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 ORAPHARMInternational483responses@fda.hhs.gov	04/18/2023-04/26/2023
	FEI NUMBER 3005977675

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Mr. Sujit Kumar Rath, General Manager Operation and Site Head

FIRM NAME	STREET ADDRESS
Ipca Laboratories Ltd.	Plot 65,99, and 126 Danudyog Industrial Estate
CITY, STATE, ZIP CODE, COUNTRY Piparia, Silvassa, Union Territory of Dadra & Nagar Haveli, India 39630	TYPE ESTABLISHMENT INSPECTED Drug product 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

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.

Specifically,

OOS

A. Your firm failed to follow validated analytical test method Ref. Protocol No. SIL (b)(4) AMV/SIM/07/00 (Effective date 6 Jul 2007) for (b)(4) Assay by HPLC and failed to conduct a complete investigation as established by OOS procedure, CSOP/2017/115 (b)(4) Out of Specification Result Management (Effective date 14 May 2022).

For example, on 29 Nov 2022, your firm reported an OOS No. SIL/OOS/2022/013 for (b)(4) assay test by HPLC for (b)(4) (b)(4) mg tablets Batch No. (b)(4) (non-US market). This OOS result was reported for the low assay value of (b)(4) % (Specification (b)(4) % - (b)(4) %). The Phase I investigation did not reveal any assignable root cause. Your firm proceeded to Phase IIB without conducting the Phase IIA-Manufacturing Investigation. Based on the higher assay results obtained from the (b)(4) samples (non-validated method) compared to (b)(4) samples (validated

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method), your firm determined the root cause as "probably [redacted] occurring at the time of [redacted] which lead to lower result." The assay results for the two batches that were analyzed in the same sequence under hypothesis testing are as follows: Batch No. [redacted] %, [redacted] %), and Batch No. [redacted] ([redacted] % and [redacted] %). Y to establish a scientifically sound justification for the root cause before concluding that the [redacted] due to [redacted] will only cause a lower value of assay for Batch No. [redacted] (batch with OOS result) and not the passing batch, Batch No. [redacted] Your firm used this probable root cause to retest the [redacted] sample for passing assay value and invalidated the initial OOS result. Your Senior Manager QC (PP) stated that a [redacted] s used to [redacted] in the validated test method. Yet, your firm used an [redacted] sample to retest the batch to invalidate the initial OOS result.

B. Your firm invalidated an OOS result without a scientifically justified root cause. For example, on 29 Jan 2020, your firm reported an OOS No. SIL/OOS/2020/004 for assay test by HPLC method for [redacted] mg [redacted] tablets [redacted] Batch No. [redacted] (non-US Market). The OOS for low assay value of [redacted] % (Specification [redacted]). The Phase I investigation did not reveal an assignable root cause and no deficiency was noted with sample preparation. According to the Record of Analysis A.R. No. [redacted] dated 12 Oct 2019, your analyst [redacted] yet your firm suspected that the tablets did not [redacted] To prove this probable root cause for low assay, your firm designed a hypothesis test and prepared the test sample without [redacted] to compare with a [redacted] which resulted in two (2) completely different [redacted]. Your firm used this probable root cause to retest the new sample for passing assay value and invalidated the initial OOS result. Your firm has not derived data to confirm that [redacted] will not [redacted] Analytical method validation report AMV-R/US [redacted] AS/039/14/R01 (Effective date 12 May 2016) confirmed that test sample is prepared by [redacted]

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OOT

C. Your firm failed to follow validated analytical test method Ref. Protocol No. SIL (b) (4) AMV/SIM/07/00 (Effective date 6 Jul 2007) for (b) (4) Assay by HPLC and failed to cond omplete investigation as established by OOT procedure, CSOP/2018/155/R09 Out of Trend (OOT) Identification and Investigation (Effective date 18 Jan 2023).

