WARNING LETTER

Aspen Biopharma Labs Private Limited

MARCS-CMS 698665 — MARCH 05, 2025

Delivery Method:

VIA UPS

Reference #:

320-25-50

Product:

Drugs

Recipient:

Mr. K. Sateesh Reddy

CEO

Aspen Biopharma Labs Private Limited

Plot 10, Phase - II; Lalgadi Malakpet Village, Rangareddy

Hyderabad 500078 Telangana

India

Issuing Office:

Center for Drug Evaluation and Research (CDER)

United States

Warning Letter 320-25-50

March 5, 2025

Dear Mr. Reddy:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, at Aspen Biopharma Labs Private Limited, FEI 3012796281, at Plot 10, Phase – II; Lalgadi Malakpet Village, Rangareddy, Hyderabad, Telangana, 500078, India, from September 16 to September 21, 2024.

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 11, 2024, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence

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

1. Failure to design and construct buildings and facilities used in the manufacture of your API in a manner to minimize potential contamination, facilitate appropriate cleaning, maintenance, and operations.

You produce higher-risk APIs in an inadequate facility including one that lacks appropriate separation for high pharmacological activity or toxic materials including **(b)(4)** drugs. During the inspection, our investigator observed your facility was in a state of disrepair, with manufacturing areas open to the outdoor environment with inadequate protection of materials. Our investigator also observed that **(b)(4)** drugs were manufactured in a common area.

For example, your firm stated that "all the operations are conducted under one roof in **(b)(4)** Block Annex without proper segregation" and that "**(b)(4)** Block Annex manufacturing facility is in the process of demolish." Of note, FDA collected batch indicating you produced drugs during this time period.

In your response you indicate that your facility is undergoing renovations. Your response is inadequate because you did not provide sufficient details of how your facility design will prevent contamination of drug substances from the open environment, as well as cross-contamination of non-toxic drug substance from highly toxic components.

It is expected that buildings used in the manufacture of APIs are designed and constructed to minimize potential contamination.

In response to this letter provide:

- Your corrective action and preventive action (CAPA) plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of equipment/facilities performance issues, effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing management review.

2. Failure to demonstrate that your manufacturing process can reproducibly manufacture an API meeting its predetermined quality attributes and failure to adequately validate written procedures for the cleaning and maintenance of equipment.

Process Validation

You failed to appropriately validate your processes and adequately qualify the equipment used to manufacture your drugs. Specifically, you have not completed process validation for commercial size lots of your APIs. For example, you rely on studies conducted on development lot sizes for **(b)(4)** API intermediates manufactured utilizing different equipment than that used for commercial production.

In your response, you state that you compared commercial lots to the smaller development validation lots, found no significant variations, and will perform commercial size process validations. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant **(b)(4)** of a manufacturing process must be designed appropriately to assure the quality of raw material inputs, in-process materials, and finished APIs. Process qualification studies determine whether an initial state of control has been established.

Successful process performance qualification (PPQ) studies incorporating the use of appropriately qualified equipment and validated test methods are necessary prior to commercial distribution. Thereafter, ongoing vigilant oversight of process performance and drug quality is necessary to ensure you maintain a stable manufacturing operation throughout the drug lifecycle. Failure to implement adequate analytical method validation practices can result in insufficient understanding of process variables or failure to detect a drift in capability, which increases the risk of drug quality defects. See FDA's guidance document Process Validation: General Principles and Practices for general principles and approaches that FDA considers appropriate elements of process validation at https://www.fda.gov/media/71021/download.

Cleaning Validation

You lacked cleaning validation studies that demonstrate your cleaning procedures are adequate. For example, you previously identified the need to implement a cleaning validation based on your internal deviation report, yet our investigator observed that you lack cleaning validation.

In addition, our investigators observed manufacturing equipment labeled “Cleaned” that contained liquid with a **(b)(4)** floating substance or residue on product-contact surfaces.

In your response you indicate that you plan to perform cleaning validation for your drugs and perform hold time studies. Your response is inadequate because you did not provide supportive documentation or your interim plans for drug production while you complete corrective and preventive actions.

Inadequately cleaned and maintained manufacturing equipment can lead to potential cross-contamination that could compromise your API’s quality and safety. Cleaning procedures should consider solubility, cleaning difficulty, and residue limits, while reproducible and effective for the removal or obliteration of previous lot identification and protection of clean equipment from contamination prior to use. Furthermore, the use of dedicated production areas should be considered for higher-risk material of an infectious nature or high pharmacological activity or toxicity (e.g., certain steroids or **(b)(4)** agents) where cleaning and inactivation alone are not sufficient controls.

