WARNING LETTER

Pfizer Healthcare India Private Limited

MARCS-CMS 594972 — MARCH 25, 2020

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Albert Bourla

Chairman and Chief Executive Officer

Pfizer Healthcare India Private Limited

235 East 42nd Street
New York, NY 10017-5703
United States

Issuing Office:

Center for Drug Evaluation and Research | CDER

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Warning Letter 320-20-31

March 25, 2020

Dear Mr. Bourla:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Pfizer Healthcare India Private Limited, FEI 3008316085, at Plots 116-117-118-119-111-123 (part), Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam, Andhra Pradesh, India, from August 29 to September 6, 2019.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (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 September 27, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

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

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 facility manufactures **(b)(4)** injectable products. Your firm failed to conduct adequate investigations, including timely implementation of effective corrective action and preventive action (CAPA) plans.

Failed Sterility Testing

You did not adequately investigate root causes and implement CAPA to address deficiencies regarding your sterility testing **(b)(4)**. For example, in February 2019, you investigated the sterility failure of **(b)(4)** injection batch **(b)(4)**. You determined the most probable root cause of this sterility failure was the "lack of robust **(b)(4)** integrity testing and possible non-integral drug product vials." You also stated that the source of the microbial contamination may have been a faulty **(b)(4)**. This batch was rejected. However, you continued to use the same **(b)(4)** and performed sterility testing for a substantial number of additional batches before you made corrections, including replacing the suspect **(b)(4)**.

Your response stated that you will implement automated **(b)(4)** integrity testing, which is planned for July 2020. Previously, you lacked an automated integrity test, and instead relied on a visual check that was insufficient on its own to reliably detect **(b)(4)**.

You also indicated that, effective January 2020, you would inspect sterility test samples for integrity before introduction to the sterility **(b)(4)**.

The timeliness of the CAPA to resolve these significant root causes was insufficient. Your response did not adequately address the delay in CAPA implementation. Your response also indicated that you had made revisions to the investigation and that these revisions were completed on September 27, 2019. However, your response lacked the revised investigation and the status of your CAPA progress.

Environmental Monitoring Program

You did not adequately investigate serious deficiencies in microbiology laboratory conditions and practices. Among the deficiencies were excessive occurrences of negative control plate contamination, high levels of contamination in environmental monitoring (EM) samples of the sterility test **(b)(4)**, and disregarded EM data because of delayed plate readings. More specifically:

• You did not thoroughly investigate negative environmental trends observed in the **(b)(4)** used to support sterility testing. Repeated recoveries were observed in the **(b)(4)**, including excessively high levels (e.g., **(b)(4)**, too-numerous-to-count (TNTC) CFU/m3), in some cases, over a three month period.

• You did not adequately investigate numerous instances over a one year period of microbial growth on negative control plates. These plates were used to support the EM program in both your production and laboratory areas.

• You invalidated microbial results without adequate scientific justification. Between September 26 and December 23, 2018, your biological quality laboratory allowed EM and testing plates used for monitoring your facility to be incubated beyond the days established in procedures. You attributed this recurring issue to a lack of qualified personnel. These plates included but are not limited to EM of the **(b)(4)**, negative control plates, and product bioburden analysis. The testing results were repeatedly invalidated as the counts were considered unreliable, although the risks posed by the potentially valid contamination findings and related impact were not sufficiently addressed. Approximately **(b)(4)** batches were made during this period.

Your investigation into the extended incubation of plates indicates that they were being read on a "**(b)(4)**" basis. While you indicate you were reading plates **(b)(4)**, you lacked documentation of earlier readings performed before the extended incubation times. The investigation also discusses the commingling of media plates in the same bag that were overgrown to the point that one plate may have contaminated another plate.

Laboratory data accuracy deficiencies were also cited in our September 2018 inspection.

In your response, you indicated there are ongoing investigations to address the root causes of the recurring growth on negative control plates. You indicated that you have taken initial measures such as adding a new media vendor and improving incubator maintenance.

