

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER

Email Responses to: CDER-OC-OMQ-
International483Response@fda.hhs.gov

DATE(S) OF INSPECTION

11/07/2024-11/13/2024

FEI NUMBER

3002806691

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Mr. Vijayasarithi R, Global Chief Quality Officer

FIRM NAME

CIPLA Limited

STREET ADDRESS

Old Madras Road

CITY, STATE, ZIP CODE, COUNTRY

Bengaluru, Karnataka, 560049, India

TYPE ESTABLISHMENT INSPECTED

API 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.

The observations noted in this Form FDA-483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the quality system requirements.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

Facilities and Equipment Systems

Observation 1

Repeat Observation

Equipment used to control and monitor critical process parameters identified in the manufacture of APIs and API intermediates is not adequately, designed, installed, or qualified.

Specifically,

Failure to maintain adequate controls for maintenance, cleaning, and transport of equipment used in non-dedicated manufacturing areas.

Specifically,

A. During the inspectional walkthrough on 7 Nov 2024, visible (b) (4) stains were observed throughout (b) (4) 19, Capacity: (b) (4) used to perform (b) (4) steps for (b) (4) API. This included visible stains observed throughout the top and bottom of the (b) (4) body, (b) (4) 19 was lasted used on 16 Oct 2024 for

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Guerlain Ulysse, Drug Specialist

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processing (b)(4) API, batch # (b)(4) Type B equipment cleaning was documented on the Equipment Cleaning Record (ECR) as being fully completed between 18 Oct 2024 – 3 Nov 2024. This included complete dismantling of the equipment and it being cleaned with (b)(4) water and (b)(4) solvent as per SOP GC 57 Cleaning Procedure for (b)(4) Effective Date: 27 Sept 2023. Approximately (b)(4) Quality Control (QC) swabs were also taken on 3 Nov 2024 of various parts of (b)(4) 19, with all test results: Not Detected for Content of (b)(4) However, the following test results were reported after swab sampling performed as per the current inspection request for the same equipment on November 8th, 2024:

- Location: (b)(4) (swab (b)(4) Content Result: (b)(4) ppm, Limit: Not more than (NMT) (b)(4) ppm.
- Location: (b)(4) (swab (b)(4) Content Result: (b)(4) ppm, Limit: Not more than (NMT) (b)(4) ppm.
- Location: (b)(4) Body (swab (b)(4) Content Result: (b)(4) ppm, Limit: Not more than (NMT) (b)(4) ppm.
- Location: (b)(4) (swab (b)(4) Content Result: (b)(4) ppm, Limit: Not more than (NMT) (b)(4) ppm.

In addition, (b)(4) degradation peaks were reported and identified on each of the sampling swabs. According to the Head of Quality Operations - API, the black and brown matter also recovered on the swab samples were likely due to oil leak due to mechanical failure of (b)(4) 19. An investigation was opened during the current inspection, to determine the root cause of the OOS (b)(4) content results and (b)(4) liquid stains observed within the (b)(4) during the current inspection. This is despite Type B equipment cleaning being documented as completed and Not Detected results being reported for (b)(4) 19 QC sample swabs.

B. During a walkthrough of the facility on 07 Nov 2024, we observed the (b)(4) 74) in suite (b)(4) to have visible (b)(4) residues, despite documented cleaning.

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Swabbing of the (b) (4) product-contact surfaces revealed residues identified as (b) (4) compound (intermediate for (b) (4)), a product previously manufactured in Room (b) (4) despite this equipment not being part of the manufacturing equipment train for (b) (4) compound. The residue levels detected on the (b) (4) chute, such as (b) (4) ppm, significantly exceeded the acceptable limit of NMT (b) (4) ppm. Additionally, swab samples tested by HPLC revealed unknown peaks exceeding the limit of quantitation (LOQ), further indicating insufficient cleaning.

