U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Via email
Return Receipt Requested

September 18, 2023

Mr. Amit Chadah
Chief Executive Officer
Nectar Lifesciences Ltd.
SCO 38-39, Sector 9-D
Chandigarh-160 009
India

Dear Mr. Chadah:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Nectar Lifesciences Ltd., FEI 3008932049, at Unit VI, Village Bhatolikalan, adjoining Jharmajri, E.P.I.P. Post Office Barotiwala, Tehsil Baddi, District Solan, 174103 (Himachal Pradesh), from March 2 to March 10, 2023.

This untitled letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (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 April 14, 2023, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific CGMP violations including, but not limited to, the following:

1. **Your firm failed to establish appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).**

Media Fills

Your process simulation studies (media fills) failed to accurately simulate your aseptic manufacturing operations. Our inspection found numerous critical interventions performed that were not represented in your media fills conducted in August 2022, summarized in report No. RPT/PVL/MFS/01/22, dated August 21, 2022. For example, (b) (4) operators were observed performing multiple simultaneous (b) (4) interventions during aseptic filling. Your

firm confirmed during the inspection that these activities were not represented in any media fill studies.

In addition, your media fill batch size represents a small portion of your actual production batch size. Your media fill studies should closely simulate aseptic manufacturing operations and incorporate appropriate worst-case activities and conditions. A larger media fill batch size close or equal to the full production size should be used for your simulations, based on the process design and contamination risks associated with your manually intensive filling line.

In your response, you commit to implement some procedural and design modifications to improve your aseptic operations. We acknowledge your commitment to implement a (b) (4) (b) (4) system to ensure that not more than (b) (4) can be opened at any given point in time.

Your response is inadequate because it does not indicate whether you have conducted investigations and reviewed available information (e.g., aseptic processing videos, past deviations) to fully identify where your aseptic processing operation requires improvements. Additionally, you do not explain how your media fill studies will more appropriately mimic production conditions and evaluate contamination risks of your aseptic process.

Smoke Studies

You lacked smoke studies that determine dynamic conditions of the aseptic line. For example, our review of your smoke study videos found:

- Inadequate unidirectional airflow during movement of open vials towards the (b) (4) (b) (4) station.

- Inadequate visualization of airflow during non-routine intervention to remove open vials under the (b) (4)

Without adequate smoke studies, you cannot substantively assess whether unidirectional ISO 5 airflow is protecting your drug product from contamination.

In your response, you commit to revising the airflow visualization study protocol by incorporating all conditions identified to have possible adverse impact to the airflow pattern in the aseptic processing area.

Your response lacks a commitment to perform an investigation and assess impact on products manufactured on an aseptic processing line without adequate smoke studies.

Aseptic Behaviors

Your aseptic filling production videos indicated numerous instances of poor aseptic technique by your operators while performing manual interventions. For example:

- Operators left an aseptic processing line (b) (4) open for an extended period.

- Operators used the same forceps for multiple interventions. The forceps were stored below the filling line station in a manner which increases the potential for their contamination.

- An operator reached over open vials during a routine intervention to remove empty or fallen sterile vials.

To safeguard sterility of the drug product in aseptic processing operations, you must establish robust operational design and procedures, and personnel must employ strict discipline. Poor aseptic techniques can directly lead to non-sterility.

In response to this letter, provide the following:

- A comprehensive, independent risk assessment of all contamination hazards with respect to your aseptic processes, equipment, and facilities, that includes but is not limited to:
  - All human interactions within the ISO 5 area
  - Equipment placement and ergonomics
  - Air quality in the ISO 5 area and surrounding room
  - Facility layout
  - Personnel flows and material flows (throughout all rooms used to conduct and support sterile operations)

- A detailed remediation plan with timelines to address the findings of the independent contamination hazards risk assessment. Describe specific tangible improvements to be made to aseptic processing operation design and control.

