DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave,Bldg 51,Rm 4225 Silver Springs, MD 20993 (301) 796 3334 Fax:(301) 847 8738 Industry Information: www.fda.gov/oc/industry	10/13/2014 10/17/2014 FEI NUMBER 3007574780

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: V.S.S. Kushwaha, Vice President Technical

FIRM NAME	STREET ADDRESS
Ipca Laboratories LTd	1 Pharma Zone, SEZ Phase II,Sector 3 District Dhar
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Pithampur 454 775, India	Finished 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

Drug products failing to meet established specifications are not rejected.

Specifically, during our review of your firm's electronic HPLC chromatography data, we noted what appeared to be the laboratory practice of performing sample pre-analysis ("trial") injections prior to initiating the official/reported analyses. These sample pre-analysis "trial" injections are not reviewed and/or reported.

1) Our limited review of randomly selected pre-analysis "trial" unreported sample chromatograms found results that appear to fail your firm's established specifications. No Out-Of-Specification (OOS) investigation was initiated as required per SOP PIT/QAD/059/05 "Procedure for Investigation of Out of Specification Results in Quality Control Laboratory", and no other documentation and/or explanation was provided to describe actions taken to achieve desirable/passing results.

For example:

(b) (4) Tablets USP (b) (4) Assay by HPLC

- The first "trial" sample injection was performed on 01/0 1/13 @ (b) (4)
  - A calculation of this result performed upon our request found the Assay result to be (b) (4) % vs. a specification limit of (b) (4) - (b) (4)
- The second "trial" sample injection was performed on 01/01/13 @ (b) (4)
  - A calculation of this result performed upon our request found the Assay result to be (b) (4) % vs. a specification limit of (b) (4) % - (b) (4)
- The third and fourth (reported/official) sample injections were performed on 01/01/13 @ (b) (4) and (b) (4) respectively.
  - The Assay result for this batch was reported as (b) (4)

2) Our limited review of randomly selected pre-analysis "trial" unreported sample chromatograms also found results that appear to differ significantly from the official/reported results, however, appear to meet your firm's established specifications.

For example:

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	Peter E. Baker, Investigator Dipesh K. Shah, Investigator	10/17/2014

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(b) (4) Tablets USP (b) (4) Assay by HPLC

- The first "trial" sample injection was performed on 01/01/13 @ (b) (4)
  - A calculation of this result performed upon our request found the Assay result to be (b) (4) vs. a specification limit of (b) (4) % - (b) (4)
- The second "trial" sample injection was performed on 01/01/13 @ (b) (4)
  - A calculation of this result performed upon our request found the Assay result to be (b) (4)
- The third "trial" sample injection was performed on 01/01/13 @ (b) (4)
  - A calculation of this result performed upon our request found the Assay result to be (b) (4) %
- The fourth "trial" sample injection was performed on 01/01/13 @ (b) (4)
  - A calculation of this result performed upon our request found ay result to be (b) (4) % vs. a specification limit of (b) (4) % - (b) (4) %
- The fifth and sixth (reported/official) sample injections were performed on 01/01/13 @ (b) (4) and (b) (4) respectively.
  - The Assay result for this batch was reported as (b) (4) %

3) Our limited review of randomly selected pre-analysis "trial" unreported sample chromatograms also found that this practice extends to laboratory investigation processes.

For example:

During our review of the electronic data collected in support of the Out-Of-Specification (OOS) #OOS/030/13/B regarding the content uniformity by HPLC failure for (b) (4) Tablets USP (b) (4) mg (b) (4) we found that prior to the official/reported OOS investigational analyses, pre-analysis "trial" sample injections were performed.

- Prior to the investigational analysis performed by the second analyst on 08/24/13 beginning @ 10:55am, at least one sample trial injection was performed @ 10:39am
  - The Assay result for OOS sample pre-analysis trial was found to be ~(b) (4) %
  - The average value of the official/reported content uniformity investigation results from this second analyst testing was found to be (b) (4) %

Due to the apparent laboratory practice of directing raw data "trial" chromatogram paths randomly throughout your firm's hard drive in no apparent organized fashion, in what appears to be an attempt to hide results from review, the number of such pre-analysis trial samples performed in relation to each raw material, in-process, and finished drug product analyzed by HPLC at your firm could not be determined.

According to your written procedure PIT/QCD/115/04 "Procedure for Standard Practice in Chromatography", "Trial chromatograms and any other chromatogram (if any) should be attached with relevant documentation and should be stamped with blue color "INVALIDATE" with justification". However, during our review of a representative number of examples,

including those mentioned above, it appears that "trial chromatograms" are not attached to the QC records and invalidated as required.