Additionally, there is no established procedure for documenting transport of mobile equipment, and the (b) (4) had been moved without prior approval or record, contributing to contamination risk. Throughout the (b) (4) manufacturing blocks for US products, there are (b) (4) critical process equipment that are transported for use without documentation.

Furthermore, your firm failed to verify and control cleaning effectiveness over extended periods. Despite multiple cleanings since the last use of the (b) (4) in a manufacturing process, residues persisted. The (b) (4) underwent four product changeover cleanings (Type B) and one general cleaning (Type G) since its last use on 15 August 2023, yet was still visibly unclean on 07 November 2024 (15 months later), indicating a lack of effective cleaning and monitoring over an extended period. Your established dirty hold time for equipment is (b) (4).

C. The cleaning validation program does not include evaluation of all equipment configurations and parts to appropriately determine representative swab locations and the most difficult to clean areas. For example:

The same swabbing locations are predetermined for all (b) (4) including (b) (4) (b) (4) used for different steps in the (b) (4) process of U.S marketed APIs as per Annexure 1035-A-0043/A1, SOP Surface Area Calculations and Swab/Rinse Sampling of Equipment and Accessories, Version 6, Effective Date: April 16, 2024.

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In addition, a generic equipment engineering drawing containing a (b) (4) shaft was referenced in the equipment cleaning validation protocols for (b) (4). However, the harder to clean equipment configurations were not assessed as part of the cleaning validation program. This includes (b) (4) 19 equipment containing additional (b) (4) (b) (4) than the diagram referenced for swab sampling locations.

D. (b) (4) preventive maintenance (PM) activities for (b) (4) 19, Capacity: (b) (4) has not been performed since May 2024. As per the “ (b) (4) Preventive Maintenance Planner” for API (b) (4) block, PM was not performed by the scheduled due date of August 2024 since the equipment was undergoing a campaign cleaning study, start date: June 2024. However, multiple batches of (b) (4) API have been manufactured using (b) (4) 19 with an overdue PM. In addition, visible (b) (4) stains were observed throughout (b) (4) 19, Capacity: (b) (4) used to perform (b) (4) steps for (b) (4) API during the inspectional walkthrough on 7 Nov 2024. According to the Site Head, the stains were likely leakage from a mechanical failure in the same (b) (4) (b) (4) 19 with a PM overdue since August 2024 and which has been continually used to manufacture commercial batches.

E. During the inspection walkthrough of 7 Nov 2024, (b) (4) bags stored within the equipment storage area of API Block (b) (4) with torn (b) (4) coverings, torn and/or absent item code labels, and torn /or absent quality approval labels. This included torn primary (b) (4) coverings that exposed the (b) (4) bag primary surface to the surrounding drawer environment.

Production System

Observation 2

Clear instructions and controls are not established and implemented to ensure that critical process parameters (CPPs) are consistently monitored and documented to ensure process consistency and reduce variability in the quality of drug substances.

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Specifically, your firm failed to identify and include all critical process parameters in the master batch record.

For example.

A. Section (b)(4) of the batch record for (b)(4) permits the use of either the (b)(4) or the (b)(4) for the (b)(4) step.

However:

- o If the (b)(4) is used, Section (b)(4) must be documented as a CPP.
- o If the (b)(4) is used instead of the (b)(4) Section (b)(4) must be documented as a CPP.

Your Senior Manager, Production reported Section (b)(4) to be a critical process parameter if the (b)(4) is used; however, Section (b)(4) is not included in the master batch record as a critical process parameter (CPP).

Additionally, there are no instructions in the batch record guiding operators on when to complete Section (b)(4) or Section (b)(4) based on the equipment selected.

