling nozzles became clogged. You released the filled portion of the batch and discarded the remaining **(b)(4)** of drug product.

Your response indicates that a formal incident was not initiated because there was no procedure to document unusual occurrences. Your corrective actions include revising SOP *Preparation and Issuance of Batch Documents* to require the documentation of all interventions and revising the SOP for *Incidence Notification* to require the initiation of an incident report for occurrences not listed as deviations. Your response also states that the team discussed the incident and decided the nozzle clogging was caused by the interference of the "**(b)(4)**" of the dosage vials and the filling nozzles at the time of the filling process. In your response to this letter, provide evidence to support your conclusion, as well as your corrective actions implemented to prevent nozzle clogging.

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations.

The Agency has concerns with the drug products manufactured by your firm under poor aseptic practices. To help ensure that your drug products meet the quality and purity characteristics that they purport, or are represented to possess, please reference the FDA-guidance entitled *Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice* located at the following link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf[1].

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, your failure to correct these violations may result in FDA continuing to refuse admission of articles manufactured at Promed Exports Private Limited located at Promed Exports Private Limited,Khera Nihla Village, Tehsil Nalagarh, Solan District, Himachal Pradesh, 174101, India, into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The articles may be subject to refusal of admission pursuant to Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3), in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of Section 501(a)(2)(B) of the Act, 21 U.S.C. 351(a)(2)(B).

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct and prevent the recurrence of violations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute the **(b)(4)**, provide the date and reason you ceased production. Please identify your response with FEI # 3008250236.

Please send your reply to:

Allison A. Aldridge, Ph.D.
Compliance Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Manufacturing and Product Quality
Division of International Drug Quality
White Oak, Building 51, Room 4254
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-0483
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Sincerely,
/S/
Michael D. Smedley
(Acting) Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

Page Last Updated: 08/20/2013
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

U.S. Food and Drug Administration
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Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
Email FDA

Links on this page:

1. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf