WARNING LETTER

Shree Jaya Laboratories PVT. LTD.

MARCS-CMS 698690 — FEBRUARY 28, 2025

Delivery Method:

VIA Electronic Mail

Reference #:

320-25-49

Product:

Drugs

Recipient:

Mr. V. Vishnu Murthy Raju

Managing Director

Shree Jaya Laboratories PVT. LTD.

Plot No. 11, Road No. 3, ALEAP Industrial Estate

Near Pragathi Nagar, Kukatpally Hyderabad

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India

Issuing Office:

Center for Drug Evaluation and Research (CDER)

United States

Warning Letter 320-25-49

February 28, 2025

Dear Mr. Raju:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Shree Jaya Laboratories PVT. LTD., FEI 3011845012, at Sy. No. 299, Malkapur Village and Post, Choutuppal Mandal, Yadadri Bhuvanagiri District, Telangana from September 4 to 12, 2024.

This warning letter summarizes significant deviations from Current Good Manufacturing Practice (CGMP) for active pharmaceutical ingredients (APIs).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your APIs 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 1, 2024 response to our Form FDA 483 in detail.

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

1. Failure to clean equipment and utensils to prevent contamination or carry-over of a material that would alter the quality of the intermediates beyond the official or other established specifications.

You failed to have adequate procedures for the cleaning and maintenance of manufacturing equipment and facilities. Our inspection found manufacturing equipment labeled as “Cleaned” and found the following deficiencies. For example:

• **(b)(4)** #B-**(b)(4)**-404 in Production Block-**(b)(4)** was documented on the equipment usage log as “Cleaned as per SOP” on September 5, 2024; however, excessive **(b)(4)** colored residues were observed inside the **(b)(4)** later this same day. This **(b)(4)** is used to manufacture **(b)(4)**.

• **(b)(4)** #BI/**(b)(4)** in Room #**(b)(4)** used to manufacture **(b)(4)** intermediate, was documented on the equipment usage log as “Cleaned as per SOP” on August 30, 2024; however, **(b)(4)** was observed on the inside and outside of the equipment’s product discharge area.

In addition, buildings used in the manufacture of key starting materials and intermediates used in the production of APIs are not maintained in a good state of repair. For example, the ceiling above **(b)(4)** located outside Production Block-**(b)(4)** was observed to be heavily stained, and with cracks and fallen plaster. These **(b)(4)** are used to manufacture **(b)(4).**

In your response, you state that the equipment used in the **(b)(4)** processing areas is dedicated and the **(b)(4)** found on the equipment surfaces corresponds to the same compound, therefore, no cross-contamination is expected. You acknowledge there was insufficient oversight in ensuring compliance with cleaning procedures and inadequate monitoring of cleaning intervals. In addition, you state that daily sanitation procedures were not adequately enforced to prevent material accumulation, but they will be reinforced. You also state that an immediate corrective action was to repair and restore the ceiling outside Production Block-**(b)(4)**.

Your response is inadequate. Although you indicate cross-contamination may not be expected, product carryover and unknown impurities may form as a result of product build up on unclean equipment. You also do not acknowledge why personnel signed off on equipment usage logs as equipment being clean when it was not clean. In addition, no evidence of the ceiling repair was provided.

- In response to this letter, provide the following:
  A comprehensive, independent retrospective assessment of your cleaning effectiveness to evaluate the scope of cross-contamination hazards. Include the identity of residues, other manufacturing equipment that may have been improperly cleaned, and an assessment whether cross-contaminated products may have been released for distribution. The assessment should identify any inadequacies of cleaning procedures and practices, and encompass each piece of manufacturing equipment used to manufacture more than one product.
- A corrective action and preventive action (CAPA) plan, based on the retrospective assessment of your cleaning program, that includes appropriate remediations to your cleaning processes and practices, and timelines for completion. Provide a detailed summary of vulnerabilities in your process for lifecycle management of equipment cleaning. Describe improvements to your cleaning program, including enhancements to cleaning effectiveness; improved ongoing verification of proper cleaning execution for all products and equipment; and all other needed remediations.