OBSERVATION 2

Established laboratory control mechanisms are not followed. Electronic records are used, but they do not meet systems validation requirements to ensure that they are trustworthy, reliable and generally equivalent to paper records.

Specifically,

1) During our review of your firm's electronic GC chromatography data audit trails, we noted what appears to be the laboratory practice of overwriting and deleting raw data files.

For example:

A) (b) (4) Tablets (b) (4) ng (b) (4) by GC

- The first four injections of the sample set were collected on 10/09/13 from 12:12pm to 5:14pm under the sequence titled (b) (4) Tabs (b) (4) mg 09.10.13.seq"
- These four injections were later overwritten and deleted on 10/09/13 starting at (b) (4) using the same sequence and raw data file path
    - As a result, the original chromatogram results are not available for review

B) (b) (4) USP (raw material) (b) (4) by GC

- The first three injections of the sample set were collected on 01/08/14 from 1:51pm to 3:13pm under the sequence titled (b) (4) USP 08.01.14.seq"
- These three injections were later overwritten and deleted on 01/08/14 starting at 4:05pm using the same sequence and raw data file path
    - As a result, the original chromatogram results are not available for review

C) (b) (4) (raw material) method verification for (b) (4) Content by GC

- The first five injections of the sample set were collected on 01/02/14 from 1:24pm to 4:07pm under the sequence titled "System suitability and Method Precision 02.01.14"
- These five injections were later overwritten and deleted on 01/02/14 starting at 5:04pm using the same sequence and raw data file path
    - As a result, the original chromatogram results are not available for review

D) GC #353 (b) (4) Instrument Calibration

- The calibration sequence was performed and completed on 10/01/12 under the sequence titled "Calibration_Pack column_.seq" (16 total injections)
- The results of this calibration were later overwritten and deleted on 10/03/12 starting at 8:23am using the same sequence and raw data path
    - As a result, the original chromatogram results are not available for review

2) During our review of your firm's electronic FTIR data, we noted duplicate results for the same sample. Our review of the QC data package found that the original result was not included/reported, and no justification was provided regarding the reason for retest.

Additionally, the system audit trail for your (b) (4) FTIR instrument could not be reviewed during our inspection due to software issues.

OBSERVATION 3

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

Specifically, one of your firm's (b) (4) GC instruments (Perkin Elmer #072) is not equipped with a system audit trail that independently records the date and time of actions that create, modify, or delete electronic records.

OBSERVATION 4

Written records of investigations into the failure of a batch or any of its components to meet specifications do not include the conclusions and follow-up.

Specifically, your firm's "Minor" deviation investigation #3015, initiated on 05/02/14 due to:

"Meta data can be deleted in GC (Make - Agilent) and FTIR (Make - Shimadzu) by changing permission from respective instrument user windows login",

did not include:

1) a comprehensive review of the electronic "Meta data", and
2) a product impact evaluation.

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This deviation investigation was closed on 06/06/14 and found "no impact on the product quality", however, no scientific rationale and/or justification was included to substantiate this claim. Your Quality Representative claims that "the details of the analysis are available in the activity log" (e.g. audit trail), however,

1) one of your firm's (b) (4) GC's does not include an "activity log", and
2) your review of the GC activity log for GC#353 did not identify the systematic deletion of electronic raw data (meta data).

OBSERVATION 5

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

Specifically, during our inspection of the manufacturing unit on 10/14/14, we identified uncontrolled Quality Unit document control stamps within the unlocked In-Process Quality Assurance (IPQA) office located next to the compression and (b) (4) areas. These stamps are used to create QA controlled records printed from the PC located within this office.

There are no written procedures established to control these QA stamps in order to prevent violation of your document control system.

OBSERVATION 6

Employees are not given training in written procedures required by current good manufacturing practice regulations.

Specifically, during our walk-through inspection your manufacturing unit, we identified partially shredded "Training Evaluation" forms for multiple operators that had been completed and signed on 09/23/14 regarding SOP PIT/QAD/019/07 "Procedure for In-process Checks during Tablet Compression/Capsule Filling". We requested and reviewed the official training binders for these operators, and found that the training had been completed on 09/23/14 by your QA Officer, however, no Training Evaluation forms were included as required per section 5.11 of SOP PIT/HRD/003/13 "Procedure for Training of Plant Personnel".

According to the QA Officer who presented the training, he shredded and discarded the Training Evaluation forms for these manufacturing operators "by mistake".

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