WARNING LETTER

# Centaur Pharmaceuticals Private Ltd.

MARCS-CMS 651080 — JUNE 05, 2023

**Delivery Method:**

VIA UPS

**Product:**

Drugs

**Recipient:**

Mr. Shreekant Dattatraya Sawant

Joint Managing Director

Centaur Pharmaceuticals Private Ltd.

Centaur House
Shantinagar, Vakola, Santacruz-East
Mumbai 400055
India

**Issuing Office:**

Center for Drug Evaluation and Research | CDER

United States

## Warning Letter 320-23-15

June 5, 2023

Dear Mr. Sawant:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Centaur Pharmaceuticals Private Ltd., FEI 3003973520, at Plot No. 75, 76 & 76/1, Chikhloli MIDC, Ambernath-West, Thane – 421501, Maharashtra, from November 14 to November 21, 2022.

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 December 7, 2022 response to our Form FDA 483 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 of your quality unit to exercise its responsibility to ensure the API manufactured at your facility are in compliance with CGMP.**

A. Your Quality Unit (QU) failed to ensure adequate document control over paper and electronic records.

For example,

- Analytical worksheets, incident report forms, non-conformance reports, batch release copies, and pre-printed blank forms were stored in laboratory drawers and cabinets with unrestricted access and inadequate controls.
- The CGMP document "Blank Analytical Worksheet" recording a high performance liquid chromatography (HPLC) test result for **(b)(4)** stability at the 48-month timepoint (25°C/60%RH) was issued under control form number 2261. A second CGMP Document "Blank Analytical Worksheet" was issued with the same control number, 2261.
- Original CGMP documents were discarded and shredded without a review and a meaningful description in the logbook. For example, the document titled "Logbook of Shredding Machine" described a document being shredded as "discard waste papers." The discarded records, however, included analytical worksheets, laboratory incident forms, and training records.

In your response, you state that document control SOPs are consolidated, and document issuance and destruction is under the control of your Quality Assurance (QA) Unit. In addition, an analytical QA team has been implemented to review all Quality Control (QC) records. Employees who have been involved in data integrity concern were either reassigned or removed from their duties. Your response acknowledges that you have created "uncontrolled documents" and destroyed CGMP documents without adequate controls and accountability.

Your response is inadequate. You have not identified and addressed the scope and extent of your practice of discarding and shredding critical CGMP documents (e.g., raw data and analytical worksheets with weights and calculations). In addition, your response does not address the deficiency of assigning multiple CGMP documents with the same control number.

B. Your Quality Unit failed to ensure that materials are appropriately tested, and the results are reported.

For example, an HPLC system processed unlabeled vials of solution. You could not provide evidence that these unlabeled vials contained the solution described in the HPLC system sequences.

Reliability of data is compromised when there is a failure to maintain complete records of the conditions and data associated with all tests. Furthermore, the lack of complete data compromises the QU's ability to exercise its function of ensuring compliance to applicable standards.

Your response acknowledges that the first analyst did not label the HPLC vials and a second analyst did not conduct a verification of the labeling. You state that your SOP titled "Good Chromatography and Analytical Techniques" will be revised to incorporate the vial verification checklist for use by QC supervisors. Furthermore, you planned on providing trainings for vial labelling.

Your response is inadequate. You did not determine the scope of this deficiency. In addition, you did not provide the root cause analysis. Finally, the effectiveness of your firm's CGMP training program appears to be inadequate.

Adequate QU oversight of all manufacturing operations is necessary to consistently ensure drug product quality.

In response to this letter, provide:

- A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should also include, but not be limited to:

o A determination of whether procedures used by your firm are robust and appropriate
o Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices
o A complete and final review of each batch and its related information before the QU disposition decision
o Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products

- A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed corrective action and preventive action (CAPA) plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.
- A comprehensive review of your material system to determine whether all suppliers of components, containers, and closures, are each qualified and the materials are received, tested, and reported in accordance with an approved specification aligned with the suppliers. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.
- A comprehensive assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
- Assessment of your firm's CGMP training program effectiveness involving QC laboratory operations.

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

You failed to have adequate procedures for cleaning and maintenance of manufacturing equipment. Our investigators observed manufacturing equipment labeled "Cleaned" and found the following deficiencies. For example:

- **(b)(4)** material was peeling off from the inner side of a **(b)(4)** discharge **(b)(4)** of **(b)(4)**-303 and **(b)(4)** material was encrusted on the **(b)(4)**.
- **(b)(4)** residues were present on the inner surface areas of your **(b)(4)** RV-403.

In your response, you explain that the **(b)(4)** material, observed in the **(b)(4)**-303, is insignificant and non-reactive. You commit to implementing preventive measures, which include updating the SOP for the **(b)(4)** to manage the peeling **(b)(4)** material and adding a check point for verification.

Your response is inadequate. You did not evaluate the potential risk of the peeling **(b)(4)** on all the APIs that you manufacture. You did not provide evidence that this **(b)(4)** material does not react with APIs, other than **(b)(4)**. You also failed to include a gap assessment of the root cause of this cleaning deficiency.

Inadequately cleaned and maintained manufacturing equipment can lead to potential cross-contamination that could compromise your API's quality and safety.

In response to this letter, provide:

- 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 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.
- 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 introduction of new manufacturing equipment or a new product.

- A summary of updated SOPs that ensure an appropriate program is in place for verification and validation of cleaning procedures for products, processes, and equipment.
- Provide a holistic review of cleaning procedures and the associated cleaning validation strategy for all manufacturing equipment to determine whether similar deficiencies exist.

**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 Centaur Pharmaceuticals Private Ltd., FEI 3003973520, at Plot No. 75, 76 & 76/1, Chikhloli MIDC, Ambernath-West, Thane – 421501, Maharashtra, India 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 3003973520 and ATTN: Liming Zhang.

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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