DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	6/9/2025-6/19/2025* FEI NUMBER 3004540906

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Dr. Donthineni Linga Rao, President Technical Affairs

FIRM NAME	STREET ADDRESS
NATCO Pharma Limited	Pharma Division, Kothur Village
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Rangareddy, Telangana, 509228 India	Sterile and Non-Sterile Drug Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Your firm operates (b) (4) non-viable particle monitoring equipment (b) (4) (b) (4) used to perform and generate test data for non-viable (NVP) count used in environmental monitoring and cleanroom qualification activities in Grade A, Grade B, Grade C, and Grade D areas in support of aseptic manufacturing operations in your Unit (b) (4) Aseptic processing area, used for manufacturing of (b) (4) mg (b) (4) ml and (b) (4) mg (b) (4) ml for the US Market. During our review, we observed that your quality unit does not review the electronic data generated, stored and archived, only using printout as primary data. During our review of the electronic data, environmental monitoring for non-viable particles (NVP) during aseptic operations was found to be inadequate. For Example,

A. For eleven (11) final sample report results for (b) (4) µm and (b) (4) µm particles retrieved from the software (electronic data) for (b) (4) discrepancies were observed between the electronic data and the official reported hardcopy final results attached to production batch records. This issue affected (b) (4) batches from 11/02/2023 to 04/16/2024: (b) (4) Injection (b) (4) mg/vial, non-US commercial batch). Upon comparison of the electronic data reports (soft copy) to the printed data reports in the batch records (hard copy), it was observed that results had been altered from over the action limit (non-conforming) to below the action limit. The firm's management acknowledged that prior to July 2024, operators saved data on

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Arsen Karapetyan, Investigator - Dedicated Drug Cadre Wayne D Mcgrath, Investigator	X Arsen Karapetyan Investigator - Dedicated Drug Cadre Signed By: Arsen Karapetyan -S Date Signed: 06-19-2025 02:14:53	6/19/2025

USB drives and supervisors printed test reports on their assigned desktops, a practice since discontinued. This workflow appears to have allowed for potential manipulation of data between the point of generation and official reporting, representing a significant gap in your firm's data integrity program.

B. For (b) (4) batches (b) (4) (b) (4) Injection from 04/16/2024 to 06/06/2025, your firm failed to follow your own standard operating procedure (SOP No. VPD/137-12, "Procedure for Operation and Monitoring of Non-Viable Particle Count by (b) (4) " effective 02/17/2025) for handling out-of-limit NVP results. The SOP stipulates that if a sampling location fails to be within the limit (b) (4) an incident should be initiated to perform an investigation. However, for all (b) (4) batches, the same locations were sampled multiple times (b) (4) with failing results until a passing result was eventually obtained, without initiating the required incident reports or investigations. Furthermore, operators printed all data reports, including those with failing results, and attached them to the batch records. Despite Quality Assurance review of these hardcopy printouts, this deviation from the SOP was not identified or addressed. This practice demonstrates a lack of adherence to established procedures and inadequate quality oversight.

C. Additionally, across (b) (4) NVP equipment unit (b) (4) at least 57 different instances were identified where the first sample failed, and the sample was subsequently retested and passed. While this aligns with your SOP's allowance for retesting, the procedure specifically states, 'if a sampling location fails to be within the limit, and the high counts are due to personnel movement, repeat the sampling at the same location.' However, there was no documentation by operators to indicate whether the failures were indeed due to personnel movement, making it impossible to verify if the retesting was justified according to the procedure.

D. Finally, your operators failed to print and attach to batch records environmental monitoring data during aseptic operations that appeared to be within specification, resulting in the omission of

relevant data from batch documentation and preventing proper review by the Quality Unit. Additionally, your firm failed to properly document and review environmental monitoring activities in the change room. Despite a procedure requiring monitoring (b) (4) more than 300 data reports were not printed out, documented, or reviewed by your production or quality units.

OBSERVATION 2

Equipment and utensils are not maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

On 10 June 2025, we observed the following discrepancies in your Unit (b) (4) aseptic processing area, which includes a Grade B supporting room and a Grade A (b) (4) restricted access barrier system (b) (4) RABS):

-Damage on the wall above and below the clean room phone panel in the Grade A extended laminar airflow (LAF) area at the start of the (b) (4) RABS, creating rough surfaces.

