Inspections, Compliance, Enforcement, and Criminal Investigations

Apotex Pharmachem India Pvt Ltd. 6/16/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration

Warning Letter

WL: 320-14-11

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

June 16, 2014

Jeremy B. Desai, PhD
President and Chief Operating Officer
Apotex, Inc.
150 Signet Drive
Toronto, ON, Canada M9L 1 T9

Dear Dr. Desai:

During our January 27, 2014 through January 31, 2014 inspection of your pharmaceutical manufacturing facility, Apotex Pharmachem India Pvt. Ltd. located at Plot # 1A Bommasandra Ind. Area, 4th Phase, Jigani Link Road, Bangalore, India, investigators from the U.S. Food and Drug Administration (FDA) identified significant deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (APIs). These deviations cause your APIs to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 USC § 351(a)(2)(B), in that 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 have conducted a detailed review of your firm's response dated February 20, 2014 and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated April 4, 2014, and May 27, 2014.

Our investigators observed specific deviations during the inspection, including, but not limited to, the following:

1. Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.

Your firm lacked accurate raw laboratory data records for API batches shipped by your firm. The inspection revealed that batch samples were retested until acceptable results were obtained. In addition, your quality control (QC) laboratory failed to include complete data on QC testing sheets. Failing or otherwise atypical results were not included in the official laboratory control records, not reported, and not investigated. For example,

- A review of the Gas Chromatograph (GC) electronic records from July 13, 2013, for **(b)(4)** USP batch #**(b)(4)** revealed an out-of-specification (OOS) result for the limit of residual solvents that was not reported. However, the QC test data sheet included passing results obtained from samples tested on July 14, 2013 and July 15, 2013. The inspection documented that your firm discarded sample preparation raw data related to the OOS results. In your response you indicate that the electronic chromatographic data and the weighing log books were available and reviewed during the inspection. However, the raw data and sample preparation information used for the calculation of the test results that were found OOS or disregarded were not in fact available for review.

- A review of the High Performance Liquid Chromatograph (HPLC) electronic records from July 3, 2013, for **(b)(4)** batch #**(b)(4)** revealed an Out-of-Trend (OOT) result. The sample preparation raw data was discarded and not reported. A QC analyst indicated that these results were discarded due to some small extra peaks identified in the chromatogram fingerprint and an unexpected high assay result. The QC test data sheet reported two new results that were obtained from samples tested on July 4, 2013 and July 5, 2013, using a different HPLC instrument.

- A review of the Karl Fischer electronic records from November 21, 2013, for **(b)(4)** EP batch #**(b)(4)** revealed an OOS result that was not reported. The passing results reported on the data sheets were generated from another sample tested an hour after the initial OOS results were obtained on the same day, November 21, 2013.

According to laboratory analysts interviewed during the inspection, the common practice was to complete the analysis and to record the sample preparation data only if the results were acceptable. If the results obtained were atypical, a fresh sample was to be prepared and analyzed. The original sample testing was not recorded.

Your firm's response states that the observations listed in the Form FDA 483 refer to work performed by analysts who did not follow the established procedures found in standard operating procedure (SOP) QC027 "Out of Specification Test Results and Investigation," SOP QC098 "Laboratory Incidents Investigation and Resolution," and SOP QA006 "Deviations." In addition, your response states "[t]he examples cited in this and other observations where additional testing was conducted by the analyst resulted from a number of factors ranging from system suitability parameters not being met to equipment malfunction to available in-process test data results that were inconsistent with release results."

In addition, your response to the FDA Form-483 indicates that your firm identified similar variances from established procedures that occurred in September 2013. Your response goes on to indicate that, following this discovery, you reviewed data from the month of August 2013, and identified nine additional incidents in which extra testing was performed without maintaining appropriate laboratory records. You fail to explain why, given these troubling findings, you did not then expand your investigation to discover the full scope of such variances from established procedures. Based on findings from these two months, it would be reasonable to believe that improper variances occurred in prior months as well.

The above examples demonstrate a general lack of reliability and accuracy of data generated by your firm's laboratory, which is a serious CGMP deficiency that raises concerns about the integrity of all data generated by your firm. We are concerned that your laboratory allowed the practice of retesting for GC, HPLC, and Karl Fischer methods without appropriate documentation, justification, and investigation. It is critical that you investigate these data integrity issues and identify the extent of these practices in your laboratory and manufacturing operations as part of a comprehensive data integrity audit. In your response, please also provide copies of the procedures in place that set forth the requirements to review and preserve complete data generated from your operations.

