WARNING LETTER

Aurobindo Pharmaceutical Limited

MARCS-CMS 618091 — JANUARY 12, 2022

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Narayanan Govindarajan

Managing Director

Aurobindo Pharmaceutical Limited

Floor No.'s 22, 23 & 24 Galaxy
Plot No-1, Survey No: 83/1, Hyderabad Knowledge City Raidurg Panmaktha, Ranga Reddy District
Hyderabad 500081 Telangana
India

Issuing Office:

Center for Drug Evaluation and Research | CDER

United States

Warning Letter 320-22-10

January 12, 2022

Dear Mr. Govindarajan:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Aurobindo Pharmaceutical Limited Unit I, FEI 3004021253, at Survey 379, 385, 386, 388 – 396, Borpatla Village, Doultabad, Telangana, 502296 India, from August 2 to 12, 2021.

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).

We reviewed your August 12, 2021, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

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

1. Failure to evaluate the potential effect that changes may have on the quality of your intermediates and API.

Your firm failed to fully evaluate whether increasing your acceptable **(b)(4)** limit by **(b)(4)** in an **(b)(4)** API starting material **(b)(4)** would impact the quality of **(b)(4)** API. Following the initial rejection of several lots of the **(b)(4)** starting material for failing to meet specified **(b)(4)** limits (e.g., **(b)(4)** ppm observed, **(b)(4)** ppm specification), you performed a lab scale study to justify an increase in the acceptable **(b)(4)** limit. You only evaluated **(b)(4)** potential impurities formed via **(b)(4)** where **(b)(4)** and did not consider the generation of the other substituted potential impurities before increasing the **(b)(4)** limit in your **(b)(4)** starting material from **(b)(4)** ppm to **(b)(4)** ppm

Further, instead of fully evaluating the effect of increasing the **(b)(4)** limit in the **(b)(4)** starting material, you relied on an **(b)(4)** step as part of your lab scale study, which was not a part of the approved or implemented large scale manufacturing process for the **(b)(4)** API at the time, to purge potential impurities without demonstrating that any potential impurities would be removed by **(b)(4)**. Lastly, you relied on the existing related substances analytical method to detect the new impurities without determining their relative response factors to assess if this analytical method was appropriate for the new impurities.

In your second response, you provided the spike and purge studies results to demonstrate how these impurities are removed as part of the manufacturing process. However, your responses are inadequate as these studies were not completed before the implementation of this change to the **(b)(4)** starting material.

In response to this letter, provide a comprehensive, independent assessment of your change management system. This assessment should include, but not be limited to, your procedure(s) to ensure changes are justified, reviewed, and approved by your quality unit. Your change management program should also include provisions for determining change effectiveness.

2. Failure of your quality unit to ensure that critical deviations are investigated and resolved.

Your firm does not fully investigate discrepancies. During method transfer for the gas chromatography–mass spectrometry (GC-MS), method for **(b)(4)** determination in **(b)(4)**, a starting material for **(b)(4)**, you failed to pass the method transfer acceptance criteria for inter laboratory precision because of observed peak splitting. Although you conducted an investigation, it was not adequate as your investigation failed to consider all potential equipment sources. The failing result was invalidated without a scientific rationale and was not reported in the "problems faced" or "corrective actions taken" sections of the approved method transfer report. Ultimately, you attributed the failing result to a dirty and/or degraded column, replaced the column, and obtained a passing result with a fresh sample. Likewise, after attributing the failure to the deteriorated column, you did not establish controls to ensure that only acceptable columns would be used in future analyses.

In your response, you re-confirmed your confidence that the column was the root cause for the failing result and that the GC-MS **(b)(4)** method had been adequately transferred. You stated that the failing result was an isolated incident. In your second response, you noted that there was an "interaction of [the] sample **(b)(4)** with the deteriorated **(b)(4)** of the **(b)(4)** column" to explain why **(b)(4)** standards in the failing sample set did not show peak splitting. However, if the assigned root cause is an inherent instability between with the sample and a deteriorated GC-MS column, you failed to provide any equipment controls to prevent peak splitting in the future, nor did you consider whether the analytical method was appropriate for the intended **(b)(4)** testing.

In response to this letter, provide the following:

• A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, out-of-specification (OOS) 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, corrective action and preventive action effectiveness, quality assurance unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.

• A retrospective, independent review of all invalidated OOS (including in-process and release/stability testing) results for US products irrespective of whether the batch was ultimately distributed in the US for the last three years from the initial date of inspection and a report summarizing the findings of the analysis, including the following for each OOS:
  o Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error.
  o For investigations that conclusively establish laboratory root cause, provide rationale and ensure that all other laboratory methods vulnerable to the same or similar root cause are identified for remediation.
  o For all OOS results found by the retrospective review to have an inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, suitability of equipment/facilities, variability of raw materials, process capability, deviation history, complaint history, batch failure history). Provide a summary of potential manufacturing root causes for each investigation, and any manufacturing operation improvements.

• Review all analytical and microbiological method transfers for any discrepancies not described in the approved method transfer reports. Take appropriate actions to ensure methods have been accurately transferred and are acceptable for use.

Repeat Deviations at Facility

In a previous Regulatory Meeting held July 29, 2019, FDA cited similar CGMP deviations. You proposed specific remediation for these deviations in your response. Repeated failures demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

CGMP Consultant Recommended

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

Conclusion

The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility. You are responsible for investigating and determining the causes of any deviations and for preventing their recurrence or the occurrence of other deviations.

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 (//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.

Correct any deviations promptly. FDA may withhold approval of new applications or supplements listing your firm as a drug manufacturer until any deviations are completely addressed and we confirm your compliance with CGMP. We may re-inspect to verify that you have completed corrective actions to any deviations.

Failure to address any deviations may also result in the FDA refusing admission of articles manufactured at Survey 379, 385, 386, 388 – 396, Borpatla Village, Doultabad, Telangana 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 that appear to be adulterated may be detained or refused 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).

This letter notifies you of our findings and provides you an opportunity to address the above deficiencies. After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done to address any deviations and to prevent their recurrence. In response to this letter, you may provide additional information for our consideration as we continue to assess your activities and practices. 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. Identify your response with FEI 3004021253.

Sincerely,
/S/

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

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