Hospira Healthcare India Pvt. Ltd. 3/4/19

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-19-14

March 4, 2019

Mr. Albert Bourla
Chairman and Chief Executive Officer
Worldwide Pfizer
235E 42nd St.
New York, NY 10017

Dear Mr. Bourla:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Hospira Healthcare India Pvt. Ltd., at Plots B3, B4, B5 (pt); B6 (pt); B11-B18 and B21-B23, SIPCOT Industrial Park, Irungattukottai, Sriperumbudur, Kancheepuram District, Tamil Nadu, India, from March 27 to April 3, 2018.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your April 24, 2018, response in detail and acknowledge receipt of subsequent correspondence.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

1. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

Your microbiology laboratory did not accurately report test results. On March 27, 2018, during a walk-through of your laboratory, our investigator observed microbial growth on **(b)(4)** personnel/environmental monitoring media plates associated with **(b)(4)** aseptic processing lines. However, our review of laboratory records found that analysts had recorded a result of "Nil" (no growth) for each of these plates. On the same day, our investigator also observed that your microbiologist had significantly underreported microbial results for three **(b)(4)** samples.

During the inspection, your staff confirmed that laboratory records did not accurately reflect the actual microbial growth observed on plates.

Your written response acknowledged the significance of these microbial growth count discrepancies. Your firm also stated that, after implementing extra plate-reading oversight in the microbiology laboratory, a notable increase in counts emerged in environmental monitoring results, with a particularly "sharp" increase in personnel monitoring excursions across the facility.

Accurate microbiological data is fundamental to evaluating and maintaining the state of control of an aseptic processing operation. Awareness of microbial excursions in an aseptic processing operation is essential to trigger prompt actions that maintain environment control. Your failure to report accurate data compromised the sterility assurance of drug products released from the facility and may have increased risks to patients.

The critical data integrity breaches identified in our inspection also raise serious concerns regarding the validity of all results reported by your quality control laboratory. We acknowledge your decision during the inspection to suspend release of drug products until the data integrity issues were thoroughly investigated. We also note that during the FDA regulatory meeting held on May 8, 2018, your management further acknowledged the significant data integrity problem identified in the inspection and discussed a comprehensive plan to address root causes.

Your response included adding corporate and third-party oversight of microbiology laboratory tests and data reporting, and several other remediation measures. However, your response did not describe the scope of inaccurate reporting of data, and the extent of management and staff involvement with data manipulation.

In your response to this letter, include:

- A final report on corrective actions and preventive actions (CAPA) that were implemented to assure that aseptic processing operations are maintained in a state of control, including fully requalifying personnel involved in these operations.
- The final report on changes implemented in the site's quality control (QC) laboratories to enhance procedures, training, and CGMP documentation practices observed during the inspection and as a result of post-inspection assessments.
- A comprehensive, retrospective review of reliability of all microbiology laboratory data, including but not limited to data relating to water system control and environmental monitoring (personnel, surfaces, air). Assess all batches within expiry and distributed in the United States.

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).

Your firm failed to adequately investigate poor control and critical defects in your **(b)(4)** manufacturing process.

Our inspection found that you initiated multiple investigations because batches exceeded critical defect limits for visual inspection. For example, during four months in 2017, three batches yielded excessive critical defect rates ranging from **(b)(4)**% to **(b)(4)**%. The limit is no more than **(b)(4)**%.

Manufacturing investigations indicated that high rates of significant **(b)(4)** appearance defects were caused by power failures and **(b)(4)** that disrupted the **(b)(4)**. These events delayed reaching appropriate **(b)(4)** during the **(b)(4)**, leading to insufficient and non-uniform **(b)(4)**. However, your investigations did not sufficiently determine the root cause of recurring batches with significant **(b)(4)** defects when no power interruptions and cycle deviations were documented. Your process control problems permitted excessive **(b)(4)** to remain in finished product units and caused persistent defects. The **(b)(4)** caused by these **(b)(4)** process control difficulties were found to lead to quality attribute specification failures including impurities, assay, or **(b)(4)**.

The extent of these critical drug quality defects was further revealed when examination of reserve samples identified many **(b)(4)** appearance defects, although the lots had undergone the required 100% visual inspection and had met AQL sampling criteria.

The investigations did not include a timely CAPA plan to address **(b)(4)** design deficiencies and inappropriately high tolerances for critical defects such as **(b)(4)**. You also did not adequately address the need to highly scrutinize variances in pressure control in your **(b)(4)** equipment, including better triggers for investigation.

Excessive defects and major manufacturing deviations are both signals of unacceptable manufacturing variation and the need for thorough investigation into the sufficiency of process design and controls. The failure of your firm's operations and quality departments to promptly detect adverse signals in manufacturing permitted the conditions that allowed several batches with critical quality defects to be distributed.

We acknowledge your decision to recall all batches of **(b)(4)** injection USP **(b)(4)** and **(b)(4)** within expiry in the U.S. market, after your testing of retain samples showed subpotent test results.

