Food and Drug Administration
Silver Spring, MD 20993

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

April 16, 2014

Dr. C.B. Rao, Managing Director
Hospira Healthcare India Pvt. Ltd.
Plot No. B3, SIPCOT Industrial Park
Irungattukottai, Sriperumbudur (T.K.)- 602 105
Kancheepuram District, Tamil Nadu
India

Dear Dr. Rao:

During our December 2-10, 2013 inspection of your pharmaceutical manufacturing facility, Hospira Healthcare India Pvt., Ltd., located at Plot No. B3, SIPCOT Industrial Park, Irungattukottai, Sriperumbudur (T.K.), India, investigators 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 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), 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 and note that it lacks sufficient corrective actions.

Our investigators observed specific violations during the inspection, including, but not limited to, the following:

CGMP VIOLATIONS

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

   For example, the investigator found several (b) (4) sterile (b) (4) pairs of gloves in the warehouse (batches #(b) (4), #(b) (4), and #(b) (4)) with defects in the heat-sealed barrier packaging that may compromise the sterility of the gloves. The examination of batch #(b) (4) found packages of gloves with what

appeared to be a black stain and breakage of the plastic material near the heat seal, as well as de-lamination of the heat-seal. Your firm classified these defects as "cosmetic" and the protocol for qualification of (b) (4) sterile gloves, VMS-0899 (S-03) was amended to include "…*that these defects were "cosmetic" in nature and had no impact to the integrity/quality of the gloves…*" with no data to support your conclusion. Consequently, your quality unit (QU) released these batches for use in aseptic production.

Your firm's response indicates that a defect library, including examples of integral glove pouches, cosmetic defects, and gloves containing pinholes, will be created along with training involving the inspection process across your facility. However, your response does not include a study to ensure that a defect does not have an impact on the sterility of the gloves before being classified as "cosmetic." It is unclear how you distinguish a "cosmetic" defect from one that would warrant rejection of glove batches.

Additionally, your firm's response states that a review of gloves defects found during visual inspection concluded that there is no impact on marketed product. However, we are concerned that your QU is relying solely upon the final release specification of finished drugs to ensure that your glove inspection is effective. Quality should be built into the product, and testing alone cannot be relied upon to ensure product quality.

Please provide your rationale for stating that there is no impact on marketed drug products, as your risk assessment does not adequately support your conclusion.

The warning letter issued to your facility on May 28, 2013 cited deficiencies related to glove integrity. The current inspection found additional issues related to the sterile gloves, which causes us to question your overall vendor qualification program. The sterile gloves' integrity should be considered in your firm's quality risk management practices for aseptic processing. With your additional corrective actions and preventative actions (CAPAs) and defects library, it appears that previously your sterile gloves were not considered as an element in the quality risk management for your aseptic process. We are concerned that your firm's quality risk management system does not reflect an understanding of your process, how to improve it, and consequently assure patient safety.

2. Your firm failed to establish the reliability of the component supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals (21 CFR 211.84(d)(2)).

For example, your firm has not verified the sterility of incoming active pharmaceutical ingredients (APIs) during the supplier qualification exercise. Your firm released incoming API for further manufacturing based on the sterility test result from the supplier's certificate of analysis (CoA).

The API supplier qualification for (b) (4) and (b) (4) USP does not include sterility analysis by your quality control (QC) laboratory on a representative number of shipments.

In response to this letter provide a summary report for the evaluation of your vendors to ensure they are compliant with the revised standard operating procedure (SOP), "Vendor Qualification" section 3.4. If they are not, provide a timetable as to when your critical vendors will be in compliance with such SOP.

3. 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).

   For example, your firm did not investigate deviations documented in "Inter-Office-Memos" related to the visual inspection of drug product vials. During the visual inspection of (b) (4) injection, performed on April 14, 2013, operators documented in an "Inter-Office-Memo" that 500 vials with black marks on the outer surface. These vials were rejected without any investigation to determine root cause, and corrective and preventive action needed. Subsequently, on September 20, 2013, your firm implemented SOP QA023-06 which requires that all deviations be investigated.