On 24 Nov 2022, your firm reported an OOT No. OOT/QC/SIL/015/22 for (b) (4) Assay by HPLC for (b) (4) mg tablets Batch No (b) (4) (non-US Market). The OOT result was reported for lower (b) (4) assay value (b) (4) % (OOT Limit (b) (4) % - (b) (4) %). Phase I investigation did not reveal any assignable root cause. Your firm proceeded to Phase IIB without conducting the Phase IIA-Manufacturing Investigation. Based on the higher assay results obtained from the (b) (4) (non-validated method) compared to (b) (4) (validated method), your firm determined the root cause as "probably (b) (4) occurring at the time of (b) (4) which lead to lower result". or the batches analyzed re Batch No's. (b) (4) (b) (4) The batches (b) (4) initially recorded OOT and OOS results whereas (b) (4) as a passing batch. Your firm failed to establish a scientifically sound justification for the root cause before concluding that the (b) (4) (b) (4) due to (b) (4) causes a lower assay value for the initially recorded OOT and OOS results (b) (4) and not to the passing batch, Batch No. (b) (4) Yet, your firm used an (b) (4) to retest the batch to invalidate the initial OOT result.

Your firm failed to follow established OOT procedure CSOP/2018/155/R09 Out of Trend (OOT) Identification and Investigation (Effective date 18 Jan 2023) such that you did not conduct Phase IIA Manufacturing Investigation as per Section 5.4.5. In addition, analytical test method validation report Ref. Protocol No. SIL (b) (4) AMV/SIM/07/00 (Effective date 6 June 2007) confirmed that powder was used. Although, the specific procedure to obtain (b) (4) is not mentioned in the procedure, your Senior Manager QC (PP) s (b) (4) is used to

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(b) (4) Yet, you used an (b) (4) to retest the batch to invalidate the initial OOT result.

D. On 24 Nov 2022, your firm documented market complaint MKT/004/2020 for a (b) (4) spot on the (b) (4) tablets Batch No. (b) (4) (non-US Mar r (b) (4) (non-US Market) Mfg. Date Aug 2018, Exp date July 2021. Your investigation stated that the (b) (4) spot was due to reaction of (b) (4) However, (b) (4) in the manufacturing of API. The process flow diagram of the API consists of at least (b) (4) operations with (b) (4) Your firm failed to establish the connection between the (b) (4) API manufacturing, and the presence of (b) (4) n the finished drug product to support your root cause. Your investigation stated that (b) (4) arried out in Grade D (ISO 8) manufacturing areas under (b) (4) conditions; ho r firm monitors particle counts (b) (4) during HVAC qualification. Your firm failed to document in the investigation how your firm ensures adequate exhaust systems to control the contaminants in areas where contamination can occur during production. Additionally, your firm failed to rule out possible contamination from the HVAC system, as your firm did not evaluate data to verify the room classification for Grade D (ISO 8) for the other (b) (4)

OBSERVATION 2

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

A. Your firm failed to ensure deviation investigations and associated corrective and preventive actions (CAPAs) are timely, accurate, and documented contemporaneously. For example, investigations and the associated CAPAs including but not limited to:

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a. PR #206678 dated 20 Jul 2021-where the tablet inspection system was not working and steps in the investigation were not documented and was not closed for a total of 10 months without justification.

b. PR#185131 dated 12 Dec 2020 and associated CAPA No. 194953 dated 17 Mar 2021 -where during the analysis of (b)(4) test (b)(4) pre-documentation done by analyst.

c. PR#142411 dated 03 Sept 2019 and associated CAPA 210533 dated 28 Aug 2021-where during the Dissolution Test by UV for (b)(4) Capsules, sample absorbance was (b)(4) in the (b)(4) (Reviewed by 3rd party consultant)

d. PR #152326 dated 17 Dec 2019 and associated CAPA 207112 dated 27 Jul 2021-where the wrong manufacturer name was added to the (b)(4) (Reviewed by 3rd party consultant) were re-opened; however, the date that the remediation activities began is not captured, so it cannot be determined how long the deviation investigations were open, and if appropriate time frames were met. Furthermore, your QA Manager reported that your firm did not want it to appear as though the investigations were open long due to not being control of the investigations because the 3rd Party Consultant was involved.

