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 CDER-OC-OMQ-International483Response@fda.hhs.gov	03/10/2025-03/14/2025
	FEI NUMBER 3005466325

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Mr. Panem Yoganjaneya Reddy, Vice-President & Site Head

FIRM NAME	STREET ADDRESS
Apotex Pharmachem India Pvt Ltd.	Plot 1a Bommasandra Industrial Area 4th Phase, Jigani Link Road Bommasandra Ind. Estate,
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Bangalore Karnataka 560099 IN, India	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:

QUALITY SYSTEM
OBSERVATION 1

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch whether or not the batch has been already distributed in the US market. Specifically,

A. PR #146169 (Stability, Invalidated): An OOS result of (b) (4)% against the specification limit of NLT (b) (4)% and NMT(b) (4)% (b) (4) for Assay by potentiometry was obtained on 05/17/2024 for (b) (4) stability Batch #(b) (4) during 18M long-term stability timepoint. No assignable root cause was identified during Phase I & II. You attributed the root cause under the hypothesis-1 testing where the analyst sonicated the sample during preparation for(b) (4) to dissolve the sample in diluent and there is no instruction to sonicate the sample to dissolve in diluent in STP #FPM 179/04 (b) (4). Per LIMS # (b) (4) 1 record, the analyst prepared the sample per STP #FPM 179/04.

Your QA Deputy Manager stated they inquired about the issue online and they will be "Air Bubble Entrapment" through the connected tube on the equipment which will lead to inaccurate titrimetric value which will lead to abnormal results. You performed an hypothesis with air bubble which yielded a failure results. You then retested the sample using the same STP, obtained a passing result, and invalidated the initial results. (b) (4) has a storage condition of 2-5^0 C. However, you failed to include in the investigation report when the sample was pulled from the chamber #QC/CC/203 and

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actually tested. In addition, your STP #FPM 179/04 method does not state how much time is allowed to analyze the sample when pulled from the 2-8C chamber.

B. PR # 149624 (Stability, Invalidated), An OOS for assay results of (b) (4) % (Limit: NLT (b) (4) % and NMT (b) (4) % (b) (4) was obtained on 08/30/2024 for (b) (4) stability batch (b) (4) for 12M_LT stability (US marketed product). You attributed the root cause for obtaining lower (b) (4) result is due to keeping the (b) (4) bottle with sample in open condition inside (b) (4) containing compromised (b) (4) However, you have tested (b) (4) batches of (b) (4) (b) (4) API using the same STP FPM 046/19) and GTP 006/03 (b) (4) 08/03/2020 effective date) and the instructions and pictorial listed in GTP 006/03 have not changed since testing the finished API. You then retested the stability sample by closing the sample with (b) (4) which yielded a passing retest result, and invalidated the initial results without scientific rationale.

C. From August 2021 to October 2021, approximately 8 OOS deviations for (b) (4) (b) (4) have been obtained for (b) (4) at step no (b) (4) Yet, implemented CAPA are ineffective to prevent recurrence. You implemented several CAPAs including **PR #98687 on 12/14/2021 and CAPA PR** #98688 on 11/23/2021. Yet, you encountered a recurrence under PR #103412, 128792, and 137037. You attributed the root cause during these events as Facility/Manufacturing Equipment or System and Process. These batches were released to US markets including (b) (4) Batch # (b) (4)

Batch Number	Manufacture Date	Shelf-Life	Shipped to US Market
(b) (4)			

OBSERVATION 2

The responsibilities and procedures applicable to the quality control unit are not in writing or fully followed by your personnel. Specifically,

A. You established a maximum of (b) (4) batches for product campaign cleaning. However, you have not performed any documented cleaning validation studies to support the (b) (4) batches. In addition, you established (b) (4) batches as the maximum for changing the (b) (4) bags, but you have not performed any cleaning studies to support that number per your Production GM.

B. You have not performed a product changeover cleaning validation for (b) (4) Intermediates) and (b) (4) (finished API), US marketed APIs.

C. You manufactured and shipped (b) (4) (2-8^0 C Storage Condition) to US market. Protocol #B-QA-GEN-P-0042 Rev-0 (*Protocol for Transportation Study*, 01/12/2024 effective date) requires a minimum of (b) (4) shipments for all zones to be completed. You performed the (b) (4) However, you have not completed the shipping study for (b) (4) (US marketed API) although you have shipped approximately (b) (4) batches to US market since the last study. Per your Sr. Manager, QA, they missed to complete it for the subsequent shipments sent to US.

In addition, Protocol #B-QA-GEN-P-0042 Rev-0 (*Protocol for Transportation Study*, 01/12/2024 effective date) is deficient and does not justify the selection of the products and the seasons (i.e. hottest and coldest) to be covered.