B. Acceptance criteria for certain critical process parameters are not clearly defined in process validation. For example,

- For Step No. (b)(4) the parameter "(b)(4)" lacks a specific (b)(4) in the acceptance criteria, listing only "(b)(4)" as the limit for the (b)(4).
- Validation batch document the following (b)(4) for this parameter:
 - o Batch # (b)(4)
 - o Batch # (b)(4)
 - o Batch # (b)(4)

These (b)(4) exc (b)(4) cepted (b)(4) of (b)(4) as defined in (b)(4) with limited excursions permitted between (b)(4) for short periods. The absence

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of defined (b) (4) limits for this CPP could result in uncontrolled process variability impacting product quality and consistency.

Observation 3

Current manufacturing practices do not ensure that operators are present and actively monitoring critical process parameters and environmental controls during each step of production when equipment is automated.

Specifically, your firm has not established and implemented procedures which require operators to be physically present during critical manufacturing steps.

For example, during the walkthrough of your facility on 7 Nov 2024, we observed production computer tablets left unattended while manufacturing operations were ongoing. Your Site Head reported that these Tablets are used to monitor the manufacturing process. This practice undermines your firms' ability to ensure continuous oversight and intervention, as operators are not physically present to observe or address critical conditions in real-time.

Additionally, your firms environmental monitoring is deficient. For example, during the walkthrough of your facility on 7 Nov 2024, for the (b) (4) step, we observed the magnehelic gauge to be non-operational, used to control and monitoring environmental conditions. No operators were present to identify, address, and report this issue in a timely manner. This lapse demonstrates a lack of adequate monitoring for parameters that can contribute to quality deficiencies.

Observation 4

Appropriate line clearance checks are not conducted to ensure that materials are removed, and equipment is fit for us before the start of new production to prevent cross-contamination.

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TYPE ESTABLISHMENT INSPECTED

API Manufacturer

Your firm failed to document line clearance activities in batch records to ensure all traces of raw materials and previous batch materials are removed from the area and equipment is fit for use prior to the start of a new batch.

Quality System

Observation 5

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

Specifically, your Quality Unit failed to adequately exercise its authority and responsibilities, including but not limited to, implementing effective procedures, and conducting adequate oversight to support the safety, effectiveness, and quality of the active pharmaceutical ingredient (API) you manufacture. For example, but not limited to:

A. Your Quality Unit failed to establish and implement site specific procedures.

1. Your firm lacks a site-specific Validation Master Plan (VMP), including site-specific qualification schedules and validation plans for facilities, systems, equipment, and utilities. This omission persists despite the methodology outlined in Change Control #1024-F-22-00006 (Initiation Date: 08 Mar 2022), which mandates that the VMP be updated to reflect any area and equipment changes.
2. Your firm failed to integrate ICH Q7 into the cGMP training program. Your firm's current cGMP training materials do not include specific requirements from ICH Q7, which provides critical guidance on Good Manufacturing Practices for Active Pharmaceutical Ingredients (APIs). This omission limits personnel understanding of essential quality standards specifically relevant to API production.

B. (b) (4) 23 has been used to manufacture multiple batches of (b) (4) (b) (4) API since March 2022. However, Change Control #1024-F-22-00006, Initiation

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Date: 08 Mar 2022, for (b)(4) area (b)(4) facility changes for relocation of (b)(4) 33 and installation of (b)(4) 23 and (b)(4) in API Block (b)(4) remains open as of the current inspection. In addition, the following deficiencies were noted with the change control:

- (b)(4) area (b)(4) room was modified and reconstructed to remove (b)(4) 04) and (b)(4) (b)(4) 07) was then added and fitted to another (b)(4) previously (b)(4) within the same room. However, maintenance, engineering, and quality controls for installation of (b)(4) 07 into a new (b)(4) within the (b)(4) area (b)(4) room, also containing (b)(4) (b)(4) 33 and (b)(4) 23, was not documented.
- The change request Impact Assessment and Action Plan has not been completed as per SOP 1035-G-0249 Handling of Change Request through TrackWise, Effective Date: 18 Jul 2024 requirement.
- The quality unit did not sign off on final review of training records imparted since March 2022.

