Apotex Research Private Limited 1/30/15

Department of Health and Human Services

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

Warning Letter

WL: 320-15-06

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

January 30, 2015

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 June 23, 2014 through July 1, 2014, inspection of your pharmaceutical manufacturing facility, Apotex Research Private Limited (ARPL) located at Plot #1 & 2, Bommasandra Ind. Area, 4th Phase, Jigani Link Road, Bangalore, India, investigators from the U.S. Food and Drug Administration (FDA) identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 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 July 22, 2014 and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated August 11, 2014, August 29, 2014, September 30, 2014, October 31, 2014, December 5, 2014 and January 9, 2015.

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

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 (21 CFR 211.194(a)).

The inspection of your facility documented multiple incidents of performing "trial" testing of samples, disregarding test results, and reporting only those results from additional tests conducted. For example,

a. The official release data for **(b)(4)** and **(b)(4)** Tablets **(b)(4)** mg batch **(b)(4)** for unknown impurities was reported to be within specification (NMT **(b)(4)**%). However, the chromatographic data showed that the "trial" injection data for this batch failed the unknown impurities specification with a result of **(b)(4)**%.

b. The official High Performance Liquid Chromatography (HPLC) impurity data for **(b)(4)** mg Tablets batch **(b)(4)** (**(b)(4)**), 3-month stability time-point @ 25°C/60% RH only included the most favorable result obtained from multiple test results without any justification. The data from this batch was submitted to the U.S. FDA as an exhibit batch.

In addition to the examples above, our inspection found that 2,803 of 44,643 injection results were not processed or reported in the official data folder for dissolution analysis via HPLC for **(b)(4)** Tablets. Our inspection identified numerous examples of "trial" injections for various drug products (U.S. and non-U.S. markets), which suggests that this is a common practice.

Your response to our findings of "trial" injections attempts to explain the rationale for retesting **(b)(4)** and **(b)(4)** (1a above). You state that "the unknown were intermittent spikes resulting in aberrant chromatography caused by electronic disturbance or pressure fluctuation." Your subsequent investigation into the observation concluded that "the unknown impurity peak…is not characteristic of the product and was not observed in the analysis of all commercial and exhibit batches." The fact that you did not observe the peak in commercial and exhibit batches does not justify disregarding the test run or failing to follow up with appropriate corrective actions and preventive actions.

According to your response, your laboratory supervisor confirmed that he was aware of the repeated testing of the **(b)(4)** stability samples (1b above) and that he allowed the analyst to repeat the analysis without conducting further investigation. Your response also states the following: "sample injections were not processed as the analyst failed to record the sample preparations in the analytical laboratory notebook and did not integrate the chromatograms for reporting." This explanation does not resolve the Agency's concerns, but instead raises further issues.

You indicate in your response that you initiated investigations for these incidents, some of which occurred over two (2) years ago; however, you did not provide documentary evidence to support your assertions about the repeat testing and related activities. Your response is inadequate because you did not extend the scope of the investigation to the other electronic systems used in each of your laboratories. As part of your corrective action and preventive action plan, address how your firm intends to ensure the reliability and completeness of all analytical data generated at your facility.

2. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

QC personnel created unauthorized folders on laboratory computerized systems without appropriate oversight. Our review of the HPLC Empower III data collected in 2013-2014 in the commercial QC laboratory found a data folder entitled "WASH." According to your management, the folder was intended for column wash injections using blank solvent prior to and following sample runs, although you have no standard operating procedure (SOP) detailing this process. One of your laboratory analysts stated that this folder does not contain

any standard or sample injection results. However, our investigator found that this folder contained a total of 3,353 injection results, some of which appeared to be samples.

Your analyst confirmed that the single injection titled “19” in the “WASH” folder represented a trial sample injection performed prior to the official analysis of **(b)(4)** Tablets on December 19, 2013. From this chromatogram in the “WASH” folder, our investigator documented an unidentified impurity at relative retention time (RRT) **(b)(4)** calculated at a concentration of **(b)(4)**%. However, the specification for any unidentified impurity is **(b)(4)**%. You neither investigated nor reported this out-of-specification (OOS) result.

Your firm acknowledged that the analysts involved in performing single injections failed to follow good laboratory practices described in the SOP “General Laboratory Working,” and that the analysts conducting the injections in question made decisions to perform unauthorized, unapproved injections. Your response indicates that, during an interview of the laboratory analyst conducted approximately six months after the incident, you determined that he may inadvertently have used an old sample vial from the LC tray for the single injection made for the purpose of a column wash. We question your conclusion about the likely cause without having any supporting documentation or record, and based only on memory of what may have happened six months earlier.

