Inspections, Compliance, Enforcement, and Criminal Investigations

Apotex Inc. 2/21/13

Department of Health and Human Services

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

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Warning Letter

WL: 320-13-09

February 21 , 2013

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 August 13, 2012 through August 24, 2012, inspection at your pharmaceutical manufacturing facility, Apotex, Inc., located at 150 Signet Drive, Toronto, Canada, and our October 18, 2012 through October 26, 2012, inspection of your pharmaceutical manufacturing facility, Apotex, Inc., located at 380 Elgin Mills Road East, Richmond Hill, Ontario, Canada, 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, Part 210 and 211. These violations cause your drug product(s) 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 responses of September 14, 2012 and November 16, 2012, and note that they lack sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated October 11, 2012 and December 14, 2012.

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

A. Apotex, Inc., 150 Signet Drive, Toronto, Canada

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be

> sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

For example, you failed to perform adequate unidirectional airflow pattern studies (i.e., smoke studies) for the aseptic filling line used for the production of **(b)(4)** Injection. The smoke studies did not include examination of airflow during set-up and at points of process intervention. Moreover, your airflow patten studies for the class 100 area of the **(b)(4)** filling line show clear evidence of turbulent airflow in your filling line located in Room **(b)(4)** both above the **(b)(4)** just prior to entry into the filling zone and over the stopper bowl adjacent to the filling zone. Although this lack of unidirectional airflow can compromise sterility, you failed to take appropriate action to ensure that your parenteral drug products were protected from these contamination hazards.

An *in situ* air pattern analysis should be conducted in all critical areas under dynamic conditions, to demonstrate unidirectional airflow and sweeping action at critical work areas.
These studies should evaluate the impact of aseptic manipulations (e.g., interventions) and equipment design, document the activities performed, and include written conclusions. In your response to this letter, provide a copy of your new smoke study recordings along with supporting documentation.

According to your September 14, 2012 response, you committed to conduct smoke studies by December 31, 2012. In your response to this letter, provide an update of all airflow pattern studies conducted, your evaluation of the results, and your proposed corrective and preventive actions. In addition, provide your risk assessment for all sterile products within expiry that were manufactured under these unacceptable conditions.

In addition, your firm failed to establish maximum holding times for vials used in media fills, prior to incubation. Your media fill protocol for batch **(b)(4)** does not establish a set timeframe between completion of filling vials and placing filled vials in the incubators. Our investigator found that, during a media fill operation you filled the vials on July 24 and July 25, 2012, and did not incubate them until July 30, July 31, and August 1, 2012. Your manager attributed the delay to lack of space to perform the visual inspection and to personnel resource constraints. Upon completion of filling the media fill vials, the vials should be incubated under conditions (time and temperature) adequate to allow detection of microorganisms that might otherwise be difficult to culture. Data should be maintained to show monitoring of, and conformance to, those conditions.

Your response indicates that you initiated a change control to have a maximum hold time of **(b)(4)** from end of filling to start of incubation of the media fill vials. In your response, provide your justification for the **(b)(4)** maximum hold time. In addition, specify the required storage conditions for the media vials during this hold period and their justification. In you response please also provide a summary of your assessment regarding whether the vial hold conditions between filling and incubation for batch **(b)(4)** affected the conclusions of your media fill studies, including whether you plan to repeat the studies and the rationale supporting this decision.

> 2. 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).

Our investigator found that your firm released partial batches to the U.S. market without specific criteria for the partial release decision and without appropriate investigations. You have been cited for the same practice in previous warning letters. Indeed, your firm released at least 76 sublots from January 2011 to August 2012 without adequate investigations.

For example, on April 13, 2011, while **(b)(4)** the **(b)(4)** during the **(b)(4)** step for **(b)(4)** tablets, batch **(b)(4)**, your operator noticed five tablets with breached **(b)(4)** in **(b)(4)**, a critical defect. The documentation available indicates that the **(b)(4)** used for **(b)(4)** of the

tablets was **(b)(4)** prior to the start of **(b)(4)**, and your firm re-sampled **(b)(4)** and found that **(b)(4)** had one critical defect. Your firm permits zero critical defects at the **(b)(4)** step. Your firm rejected **(b)(4)**. On May 4, 2011, your firm released the tablets from **(b)(4)** to market as batch #**(b)(4)**. Your investigation and your response indicate that the breached **(b)(4)** was attributed to the use of a **(b)(4)** with rough edges and variation of the **(b)(4)** technique. However, your firm failed identify the control to be used during the **(b)(4)** step in the future to ensure that the **(b)(4)** condition does not affect product quality. Please explain the basis for your conclusion that the only affected part of the batch was the rejected portion.

