Alchymars ICM SM Private Limited 2/16/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS

Warning Letter 320-18-35

February 16, 2018

Mr. T.G. Velumani
Chief Executive Officer
Alchymars ICM SM Private Limited
Adwave Towers C/4
III Floor, #17 South Boag Road
T. Nagar, Chennai 600 017
India

Dear Mr. Velumani:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Alchymars ICM SM Private Limited at A-14 & 20 Complex, Alathur, Tamil Nadu, from September 11 to 15, 2017.

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 October 6, 2017, 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.

1. Failure to have laboratory control records that include complete data derived from all laboratory tests conducted to ensure your API complies with established specifications and standards.

Our investigator found that your firm was falsifying laboratory data. For example, the number of colony-forming units (CFU) found on **(b)(4)** plates for **(b)(4)** water point-of-use tests differed substantially from the number recorded on your **(b)(4)** water report. For multiple points of use, your analyst reported far fewer CFU than observed on the plate by our investigator. In addition, while you reported absence of growth on a selective media plate used to detect objectionable microorganisms, our investigator observed growth on this plate. This is concerning because you use **(b)(4)** water to manufacture products, such as **(b)(4)** API, that are intended for use in sterile injectable dosage forms.

We acknowledge your decision to suspend production of **(b)(4)** and **(b)(4)** API based on your risk assessment, and your commitment to a third party data integrity assessment. We also acknowledge your commitment to conduct a risk analysis and data review for distributed products, and to sanitize and validate the **(b)(4)** water system. We request that you notify FDA before resuming production of **(b)(4)** and **(b)(4)** API for U.S. supply.

In response to this letter, provide your data integrity remediation efforts as requested in the Data Integrity Remediation section of this letter below. In addition, provide the following:

- An independent assessment of your water system design, control, and maintenance;
- A comprehensive corrective action and preventive action (CAPA) plan for improving design, control, and maintenance of your water system;
- Your **(b)(4)** water system validation report;
- A summary of improvements made to your water system design, as well as to your program for ongoing control and maintenance;
- The total count and endotoxin limits that you currently use for this system.

2. Failure to properly maintain equipment and to keep complete records of major equipment maintenance.

Our investigator found damaged product-contact surfaces on your multi-product equipment. For example, the manhole gasket of **(b)(4)**111 was deteriorating and wrapped in peeling tape. A gasket on the **(b)(4)**102 was also cracked in one area and wrapped in peeling tape.

Your SOP/ENG/39-1, *Gasket Management for Equipments and Pipelines which are in Direct Contact with the Product*, section 4.18, requires you to replace gaskets in critical areas, including gaskets for **(b)(4)**111 and **(b)(4)**102, **(b)(4)**. Your firm was unable to provide gasket replacement records for this equipment during the inspection.

Furthermore, the most recent records of your firm checking the condition of the gaskets for **(b)(4)**102 were from January 2017, more than **(b)(4)** before our inspection.

This is a repeat observation from our February 2015 inspection. We also note that you have found deteriorating gaskets to be the root cause for finished API particle complaints.

Your response is inadequate. You stated that the “involved gasket was immediately substituted” but did not evaluate all other gaskets on your manufacturing equipment. You indicated that you will update your procedure to require a supervisor walk-through to assess product contact surfaces, but did not include sufficient detail (e.g., frequency of equipment inspection). You also failed to address the lack of gasket maintenance records.

In response to this letter provide a comprehensive assessment and corrective action and preventive action (CAPA) plan to address the adequacy of your maintenance program for all equipment. This systemic assessment and CAPA should also remediate your maintenance record deficiencies. In addition, provide procedures that specify the frequency of gasket assessment and your preventive maintenance replacement requirements.

3. Failure of your quality unit to ensure that quality-related complaints are investigated and resolved.

Your quality unit did not thoroughly investigate customer complaints for **(b)(4)** API. For example, you classified the December 31, 2015, CC1/P/11 complaint about black spots in finished **(b)(4)** API as “minor and unjustified” without a thorough review. You did not perform a detailed review of production records or equipment cleaning and maintenance logs, even though equipment gaskets were found to be the root cause of similar past complaints.

In addition, you classified the April 20, 2015, CC1/P/01 complaint about out-of-specification results for **(b)(4)** moisture content as “minor and unjustified” without a thorough review. While you tested the retention samples for the complaint batch and three previous batches, your investigation lacked a review of production records, such as those for the API drying process.

In your response you commit to an independent review of all investigations and to updating written procedures on deviations, complaints, and investigations. However, your response lacks sufficient detail on how your firm intends to comprehensively remediate the investigation system.

In response to this letter, provide a comprehensive independent review and remediation of your systems used to ensure thorough, timely, and effective investigations of deviations, complaints, defects, out-of-specification results, and failures.

4. Failure to properly maintain buildings and facilities used in the manufacture of intermediates and API.

The equipment washroom in your Section **(b)(4)** manufacturing block was found in a filthy condition with damaged tiles and standing water. In addition, the handwashing stations intended for the class-100,000 (ISO-8) areas in sections **(b)(4)** and **(b)(4)** of your facility were visibly dirty.

Your response commits to reconstructing these areas. However, you did not provide any detail on routine cleaning and preventative maintenance for these areas.

In response to this letter, provide a comprehensive evaluation of your facility cleaning and maintenance program. Please also provide your CAPA plan to improve routine cleaning and preventative maintenance at your facility, including but not limited to your equipment washrooms and handwashing stations.

5. Failure to provide personnel with adequate clean washing and toilet facilities.

Your handwashing stations were inconveniently located and not fully functional. For example, the handwashing stations intended for the class-100,000 areas in sections **(b)(4)** and **(b)(4)** of your facility were in the equipment washrooms, accessible only to operators who had already put on gowns and gloves. Handwashing stations did not have hot water, soap, or hand drying equipment. This is a repeat observation from our February 2015 inspection.

We acknowledge your commitment to implement temporary handwashing stations and construct permanent stations within the gowning areas of the class-100,000 cleanrooms.

In response to this letter, provide updated installation timelines and additional detail on hot water availability for these handwashing stations.

Repeat Deviations

In a previous inspection dated February 2 to 6, 2015, FDA cited similar CGMP deviations. In your responses to the 2015 and 2017 inspections, you proposed specific remediation for these deviations. However, repeated deficiencies demonstrate that your facility's oversight and control over the manufacture of drugs is inadequate.

CGMP consultant recommended

Because you failed to correct repeat deviations, we strongly recommend engaging a consultant qualified to evaluate your operations, and assist your firm in meeting CGMP requirements. The consultant should immediately and comprehensively assess your company's manufacturing operations to ensure that systems and processes, and ultimately, the products manufactured, conform to FDA requirements. In particular, this qualified third party should thoroughly assess and assist with remediation of data integrity, laboratories, investigations, the maintenance program, and quality oversight at your firm. 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 ensuring ongoing CGMP compliance.

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. In response to this letter, provide the following.
A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting, including results of the data review for products distributed to the United States.
B. 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 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.

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 your facility.

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.

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 Alchymars ICM SM Private Limited at A-14 & 20 Complex, Alathur, Tamil Nadu, 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 or mail your reply to:

Ms. Marisa Heayn
Consumer Safety 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 3005216842.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research