In correspondence with the Agency, you indicate that no malicious data integrity patterns and practices were found. Also, you state that no intentional activity to disguise, misrepresent or replace failing data with passing data was identified and no evidence of file deletion or manipulation was found. Your response and comments focus primarily on the issue of intent, and do not adequately address the seriousness of the CGMP violations found during the inspection. In addition, FDA’s inspection did not include observations related to deletion of specific files, intentionally or otherwise. Rather, FDA’s concern pertains to the practice of disregarding failing results, conducting trial injections and retesting products without any investigation. We are also concerned that you do not have documentation to support your decision to retest samples of lots that had initially failed to meet specifications, and you allowed manufacturing activities to occur without the oversight of your quality unit.

As part of your comprehensive evaluation and risk assessment, include a detailed description of all computerized systems in your facility used for testing drugs. This description should include information on each electronic folder that was not created pursuant to a valid SOP and an assessment of every file in each such folder, including information about the sample (product), date of test, lot number and original test result over the last five (5) years, except for data relating to exhibit batches, in which case there is no time limitation. Also provide specific information about all retests during these time frames, where an initial out-of-specification or out-of-trend result was disregarded without an investigation and the date on which you became aware such information had been disregarded. In addition, for each batch, provide the number of injections performed and chromatograms reviewed, and of those, the number that were used to generate a reported result. Furthermore, provide an updated assessment on the possible effects of your firm’s practices on the quality, safety, and efficacy of the drugs you manufacture or plan to manufacture, including drugs covered by approved or pending applications.

In your corrective action and preventive action plan, describe in detail your revised control process for ensuring that batches with retest results are not released until a thorough investigation is conducted. Also describe how you intend to prevent these failures from recurring in the future, and how you will measure the effectiveness of your corrections. Also describe the procedures established to manage and retain all computerized data.

3. Your firm failed to establish and follow appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile (21 CFR 211.113(a)).

On June 23, 2014, during the inspection of the QC Microbiology Laboratory, our investigators observed missing in-progress microbiological test plates for various finished drug products, in-process products, water, and media growth promotion samples. For example:

a. Finished drug product **(b)(4)** Tablets **(b)(4)**mg batches **(b)(4)** and **(b)(4)** microbial sample plates/tubes were placed in the incubators on June 19-20, 2014, as documented in your LIMS computer system. The plates should have been incubated for **(b)(4)** days, per your procedures. On June 23, 2014, no plates/tubes for this batch were observed in any of the incubation chambers.

b. Finished drug product **(b)(4)** Tablets **(b)(4)** mg Exhibit Batch **(b)(4)** sample for microbial testing was prepared on June 13, 2014. Your firm failed to provide the FDA investigator with the worksheet to document the incubation times and media used for the analysis. Your analyst described that the entire microbial test for this batch had already been completed the previous week but that the analyst had "forgotten" to document the details on the worksheet.

The FDA investigator noted other instances of missing samples/plates for in-process drug products, potable water, and growth promotion, even though records indicated that they were in the incubator.

As a result of the above observation, your firm initiated an investigation and reported that 290 **(b)(4)** plates and 36 media tubes under testing were missing, affecting 45 product sample batches, 12 growth promotion test batches, and 37 negative control plates. Your firm also found discrepancies between the documentation and location of samples/plates and you indicated that the majority of the missing plates were found in the decontamination area for disposal.

In your response, you refer to an investigation and indicate that "…two analysts momentarily panicked (upon (1) learning that FDA Investigators were approaching the microbiology Lab and (2) seeing used petri plates from the weekend scattered throughout the laboratory)[*sic*] and directed the lab technician to immediately remove the petri plates from the microbiology lab … in an utterly misguided and ill-conceived attempt to clean up the microbiology lab prior to the start of the FDA inspection."

Your response lacks a comprehensive risk assessment of your failure to follow procedures, your inadequate documentation system and your inadequate practices related to microbiological control. Your response failed to evaluate the effect of these violations on product quality, and did not include an assessment as to whether any other batches have been compromised.

ARPL's inability to prevent and detect poor recordkeeping practices raises serious concerns regarding the quality system in place at the time of the inspection. Appropriate controls are essential to assure that the information used for making decisions is trustworthy, accurate, and reliable.

