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	8/19/2019-8/23/2019
	FEI NUMBER 3005977675

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Mr. Sujit Kumar Rath, Senior General Manager Operations

FIRM NAME	STREET ADDRESS
Ipca Laboratories Limited	Plot No. 65 And 99, Danudyog, Ind. Estate, Piparia
CITY, STATE, ZIP CODE, COUNTRY Silvasa (D And Nh), 396230 India	TYPE ESTABLISHMENT INSPECTED Finished 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

Deviations from written test procedures and laboratory mechanisms are not recorded and justified.

Specifically,

Your Quality Unit has not been effective in carrying-out its duties of ensuring that drug products are manufactured in accordance with current good manufacturing practices (cGMP) to ensure safety, efficacy, purity and overall quality of drug products manufactured at your firm. This is demonstrated by a cascade of failure in your Quality Unit responsibilities related to controls on issuance of GMP forms, review of laboratory testing data, conducting investigations and conducting activities per written procedures. The inspectional observations listed on this form document that your consultants have not performed the adequate assessments / reviews to ensure the quality of drug products tested at your firm. For example, but not limited to:

A) During the inspection, we observed your firm did not investigate the issues of unknown peaks eluted sporadically at different retention time (RT) in blank injections, reference standards (system suitability and (b) (4) injections and sample solution injections during Residual solvent by GC test. During the inspection, we observed unknown peak's combined % Area as high as 15%. The following drug substances tested for Residual Solvent by GC test showed the presence of unknown peaks:

1) (b) (4) USP;
2) (b) (4) USP;
3) (b) (4) USP;

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Arsen Karapetyan, Investigator - Dedicated Drug Cadre Pratik S Upadhyay, Generic Drug User Fee Amendments (GDUFA)	X Arsen Karapetyan Investigator - Dedicated Drug Cadre Signed By: Arsen Karapetyan -S Date Signed: 08-23-2019 08:40:55	8/23/2019

4) (b) (4) USP; and
5) (b) (4) USP

- Your firm did not integrate, identify, document, trend, calculate and investigate the root cause for presence of unknown peaks and type of impurities present in above APIs that are ultimately used for manufacturing (b) (4) drug products at your firm.

- Your firm used "inhibit integration" function each time while processing GC chromatograms to only select peaks of interest and avoid integration of unknown peaks observed in Residual Solvent by GC test. Unknown peaks were also observed during the verification of the following documents and electronic data:

- Representative chromatograms attached with standard Test Procedures (STPs);
- QC Analyst's on the job training record for Residual Solvent by GC; and
- Method Verification Chromatograms for (b) (4) USP.

B) Your Quality Unit lacked adequate oversight on employee practices for conducting QC tests and reviewing test data prior to batch release. Your Quality Unit inadequately reviewed out-of-specification (OOS) and out-of-trend (OOT) investigations, routine QC testing laboratory worksheets, electronic data, etc., and approved batch release without thoroughly reviewing QC test data to ensure adherence of QC Analysts to follow the standard test procedures (STPs) while conducting QC tests such as Assay by HPLC, Related Substances by HPLC and Dissolution tests. For example, but not limited to:

1) Your QC Analysts deviated from STPs for over twelve (12) years while conducting Dissolution by UV tests for (b) (4) Tablets. The following issues were observed:

- Your analytical method validation protocol (approved on August 30, 2007) references to "(b) (4) (b) (4) and (b) (4) under (b) (4) evaluation study (section 10.6). Your QC

Analyst used (b) (4) with no traceability regarding the (b) (4) reference and no justification was provided for referring (b) (4) " in the method validation protocol and report. This oversight in the method validation was not identified and timely investigated. The method validation report was approved on September 27, 2007.

- Your QC Analysts were using (b) (4) instead of (b) (4) during sample and standard test solutions preparation during (b) (4) step. Your firm has not performed (b) (4) equivalence assessment between (b) (4) and (b) (4) This issue underwent undetected for over 12 years.

