Inspections, Compliance, Enforcement, and Criminal Investigations

Hospira Healthcare India Pvt. Ltd. 5/28/13

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: 320-13-18

May 28, 2013

Mr. Michael Ball
Chief Executive Officer (CEO)
Hospira
275 N Field Drives
Lake Forest, IL 60045

Dear Mr. Ball:

During our October 3-10, 2012 inspection of your pharmaceutical manufacturing facility, Hospira Healthcare India Pvt., Ltd., located at Plot No. B3, SIPCOT Industrial Park, Irungattukottai, Sriperumburdur (T.K.), 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 deviations cause your drug product(s) 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. We also acknowledge receipt of your firm's additional correspondence dated January 29, 2013.

Our investigator(s) 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:

a. Surfaces are not always sanitized prior to use. During the filling of **(b)(4)** Injection USP **(b)(4)** g lot #**(b)(4)**, the investigator observed an operator bringing the **(b)(4)** vial

transfer belt from outside the primary HEPA area and re-attaching it to the line without sanitizing the belt. This was observed four times during the inspection. Your management instructed the operators to cull out the implicated vials only after the investigator brought this to your management's attention.

b. Aseptic manufacturing interventions are not performed in a manner to protect sterile drug products from contamination. During the manufacture of **(b)(4)** Injection USP **(b)(4)**g lot #**(b)(4)** and **(b)(4)** Injection USP **(b)(4)** g lot #**(b)(4)**, the investigator observed at least two instances in which operators performed interventions requiring them to reach over unstoppered vials. In both cases, the exposed vials were not removed and line clearance was not performed. We are concerned because these types of interventions can
contaminate open vials and can affect the unidirectional airflow used to protect the sterile equipment, surfaces, and products.

c. No dynamic airflow studies (e.g., smoke studies) have been performed to demonstrate unidirectional airflow and to determine risk to product sterility for certain routine aseptic interventions, including: removal of jammed stoppers within the **(b)(4)**, re-loading **(b)(4)** stoppers, and removal of jammed vials in the automatic weight checker. Your firm's response states that these interventions have now been simulated, but you provided no documentation or evidence of these simulations. In response to this letter provide a copy of the video/DVD containing the dynamic airflow studies (e.g., smoke studies) performed to demonstrate unidirectional airflow during these interventions.

d. Your media fill batch records do not describe the rationale for not incubating vials following media fills. For example, your firm rejected 272 vials during the media fill batch **(b)(4)** for **(b)(4)** conducted in May 2012, while having no documentation for the specific reasons why the vials were rejected. Your management told the investigator that the vials rejected are most likely non-integral, but had no documentation to support this position. Media fill reconciliation documentation should include a full description of units rejected from a batch and an accounting for the rejection of each.

e. Gloves used during manufacture of sterile products are used without adequate assurance of their sterility. For example, during the inspection, the investigator evaluated the **(b)(4)** gloves used during aseptic processing and found significant damage to the integrity of a large percentage of the boxes as well as to the individual packaging for the gloves. The investigator also noticed that one of the boxes containing individually packaged sterile gloves was incorrectly labeled as "non-sterile surgical gloves." Your quality management informed the investigator that these gloves are not sterilized prior to use in the aseptic manufacturing suites. We are concerned that your environmental excursion investigations or other quality oversight did not uncover the potential for use of gloves whose sterility was compromised.

f. The revised SOP, "Handling of damage container" WH012, that you provided in your response is inadequate because it does not indicate how you will handle the quarantined supplies. Also, clarify whether the procedure WH019-04 "Procedure for receipt, storage, approval and issue of sterile gloves" establishes that all glove packaging is inspected before acceptance to verify that your firm receives and uses sterile gloves.

We are concerned that similar violations were found during a recent inspection of February 12 through March 1, 2013 conducted at you Rocky Mount Hospira facility located in North Carolina, USA. Please provide a current global corrective action plan for your facilities (US and foreign sites). Include a comprehensive training module on aseptic process techniques for all employees involved in aseptic process operations and how you plan to measure the effectiveness of any training being provided.

2. Your firm failed to have facilities used in the manufacture, process, packaging and holding of a drug product of appropriate construction to facilitate cleaning, maintenance, and proper operations (21 CFR 211.42(a)).

a. The FDA investigator observed two holes of approximately 1 cm x 0.5 cm each, between the Class 100,000 (ISO 8) "circulation corridor" and the Class 100 (ISO 5)

"component receipt area" of sterile **(b)(4)** facility.

b. The entry/exit door into the vial filling/stoppering suite has not been designed in a way that protects the aseptic filling area from disruption of airflow from room entries and exits; for example, there is no mechanism to control the door operation from disrupting the air flow within the filling area when personnel enter and exit the room. This disruption may affect the air flow in this critical area.

c. The investigator also noted that air was flowing from the circulation corridor into the component receipt area, adjacent to where the aseptic **(b)(4)** filling of **(b)(4)** Injection USP **(b)(4)** mg, lot #**(b)(4)** was in progress. The circulation corridor, where the holes were observed, is an unclassified area. The component receipt area is directly connected and adjacent to the aseptic vial filling/stoppering suite and is where sterile components are unloaded from the **(b)(4)**.

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.

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 refusing admission of articles manufactured at Hospira Healthcare India Pvt., Ltd. into the United States. The articles are 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 drug product(s) at issue, provide the date(s) and reason(s) you ceased production.
If, as a result of receiving this Warning 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.

Your failure to correct these deviations may result in FDA to refuse admission of articles manufactured at Hospira Healthcare India Pvt., Ltd Irungattukottai, Sriperumburdur (T.K.) India into the United States. The articles are 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 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 deviations, 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 drug

product(s) at issue, provide the date(s) and reason(s) 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,
/Michael D. Smedley/
Michael D. Smedley
Acting Director
Office of Manufacturing and Product Quality
Office of Compliance

Page Last Updated: 06/04/2013
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