Regarding the significant adverse environmental monitoring trends in your sterility testing **(b)(4)**, your response stated that no additional EM excursions had occurred in your **(b)(4)** since you initiated your CAPA. The CAPA steps included addition of a **(b)(4)** to the **(b)(4)**, better disinfection of supplies, slower **(b)(4)** movements, and retraining.

You also stated that you are improving overall laboratory capabilities and investigations systems.

However, your response did not fully address how deficient laboratory controls, inadequate investigations, and delays in implementing CAPA compromised your firm's microbiological control program.

In response to this letter, provide the following:

• A comprehensive assessment of your overall system for investigating deviations, discrepancies, complaints, out-of-limit results, out-of-specification results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality assurance oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.

• An assessment and remediation plan for your CAPA program. Provide a report that evaluates whether your firm effectively conducts root cause analysis, ensures CAPA effectiveness, regularly reviews investigations trends, implements improvements to the CAPA program when needed, ensures appropriate quality assurance decision rights, and is fully supported by executive management.

• A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.

• A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, analyst competencies, and resources. Regarding the latter, the assessment should address the adequacy of qualified staff needed to produce reliable results within appropriate timelines as well as your practices for managing the tracking of samples and timely reading of test results. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.

• Your revised investigations regarding the sterility failure and the loss of environment control in the sterility testing **(b)(4)**. The updated investigations should include, but not be limited to:
  o A final summary of all factors that may have compromised **(b)(4)** integrity, corrective actions, and your re-qualification results.
  o Further explanation of the potential product container-closure integrity root cause that appears to have been ruled out as a cause of the sterility failure. Provide a detailed summary of the defect and deviation rates that are relevant to container-closure integrity from your batch records over the last two years. In addition, explain the atypical manufacturing conditions that could impact container-closure integrity.

• A summary of your completed negative control plate investigations that were ongoing at the close of the inspection.

• Your response concerning extended incubation of media plates leading to the invalidation of EM results. Include a summary worksheet that documents the date that each plate was read, the date each plate was scheduled to be read, and the difference in the number of days between the actual date and the scheduled date. Clarify if you read and document microbial plates samples more than once during the incubation period and whether you document the results each time. Also provide your investigation for the TNTC result documented in PR#2466588. Include the methods used for bioburden, dilutions, and counting of microbes.

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. For guidance on establishing and following CGMP compliant data integrity practices, see FDA's guidance documents Data Integrity and Compliance With Drug CGMP at https://www.fda.gov/downloads/DRUGS/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf (https://www.fda.gov/downloads/DRUGS/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf) and Questions and Answers on Current Good Manufacturing Practices—Laboratory Controls at https://www.fda.gov/DRUGS/Guidances-Drugs/Questions-And-Answers-Current-Good-Manufacturing-Practices-Laboratory-Controls#17 (https://www.fda.gov/DRUGS/Guidances-Drugs/Questions-And-Answers-Current-Good-Manufacturing-Practices-Laboratory-Controls#17).

We acknowledge that you engaged a consultant to audit your operation and assist in meeting FDA requirements.

In response to this letter, provide the following:

• A comprehensive investigation into the extent of the inaccuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.

• A current risk assessment of the potential effects of the 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.

• A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

Conclusion

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 these violations and for preventing their recurrence or the occurrence of other violations.

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). This also 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.

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

Failure to correct these violations may also result in the FDA refusing admission of articles manufactured at Pfizer Healthcare India Private Limited, FEI 3008316085, at Plots 116-117-118-119-111-123 (part), into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority 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 or mail your reply to:

Michael Klapal
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 3008316085.

Sincerely,
/S/

Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

CC:
(b)(6)
Site Leader
Pfizer Healthcare India Private Limited
Plots 116-117-118-119-111-123 (part)
Jawaharlal Nehru Pharma City, Parawada
Visakhapatnam, Andhra Pradesh, 531019
India

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)