2) Your QC Analysts deviated from STPs for over two (2) years while conducting Assay and Related Substances by HPLC tests for (b) (4) Tablets and (b) (4) Tablets. During the inspection, we observed your employees were using (b) (4) other than (b) (4) (b) (4) by deviating from the STPs for over two (2) years or more.

Your Quality Unit failed to identify and investigate Analyst deviation from STPs as one of the potential root causes for Out of Specification (OOS), Out of Trend (OOT), and customer complaints pertaining to lack of effectiveness (see Observation 3A).

C) Your firm's electronic data assessment based on IQVIA™ final report "Forensic Analysis & Electronic Data Assessment", dated 08/17/2018, for chromatographic data systems in response to Warning Letter 320-16-07, dated 01/29/2016 appears to be incomplete. Specifically,

- Your firm's electronic data assessment based on IQVIA™ final report "Forensic Analysis & Electronic Data Assessment", identified some instances, but not all, where interrupted sample injections due to power failure or communication error show that the sample did not run and concluded that the chromatographic data was not available for review. During the current inspection, we demonstrated that

such interrupted sequences which show "Incomplete Data", are in fact able to be retrieved and reviewed using the "Verify Incomplete Data" function on your chromatographic software.

- At the time of the IQVIA™ assessment your firm did not have the knowledge that such interrupted sequences mentioned above could be filtered by "Project Integrity Failures" in your chromatographic software. Subsequently, on or around 08/16/2019, approximately three days prior to the start of the current inspection, your firm finalized an additional assessment report titled "Report for the retrospective assessment of 'Project Integrity Failure' and 'Incomplete Raw Data files' In Empower Chromatographic data software (CDS)". This assessment resulted in approximately fourty eight (48) instances of "Project Integrity Failures', of which only fourteen (14) instances had been identified during the final IQVIA™ assessment.

-Your firm performed an assessment of the "Project Integrity Failures" which show no chromatograms, with either the term "Data Missing" or "Incomplete Data" written on top of the chromatogram. This assessment is inadequate in that your firm was not aware of the "Verify Incomplete Data" function to retrieve data and observe chromatographic data. Your firm's QA reviewers were observed to have this privilege in your chromatographic software, however did not know about this function until we demonstrated it during the inspection. During our review of retrospective and current data, we observed interrupted sequences, two of which involved a rider peak and retention time shift where the principal peak of the sample solution was observed to be eluted after "verify incomplete data" function was applied as recent as June 2019: For Example:

1) On or around 10/12/2014, during dissolution testing for product (b) (4) Tablets USP (b) (4) mg Batch No. (b) (4) for 9-month accelerated stability study, the third sample injection was interrupted at around (b) (4) pm per your firm's Deviation report 6498 due to analyst "inadvertently clicked on hibernate instead of log off option on computer". During our review, we observed a rider peak on chromatogram for first injection around (b) (4) pm. Due to sample

interruption at around (b) (4) pm on 10/12/2014, the analyst started another sequence for a retest starting around (b) (4) pm on 10/12/2014.

2) During assay testing for product (b) (4) Tablets USP (b) (4) mg batch numbers (b) (4) and (b) (4) for stability study, the initial duplicate sequence sample injections for sample (b) (4) started around 08/19/2014 a (b) (4) pm, with second injection of sample (b) (4) starting at (b) (4) pm interrupted per your firm's LI/SIL/2014/057 due to "power failure HPLC system went in idle condition" and showing "Incomplete Data". After we verified the data during the inspection, it was observed that the sample injection had partially eluted starting around (b) (4) minutes, with all three injections prior also eluting around (b) (4) minutes. Per your test method, principal peak for (b) (4) is about (b) (4) minutes. Approximately, two days later on 08/21/2014, a new sample solution preparation as performed, and the two batches were retested starting around 1:29 pm with all reported principal peaks eluting at around (b) (4) minutes.