The failure to create and maintain accurate documentation is a repeat observation reported to your facility during the 2006 and 2010 inspections.

2. Failure to investigate and document out-of-specification results.

For example,

- Your firm failed to investigate unknown peaks found during the HPLC testing for related compounds of API **(b)(4)** USP batch #**(b)(4)**. A reviewer of the raw data reported on the "finished product report review data" worksheet that unknown peaks were observed due to vial contamination. The electronic records indicate that the first analysis performed on August 20, 2013, failed the specification (**(b)(4)**) limit for both any single unknown impurity (**(b)(4)**% vs. NMT **(b)(4)**%) and total impurities (**(b)(4)**% vs. NMT **(b)(4)**%). These OOS results were not reported or adequately investigated, and the raw data was discarded. The sample was re-analyzed on August 21, 2013, at which time it met specifications and the results were recorded. According to a laboratory analyst, the sample preparation printout corresponding to the initial testing (on August 20, 2013) was destroyed.
- Your firm's investigation of the data from the Empower software identified instances where additional testing was performed but not properly documented in laboratory records. This investigation was limited in scope to only a short timeframe, the month of August 2013, and to only one type of laboratory instrumentation, HPLC. During FDA's inspection, the QC manager explained that the scope of the risk assessment was limited to the month of August 2013 because he was busy with other laboratory responsibilities. According to your response to the Form FDA-483, some of the corrective actions implemented as a result of this investigation include: re-training of QC analysts, revision of the laboratory incident investigations SOP, and enhancements to the documentation and sample handling practices. As failures to investigate and document OOS results have persisted, it is clear that your corrective actions were not sufficient.
- An email chain from December 26, 2013 to January 21, 2014, reviewed during the inspection, discussed an unexpected unknown peak observed in the residual solvents release test for **(b)(4)** batches **(b)(4)** and **(b)(4)**. Your firm acknowledged during the inspection that SOP QC 098/01 "Laboratory Incident Investigation and Resolution" was not followed. During the inspection, a Quality Control manager stated that this incident was not investigated and resolved because this was an unknown peak and no failure had been identified.

Your management failed to prevent the practices of product sample retesting without investigation, and rewriting and/or omission of original CGMP records persisted without implementation of controls to prevent data manipulation.

Your firm's response to the Form FDA-483 acknowledges the deficiencies regarding data integrity observed during this inspection. Nevertheless, your firm's health hazard evaluation "Drug Safety Analysis" conducted in response to the Form FDA-483 concluded that there was no effect on product quality or patient safety. However, this evaluation was based on unreliable and incomplete data, as undesired records appear to be excluded. For instance, your report failed to include all of the batches tested, and did not list all of the customers you notified other than Apotex, Inc. Your response to the previous 2010 inspectional findings stated that "We are confident that … SOPs covering OOS … and Deviation … will provide the necessary control over the system to ensure consistent application and on-going compliance to this requirement." However, you clearly failed to detect and investigate the inaccurate data found by our investigators during this recent inspection.

In response to this letter, you should provide documentation of all corrective actions taken by your firm to address these failures to initiate investigations as required by your procedures and determine root cause(s) of OOS results.

The failure to perform adequate investigations is a repeat observation reported to your facility during the 2006 and 2010 inspections.

3. Failure to include adequate documentation during complaint investigation.

Your firm received complaint #**(b)(4)** for **(b)(4)** USP batch #**(b)(4)** due to failing assay results. The original investigation, approved on March 29, 2013, indicated that the complaint was received on February 26, 2013. During the review of that investigation, our investigators found a test record from January 8, 2013 (prior to the date you documented receiving the complaint) that reported failing HPLC assay results of the retain sample of batch **(b)(4)**. This record was not included in the investigation report. Your response to the Form FDA-483 observation included an addendum to the investigation report that indicated the complaint/query was actually received on January 8, 2013.

