WARNING LETTER

Aurobindo Pharma Limited

MARCS-CMS 577033 — 20/06/2019

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. N. Govindarajan

Managing Director

Aurobindo Pharma Limited

Plot No. 2, Maitrivihar, Ameerpet
Hyderabad 500038 Telangana
India

Issuing Office:

Center for Drug Evaluation and Research

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Via UPS **Warning Letter 320-19-27**

Return Receipt Requested

June 20, 2019

Mr. N. Govindarajan
Managing Director
Aurobindo Pharma Limited
Plot No. 2, Maitrivihar, Ameerpet
Hyderabad-500038, Telangana
India

Dear Mr. N. Govindarajan:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Aurobindo Pharma Limited (APL), Unit XI at Sy. No. 61-66, IDA, Pydibhimavaram, Ranasthalam (Mandal), Srikakulam District, AP, from February 4 to 9, 2019.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API 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).

In addition, the inspection revealed that your firm failed to submit supplemental **(b)(4)** to report the pertinent specification changes in Drug Master File (DMF) **(b)(4)**, as required by 21 CFR 314.97(a).

We reviewed your March 4, 2019, response in detail and acknowledge receipt of your subsequent correspondence.

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

CGMP Deviations

1. Failure to extend investigations to other batches that may have been associated with a specific failure or deviation.

Your investigation into the root cause of **(b)(4)** impurities, such as **(b)(4)**, in your **(b)(4)** and **(b)(4)** API was deficient. Your initial assessment determined that the synthetic mechanism for the manufacture of **(b)(4)** API did not have the potential to produce **(b)(4)** impurities such as **(b)(4)** and **(b)(4)**. This assessment did not include an evaluation of the potential for key starting materials (KSM), other raw materials, and solvents to result in the presence of **(b)(4)** and **(b)(4)**.

After you were informed by the European Directorate for the Quality of Medicines (EDQM) that their test results showed your **(b)(4)** API contained **(b)(4)**, your firm tested more than **(b)(4)** API batches and determined that **(b)(4)** batches, approximately **(b)(4)**%, contained **(b)(4)** contamination at levels above the acceptable limit. You subsequently recalled these batches.

Your risk assessment dated January 29, 2019 documented that **(b)(4)** contamination in **(b)(4)** API originated from recovered **(b)(4)** and **(b)(4)** solvents. You reported that recovered **(b)(4)** is generated from a **(b)(4)**, which is recovered at your contract manufacturer, **(b)(4)**. Your investigation concluded the **(b)(4)** contamination was due to the use of recovered **(b)(4)** supplied by **(b)(4)**. You attributed the **(b)(4)** contamination to **(b)(4)** inadequate cleaning procedures.

In your response you state that you are not using recovered solvents to manufacture **(b)(4)**. Your response is inadequate. While you were no longer using **(b)(4)** as a supplier of recovered solvent **(b)(4)** for the manufacture of **(b)(4)** at the start of the FDA inspection, you did not identify corrective actions to ensure adequate quality oversight of operations for all contractors performing functions that could affect drug quality.

We acknowledge that you have initiated additional process controls and are now testing all manufactured batches of **(b)(4)** API for **(b)(4)**, including **(b)(4)**, as batch release criteria.

In response to this letter:

- Identify corrective actions to ensure adequate quality oversight of operations for contract manufacturers performing functions that could affect drug quality, including any revised qualification and evaluation procedures.
- Provide an update on investigations and corrective action and preventive action (CAPA) plans initiated to address the presence of **(b)(4)** and other potential **(b)(4)** impurities in all API manufactured at your firm.
- Provide test results for all **(b)(4)** and intermediates for the presence of **(b)(4)**, and other potentially **(b)(4)** impurities.
- Conduct a retrospective review of **(b)(4)** batches for identification of **(b)(4)** impurities in chromatograms. Provide corrective actions for identifying unknown peaks in chromatograms using a properly validated method for **(b)(4)** impurities.
- Submit risk assessments for all API and intermediates manufactured at your facility for the potential presence of mutagenic impurities.

For FDA's current thinking on control of potentially mutagenic impurities, see FDA's guidance document *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* for approaches that FDA considers appropriate for evaluating mutagenic impurities, at https://www.fda.gov/media/85885/download (https://www.fda.gov/media/85885/download).

2. Failure to ensure that equipment surfaces in contact with API do not alter the quality of the API beyond the official or other established specifications.

Your investigations into poor equipment maintenance are inadequate. Our investigators observed what appeared to be rust on more than **(b)(4)**% of **(b)(4)** SRJ014, used to manufacture **(b)(4)** API. Your investigation into this finding did not sufficiently extend to other drug manufacturing equipment that may also not be properly maintained.

In your response, you acknowledged that your firm did not check the dryness of the inner surface of the **(b)(4)** after cleaning: therefore, moisture remained in the **(b)(4)** and caused discoloration. You determined the stains were due to the formation of iron oxide (rust) inside the **(b)(4)**. In your response, you explained you would replace **(b)(4)** SRJ014 with a **(b)(4)** that is not susceptible to formation of rust. However, your response is inadequate because you did not identify corrective actions to ensure other equipment used to manufacture drugs have contact surfaces that are also made of adequate material.