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

You failed to adequately investigate a complaint of **(b)(4)** particles in the intermediate, **(b)(4)**, Stage-**(b)(4)**, batch **(b)(4)**. The root cause was attributed to improper cleaning/usage of the **(b)(4)** bag. A CAPA to change the **(b)(4)** bag more frequently (i.e., after **(b)(4)** batches instead of **(b)(4)** batches) was proposed.

The complaint investigation was deficient because it did not extend to other batches, as required by your procedure, and it failed to identify other potential causes of the **(b)(4)** particles. Despite CAPA implementation of more frequent **(b)(4)** bag changes, the **(b)(4)** in Production Block – **(b)(4)** was observed during the inspection to be in disrepair, with the interior lining worn and corroded. The **(b)(4)** is located outdoors, exposed to the outside environment, and was also observed to contain heavy rust and a dead insect. Your management acknowledged the condition of the equipment and environmental conditions were not evaluated as potential source(s) of the contamination.

In your response, you acknowledge your procedure for handling complaint investigations, but did not account for environmental conditions, which likely contributed to the complaint. You provided an addendum investigation report extending the investigation to other batches and including environmental conditions. You also state that the **(b)(4)** equipment will be upgraded and enclosed to create a controlled environment.

Your response is inadequate. You do not commit to conduct a retrospective review of all complaints to ensure they were adequately investigated, extended to other batches, and considered environmental conditions, if necessary.

In response to this letter, provide a comprehensive assessment of your overall system for investigating deviations, discrepancies, complaints, 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 unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.

3. Failure of your quality unit to exercise its responsibility to ensure the intermediates manufactured at your facility are in compliance with CGMP.

Several original batch production records were found torn in your scrapyard. The investigator asked to review the batch records associated with the torn documents. Your management then provided a second set of these batch records in question. During the inspection, no explanation was provided regarding how there could be two sets of original batch production records or who authorized the disposition of these documents.

In addition, batch production records are not completed contemporaneously. Batch records were observed to be stored in the Quality Assurance (QA) department while manufacturing operations were ongoing. Production tasks performed by operators were recorded later by the production supervisor, who was overseeing five production rooms at the same time.

In your response, you state that some of the batch production record pages were damaged by chemical spillages and the pages were replaced by the QA department. The damaged pages were

not returned to QA and were sent to the scrapyard. You explain that your production supervisor fills out the batch production records because your operators lack proficiency in English. You also state that several production staff members were unable to attend work due to illness, which is why one production supervisor had to oversee and record operations in multiple areas.

Your response is inadequate. You failed to provide supporting evidence of any incident or deviation regarding chemical spills on CGMP documents. You also do not address your practice of tearing CGMP documents and its potential impact, including ensuring accurate results were reported when the batch production records were recreated. In addition, there is no assurance that CGMP activities are adequately performed and documented, given that the records are not in a language understood by your employees executing such activities.

Complete and accurate batch production and control records must be contemporaneously documented to ensure that manufacturing processes are consistently followed and reproducible. Additionally, incomplete manufacturing records deprive you of the ability to adequately investigate deviations.

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/media/119267/download. (https://www.fda.gov/media/119267/download.)

In response to this letter provide 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.

Additional API and Intermediate CGMP Guidance

FDA considers the expectations outlined in ICH Q7 when determining whether APIs and intermediates 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 APIs and intermediates at https://www.fda.gov/files/drugs/published/Q7-Good-Manufacturing-Practice-Guidance-for-Active-Pharmaceutical-Ingredients-Guidance-for-Industry.pdf.

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, 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 Shree Jaya Laboratories PVT. LTD., at Sy. No. 299, Malkapur Village and Post, Choutuppal Mandal, Yadadri Bhuvanagiri District, 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[1]. 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 3011845012 and ATTN: Emily Stoklosa.

Sincerely,
/S/

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

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1 Under program enhancements for the Generic Drug User Fee Amendments (GDUFA) reauthorization for fiscal years (FYs) 2023-2027, also known as the GDUFA III Commitment Letter, your facility may be eligible for a Post-Warning Letter Meeting to obtain preliminary feedback from FDA on the adequacy and completeness of your corrective action plans.

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