Your firm's response acknowledges that the assay result for the retain sample was omitted, but also claims additional investigations are ongoing and that preventive and corrective actions will be implemented as appropriate. However, your response to the previous 2010 inspectional findings included a similar corrective action plan regarding OOS, deviations, stability, product complaint and CAPA investigations. In this plan, you committed "to address this omission and provide assurances that the scope and detail related to future investigations is appropriately documented … to ensure consistent consideration for failure investigations."

In response to this letter, you should provide evidence of the additional investigation conducted and the corrective actions implemented to prevent the omission of data. Provide records of all complaints relating to your APIs, including returned API and the disposition of each returned batch. Discuss the expansion of your investigation to other batches and APIs that could be affected by failing assay results. Furthermore, explain the failure of your firm's complaint system and how you will implement proper management oversight to ensure adequate corrections to this deficiency.

Your complaint investigation system was also identified as an observation during the 2010 inspection of your facility.

4. Failure to record activities at the time they are performed.

Specifically, your staff used "finished product reports review data" worksheets to document critical laboratory information days after the actual testing was performed. The worksheets reported observations from your firm's secondary reviewer, and next to each of these listed observations the analyst marked them as corrected. A review of these worksheets revealed that your analysts did not always record data in the laboratory records in a contemporaneous manner as noted in the following examples:

- **(b)(4)** USP batch #**(b)(4)** worksheet dated September 18, 2013, reports "sample wt. taken wrongly." However, the correction to the stability data sheet for this lot gives the appearance that sample weighing was performed on August 10, 2013.

- **(b)(4)** USP batch #**(b)(4)** worksheet dated September 19, 2013, reports "all tests completed but appearance not reported." However, the correction to the test record indicates the test was performed on September 15, 2013, the date of the original testing.

- **(b)(4)**% batch #**(b)(4)** worksheet dated June 11, 2013, reports "resolution b/t **(b)(4)** & **(b)(4)** in ID std not in working std & it is **(b)(4)** not **(b)(4)**." However, the correction to the stability test data sheet for this lot gives the appearance that the resolution was performed on June 9, 2013.

Your firm's procedure SOP QA008/02 "Documentation Practices" prohibits backdating or re-creating document entries without supporting documents, and instructs your staff that the data must be recorded on the CGMP document at the time the activity is performed. Your response indicates that you revised SOP QA008/02 "Documentation Practices" to clarify how to document missed entries with appropriate retraining. While we acknowledge your commitments for retraining on the revised procedure, we remain concerned about the capability and credibility of your quality control laboratory.

Our inspection revealed that your firm selectively omitted CGMP records directly related to the testing and manufacturing of your products. You are responsible for the accuracy and integrity of the data generated by your firm. A firm must maintain all raw data generated during each testing and manufacturing operation, including graphs, charts, and spectra from laboratory instrumentation. You must properly identify these records to demonstrate that each released batch was manufactured in accordance with validated parameters, was tested appropriately, and met release specifications. Your firm's executive management is responsible for ensuring the quality and safety of your products. Implementing adequate controls and systems to prevent omission and manipulation of laboratory data is at the foundation of fulfilling this critical responsibility.

The above examples raise serious concerns regarding the integrity, reliability and accuracy of the data generated and available at your facility. In your response to this letter, provide a comprehensive evaluation of the extent of the omission, deletion and destruction of records, a risk assessment regarding the potential impact on the quality of products, and a comprehensive corrective and preventive action plan. Your response should include a summary of your investigation into missing, inaccurate or unreliable tests results with a description the findings. Your investigation should assess the impact of these and any similar incidents on the quality of the drug products produced with your APIs, and should describe the steps that will be taken to prevent these fundamental breaches of data integrity and management oversight in the future.

Your plan should also ensure that controls are put in place that are sufficient to prevent omissions of data and prevent unauthorized changes to existing data. Any changes to data should only occur in strict accordance with approved established procedures, and the date of change, identity of person who made the change, and an explanation or reason for the change should always be recorded. Your firm also needs to improve its procedures for analyzing complaints, handling OOS results, and assuring effectiveness of corrections following investigations into deviations and OOS results.

Accordingly, you should include a detailed description of your plan to implement a robust quality system in your response to this letter. This remediation plan should describe the broader steps taken to ensure direct and effective corporate oversight of the quality and operation functions of this facility. This system should ensure sustainable compliance with CGMP, including the basic capability to prevent data manipulation and destruction or deletion of records.