C. Transportation shipment studies have not been performed to ensure that (b)(4) (b)(4) API batches distributed to the U.S market were shipped under the required environmental and temperature packing conditions at 2-8 degrees Celsius. According to the Site Quality Head, (b)(4) (API) is temperature-sensitive and requires specific handling conditions during storage and shipment to maintain its stability and potency. In addition, Forced Degradation Study, Protocol No. S/SN/1802015 has concluded that (b)(4) (b)(4) API is sensitive to (b)(4) and (b)(4) condition which can increase organic impurities.

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Observation 6

Failure to conduct comprehensive failure investigations, implement effective corrective actions, and ensure adequate controls.

Specifically,

Your firm failed to conduct adequate investigations and prevent or minimize the likelihood of reoccurrence into three complaints received for failure of the primary packaging material, PRID 271554 dated 12 May 202, PRID 272935 dated 20 May 2022, PRID 296334 dated 20 Sept 2022. For example, but not limited to the following:

- Inadequate investigation and lack of root cause identification.
- Failure to extend the investigation to other batches.
- Failure to include the Supplier in the investigation.
- Deficient corrective and preventive actions (CAPA) and lack of change control
- Failure to assess stability impact with the new packaging configuration.

Packaging and Labeling System

Observation 7

Failure to establish adequate acceptance criteria to ensure consistent quality of packing materials and their fitness for use in the manufacturing process.

Specifically, your firm failed to ensure adequate and current acceptance criteria for primary packaging materials, specifically for (b) (4) bags, after a configuration change. For example,

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A. Your firm failed to update acceptance criteria for (b)(4) bags upon receipt and for use in packaging operations.

Following a change to the configuration of the (b)(4) bags, the acceptance criteria were not updated to include an appropriate description and specifications for the new bag configuration, as seen in Complaint PRID 27115. Additionally, the adequacy and presence of the new (b)(4) seal is not evaluated when accepting the material or before its use in the process.

Your Quality Unit failed to establish and implement a sampling plan/size for (b)(4) bags and document the number of bags inspected for defects prior to use. Procedure, "1035-A-003, Repacking and Relabeling of Active Pharmaceutical Ingredients and Intermediates, Version Number, 8.0, Effective Date: 13 Jan 2022" establishes in section (b)(4) that all (b)(4) bags to be used for packing are to be inspected for cleanliness pinholes, and improper sealing. Your firm's management reported, 100% of bags are inspected, but is not documented.

B. Your firm's certificate of analysis (COA) for packaging material is inadequate. The COA establishes acceptance criteria for the (b)(4) bags as "a (b)(4) bag manufactured from (b)(4)" without verification testing to confirm:

- The bag's material composition is "(b)(4)".
- The presence, adequacy, and integrity of the (b)(4) seal upon receipt.

Your firm's management confirmed the COA was not updated following the change in the bag's configuration.

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Laboratory Control System
Observation 8

Laboratory control mechanisms are not established.

During the inspection walkthrough on 8 Nov 2024, late samples were listed and observed within the firm's Laboratory Management System (LIMS). This included the following:

- A. The preventive maintenance (PM) for HPLC I-283 was overdue since 8 Oct 2024, and has not been performed as of the current inspection. However, HPLC I-283 was continually used to perform HPLC testing for API batches intended for the U.S market including: (b) (4) USP, batch # (b) (4) USP batch # (b) (4) and (b) (4) USP, (b) (4) PM for instruments is essential for ensuring regular inspection of the equipment, component tests, adjustments, and parts replacement.
- B. A 3-month stability batch for a non-U.S. marketed API was pulled on 11 Jul 2024. However, the analysis was completed on November 10, 2024, which was during the current inspection. There is no document quality assessment for the stability batch tested past the (b) (4) testing period required as per SOP 1035-L-0100, Stability Studies Version 13, Effective Date: 23 May 2024.

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