In response to this letter:

- Provide a comprehensive assessment of the state of maintenance of all equipment that can be used in the manufacture of drugs for the United States.
- Provide a CAPA plan that includes a full review of all equipment contact surfaces to determine if they are reactive/additive to your drugs and whether contact surfaces are suitable for intended use. If any raw material, intermediate, or API contact surfaces are found to be deficient, provide a risk assessment, including the impact on potentially affected batches, and actions taken to prevent recurrence.

Failure to Comply with Submission Requirements for Supplements and Other Changes to an Approved (b)(4)

1. Changes to methods or controls were not reported to FDA through a supplement to an approved (b)(4). (21 CFR 314.97(a) and 314.70(c)(6)(i))

Investigators observed, in your **(b)(4)** API, non-carcinogenic impurities of **(b)(4)** and **(b)(4)** at levels up to **(b)(4)**% and **(b)(4)**%, respectively, in residual solvent testing for **(b)(4)** API batches. These impurities are present in drug substances at levels exceeding the **(b)(4)** USP specification limit for *Any other individual impurity* (i.e. NMT **(b)(4)**%). These impurity levels are also above the ICH Q3A(R2) reporting threshold for drug substance impurities.

Your Quality Unit failed to report to FDA these impurities, which were also above your internal reporting threshold limit of no more than **(b)(4)**%. You updated the information in your Drug Master File (DMF) only after FDA investigators communicated during the inspection that you should be reporting all observed impurities above the reporting threshold.

In your response, you explained a "scheduled regulatory update skipped our attention." In addition, you stated you would undertake an additional CAPA for controls of residual solvents. Your response is inadequate, as you did not commit to conduct a full review of all impurities observed in all your APIs above the reporting threshold and ensure that your DMFs and **(b)(4)** are updated accordingly.

As the applicant of **(b)(4)** and **(b)(4)** you must comply with the requirements of 314.70(c)(6)(i) regarding the submission of supplemental **(b)(4)** and other changes to an approved **(b)(4)**. The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved **(b)(4)** may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include but are not limited to addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess.

As the DMF holder of **(b)(4)** API DMF **(b)(4)**, we remind you that any addition, deletion, or change to the information in your DMF is required to be submitted to the FDA under 21 CFR 314.420. Additionally, you are required to notify each person authorized to reference the information in your DMF of the pertinent changes.

In response to this letter:

- Conduct a thorough review of all batches of API made at Aurobindo that shows unknown impurities above the reporting thresholds. Identify any impurities that are present at a level greater than the ICH Q3A(R2) identification thresholds and update your DMFs and **(b)(4)** as required. Any DMF update should also result in notifications to any authorized person for the DMF. Provide copies of these notifications to FDA.
- Provide a thorough, independent assessment of your overall system for investigating unknown peaks, deviations, discrepancies, out-of-specification (OOS) results, complaints, and other failures. In addition, provide a retrospective review of all distributed batches within expiry to determine if your firm released batches that did not conform to established specifications, official compendium, or appropriate manufacturing standards.

Additional API CGMP guidance

FDA considers the expectations outlined in ICH Q7 when determining whether API are manufactured in conformance with CGMP. See FDA's guidance document *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* for guidance regarding CGMP for the manufacture of API at https://www.fda.gov/media/71518/download (https://www.fda.gov/media/71518/download).

CGMP consultant recommended

We acknowledge that your firm engaged a consultant to assist your firm in meeting CGMP requirements. Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

Repeat Observations at Multiple Sites and Regulatory Meeting

FDA cited similar CGMP observations at other facilities in your company's network. Aurobindo Unit I and Aurobindo Unit IX were also inspected and cited for CGMP deficiencies related to the manufacture of **(b)(4)** API and intermediates. These facilities are also considered to be in an unacceptable state of compliance with regards to CGMP. These repeated failures at multiple sites demonstrate that management oversight and control over the manufacture of drugs are inadequate.

Contact Nabeel Babaa, by e-mail at Nabeel.Babaa@fda.hhs.gov (mailto:Nabeel.Babaa@fda.hhs.gov), within five business days of receipt of this letter to schedule a regulatory meeting to discuss CGMP compliance at Aurobindo Unit XI (FEI: 3004611182), Aurobindo Unit I (FEI: 3004021253), and Aurobindo Unit IX (FEI: 3006370489).

Conclusion

Deviations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these deviations, for determining the causes, for preventing their recurrence, and for preventing other deviations 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 (mailto: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.

Until you correct all deviations 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 deviations may also result in FDA refusing admission of articles manufactured at Aurobindo Pharma Limited, Unit XI, Sy. No. 61-66, IDA, Pydibhimavaram, Ranasthalam (Mandal), Srikakulam District, AP, 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 deviations 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:

Tamara Rosbury

Compliance Officer

U.S. Food and Drug Administration

White Oak Building 51, Room 4359

10903 New Hampshire Avenue

Silver Spring, MD 20993

USA

Please identify your response with FEI 3004611182.

Sincerely,

/S/

Francis Godwin

Director

Office of Manufacturing Quality

Office of Compliance

Center for Drug Evaluation and Research

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