**WARNING LETTER**

# Centurion Laboratories Private Limited

**MARCS-CMS 571255 — 04/05/2019**

**Delivery Method:** VIA UPS
**Reference #:** 320-19-21
**Product:** Drugs

**Recipient:**

Hemin Patel

Director

Centurion Laboratories Private Limited

Plot P-2, Bio-Tech Park at Manjusar
Tal - Savli, GIDC
Manjusar 391775 Gujarat
India

**Issuing Office:**

Center for Drug Evaluation and Research

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Dear Mr. Patel:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Centurion Laboratories Private Limited, FEI 3008342939, located at Plot P-2, Bio-Tech Park at Manjusar, Tal-Savli, GIDC, Manjusar, Gujarat, from October 22 to 26, 2018.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products 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 November 15, 2018, response in detail.

During our inspection, our investigator observed specific violations including, but not limited to, the following.

**1. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to ensure compliance with established specifications and standards (21 CFR 211.194 (a)).**

On October 24, 2018, our investigator observed torn documents of stability study data, analytical testing sheets, analysis calculations, and release forms that were placed into clear trash bags. Stability study documents for three batches of **(b)(4)** mg tablets were salvaged from the trash and compared to the official and approved records. Out-of-specification (OOS) results were among the data found, however the official results were recorded as within specification. Additionally, it was observed that blank stability study forms were prepared, pre-signed, and approved by the quality unit before recording the test data.

In your response, you acknowledged the multiple trash bags containing torn quality control documents and the practice of signing documents before recording the data. You stated the torn documents were from scale-up batches in which you tore the documents so as "not to create confusion in the mind of the investigator." Your response was inadequate because you did not explain the discrepancies between the torn documents with OOS values and the documents retained by the quality control laboratory that included passing values. Additionally, you did not complete a retrospective evaluation of all potentially affected quality-related records to determine the scope of data integrity practices, including, but not limited to, the signing of blank documents before performing laboratory tests.

In response to this letter, provide your corrective action and preventative action (CAPA) plan as requested in the Data Integrity Remediation section of this letter below.

**2. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).**

Your firm's laboratory equipment used for batch release and stability testing purposes did not have appropriate controls and procedures to ensure changes were only made by authorized personnel. For example, quality control analysts, a company executive, and your software service provider all shared a username and password for your high-performance chromatography systems. In addition, analysts were authorized full system administrator privileges. These privileges allowed modification and deletion of data files and folders. Furthermore, you lacked a procedure for controlling staff use and privileges of your computer systems.

In your response, you acknowledged the lack of appropriate controls over computer systems and provided your CAPA. Your response was inadequate because you did not determine if the integrity of your data was compromised. In response to this letter, provide an assessment of all computer systems used for CGMP activities at your facility. Also explain how you will ensure that audit trails are continually enabled.

**3. Your firm failed to follow written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).**

During the inspection, our investigator observed that equipment used to manufacture more than one product was inadequately maintained and cleaned.

For example, our investigator observed in the **(b)(4)** room a **(b)(4)** identified as "cleaned." However, this **(b)(4)** was found to have visible product build-up inside the **(b)(4)** and **(b)(4)** of the **(b)(4)**. Furthermore, the air filter of the equipment was damaged with multiple holes. This equipment was used to manufacture finished drug products shipped to the United States such as **(b)(4)** tablets, **(b)(4)** tablets, **(b)(4)** tablets, and **(b)(4)** tablets. Additionally, a memo provided during the inspection stated these cleaning and equipment maintenance deficiencies were because of a shortage in manpower related to a nine-day dancing festival and government holiday. Inadequately cleaned and maintained equipment can lead to cross-contamination and variability of drug products.

In your response, you acknowledged the observation and stated you have implemented procedures to adequately clean and maintain equipment. Your response was inadequate because you did not include a review of the condition of all your manufacturing equipment. Additionally, you did not perform a risk assessment of drug products distributed to the U.S. market that were manufactured on multi-use equipment which lacked adequate cleaning and maintenance.

In response to this letter, provide:

• A comprehensive plan to evaluate the adequacy of cleaning procedures, practices, and validation studies for each piece of manufacturing equipment used to manufacture more than one product.

• Scientific rationale for your cleaning validation strategy to ensure the efficacy of your cleaning procedures is adequately assessed.

• A summary of updates to your cleaning validation protocol to better incorporate conditions identified as worst case. This should include, but not be limited to, evaluating drugs that are of highest toxicity, drugs that are lowest solubility in their cleaning solvents, drugs that have characteristics that make them difficult to clean, and swabbing of various equipment locations that are most difficult to clean.

• A summary of standard operating procedures that have been updated to ensure an appropriate program for verification and validation of cleaning procedures for new products, processes, and equipment.

• A detailed retrospective risk assessment addressing the potential effects of the inadequate cleaning and maintenance activities on the quality of all drug product batches in U. S. distribution within expiry. Provide any CAPA plan(s) related to your assessment.

• A comprehensive, independent assessment of your cleaning and maintenance programs, practices, and procedures.

**Data Integrity Remediation**

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, efficacy, 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/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf).

We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following:

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

• A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.

• Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.

• An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.

• A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all 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 corrective action and preventive action plan. Your strategy should include:

• A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate including analytical data, manufacturing records, and all data submitted to FDA.

• A comprehensive description of the root causes of your data integrity lapses including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.

• Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.

• Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.

• A status report for any of the above activities already underway or completed.

**CGMP Consultant Recommended**

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements if your firm intends to resume manufacturing drugs for the U.S. market. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and effectiveness 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**

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations.

FDA placed your firm on Import Alert 66-40 on March 11, 2019.

Until you correct all violations 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 violations may also result in FDA continuing to refuse admission of articles manufactured at Centurion Laboratories Private Limited, FEI 3008342939, located at Plot P-2, Bio-Tech Park at Manjusar, Tal-Savli, GIDC, Manjusar, Gujarat, 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 violations 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 (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov) or mail your reply to:

Joseph Lambert, Pharm.D.
Compliance 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 3008342939.

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

CC:
Mr. Ambalal Patel
Managing Director
Centurion Laboratories Private Limited
Plot P-2, Bio-Tech Park at Manjusar
Tal - Savli, GIDC
Manjusar, Gujarat, 391775
India

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