4. **Your firm failed to follow written procedures applicable to the quality control unit (21 CFR 211.22(d)) and your quality control unit failed to review and approve all drug product production and control records to determine compliance with all established, approved written procedures before a batch is released or distributed (21 CFR 211.192).**

For example:

a. Your procedure titled “Quality Unit Responsibility” (#GPOL-004 dated 07/09/2013) states that “any deviation shall be investigated to discover possible causes and prevent possible reoccurrence.” Although your written procedure clearly describes the protocols for handling deviations, your quality unit management indicated to our investigator that there were no deviation reports, no OOS investigations, nor any evaluations to address the possible root cause(s) of the deviations/OOSs. Among other failures, your quality unit did not follow your procedures for conducting investigations into the examples listed in citation #1 of this letter.

b. Your firm’s implementation of the audit program described in the Global Policy "Audit Program" document #GPOL-015 dated September 7, 2013 is inadequate in that it failed to prevent the recurrence of testing unofficial samples of drug product prior to testing the official sample and generating only those results to be reported.

c. In addition the inspection revealed that failing or otherwise atypical results were not investigated, nor included in the official laboratory control records as required by 21 CFR 211.192. We reiterate that an investigation is necessary for any out-of-specification (OOS) event. Refer to the FDA's guidance on OOS investigations *Guidance for Industry, Investigating Out-of-Specification (OOS), Test Results for Pharmaceutical Production*.

Your quality unit is responsible for assuring that your firm is operating in a sustainable state of control throughout the manufacture and lifecycle of all drugs produced at your facility. Your quality unit has the overall responsibility for oversight and approval of quality related activities. As part of your corrective action and preventive action plan, please describe how your quality unit will provide consistent, adequate review and approval of investigations and production batch records.

Be aware that Apotex was notified of our concerns with the practice of “trial” injections during FDA’s January 2014 inspection at your Apotex Pharmachem India Pvt. Ltd. located at Plot # 1A Bommasandra Ind. Area, 4th Phase, Jigani Link Road, Bangalore, India. However, our findings during this inspection suggest that corrective actions were not implemented globally. Furthermore, inadequate oversight by your firm’s site-specific quality units is a repeat finding from WL: 320-10-003 dated March 29, 2010. The need for appropriate and global quality oversight was communicated to Apotex senior management during the regulatory meetings held September 11, 2009, March 31, 2010, and April 11, 2014.

Conclusion

The foregoing examples are of serious CGMP violations demonstrating that your quality system does not adequately ensure the accuracy and integrity of the data generated at your facility to ensure the safety, effectiveness, and quality of the drug products you manufacture. We found that your quality system failed to ensure the adequate investigation and resolution of quality failures. ARPL failed to investigate OOS results, failed to contemporaneously document failures and report failures, and selected only passing results without the oversight of a quality unit. In your response and in subsequent communications with the agency, you indicated that you interviewed employees and found no evidence of data manipulation or deletion. In focusing on the issues of deletion and alteration of data, you have not sufficiently addressed or resolved other substantial CGMP issues as discussed above. In response to this letter and including the specific requests noted above, provide the following to the Agency:

1. A comprehensive evaluation of the extent of the inaccuracy of recorded and reported data. As part of your comprehensive evaluation, provide a detailed action plan to investigate the extent of the deficient documentation practices noted above;

2. A risk assessment of the potential effect of the observed failures on the quality of drug products. As part of your risk assessment, determine the effects of your deficient documentation practices on the quality of the drug product released for distribution; and

3. A management strategy for your firm that includes the details of your global corrective action and preventive action plan.

a) As part of your corrective action and preventive action plan, describe the actions you have taken or will take, such as contacting your customers, recalling product, conducting additional testing and/or adding lots to your stability programs to assure stability, monitoring of complaints, or other steps to assure the quality of the product manufactured under the violative conditions discussed above.

b) In addition, as part of your corrective action and preventive action plan, describe the actions you have taken or will take, such as revising procedures, implementing new controls, training or re-training personnel, or other steps to prevent the recurrence of CGMP violations, including breaches of data integrity.

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. We acknowledge that you are working with a third party consultant already to conduct a compressive audit of your systems and 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 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 violations and your firm’s compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, your failure to correct these violations may result in FDA continuing to refuse admission of articles manufactured at Apotex Research Private Limited located at Plot #1 & 2, Bommasandra Ind. Area, 4th Phase, Jigani Link Road, Bangalore, India into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The articles may be subject to refusal of admission pursuant to Section 801(a)(3) of the Act, 21 U.S.C. 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 U.S.C. 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 violations, 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. Additionally, if you no longer manufacture or distribute the drug products at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3006076314.

We also recommend that you contact Araceli Rey at Araceli.rey@fda.hhs.gov, or 301-796-3284, within five days of receipt of this letter to schedule a regulatory meeting with Apotex Research Private Limited and Apotex Inc.

Please send your reply to:

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

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

CC:
Dr. Parizad Elchidana
Managing Director
Apotex Research Private Limited
Plot #1 & 2, Bommasandra Ind. Area
4th Phase, Jigani Link Road
Bangalore, India – 560 099