-Exposed bolt threads in the Grade A (b) (4) LAF (referred to as a (b) (4) used to (b) (4) (b) (4) vials from the filling (b) (4) RABS to the (b) (4) RABS.

-Gaps and rough edges on both corners of the extended LAF frame by the sealing machine, which was in both Grade A space and Grade B space.

-Torn bottom of the (b) (4) used to extend the (b) (4) entry frame in Grade A (b) (4) RABS number (b) (4)

-Gap between the (b) (4) and the (b) (4) RABS frame in the Grade A (b) (4) RABS number (b) (4) which is located in front of a (b) (4)

-Broken (b) (4) plate on the (b) (4) dock on (b) (4) RABS (b) (4) in the Grade B space, which created a gap and a rough surface.

-Gap and rough sealant surface on the (b) (4) to the non-viable particle counter enclosure in (b) (4) RABS number (b) (4) The (b) (4) was in Grade B space.

This aseptic processing area is the only aseptic filling line at your firm and it is used to manufacture (b) (4) injection.

OBSERVATION 3

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include adequate validation of the aseptic process.

A. We observed the following discrepancies while reviewing the videos of the dynamic condition smoke study (airflow visualization) performed in your Unit (b) (4) aseptic processing area in December 2024:

-Only limited portions of the (b) (4) RABS were visible at a time due to the zoomed in camera angle, which prevented adequate assessment of the wholistic airflow patterns in the Grade A (b) (4) RABS.

-The smoke generation device was not visible in the majority of the videos, which prevented determination of which way the smoke was being blown by the generation device.

-The video of the (b) (4) LAF (b) (4) used to (b) (4) vials from the filling (b) (4) RABS to the (b) (4) (b) (4) RABS did not include adequate smoke to determine the airflow patterns.

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-Your report (number MSR/21/229-01) for this smoke study included multiple comments in Attachment-I about needing to reshoot certain videos due to narrow camera view or lack of smoke, but each video was signed off by QA, IPQA, Microbiology, Production, and Engineering as meeting acceptance criteria. This is in contradiction to your acceptance criteria of "The smoke should be clearly visible in the video" and "The airflow pattern shall show the logical airflow directions i.e. from the supply grill to the working level and suction from the return grill."

-Your report identified turbulent air during the intervention of (b) (4) the (b) (4) RABS (b) (4) slowly and then sanitizing the hands with (b) (4) (video 8.1). Your employees from QA, IPQA, Microbiology, Production, and Engineering all identified the turbulent air, but still signed off on this video as meeting your acceptance criteria. This is in contradiction to your acceptance criteria of "Air should be flowing smoothly in one direction with no turbulence for unidirectional air flow units."

B. Your firm does not incubate all integral vials during media fills (aseptic process simulation). During the last (b) (4) media fills (batch numbers (b) (4) and (b) (4) your firm used a (b) (4) method for conducting seal integrity checks, which resulted in the (b) (4) of (b) (4) to (b) (4) integral vials per media fill. In addition, your firm fills at the (b) (4) speed during each media fill instead of performing (b) (4) media fill at (b) (4) speed.

OBSERVATION 4

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

A. Your firm did not perform a disinfectant efficacy study when a new microorganism was identified during an OOS investigation for environmental monitoring. (b) (4) air sampling performed on 21 March 2024 in the Unit (b) (4) (Grade D) near the change room door resulted in (b) (4) CFU/cubic

meter fungi and (b) (4) CFU/cubic meter total aerobic microbial count (TAMC), which was out of the specifications of (b) (4) CFU/cubic meter TAMC and fungi should be absent. This event was investigated under out of limit investigation report number XII/EMOOL/24/011. During the investigation, two new microorganisms were identified and the report states "For the newly identified organisms Micrococcus lylae and Alternaria alstroemeriae disinfectant efficacy test shall be performed." Your firm performed a disinfectant efficacy study on Alternaria alstroemeriae in February 2025, but you never performed the study on Micrococcus lylae.