   However, your firm's response does not include a retrospective risk assessment for all deviations documented in "Inter-Office-Memos" prior to the implementation of SOP QA023-06.

   In response to this letter, provide a summary report of the quality issues documented in "Inter-Office-Memos" that were not investigated.

4. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

   For example, your firm failed to have adequate procedures for the use of computerized systems in the laboratory where residual solvent method validations were performed. During the inspection the investigator found that a gas chromatograph (Perkin Elmer model 680) controlled using TotalChrom® software does not have sufficient controls to prevent unauthorized access to, changes to, or omission of analytical raw data files. Specifically, current computer users were able to delete raw data from analyses. Also, the audit trail had not been enabled at the time of inspection, operators shared a common user ID and password, and the system administrator login in and password was not adequately controlled. All the same, your firm submitted residual solvent method validation data generated from this instrument in several FDA drug applications. These deficiencies raise serious concerns regarding the integrity, reliability and accuracy of the data generated and available at your facility.

Your response indicates that the gas chromatograph had never been used for any commercial product release activity and you concluded that there is no impact to marketed product. You also commit to repeating all residual solvent method validation work which has direct impact on the data submitted in any regulatory filing with the new controls in place.

In response to this letter provide a comprehensive computer life cycle program to assure that appropriate controls are always exercised over computer or related systems to comply with 21 CFR 211.68. Also, provide evidence that the third party audit of your computerized systems, with the new controls, is completed prior to revalidating the methods. Provide a corrective action operating plan describing the specific procedures, actions and controls that your firm will implement to ensure the accuracy of the data in each application currently submitted to the Agency and all future applications.

General Comments

On December 2, 2013, during the inspection of the quality control (QC) laboratory, our investigator observed your Supervisor of Water Testing back-dating the date of "08/11/13" (November 8, 2013) next to his signature in the Total Organic Carbon (TOC) Instrument usage log book. We are concerned with the back-dating deviation observed and what appeared to be a breach of data integrity.

In response to this letter, provide a corrective action implemented to ensure that all employees engaged in testing, manufacture, processing, packing, or holding of drug products have been trained on good documentation practices.

The deviations listed above, as well as other deficiencies our investigator found, lead us to question the basic effectiveness of your current quality system to achieve overall compliance with CGMP at your facility. It is apparent that you have not implemented a robust quality system at your firm. Be advised that corporate management is responsible for ensuring the reliability of all data produced by your firm, including data submitted to FDA to support the safety, effectiveness, and quality of marketed products.

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.

Based upon the nature of the CGMP violations identified at your firm and previous inspectional findings, it is apparent that your firm’s attempts to implement global corrective actions have been inadequate. Be advised that corporate management has the responsibility to ensure the quality, safety, and integrity of its drug products. FDA strongly recommends that your corporate management immediately undertake a comprehensive and global assessment of your manufacturing operations, including facility design, procedures, personnel, processes, and systems, including your aseptic processing capabilities, to ensure that drug products conform to FDA requirements.

If, as a result of receiving this Untitled Letter or for other reasons, you are considering a decision that could reduce the number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Program also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

Within thirty business 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 thirty 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 drug products at issue provide the dates and reason you ceased production. Please send your reply to the following address:

Rafael Arroyo
Compliance Officer
FDA/CDER/OC/OMPQ/DIDQ
10903 New Hampshire Ave.
White Oak Building 51, Room 4235
Silver Spring, MD 20993

Sincerely,

Carmelo Rosa, Psy.D.
Director, Division of International Quality
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

cc.
Mr. Michael Ball
Chief Executive Officer (CEO)
Hospira Healthcare India Pvt, Ltd
275 N Field Drive
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