Ipca Laboratories Limited 1/29/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

Warning Letter

Via UPS

WL: 320-16-07

January 29, 2016

Mr. Premchand Godha
Chairman & Managing Director
Ipca Laboratories Ltd.
48, Kandivli Industrial Estate
Kandivli (West), Mumbai 400 067
India

Dear Mr. Godha:

In 2014, the U.S. Food and Drug Administration (FDA) inspected three Ipca pharmaceutical manufacturing facilities.

A. July 14–18: P.O. No. 33 Village Sejavata, Ratlam 457 002 Madhya Pradesh (Ratlam facility)

B. October 13–17: 1 Pharma Zone, SEZ Phase II, Sector 3, District Dhar, Pithampur, Madhya Pradesh (Pithampur facility)

C. December 1–19: Plot 65 & 99, Danudyog Industrial Estate, Piparia Silvassa 396 230 (Union Territory of Dadra & Nagar Haveli) (Piparia Silvassa facility)

At your Ratlam facility, we identified significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API). At your Pithampur and Piparia Silvassa facilities, we identified significant violations of CGMP for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211.

These deviations and violations cause your drugs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 351(a)(2)(B). The methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We reviewed your firm's responses of August 8 and November 7, 2014, and January 9, 2015, in detail for all three sites and acknowledge receipt of subsequent responses.

We observed specific deviations and violations during the inspections, including, but not limited to, the following.

A. Ratlam facility (FEI: 3002807297)

1. Failure to have computerized systems with sufficient controls to prevent unauthorized access or changes to data.

During the inspection, FDA investigators discovered a lack of basic laboratory controls to prevent changes to your firm's electronically stored data. Your firm relied on incomplete records to evaluate the quality of your drugs and to determine whether your drugs conformed with established specifications and standards.

Our investigators found that your firm routinely re-tested samples without justification, and deleted analytical data. We observed systemic data manipulation across your facility, including actions taken by multiple analysts, on multiple pieces of testing equipment, and for multiple drugs. You are responsible for determining the causes of these deviations, for preventing recurrence, and for preventing other deviations from CGMP.

During the inspection, our investigators examined the computerized instrumentation and systems you used to conduct chromatographic analyses of your drugs and found that laboratory analysts had PC administrator access that they utilized to manipulate raw data and test results. We found that controls on your computerized chromatographic instrumentation were not adequate to prevent analysts from manipulating processing parameters in order to obtain passing results. We also found that your computerized systems lacked controls to prevent the back-dating of test data.

For example, we reviewed the **(b)(4)** API 12-month **(b)(4)** Commercial Stability assay test for residual solvent by gas chromatography (GC). For batch **#(b)(4)** US-DMF (**(b)(4)**), you reported an **(b)(4)**% result for **(b)(4)** residual solvent (specification **(b)(4)**-**(b)(4)**%) obtained on July 18, 2013.

We documented that the original peak had been integrated inconsistently. Standards and samples had been processed using different integration parameters with no documented reason; there were no controls in the software to prevent analysts from manipulating integration settings in order to obtain passing results that you relied on to evaluate the quality of this product. When our investigator asked you to reprocess the chromatograms using appropriate integration parameters, an out-of-specification (OOS) value of **(b)(4)**% was obtained.

In the **(b)(4)** stability interval assay test of the same API, batch **#(b)(4)** US-DMF (**(b)(4)**), you reported an **(b)(4)**% result for **(b)(4)** residual solvent (specification: **(b)(4)**-**(b)(4)**%) obtained on June 12, 2013. We again found that the original sample peaks had been re-reintegrated inconsistently. There were no controls in the software to prevent the inappropriate manipulation of integration parameters. When our investigator asked you to reprocess the chromatograms using appropriate integration parameters, the result was an OOS value of **(b)(4)**%.

For the same test, we found that on and after June 18, 2013, the date and time of the chromatographic injections for the **(b)(4)** stability test appear to have been set back to June 12, 2013. The data was reprocessed to obtain a passing result, upon which you relied to evaluate the quality of this drug.

In addition to these examples of computerized systems that permitted inappropriate manipulation of integration parameters and backdating, our investigators also found several instances of computerized data systems that failed to prevent the deletion of original injections. For example, our investigators reviewed the GC audit trail for **(b)(4)** (finished API batch **#(b)(4)**) and found that the original sample injection for related substance was on June 4, 2013 at **(b)(4)**. This injection was aborted with no justification and the computerized system that your laboratory used to

capture raw data did not retain the original results. The sample was re-injected at **(b)(4)**., which automatically deleted the original sample result. Passing results from the re-injection were reported for individual and total impurities. You used these incomplete results to evaluate the quality of this drug.