In response to this letter, provide:

- A detailed summary of your validation program for ensuring a state of control throughout the drug lifecycle, along with associated procedures. Describe your program for process performance qualification, and ongoing monitoring of both intra-lot and inter-lot variation to ensure a continuing state of control. This should include the process for selecting API lots to achieve the **(b)(4)** API blend.
- A timeline for performing appropriate PPQ for each of your marketed API. Include your process performance protocol(s), and written procedures for qualification of equipment and facilities.
- An assessment of each API process to ensure that there is a data-driven and scientifically sound program that identifies and controls all sources of variability, such that your production processes, and will consistently meet appropriate specifications and manufacturing standards. This includes, but is not limited to, evaluating suitability of equipment for its intended use, sufficiency of detectability in your monitoring and testing systems, quality of input materials, and reliability of each manufacturing process step and control.
- Appropriate improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. This should include, but not be limited to, identification and evaluation of all worst-case:
  o drugs with higher toxicities
  o drugs with higher drug potencies
  o drugs of lower solubility in their cleaning solvents
  o drugs with characteristics that make them difficult to clean
  o swabbing locations for areas that are most difficult to clean
  o maximum hold times before cleaning
  In addition, describe the steps that must be taken in your change management system before the introduction of new manufacturing equipment or a new product.
- A summary of your updated standard operating procedures that ensure an appropriate program is in place for verification and validation of cleaning procedures for products, processes, and equipment.
- 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 drugs 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 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 drugs and equipment; and all other needed remediations.

3. Failure to have originals or copies of records readily available and promptly retrievable during the retention period.

You failed to ensure adequate document control over paper and electronic records. For example, you provided a written statement on firm letterhead admitting to backdating a QC lab document and you signed a declaration confirming commercial drugs shipped to the US were not supported by appropriate original data.

In your response, you acknowledge a lack of original data and that you will improve your document management system. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

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.

We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide a management strategy for your firm that includes the details of your global CAPA 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.

4. Failure to design a documented, on-going stability testing program to monitor the stability characteristics of API and to use the results to confirm appropriate storage conditions and retest or expiry dates.

Your firm's stability program is inadequate. For example, your firm does not have adequate data to support the retest date for drugs shipped to the United States.

In your response, you acknowledge the deficiencies of your stability program and propose corrective actions including addition of stability indicating analysis. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

Without an adequate stability program, you cannot ensure that your APIs meet established specifications and all pre-determined quality criteria throughout the APIs' assigned shelf-life.

In response to this letter, provide:

- A comprehensive, independent assessment and CAPA plan to ensure the adequacy of your stability program. Your remediated program should include, but not be limited to:
  o Stability-indicating methods.
  o Stability studies for each drug in its marketed container-closure system before distribution is permitted.
  o An ongoing program in which representative lots of each drug is added each year to the program to determine if the shelf-life claim remains valid.
  o Detailed definition of the specific attributes to be tested at each station (timepoint).
- All procedures that describe these and other elements of your remediated stability program.

Drug Recall

On January 14, 2025, FDA held a teleconference with you recommending you consider removing any lots of drugs currently in distribution from the U.S. market. On January 16, 2025, you agreed to voluntary recall of all drugs in current distribution in United States.

We acknowledge that you initiated a voluntary nationwide recall on February 7, 2025, of all products distributed in the United States.

Drug Production Status

We acknowledge that you deregistered your facility on January 6, 2025, however, it is unclear whether you intend to cease production of drugs for the U.S. market. In response to this letter, clarify whether you intend to cease manufacturing drugs for the U.S. market at this facility in the future.

If you plan to resume any manufacturing operations regulated under the FD&C Act, notify this office before resuming your drug manufacturing operations. You are responsible for resolving all deficiencies and systemic flaws to ensure your firm is capable of ongoing CGMP compliance. In your notification to the Agency, provide a summary of your remediations to demonstrate that you have appropriately completed all corrective action and preventive action (CAPA).

Additional API CGMP Guidance

FDA considers the expectations outlined in ICH Q7 when determining whether APIs 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.

CGMP Consultant Recommended

Based upon the nature of the deviations we identified, you should engage a consultant qualified to evaluate your operations and to assist your firm in meeting CGMP requirements. The qualified consultant should also perform a comprehensive audit of your entire operation for CGMP compliance and evaluate the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

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.

FDA placed drugs offered for import into the U.S. from your firm on Import Alert 66-40 on January 15, 2025.

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 3012796281 and ATTN: Reba Gates.

Sincerely,
/S/

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

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