WARNING LETTER

Apotex Research Private Limited

MARCS-CMS 547439 — AUG 09, 2018

Recipient:

Dr. Ravinder Kumar

Apotex Research Private Limited

Plot 1 & 2, Bommasandra Industrial Area
4th Phase, Jigani Link Road
Bangalore 560099 Karnataka
India

Issuing Office:

Center for Drug Evaluation and Research

United States

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS

Warning Letter 320-18-69

August 9, 2018

Dr. Ravinder Kumar
Managing Director
Apotex Research Private Limited
Plot 1 & 2, Bommasandra Industrial Area
4th Phase, Jigani Link Road
Bangalore—560 099
Karnataka
India

Dear Dr. Kumar:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Apotex Research Private Limited at Plot 1 & 2, Bommasandra Industrial Area, 4th Phase, Jigani Link Road, Bangalore, from November 6 to 17, 2017.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your December 11, 2017, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

Your investigations into out-of-specification (OOS) laboratory results and manufacturing deviations are insufficient and do not include scientifically-supported conclusions. For example:

A. You tested **(b)(4)** for **(b)(4)** capsule samples collected at **(b)(4)** locations during the manufacture of **(b)(4)** capsules, **(b)(4)** mg, batch **(b)(4)**. The relative standard deviation (RSD) was OOS: **(b)(4)**% (specification is not more than **(b)(4)**%). You then tested reserve capsules and obtained additional OOS results for this batch. One unit assayed at **(b)(4)**% (specification is **(b)(4)**–**(b)(4)**%), and the RSD was **(b)(4)**% (specification is not more than **(b)(4)**%). Your firm excluded the individual sub potent assay OOS result and recalculated the RSD results as passing with a new value of **(b)(4)**%.

You did not test the reserve capsules and investigate the failing **(b)(4)** capsule **(b)(4)** results until approximately one and a half months after you used the same batch of **(b)(4)** capsules for in-vivo bioavailability studies on December 17, 2016.

Your response is inadequate. You attributed this failure to an "unknown lab error." You claimed that the low individual assay test result was an outlier and that the most probable root cause was analytical error. Outlier tests have no applicability in cases where the variability in the product is what is being assessed, such as for **(b)(4)**. You did not provide sufficient justification for disregarding the low result or supporting your unspecific conclusion of unknown laboratory root cause.

B. You initiated an investigation into OOS and out-of-trend (OOT) assay results for **(b)(4)** tablets, **(b)(4)** mg and **(b)(4)** mg, three-month stability samples (batches **(b)(4)** and **(b)(4)**). Your May 2017 investigation states that you also obtained low OOT assay values at the one-month time point. You concluded the OOS and OOT results were due to analyst error during sampling preparation but lacked data to support your conclusion. Your testing associated with the investigation did not demonstrate that sample preparation caused the aberrant results as assay values did not differ substantially when you varied sample preparation.

You did not extend the investigation to manufacturing, although your Site Incident Response Committee requested initiation of this part of the investigation. Notably, you performed the manufacturing phase of the investigation after our inspection.

Your response explains that a third party performed a retrospective review of nine invalidated OOS investigations and that in "all cases, the investigations were found to be thorough and robust and the findings were sufficiently justified." However, this is not fully consistent with your third-party report. Regarding this specific OOS investigation, your third-party report says it "did not believe sufficient scientific evidence was presented in the laboratory OOS investigation process to justify retesting. Only retesting and obtaining passing results are the basis of conclusions."

C. Variance investigation checklists (VIC) and variance investigation reports (VIR) used to investigate poor chromatography and failing results are inadequate. These VIC and VIR investigations are not subject to your OOS investigational procedures, and you do not track and trend them. Our inspection identified that you used test results obtained with your VIC and VIR investigations to replace original results. Further, your personnel stated that they retested a sample as part of a VIR investigation because they did not want to show low results to a customer.

Your response is inadequate. You have not provided the retrospective review of all VIC and VIR investigations.

D. On August 8 and 9, 2017, you observed capped and edge-worn tablets in two batches of **(b)(4)** tablets, **(b)(4)** mg. You rejected a substantial number of units from each batch due to these defects. You opened an investigation, which closed September 7, 2017, and concluded the most probable root cause was high **(b)(4)** force. You lacked scientific evidence to support this root cause as other batches had been successfully produced in that range. After observing a third batch with capped **(b)(4)** tablets, **(b)(4)** mg, in October 2017, you initiated another investigation.

Your response acknowledges that the tablet defects may be due to multiple root causes and you continue to investigate the issue. However, your response lacks a detailed update on the investigations into the capped tablets. You also did not include corrective action and preventive actions (CAPA) initiated in association with the investigations.

In response to this letter:

- Explain why **(b)(4)** mg capsule batch **(b)(4)** was shipped and used for your bioequivalence studies before testing and investigational activities were completed. Also, describe whether your procedures

require all testing and investigations to be completed prior to batch release.