The High Performance Liquid Chromatography (HPLC) audit trail for **(b)(4)** (finished API batch **#(b)(4)**) shows that the first sample injection for aliquot #2 assay test was on May 28, 2013 at **(b)(4)**. This injection result was deleted without justification. The sample was re-injected at **(b)(4)**. A passing assay result was reported from the re-injection. As with the GC system discussed above, the electronic system your laboratory used to capture HPLC results lacked sufficient controls to prevent the deletion of data without justification, and failed to retain the original data. You relied on these incomplete results to evaluate the quality of this drug.

These practices appear to be commonplace in your analytical laboratory. During the inspection, our investigators spoke with an analyst who reported that "…if we find a failure, we set back the date/time setting and re-integrate to achieve passing results…" The analyst explained that deleting, overwriting, changing integration parameters, and altering PC date and time settings were done for raw materials, in-process testing, and finished API drugs.

In your response you stated that the stand-alone chromatographic instruments in the Quality Control and Stability laboratories are no longer under full control of individual analysts and have been connected to a network-based laboratory system. You also acknowledged that you did not identify all instances of data manipulation that may have led to inaccurate conclusions regarding product quality. However, your response still lacks a comprehensive assessment and retrospective review of data generated from all of your computerized laboratory systems. This includes but is not limited to a risk assessment that evaluates all potentially-affected test data.

2. Failure to adequately investigate and resolve critical deviations.

Our inspection documented that your firm's quality unit was aware of the lack of controls in your computerized systems to prevent the manipulation and deletion of quality-related data. Your site's senior management failed to take sufficient corrective action and prevent the recurrence of these problems. For example, an anonymous email dated August 5, 2013 notified your quality management about data falsification and manipulation in your laboratory. This email stated: "…[t]here is no control of data in the department…Falsification is going on…Take action as early as possible..." Although you investigated your GC and HPLC equipment, the multi-part investigation that you opened on August 10, 2013 (CD/RTM/QA/001/2013) was incomplete and did not resolve the underlying problems of data falsification and manipulation.

Phase I: GC Investigation
Your GC Investigation was limited to review of audit trails for batches analyzed on GCs #052 and #202 between January and August, 2013. Although your investigation found multiple examples of deficient data management and retention practices, you concluded that none of the deviations were considered critical. You also concluded that there was no product or patient risk associated with these deviations. You closed this phase of the investigation on November 27, 2013, without implementing effective corrective actions and preventive actions.

Our investigator reviewed the same data and audit trail records that you included in your own investigation. In the limited time available during the inspection, our investigator found serious deficiencies and questionable data management practices that your own four-month investigation did not identify, including:

- altering time and date settings of computerized equipment using the software administrator's access privilege
- manipulating test integration parameters to obtain passing or desirable results;
- aborting on-going sample analyses
- over-writing and deleting raw data files containing original results

When presented with the results of our review of these records during the inspection, your QA manager agreed that that these examples, which you had not documented or addressed in your own investigation, were serious deviations from CGMP. Specifically, the manager concurred that these examples would be categorized as “critical” under your own system for assessing deviations.

Phase II: HPLC Investigation
Your investigation also considered HPLC data from July to December, 2013. On May 3, 2014, your investigation concluded that good documentation practices were not being followed, and your staff was insufficiently aware of requirements set forth in 21 CFR Part 11.

Our investigators confirmed these same deficiencies. When reviewing the same HPLC audit trails that you considered in your own investigation, our investigators also found that standard injections were manipulated without scientific justification. Your analyst admitted to us that he had manipulated the standard sequence injections.

Our investigator reviewed data from the same July–December 2013 time frame for **(b)(4)** finished API batch **#(b)(4)** commercial batch release assay via HPLC. As with the GC data discussed above, although your own lengthy investigation did not capture critical deviations, our investigator’s limited review of this data during the inspection identified data manipulation, including deleted injections, re-injections, and missing injections.

The investigators also reviewed HPLC data for May, 2013, which was not covered in your investigation. The information reviewed during the inspection identified data manipulation in batches **(b)(4)** for **(b)(4)** finished API assay determination, including deleted injections. Again, these deviations and their potential effects on product quality were not covered in your own investigation.

Your investigation concluded that some chromatograms were manipulated, but it failed to identify the scope or extent of such practices. It lacked sufficient rigor to demonstrate that other laboratory data were not compromised, including data supporting drug applications or stability.