- A thorough retrospective review and risk assessment that evaluates how inadequately designed media fill studies have impacted your assessment of the contamination risks to your aseptic process.

- A five-year history of all sterility positives, regardless of whether the test result was later invalidated by your firm. Include data regarding where any related batches of product were shipped.

- Independent assessment of all smoke studies, to ensure they are conducted under static and dynamic conditions and fully evaluate aseptic processing line airflow patterns.

2. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

Your aseptic processing areas are deficient regarding the system for monitoring environmental conditions. Your firm lacked adequate building management systems (BMS) to monitor and record differential pressure in your aseptic processing areas. Our investigators observed that your firm manually monitored your cleanrooms for pressure differential, temperature, and humidity on an infrequent basis (e.g., (b) (4) This frequency is not adequate to detect significant pressure deviations that could ultimately impact aseptic conditions on the filling line.

In addition, during inspection, your firm stated that the BMS system was not validated, but it was still in operation. Numerous critical alarms recorded in the BMS between January 2021 and March 2023 for Air-Handling Unit (AHU) No. ERAHF-009, dedicated to the ISO 5 and ISO 7 filling areas, were not investigated to determine product impact.

A suitable facility monitoring system is critical to maintain appropriate environmental conditions throughout all of your cleanrooms. It is important for rooms of higher air cleanliness to have a substantial positive pressure differential relative to adjacent rooms of lower air cleanliness. All deviations from established limits should be appropriately investigated to rapidly detect and address atypical changes that can compromise the facility's environment. Prompt detection of an emerging problem is essential to preventing contamination in your aseptic production operation.

In your response, you state that you have revised your procedures to require monitoring and recording of temperature, relative humidity and pressure differential be performed (b) (4) (b) (4) You also commit to designing and commissioning a custom BMS to be completed by December 2023.

Your response is inadequate. Monitoring and recording of pressure differential (b) (4) is not acceptable. In addition, your response does not address how you will ensure any differential pressure deviations will be documented and investigated.

In response to this letter, provide the following:

- A thorough, independent assessment, and corrective action and preventive action (CAPA) for your program for monitoring pressure differential, as well as temperature and humidity. Include a comprehensive evaluation of monitoring, recording, alarm documentation, deviation investigation, data retention and overall system control in your assessment. Provide a CAPA that includes but is not limited to:
  - The state of control of air balance between clean areas and adequacy of integration of each of the HVAC systems
  - Documentation for all alarms, irrespective of the length or location of the event, and retention of this data
  - Remediated procedures for investigating deviations from established limits, and specific provisions for handling deviations (e.g., atypically low pressure; pressure reversal).
  - Remediated building management system. Ensure that the system will continuously monitors and rapidly detects atypical changes of pressure, and temperature and humidity, in one or more cleanrooms simultaneously.

Repeat Violations at Facility

Similar deviations were cited in a previous inspection, conducted from January 14-17, 2014, and discussed during the regulatory meeting held on March 18, 2016. You responded by proposing specific remediations to address these observations. Repeated failures demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

CGMP Consultant

If your firm intends to manufacture drugs for the U.S. market, you should engage a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. The qualified consultant should perform a comprehensive audit of your entire operation for CGMP compliance and evaluate the completion and efficacy of your CAPA before you pursue resolution of your firm's compliance status with FDA.

Additional Guidance on Aseptic Processing

See FDA's guidance document *Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice* to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing at:
https://www.fda.gov/downloads/Drugs/Guidances/ucm070342.pdf

Conclusion

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of any violations and for preventing their recurrence or the occurrence of other violations.

Correct any violations promptly. FDA may withhold approval of new applications or supplements listing your firm as a drug manufacturer until any violations are completely addressed and we confirm your compliance with CGMP. We may re-inspect to verify that you have completed corrective actions to any violations.

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 30 working days. Specify what you have done to address any violations 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 30 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 3008932049.

Sincerely,

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