- Perform a three-year retrospective review to determine whether outlier tests have been used in previous OOS investigations, and determine whether you used them to improperly invalidate OOS results.
- Provide the report and associated CAPAs for your retrospective review of all VIRs and VICs initiated since January 1, 2015. Include a third-party assessment of each of the VIRs and VICs, and of your firm's final report.
- Assess the procedures you use to evaluate **(b)(4)** uniformity, including collecting and testing samples and evaluating results.
- Provide a comprehensive, independent assessment of your overall system for investigations of laboratory and manufacturing-related deviations, discrepancies, complaints, OOS results, and failures. Your CAPA plan should include but not be limited to improvements in investigation competencies, root cause analysis, written procedures, and quality unit oversight. Also, include an improved process for evaluating CAPA effectiveness.

For more information about handling failing, out-of-specification, out-of-trend, or other unexpected results and documentation of your investigations, see FDA's guidance document, *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*, at https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf (/media/71001/download).

2. Your firm failed to establish valid in-process specifications (21 CFR 211.110(b)).

Your firm failed to establish appropriate in-process specifications to ensure the quality of **(b)(4)**. During our inspection, your management explained that **(b)(4)** could not be tested **(b)(4)** because the material was not **(b)(4)** and could fail assay specifications. OOS **(b)(4)** should not be **(b)(4)** with other batches for the purpose of meeting specifications.

Your response included a process flow diagram which shows that **(b)(4)** of **(b)(4)** undergo separate dispensing, **(b)(4)**, and **(b)(4)** steps, and are not tested separately **(b)(4)**. You stated that assay testing at the **(b)(4)** stage is not a critical quality attribute because the **(b)(4)** is incomplete. You also acknowledged that you did not perform this **(b)(4)** testing during process validation studies. This response is inadequate. **(b)(4)** should be individually tested and found to meet appropriate specifications **(b)(4)**.

In response to this letter, remediate your current procedures to ensure that **(b)(4)** are tested for appropriate quality attributes **(b)(4)**. Provide us with any updates made to your procedures. Provide a list of all products manufactured in a similar manner and include an assessment of the effects on any batches produced in this manner which are within expiry.

Quality Unit Authority

Your inspectional history indicates that your quality unit does not fully exercise authority, such as ensuring that appropriate investigations are performed with sound conclusions, identifying root causes, and supporting scientific justification. Your firm must provide your quality unit with appropriate authority, sufficient resources, and staff to carry out its responsibilities and consistently ensure drug quality.

Quality Systems

Your firm's quality systems are inadequate. For guidance on establishing and following CGMP compliant quality systems, see FDA's guidance for industry:

- *Q8(R2) Pharmaceutical Development*, at https://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf (/media/71535/download);
- *Q9 Quality Risk Management*, at https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf (/media/71543/download); and
- *Q10 Pharmaceutical Quality System*, at https://www.fda.gov/downloads/drugs/guidances/ucm073517.pdf (/media/71553/download).

Repeat Violations and Deviations at Multiple Sites

FDA has cited similar CGMP violations and deviations at this and other facilities in your company's network. In the last five years, FDA has taken the following actions in response to CGMP violations and deviations at Apotex facilities.

1. FDA placed Apotex Pharmachem India Private Limited on Import Alert on April 1, 2014, and issued a warning letter on June 16, 2014, which cited failure to investigate and document OOS results.

2. FDA placed Apotex Research Private Limited on Import Alert on September 22, 2014, and issued a warning letter on January 30, 2015, which cited failure to follow written procedures applicable to the quality control unit.

FDA has previously communicated about the need for appropriate and global quality oversight to Apotex senior management during several regulatory meetings.These repeated failures at multiple sites demonstrate that management oversight and control over the manufacture of drugs is inadequate.

Your quality system has not implemented effective corrective actions to ensure the accuracy and integrity of the data generated at your facility, which is necessary to ensure the safety, effectiveness, and quality of the drug products you manufacture. There will be additional communications from CDER's Office of Pharmaceutical Quality regarding these issues. The Office of Generic Drugs may subsequently provide comment regarding the effect of these findings on **(b)(4)** if needed.

CGMP consultant recommended

Because you failed to correct repeat violations, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34, to assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance, and evaluate the completion and effectiveness of any corrective actions and preventive actions you have implemented before you pursue resolution of your firm's compliance status with FDA. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations in all your facilities.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA 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 or interruptions in your drug manufacture under 21 U.S.C. 356C(b) 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.

FDA placed your firm on Import Alert 66-40 on April 12, 2018.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in FDA continuing to refuse admission of articles manufactured at Apotex Research Private Limited at Plot 1 & 2, Bommasandra Industrial Area, 4th Phase, Jigani Link Rd., Bangalore, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, 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 FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov) or mail your reply to:

Brooke K. Higgins
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3006076314.

Sincerely,
/S/
Francis Godwin

Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

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