B. During review of Non-Viable Particle Count environmental data generated during aseptic operations for (b) (4) batches, the same locations were sampled multiple times (b) (4) with failing results until a passing result was eventually obtained, without initiating the required incident reports or investigations per your firm's SOP No. VPD/137-12, "Procedure for Operation and Monitoring of Non-Viable Particle Count by (b) (4)" effective 02/17/2025.

C. During the inspection, we observed at least 36 sample set projects in Empower 3 where interruptions occurred in the form of project integrity failures. We noted multiple instances where injections were interrupted, followed by the firm restarting (re-analyzing) the sample set sequence without proper documentation or investigation. Although your firm appears to have initiated investigations for these interrupted sequences at the time of occurrence, not all potential data was evaluated. Specifically, in instances where sample solutions were injected with principal peak elution, results were not evaluated to determine compliance with test specifications.

OBSERVATION 5

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written and followed.

As of 13 June 2025, your firm does not have any employees fully qualified to perform 100% visual

inspection activities on sterile drug products, including, but not limited to, [redacted] injection. In December 2024, your firm developed a new procedure for qualification of visual inspectors, with the current version of the SOP, number GQA/108, being made effective on 10 January 2025. The previous protocol-based procedure (number OIVP/2021/001-00) was made obsolete in December 2024, even though the employees performing visual inspection on sterile drug products were only qualified according to the previous procedure. Your firm currently has approximately [redacted] employees performing visual inspection activities on sterile drugs.

OBSERVATION 6

Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable construction to facilitate cleaning, maintenance, and proper operations.

Your Unit [redacted] aseptic processing area is not adequately visible from the [redacted] viewing windows. During aseptic filling operations, your employees work in a Grade B supporting room containing Grade A [redacted] RABS and Grade A extended LAFs. We attempted to observe the filling operations from the [redacted] technical area viewing window and the packaging room viewing window, but we were unable to observe the filling, stoppering, and sealing equipment, including all interventions related to these critical areas. We were unable to enter the Grade B supporting room during filling operations due to gowning qualification requirements and media fill validation data for maximum number of people in the room during filling.

This aseptic processing area is the only aseptic filling line at your firm, and it is used to manufacture [redacted] injection.

OBSERVATION 7

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The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

A. Your firm's Quality Unit has not demonstrated a clear understanding of various communication errors and circumstances that can lead to aborted, interrupted, or incomplete sequences during High-Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC) testing using Empower 3 software. During the inspection, we observed at least 36 sample set projects in Empower 3 where interruptions occurred in the form of project integrity failures. These failures were not adequately reviewed and evaluated by your Quality Unit, and no assessment was initiated until the current inspection. Our review found that your firm has not performed the necessary investigations and risk assessments to determine and understand the root cause for these interrupted sequences.

B. In response to the previous inspection deficiencies, your firm performed a retrospective review of US commercial batches for cGMP compliance sufficiency from January 2021 to December 2023, during which extraneous peaks were observed. As a result, your firm established SOP No. GQC/197-00, titled "Handling of Extraneous Peaks in Chromatographic Analysis" in August 2024. Additionally, you initiated a new protocol for retrospective review of chromatographic analysis from January 2023 to August 2024 for all remaining US commercial batches around March 2025. According to your firm, the review of all batches and analytical data has been completed. However, as of the current inspection, your firm has not assessed the results of this review.

C. Your firm's quality system does not adequately ensure that all investigations are properly documented and retained. We reviewed your firm's paper waste shred logbook, which listed draft investigations that had been discarded through shredding. The contents of these draft investigations were not available for our review due to their destruction. Furthermore, we found that your firm failed to document these draft investigations with official reported investigation reports within the Quality System.

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D. Your firm's Quality unit has failed to properly document and review environmental monitoring activities conducted during aseptic manufacturing operations, which are utilized for batch release determinations.

***DATES OF INSPECTION**

6/09/2025(Mon), 6/10/2025(Tue), 6/11/2025(Wed), 6/12/2025(Thu), 6/13/2025(Fri), 6/16/2025(Mon), 6/17/2025(Tue), 6/18/2025(Wed), 6/19/2025(Thu)

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EMPLOYEE(S) SIGNATURE

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