-This discrepancy in your firm's ability to retrieve, review and investigate all electronic raw data is a significant gap in your Data Integrity procedures. Instead of verifying the incomplete data to perform an adequate evaluation of whether the sample solution principal peak eluted or not and its impact on integrity of data, your firm-initiated Laboratory Incident (LI) reports for power failure / instrument failure / computer shut down / stoppage of HPLC system / UPS Power Supply failure / system idle condition and performed retesting of the sample. We reviewed approximately twelve (12) such LI reports, several of which resulted in "Data Missing" or "Incomplete Data". Neither your IQVIA™ or "Project Integrity Failure" assessment reports have investigated the meaning and significance of "Incomplete Data" and "Missing Data" results with respect to integrity of data, in addition to the different type of power interruptions which may cause these interruptions.

OBSERVATION 2

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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,

Your firm's OOS and OOT investigations are deficient in that failures were invalidated based on acceptable retest results without identifying the root causes of the original failures. For example:

A) OOS No.: SIL/OOS/2019/022 for Assay by HPLC failure on (b) (4) USP API lo (b) (4) and (b) (4) Your QC Unit invalidated the original test data based on the following rationales:

- Sample and standard test solutions were discarded prior to processing and verifying the analytical test results.
- Sample and standard preparations were ove (b) (4) for stability of solutions.

During the inspection, we observed your firm has not conducted evaluation of solution stability during the method validation and there was no documented evidence provided pertaining to the claim of (b) (4) (b) (4) of solution stability.

The firm compromised the integrity of OOS investigation by changing the HPLC system from HPLC equipment ID: SQC 102 to SQC 101. Additionally, a repeat analysis was performed by preparing fresh sample, standard, mobile phase and diluent solutions that resulted in a passing test result.

B) OOT No.: OOT/QC/SIL/004/18 for Dissolution by UV on (b) (4) Tablets. Your QC Unit invalidated OOT based on the assumption of not (b) (4) prior to (b) (4) the sample solution, which deviated from your STP for Dissolution by UV test. Your QC Analysts used (b) (4) by (b) (4) using a (b) (4) instead of (b) (4) This issue

went undetected for over twelve (12) years due to inadequate Quality Unit oversight (see Observation 1B1).

C) Your firm's procedure for conducting OOT investigation (CSOP/2018/155/R03) is deficient in that there is no requirement for monitoring the quality of drug products throughout its shelf life for valid OOT batches. Your firm has sold several valid OOT batches in the commercial market and none were placed on long term stability conditions (25°C/60%RH) to monitor the quality of drug products. Your firm has received multiple product complaints regarding "lack of effectiveness" that were not linked with the issues of valid OOT batches sold in the market.

OBSERVATION 3

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

Specifically,

A) Your Quality Unit deviated from written procedures and failed to timely identify and investigate root cause, take appropriate CAPA and close investigations within defined timelines. For example, but not limited to;

Product Complaint:

Your Quality Unit deviated from SOP: CSOP/2013/004/R05, titled: "Handling of Product Complaint", effective date: August 18, 2018, Section: 5.13 *"Complaint Handling Timeline"* of which sub-section 5.13.4 reads in part *"For all complaints, investigation must be completed as per timeline and closed within* (b) (4) *from sharing of response"*. Section 5.13.5 reads in part (b) (4) *extension allowed for non-critical complaints only (total* (b) (4) *of investigation)"*. Your firm deviated from CSOP/2013/004/R05 for the timely closure of the following product complaint investigations:

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1) Complaint No.: MKT/001/2019, Product: (b) (4) mg Tablets, Batch No.: (b) (4) or (b) (4) Issue: *"A hair was found embedded in the tablet"*, with complaint investigation initiated on March 04, 2019, Status: Open. This product complaint was open for over five (5) months with four (4) extensions already in place.