In your response to this letter, provide the phase 2 investigation into the HPLC systems. Include an assessment of all API batches tested. Also indicate whether senior management is taking appropriate actions in response to critical deviations, such as supporting investigations into possible reported data falsification and manipulation. Provide a status report on these efforts and any actions taken so far.

Your firm lacks a robust corrective action and preventive action (CAPA) program. Without strong investigation procedures and management support for activities of the quality unit, you cannot consistently identify root causes of product quality failures, rendering it impossible to make adequate corrections. These failures can expose patients to unnecessary risk.

3. Failure to follow and document laboratory controls at the time of performance; failure to document and explain any departures from laboratory procedures.

During the inspection of your microbiology laboratory, our investigators observed multiple examples of your firm’s practice of back-dating and falsifying laboratory data. This laboratory monitors the quality of **(b)(4)** used in the manufacture of APIs for total plate count as well as the absence of objectionable organisms. Without contemporaneous and accurate data, there is no way for you to ensure that your APIs meet specifications for the absence of objectionable microorganisms.

"Temperature Record" logbooks in microbiology laboratory
On July 14, 2014, our investigator noticed that the daily record in the 2-8°C refrigerator **#(b)(4)** temperature logbook had only been completed up to July 9, 2014. When the investigator requested the logbook later that day, he observed

that the logbook had been completed up to July 13, 2014. The entries for July 10–13, 2014, were not present when the investigator initially reviewed the log. When questioned by the investigator, the laboratory analyst responsible for performing these entries stated three times that she had documented the newly-completed temperature values at the time of performance. The same analyst's supervisor later admitted to directing the analyst to fill out the logbook after the fact. The investigator also observed another analyst actively backdating/back-filling the "Temperature Record" logbook for refrigerator #**(b)(4)** during the inspection.

(b)(4) *Sample Data*
During the inspection, investigators visually examined the **(b)(4)** quality and media growth promotion samples (plates) currently in incubation, and compared them with the QC documentation for those samples purported to be in progress (incubation). Your **(b)(4)** sampling records showed that 45 **(b)(4)** quality samples had been prepared and incubated on July 9, 2014 (**(b)(4)**, total viable aerobic count) and were in process. During the inspection, three of these plates were not in the incubator, although your **(b)(4)** sampling logbook recorded the presence of these three plates. QC worksheets for these three plates showed that documentation for the sample preparation and incubation had been created, even though the plates were not actually tested.

Your management informed the investigators that one microbial plate had been found. However, upon inspection of this plate, the investigator noted that the handwriting was different from all the other microbial plates. After questioning, your microbiologist admitted that the microbial plate was re-created (falsified) to appear as if the sample was complete.

In the 20-25°C and 30-35°C incubation chambers, our investigator reviewed documentation for 117 growth promotion samples. Only 74 samples were in the chambers; 43 were missing. According to your firm's response, the plates were missing because, during the inspection, you were moving the microbiology laboratory from the **(b)(4)** floor to the **(b)(4)** floor. No one mentioned the laboratory move during the inspection.

B. Pithampur (FEI: 3007574780)

1. Your firm failed to ensure that laboratory records include complete data derived from all tests necessary to assure compliance with established specifications and standards. (21 CFR 211.194(a))

We found documented instances of analytical test results without original data. For example, your raw data is incomplete for GC analysis performed during the **(b)(4)** method verification for **(b)(4)** USP (raw material) and **(b)(4)** (raw material).

(b)(4) tablets **(b)(4)**mg **(b)(4)** were tested for **(b)(4)** by GC on October 9, 2013. The first four injections were overwritten and deleted without justification. They were not available for review.

(b)(4) USP (raw material) **(b)(4)** was tested for **(b)(4)** by GC on January 8, 2014. The first three injections were overwritten using the same sequence and raw data file path.

(b)(4) (raw material) was tested for method verification for **(b)(4)** content by GC on January 2, 2014. The first five injections were overwritten and deleted.

We also found multiple instances of trial injections of samples. The results of additional tests were reported, but the original (trial) results were not. Chromatograms related to these original test results were overwritten by subsequent testing. No investigation related to these injections was initiated. No other documentation or explanation was provided.

In your response, you focused on reviewing your data print outs and revising your SOP. Because your quality unit did not review the original electronic raw data, you were unable to detect rewritten, deleted, or overwritten files. Without this information, you have no way to ensure that the tests you use to evaluate the quality of incoming raw materials are accurate or reliable.

C. Piparia Silvassa (FEI 3005977675)

1. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards. (21CFR 211.194(a))

During our inspection, we documented that your QC laboratory was conducting trial injections of samples but failed to report all of the data generated. For example, **(b)(4)** tablets USP **(b)(4)** mg (batch **# (b)(4)** & **(b)(4)**) were tested for assay and dissolution for finished product stability on June 26, 2013. A total of **(b)(4)** trial standard injections were performed. Only **(b)(4)** were submitted for your quality unit review. Your quality unit only reviews the data print out and had not detected your laboratory's practice of failing to submit all of the data for review.