D. SOP-QA-C-025 Rev. 3.0 (*Document Control,* 10/16/2024 effective date) is deficient. Personnel training records are only kept for (b) (4) after departure date. However, some of your finished APIs (i.e. (b) (4) has a (b) (4) shelf-life.

E. You have not audited the supplier of key starting materials (KSM) for (b) (4) (b) (4) US marketed API.

F. Empower3.8.1 (data acquisition software for HPLC and GC) does not capture in the project audit trail the users for aborted samples in the software if the cable is unplugged. Several aborted samples were observed in your Empower3.8.1 data acquisition software during my walkthrough on 03/11/2025. However, you do not perform a review of the "Message Center" during the audit trail review by QC/QA as performed during the software validation to identify the users who aborted samples.

PRODUCTION SYSTEM
OBSERVATION 3
The master production and control records for Intermediates and finished API manufacturing are deficient in that they do not include complete manufacturing, control, instructions, and sampling. Specifically,

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A. Batch Production and Control Record #MBPCR(b) (4) Material Code #(b) (4) (b) (4) US Marketed API) shows you recorded a value of "(b) (4)" in Step (b) (4) on 03/10/2025 for Batch (b) (4) as a critical control point or Step for the process. However, you have not demonstrated how you obtained that value using a "(b) (4)" which measures in (b) (4) According to your Volume Calibration Chart (Form #F/QA/258 for Equipment Code #PR(b) (4) 107), there is no a calculated value for (b) (4) using the (b) (4)

In addition, Step (b) (4) of the above batch production record states to collect in-process QC sample for (b) (4) for (b) (4) However, it does not state how to collect the sample including required sample container.

B. General Cleaning Records (product changeover) for the following equipment utilized for manufacturing US marketed API do not show how these values listed below under "Material List" were obtained. According to your Sr. Manager QA (b) (6), these equipment are considered critical.

- GCR1082724 for equipment (b) (4) ID #PR/(b) (4) 112 and Product (b) (4) (b) (4) finished API, Batch #(b) (4) show you recorded the following under material list listed below. However, you have not demonstrated how these values were obtained (not all-inclusive). According to Sr. Manager QA (b) (6), this (b) (4) is a critical instrument for the process.

(b) (4)

- General Cleaning Records for GCR1083124 for equipment PR(b) (4) /105 and Product (b) (4) (b) (4) finished API, Batch #(b) (4) show you recorded the following under material list listed below. However, you have not demonstrated how these values were obtained (not all-inclusive).

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(b) (4)

FACILIITES AND EQUIPMENT SYSTEM
OBSERVATION 4

Equipment was not maintained to prevent malfunctions during QC sampling of the finished APIs. Specifically, QC Balances (ID #QC/WB/104 and QC/WB/207) utilized to collect QC samples were observed unplugged and movable. However, you do not perform a recalibration of the QC balances in Production if moved during cleaning operations. There are no provisions in SOP #QC024 (*Operation, Verification, and Calibration of Balances*) for performing a recalibration of the QC balances in Production if moved, unplugged, and when re-plugged.

LABORATORY CONTROL SYSTEM
OBSERVATION 5

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that raw materials, in-process, intermediates, and finished APIs conform to appropriate standards of identity, strength, quality and purity. Specifically,

A. A review of retain sample for (b) (4) finished API) Batch #(b) (4) on 03/11/2025, revealed the API was manufactured on (b) (4) and the release testing has not yet performed. According to SOP #QC014 Rev. 18 (*Sampling, Testing, Release and Reject of Finished Product*, 09/12/2023 effective date), you have ≤ (b) (4) to analyze the finished API sample from sampling date. However, SOP #QC033 Rev. 30 (*Guidelines to Stability Studies*, 08/10/2024 effective date) states the stability study should be initiated within (b) (4) from the batch release date and the released testing COA results must be considered as the initial result. For example, you released

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(b) (4) finished API Batch #(b) (4) (Annual Stability Batch) under protocol #SP-(b) (4) on (b) (4), but you did not perform initial time point testing until (b) (4)

B. Finished API samples (2-8^0 C) collected by QC personnel from Production for (b) (4) (b) (4) are being stored in Cold Chamber ID #QC/CC/203. However, you do not maintain a logbook for the cold chamber that documents when these samples are placed and removed for QC analyses. In addition, there is no traceability when these samples are issued to analysts for QC analyses.

C. According to Sample Drawing Instructions form, you are to collect (b) (4) (as planned sample Qty) for (b) (4) but actually collected (b) (4) (as planned sample Qty) of (b) (4) but actually collected (b) (4) However, there are no justifications why you have not collected the requested amount.

***DATES OF INSPECTION**
03/10/2025 (Mon), 03/11/2025 (Tue), 03/12/2025 (Wed), 03/13/2025 (Thu), 03/14/2025 (Fri).

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."