- For example, CAPA No. 194953 associated with Deviation PR#18513 for an adjustment to a standard operating procedure, was not implemented and closed for (7) months.

- In another example, Deviation investigation PR#185131 dated 12 Dec 2020 was entered into Trackwise. However, once documentation began in Trackwise (2 weeks later) 24 Dec 2020, a new (later) due date was documented without justification. Your QA Manager reported that Trackwise automatically calculated this due date. However, the due date was not until (b)(4) later, which is the time frame established by your firm for completion before a justification is required.

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B. On 29 Jan 2020 your firm recorded an OOS No. SIL/OOS/2020/005 for dissolution test for (b) (4) (b) (4) mg Tablet Batch No. (b) (4) (non-US Market) (Stability Study, 1 Month, 40 ± 2 °C/75 ± 5%RH). Your firm identified human error as the root cause such that the analyst did not ensure the tablet was placed in the respective vessel of the dissolution tester. Your firm implemented CAPA 159233 and updated procedures with instructions as follows, "Analyst shall ensure that the tablets are dropped in respective bowl prior to start dissolution program". In addition, the CAPA states "Training to be imparted to concerned persons to ensure that each tablet is present in particular vessel". The procedures that were updated; SOP/QCD/201/05 Operation and Cleaning Procedures for Dissolution Test Apparatus (Effective date 9 Feb 2022), SOP/QCD/243/02 Operation and Cleaning Procedures for Dissolution Test Apparatus (Effective date 2 Apr 2022), and SOP/QCD/123/05 Procedure for Performing Dissolution Profile Study (Effective date 6 Apr 2022). On 15 Jun 2021 your firm recorded an OOS No. SIL/OOS/2021/004 for dissolution test for (b) (4) (b) (4) (b) (4) mg Tablet Batch No. (b) (4) ((Stability Study, 24 Month, 25 ± 2 °C/60 ± 5%RH). Your firm again identified human error as the root cause, as the analyst did not ensure the tablet was placed in respective vessels 10 and 11. This is the same root cause that was identified earlier and CAPA was implemented, and procedures were updated. According to the investigation, the analyst was trained on the revised procedure. This confirmed that the CAPA and /or training is not effective.

OBSERVTAION 3

Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products.

Specifically, your quality unit (QU), to include Quality Assurance (QA) and Quality Control (QC), lacked adequate responsibilities and authorities to assure reliable operations. The quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drug you manufacture.

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For example, including, but not limited to the following:

Your firm failed to initiate or close corrective and preventive actions to the data integrity issues observed during the inspection and assess the risk to patients and potential effects of the observed data integrity failures on the quality drug products affected by the lapse of data integrity and analyses of the risks posed by ongoing operations, including, but not limited to the following examples:

a. The HMI for the (b)(4) system does not have an audit trail and quality related data is lost and not retrievable. Your firm-initiated change control PR ID 258680 dated 05 Dec 2022, is still open. Your firm documented this change control as "Risk identified is low". The lapse in data integrity has not been addressed in this investigation.

b. During a walkthrough of the Microbiology Laboratory, we observed Balance #SMI062 used for media preparation and the Logbook for Daily Calibration Verification Record to have consistent non-readable printouts which were signed by the Microbiologist, Microbiology Supervisor, and the Quality Unit. For example, 16 Mar 2023, the book was signed and approved by Quality Assurance (QA) and the data was not fully printed (readable). No action was taken to rectify the problem. The balance was under maintenance by the Manufacturer, who also printed a non-readable document from the balance and signed off without acknowledging the deficiency. There is no preventive maintenance program established for this equipment and established procedures, "Cleaning Operation, and Calibration of electronic balance" and "Good Documentation Practices", and the "Preventive Maintenance Procedure" do not establish requirements for maintaining quality related data beyond how to adhere the printout to a page.

c. Your firm failed to document the start time of remediated deviation investigations; therefore, the length of investigations is unknown and unable to be controlled by the Quality Unit.

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