Your plan should also describe your commitment, procedures, actions, and controls to ensure data integrity generally. This plan should describe the corrective actions implemented to ensure that all managers, supervisors, and quality unit personnel are properly trained in detecting a lack of data integrity and data manipulation. The investigation should provide detailed descriptions of any other incidents where your quality unit failed to ensure proper testing of any materials and should include a retrospective review of all test results generated by your laboratory personnel.

Please note that the guidance document entitled "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" (ICH CGMP guidance), prepared under the auspices of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, describes current good manufacturing practice (CGMP) for the manufacture of APIs. The guidance is intended to help ensure that all APIs meet the standards for quality and purity they purport or are represented to possess. FDA considers the expectations outlined in ICH Q7, as well as alternatives intended to accomplish the same goals and provide an equivalent level of quality assurance, in determining whether a firm's APIs have been manufactured, processed, packed, and held according to current good manufacturing practice under section 501(a)(2)(B) [21 USC 351(a)(2)(B)] of the Act. To obtain the ICH CGMP guidance document for your reference, please refer to the following page of FDA's website: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf[1]

We acknowledge that you committed to hiring a third party auditor with experience in detecting data integrity problems to assist you with this evaluation and to assist with your overall compliance with CGMP. Your data integrity consultant should:

1. Identify any historical period(s) during which inaccurate data reporting occurred at your facilities.
2. Identify and interview your current employees who were employed prior to, during, or immediately after the relevant period(s) to identify activities, systems, procedures, and management behaviors that may have resulted in or contributed to inaccurate data reporting.
3. Identify former employees who departed prior to, during, or after the relevant periods and make diligent efforts to interview them to determine whether they possess any relevant information regarding any inaccurate data reporting.
4. Determine whether other evidence supports the information gathered during the interviews, and determine whether additional facilities were involved in or affected by inaccurate data reporting.

5. Use organizational charts and SOPs to identify the specific managers in place when the inaccurate data reporting was occurring and determine the extent of top and middle management involvement in, or awareness of, data manipulation.
6. Determine whether any individual managers identified in item (5) above are still in a position to influence data integrity with respect to CGMP requirements or the submission of applications; and establish procedures to expand your internal review to any other facilities determined to be involved in, or affected by, the inaccurate data reporting.
7. As part of this comprehensive data integrity audit of your laboratory, your audit report also should include any discrepancies between data or information identified in approved applications (including Drug Master Files), and the actual results, methods, or testing conditions submitted to the Agency. Include an explanation of the impact of all discrepancies. Provide a corrective action operating plan describing the specific procedures, actions and controls that your firm will implement to ensure integrity of the data in each application currently submitted to the Agency and all future applications. This should not only cover methods validation, but any other testing (e.g., stability tests, release tests) or operations you have performed for customers that may have been used to support a drug application-related submission to the agency.

Finally, in response to this letter, you should also provide a list of all the batches of APIs in distribution and those intended to be shipped to the U.S. market that relied upon missing, inaccurate, or unreliable test data.

The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility. You are responsible for investigating and determining the causes of the deviations identified above and for preventing their recurrence and the occurrence of other deviations.

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 Program immediately, as you begin your internal discussions, 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 Program 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. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

Until all corrections have been completed and FDA has confirmed corrections of the deviations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as an API manufacturer. In addition, your failure to correct these deviations may result in FDA continuing to refuse admission of articles manufactured at Apotex Pharmachem India Pvt. Ltd. located at Plot # 1A Bommasandra Ind. Area, 4th Phase, Jigani Link Road, Bangalore, India into the United States. The articles are subject to refusal of admission pursuant to section 801(a)(3) of the Act, 21 USC § 381(a)(3), in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the Act, 21 USC § 351(a)(2)(B).

Within fifteen 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 deviations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. In addition, if you no longer manufacture or distribute the APIs at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3005466325.

Please send your reply to:

Maan Abduldayem
Compliance Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Manufacturing and Product Quality
Division of International Drug Quality
White Oak, Building 51 room 4212
10903 New Hampshire Ave.
Silver Spring, MD 20993

Sincerely,
/S/
Thomas Cosgrove, J.D.
Acting Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

CC:
Dr. P.M. Akbarali
Managing Director
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1. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryinformation/Guidances/UCM073497.pdf