WARNING LETTER

Centrient Pharmaceuticals India Private Limited

MARCS-CMS 640196 — DECEMBER 07, 2022

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Manoj Sharma

Country President & Director of Operations

Centrient Pharmaceuticals India Private Limited

Bhai Mohan Singh Nagar, Toansa Dist. SBS Nagar
Nawanshahr 144533 Punjab
India

Issuing Office:

Center for Drug Evaluation and Research | CDER

United States

Warning Letter 320-23-06

December 7, 2022

Dear Mr. Sharma:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Centrient Pharmaceuticals India Private Limited, FEI 3004497364, at Bhai Mohan Singh Nagar, Toansa, Dist. SBS Nagar (Nawanshahr), Punjab from June 23 to July 1, 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 July 22, 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.

Your quality unit (QU) failed to ensure adequate document control over paper and electronic records. For example, our investigators observed numerous logbooks, forms, and partially completed "Sample Request For Analysis (Other Than SAP)" in an uncontrolled temporary storage room near your microbiology laboratory. Our investigators also observed in your document center, a document shredder labeled for "emergency use" containing shredded documents. Your document control personnel were unable to identify the documents in the shredder that were observed to contain information for relative humidity, temperature, and data recorded in writing.

You also failed to have adequate controls for your computerized systems. For example, multiple usernames and passwords for software login of several users' information were handwritten in an uncontrolled notebook of your senior executive microbiologist. The login information was for software used to control laboratory equipment, such as incubators for the storage of product and **(b)(4)** water samples. To ensure data integrity, actions performed need to be attributable to a specific individual.

Your response indicates you plan to revise multiple standard operating procedures and intend to centralize document control by forming a new document control center and document control team. Your response also indicates your senior executive microbiologist had an administrator role in the "ICDAS" software and they were subsequently reassigned to an operator role. However, your response does not provide a detailed plan to ensure your future paper and electronic record and documentation practices comply with CGMP. Your response is also inadequate because it does not include a comprehensive retrospective risk assessment of the impact and scope for the inadequate document control at your facility, and it does not fully address tiered user access and controls to ensure access is appropriate to each users' role and administrative roles are adequately controlled.

Your documentation practices are not indicative of a facility that is in compliance with CGMP. Document control is essential to maintaining an adequate quality system.

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 assessment and CAPA plan for computer system security and integrity. Include a report that identifies vulnerabilities in design and controls, and appropriate remediations for each of your laboratory computer systems.

2. Failure to ensure that all test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and purity.

You failed to ensure that your test procedures were appropriately validated and established procedures were

followed. For example, your recovery studies were not adequate to demonstrate that the method for beta-lactam environmental monitoring can recover beta-lactam residue by swab sampling. Additionally, your established procedure for swab collection was not followed. Scientifically sound test procedures are a necessary part of an effective beta-lactam containment program to prevent cross-contamination, including ensuring that API contaminated with beta-lactams can be adequately detected.

Contamination of non-beta-lactam drugs with beta-lactam drugs presents great risk to patient safety, including potential anaphylaxis and death. No safe level of penicillin contamination has been determined to be a tolerable risk. Severe allergenic responses can occur in susceptible patients exposed to extremely low levels of penicillin and other beta-lactams.

Your response indicates there is no impact to product quality. However, your response is inadequate because your justification is based on testing performed by a method used to detect beta-lactams in the buildings where non-beta-lactam drugs are manufactured that was not appropriately validated and was not followed. Additionally, your method for detecting penicillin in environmental monitoring of beta-lactams in the non-beta-lactam buildings at your facility is not sufficiently sensitive to detect very low levels of contamination. For additional information, see FDA's published analytical method that has a limit of detection (LOD) of 0.2 ppb at https://pubmed.ncbi.nlm.nih.gov/29766324/.

Because of the extremely low threshold dose at which an allergic response could occur, beta-lactam facilities need to be complete and comprehensively separated from non-beta-lactam facilities. For additional information, see FDA's guidance document *Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination* at https://www.fda.gov/media/79971/download (https://www.fda.gov/media/79971/download).

In response to this letter, provide:

• A comprehensive assessment of your laboratory practices, procedures, methods, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.

• A comprehensive assessment of your containment controls to prevent beta-lactam cross-contamination including, but not limited to, whether you perform any sampling and testing of the air exhaust of the beta-lactam manufacturing buildings and common areas (e.g., cafeteria) and associated test results for the last 2 years.

• A commitment to either validate and implement FDA's analytical method for the analysis of beta-lactam contamination in your environment and in non-beta-lactam drug products to achieve an LOD of 0.2 ppb or validate and implement an analytical method with an LOD that is equivalent or better than 0.2 ppb.

3. Failure to establish and follow written procedures for investigating critical deviations or the failure of API batches to meet specifications.

You failed to adequately investigate and determine the root cause of black particles in two batches of **(b)(4)** API. For example, your investigation report for **(b)(4)** batch **(b)(4)** stated the black particles were non-metallic charred product residue. Your report further indicated that the sample was observed by analysis to "dissolve in solution." However, during the inspection, you were unable to provide our investigator the data to support the conclusion. Well documented, thorough, scientifically sound investigations are necessary to identify the root cause in order to implement appropriate CAPAs.

Your response indicates you installed **(b)(4)** to limit the presence of metal particles in the API. However, your investigation remains inadequate because you did not provide the data to support your proposed root cause or identify an adequate CAPA. For example, your CAPA does not address non-metallic sources of contamination,

such as charred product residue or inadequate cleaning or fully address metallic sources of contamination, such as reactive, additive, or absorptive product contact surfaces.

In response to this letter, provide:

A comprehensive 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, CAPA effectiveness, quality unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.

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. 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). We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. In response to this letter, provide:

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.

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 analyses of the risks posed by ongoing operations.

C. 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.

CGMP Consultant Recommended

Based upon the nature of the deviations we identified at your firm, you should engage a consultant qualified to evaluate your operations and to assist your firm in meeting CGMP requirements if your firm intends to resume manufacturing drugs for the U.S. market. 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.

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.

FDA placed your firm on Import Alert 66-40 on November 21, 2022.

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 continuing to refuse admission of articles manufactured at Centrient Pharmaceuticals India Private Limited, at Bhai Mohan Singh Nagar, Toansa, Dist. SBS Nagar (Nawanshahr), Punjab 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 3004497364 and ATTN: Lynnsey Renn.

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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