2) Complaint No.: MKT/009/2017, Product: (b) (4) mg tablets, Batch No.: (b) (4) Issue: *"Lack of effect"*, with complaint investigation initiated on July 11, 2017. Status: Closed, Approved By date: January 03, 2018. This product complaint was open for over five (5) months and no extensions were raised for not closing the complaint investigation within (b) (4)

3) Complaint No.: MKT/013/2017, Product: (b) (4) tablets USP (b) (4) mg, Batch No.: Not provided, Issue: *"Lack of effect"*, with complaint investigation initiated on August 16, 2017, Status: Closed. Approved By date: November 16, 2017. A total of four (4) product complaints for the same issue were received by your firm and grouped together under this market complaint. This complaint investigation was open for three (3) months. There was no extension raised as required per section 5.13.5.

B) Your firm has not established a timeline for the closure of Change Control and Corrective Action and Preventative Action (CAPA) to efficiently assess and perform necessary corrections to avoid impact on the Quality of drug products manufactured. For example, but not limited to:

- Change Controls open from year 2017:

56860, Change control date created: January 06, 2017, Total days change control open: ~ 944 days;
86202, Change control date created: December 05, 2017, Total days change control open: ~ 615 days.

- Change Controls open from year 2018:

93893, Change control date created: March 07, 2018, Total days change control open: ~ 523 days;
94270, Change control date created: March 10, 2018, Total days change control open: ~ 520 days;
94709, Change control date created: March 15, 2018, Total days change control open: ~ 515 days;

Additionally, your firm has approximately eighteen (18) additional change controls that are in open status for about 235 to 440 days from year 2018. Additionally, for year 2019, there are about seventy-seven (77) change controls are in open status with the oldest being about 214 days.

- CAPAs open from years 2017 and 2018:

72700, CAPA date opened: June 30, 2017, Total days CAPA open: ~770 days;
90912, CAPA date opened: January 29, 2018, Total days CAPA open: ~561 days;
105293, CAPA date opened: July 14, 2018, Total days CAPA open: ~396 days;
106432, CAPA date opened: July 27, 2018, Total days CAPA open: ~383 days;
110990, CAPA date opened: September 14, 2018, Total days CAPA open: ~336 days;
114529, CAPA date opened: October 26, 2018, Total days CAPA open: ~294 days; and
116375, CAPA date opened: November 22, 2018, Total days CAPA open: ~268 days.

Additionally, your firm has approximately eighty-five (85) CAPAs in open status for year 2019, of which about twenty (20) CAPAs are in open status for over one-hundred (100) days.

C) Your firm's Quality Unit allows the destruction of draft and interim laboratory investigation reports using shredders maintained in your QA office area. The logbook maintained for controlling the destruction of documents showed several entries pertaining to the destruction of interim investigation reports. Additionally, we observed several GMP documents under "Q" drive of QC computers that were not under control of your Quality Unit. The documents stored under "Q" drive contained but not limited to, draft investigation reports, draft SOPs, formats (worksheets) for conducting laboratory investigations, etc. These documents can be deleted, copied and modified by all QC personnel.

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Similarly, during our review of your tablet compression equipment machine interface, we observed PDF documents with production results, changes, and alarms encountered for several batch records manufactured in 2014 on the machine interface desktop recycle bin. It was observed that the recycle bin is available without restriction to all production operators during real time compression activities. Additionally, we observed that all raw data generated in your equipment software as a result of tablet compression operations is stored on the machine interface desktop D Drive without restriction, where every production operator can access all the raw data in real time, including those generated by other operators for prior batches. Per your IT, this raw data is backed up (b) (4)

X Pratik S Upadhyay
Generic Drug User Fee Amendments (GDUFA)
Signed By: Pratik S. Upadhyay -S
Date Signed: 08-23-2019 08:42:38

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Arsen Karapetyan, Investigator - Dedicated Drug Cadre Pratik S Upadhyay, Generic Drug User Fee Amendments (GDUFA)	X Arsen Karapetyan Investigator - Dedicated Drug Cadre Signed By: Arsen Karapetyan -S Date Signed: 08-23-2019 08:40:55	8/23/2019