In your response, you committed to enhance process understanding and control. You stated that you would improve and validate a modified **(b)(4)** process and remediate deficiencies in the visual inspection program. Your response was inadequate in that:

- It did not include a reassessment of the adequacy of your CAPA to address handling out-of-specification (OOS) **(b)(4)** results obtained by your laboratory.
- It lacked sufficient details on the evaluation of additional **(b)(4)** products produced with the same manufacturing equipment used for the **(b)(4)** injection **(b)(4)** and **(b)(4)**.

In your response to this letter, provide:

- Your final report on the improvements needed to ensure that **(b)(4)** processes will reproducibly meet required quality attributes.
- An evaluation of the design and state of control of each **(b)(4)** cycle used to produce drug products for U.S. supply. Include a retrospective assessment of all investigations (e.g., process deviations, failures, complaints) related to **(b)(4)** drug products not recalled from the U.S. market. Summarize the root causes assigned for identified defects, the adequacy of the CAPA, and any further steps needed.
- Your CAPA for routine, vigilant operations management oversight of facilities and equipment to assure prompt detection of equipment performance issues, execution of repairs, completion of preventive maintenance, upgrades to equipment and facilities, and other appropriate actions.

3. Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).

From February 16 to March 20, 2018, you tested **(b)(4)** batches of **(b)(4)** API for **(b)(4)**. All results were reported as passing. However, during the FDA inspection on March 28, 2018, we requested retesting the same batches under our observation. All retest results were OOS.

A batch of **(b)(4)** finished product, initially tested on May 25, 2017, was also retested on March 28, 2018, and found to be OOS.

Further, on April 2, 2018, your management informed our investigator that the **(b)(4)** test for **(b)(4)** batch **(b)(4)** raw material was repeated and that all **(b)(4)** replicates failed to meet the specification.

Our investigators noted that your analysts did not have a timer to indicate the start and end of **(b)(4)** reported in your laboratory record of analysis. It was unclear if analysts were **(b)(4)** the **(b)(4)** samples for the full **(b)(4)** required.

In your response, you indicated that your investigation had revealed data integrity issues related to reporting **(b)(4)** test results. You also indicated that your investigation, still in progress, has identified laboratory equipment failure as a probable root cause for the failing **(b)(4)** results. More specifically, inefficient removal of **(b)(4)** from the **(b)(4)** is considered to be the cause of incomplete **(b)(4)** of the sample.

We acknowledge your decision to suspend all **(b)(4)** testing. However, you did not include an assessment to determine whether other QC laboratory tests performed in the same laboratory were compromised by data integrity issues. Your response also fails to discuss the extent of data integrity breaches in your facility.

In a Field Alert Report (FAR) of July 20, 2018, regarding OOS **(b)(4)** results, you indicated that “analysts performing the **(b)(4)** test did not perform the analysis in accordance with procedures and did not record the data accurately in the past.” Also, “there may be instances where testing results for the Karl Fisher test, gas chromatography, infrared spectroscopy and ultraviolet spectroscopy were not recorded accurately.”

In your response to this letter, include:

- A comprehensive CAPA to ensure all batches of **(b)(4)** finished product intended for the U.S. market meet all established specifications. Include your results from testing reserve samples of all drugs (active ingredient and finished drug product) that remain within retest period or expiry in the U.S. market.
- Your market action plan for all batches with reserve sample testing found to be OOS or inaccurately reported (e.g., as identified by your independent third party).

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA’s guidance document *Data Integrity and Compliance with Drug CGMP* for guidance on establishing and following CGMP compliant data integrity practices at **https://www.fda.gov/downloads/drugs/guidances/ucm495891.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm495891.pdf)**

We acknowledge that you are using a consultant to audit your operation and help you meet FDA requirements. In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. We recommend that a qualified third party with expertise in the area where potential breaches were identified, evaluate all data integrity lapses.
- The protocol and reports from your independent third parties that summarize the findings relating to data integrity at your facility. Include their findings regarding all laboratories, equipment, and staff involved with data manipulation and inaccurate reporting. Include details such as product, test type, test date, results that may have been compromised, description of data integrity issue, and any root cause identified.

B. A current risk assessment of the potential effects of these observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the root causes of your data integrity lapses including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
- A status report for any of the above activities already underway or completed.

Cessation of Manufacturing at the Facility

We acknowledge your decision to cease all production and distribution of drug products from the site due to the significant long-term loss of product demand. We also acknowledge your commitment for third-party consultants to continue performing product quality assessments, including ongoing review of adverse events and customer complaints for drugs remaining in distribution from this facility.

Note that remediating these CGMP violations will be necessary if Pfizer, a successor, or an acquirer resumes drug manufacturing operations at this site for the U.S. market.

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations in all your facilities.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) 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.

FDA placed your firm on Import Alert 66-40 on August 1, 2018.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in FDA continuing to refuse admission of articles manufactured at Hospira Healthcare India Pvt. Ltd., at Plots B3, B4, B5 (pt); B6 (pt); B11-B18 and B21-B23, SIPCOT Industrial Park, Irungattukottai, Sriperumbudur, Kanchipuram, Tamil Nadu, India into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, 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 FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to **CDER-OC-OMQ-Communications@fda.hhs.gov (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)** or mail your reply to:

Rafael Arroyo
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4235
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3008386908.

Sincerely,
/S/
Francis Godwin
(Acting) Director

Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

More in Warning Letters (/ICECI/EnforcementActions/WarningLetters/default.htm)