For **(b)(4)** tablet USP **(b)(4)** mg (batch **# (b)(4)**), the first injection (trial injection) began at 2:59 p.m. The official run began **(b)(4)** after the trial injections, at **(b)(4)**. The 2:59 p.m. injection was not reported, instead the **(b)(4)** result was reported as the official run.

Your quality unit must review all analytical data when making batch release decisions. Without complete and accurate information about the quality of the products, your quality unit cannot ensure that the products it releases comply with established specifications and standards for quality. Your response does not demonstrate how your laboratory systems and procedures prevent the deletion of data or how the managers at your facility will ensure that all records relied upon for batch release and other quality-related decisions are complete and accurate.

2. Your laboratory controls failed to establish scientifically sound test procedures to assure that your drug products conform to appropriate standards of identity, strength, quality and purity. (21 CFR 211.160 (b))

During our inspection, we found that on November 24, 2014, the in-house **(b)(4)** was inoculated with *Staphylococcus aureus* (gram-positive bacteria)and *E. Coli* (gram-negative bacteria). The medium showed *Staphylococcus aureus* growth.

On December 7, 2014, the same media was prepared and challenged with the same microorganisms, and again showed *Staphylococcus aureus* growth.

However, **(b)(4)** is selective for gram-negative bacteria. It contains an inhibitor for gram-positive bacteria. Therefore, gram-positive bacteria should not grow on **(b)(4)**.

Your QC data confirmed microbial growth for *Staphylococcus aureus* in a medium that is intended to inhibit its growth. No investigation was initiated. Despite confirmed microbial growth, this media batch was used for **(b)(4)** samples.

Your firm's response is deficient in that it is limited to the retrospective review of the growth promotion test results generated from January 2014 to December 2014. It lacks an evaluation of the acceptability of your media supplier, the adequacy of laboratory controls, and a determination whether laboratory personnel (including supervisors) are appropriately qualified to detect and correct these deviations. In response to this letter, include a copy of your investigation into this matter, including your root cause determination and CAPA.

Conclusion

Violations and deviations cited in this letter are not intended as an all-inclusive list. You are responsible for determining the causes of these violations and deviations, for preventing reoccurrences, and for preventing other violations and deviations.

Our investigators observed systemic data manipulation and other CGMP violations and deviations at three separate sites. Your quality system does not adequately ensure the accuracy and integrity of the data generated and available at your facilities to support the safety, effectiveness, and quality of your drugs. In your response to this letter, provide the following:

- A comprehensive investigation and evaluation. Describe your methodology. Results should include conclusions about the extent of data integrity deficiencies and their root causes, which may involve record control, contemporaneous recording, deletion of data, and other data integrity deficiencies.
- A risk assessment of how the observed deficiencies may affect the reliability and completeness of quality information available for your drugs. Also determine the consequences of your deficient documentation practices on the quality of drugs released for distribution.
- A management strategy that includes a detailed global corrective action and preventive action plan. Describe the actions you will take, such as contacting your customers, recalling drugs, conducting additional testing and/or adding lots to your stability programs, or other steps to assure the quality of your drugs manufactured under the deficient conditions discussed above. Also indicate measures you will take, such as revising procedures, implementing new controls, training or re-training personnel, or other actions to prevent the recurrence of CGMP deviations, including breaches of data integrity.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Staff immediately at drugshortages@fda.hhs.gov so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Until you complete all corrections, and we confirm your corrections and compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. Under Section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3), failure to correct these violations may also result in FDA refusing admission into the United States of articles manufactured at:

- Village Sejavata Ratlam (Madhya Pradesh)
- 1 Pharma Zone, SEZ Phase II, Sector 3 District Dhar, Pithampur, Madhya Pradesh
- Plot 65 & 99, Danudyog Industrial Estate, Piparia Silvassa 396 230 (Union Territory of Dadra & Nagar Haveli)

Within 15 working days of receipt of this letter, please notify this office, in writing, of the specific steps that you have taken to correct and prevent the recurrence of violations and deviations.

If you cannot complete corrective actions within 15 working days, state the reasons for your delay and the date by which you will have completed corrections. If you no longer manufacture or distribute the API or finished drug products at issue, provide the date(s) and reason(s) you ceased production. Send your reply to:

Rafael Arroyo, MS
Compliance Officer
Food and Drug Administration