In addition, on May 25, 2011, during the compression of **(b)(4)** tablets batch #**(b)(4)**, your Quality Control Unit rejected a portion of the batch due to black specks observed on the tablets. However, your firm failed to identify the contaminant(s) found in this lot, and according to your investigation report, you were not able to determine a definitive root cause. In your September 14, 2012 response you indicated that the specks may have been linked to punches and punch seals, and that you released for distribution the remaining sublot, as #**(b)(4)**.

In the foregoing and many other investigations, you did not identify the true root cause(s) of the various deficiencies. Accordingly, the actions taken often did not prevent recurrence of the problems. Your September 14, 2012 response indicates that you will further define and update sublot disposition procedures. During a TCON held on November 7, 2012 between the FDA and Apotex, you made a commitment to discontinue the practice of partially releasing batches that could be potentially affected by a quality issue, as in the referenced examples. We remain concerned about the lots affected by this practice and released into distribution; your response did not provide information to show that a thorough investigation to determine the cause of each unexplained discrepancy or failure to meet specifications had been conducted. Your response also lacks a description of appropriate corrective and preventive actions implemented, along with any risk assessment conducted prior to the release of each sublot.

Your firm's practice of rejecting portions of drug product batches is an indication that your firm does not have well-controlled manufacturing processes. In addition, it raises concerns about the quality of the portions of those batches that you released. In your response to this letter, please describe how you intend to address these concerns. It is important that your firm's investigation procedures ensure that you perform a full investigation extending to all associated lots, including determining root cause(s), prior to distribution. We will verify the implementation of your revised investigation procedures during a future inspection.

Additionally, we are concerned about your approach to process validation. Your experience with the manufacture of **(b)(4)** mg and **(b)(4)** mg tablets suggests that product and process development studies were not comprehensive enough to sufficiently understand the interaction between material properties, equipment, and processing parameters in order to establish the right control strategy. The failure of your first commercial scale validation attempt for these products necessitated significant equipment and in-process material changes. While these changes may have improved the compression and **(b)(4)** issues, you still observed defects related to tablet capping in the second validation effort. Your investigation concludes - "… reduced tablet hardness during compression contributed to generate a small number of tablets that were prone to capping." We reviewed the Process Validation Report PVS-12-056-FR and associated investigation but important questions still remain. Regarding **(b)(4)** mg tablets, please address the following points and questions in your response:

a) The appropriateness of the current lower hardness limit. Also, what is the target hardness value?

b) You included no analysis or characterization of the hardness variability in your process validation report. Provide the summary of the in-process hardness data, an appropriate statistical analysis of the data and characterization of the hardness variability in the individual validation lots and overall.

c) Do factors other than **(b)(4)** affect tablet hardness, e.g., **(b)(4)** operation and **(b)(4)** characteristics? How have you evaluated this?

d) Your analysis of root cause(s) and plans for both corrective and preventive actions.

e) With regard to batch **(b)(4)**, the **(b)(4)** acceptable quality level (AQL) failure and partial release: If the compression process was stable, softer tablets would be present throughout the tablet core batch and not limited to only one of the **(b)(4)**. We understand you collected an AQL sample from each of the **(b)(4)**and only one **(b)(4)** failed. Based on this result you rejected that **(b)(4)** and released the other **(b)(4)** of tablets. Because you believe the **(b)(4)** AQL failure was related to hardness, an attribute created in the previous unit operation, you should have thoroughly evaluated the compression operation, the tablet core batch as a whole, and the final **(b)(4)** tablet batch as a whole to ensure that the problems present in the failed batch were not also present in the released batches.

3. 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)).

For example, on August 22, 2012, an FDA investigator observed your microbiologist reading an environmental monitoring (personnel) plate. The microbiologist reported the result for that plate as zero; however, our FDA investigator observed one (1) colony forming unit (CFU) on the plate. Your microbiologist corrected this observation on the form WI-MI-150-108-J Microbiology Laboratory after the FDA investigator pointed it out to him. Your firm did not take further action to investigate and determine the impact of inaccurate reporting of your microbiological plate readings on the release of your batches.

The failure to document positive results for a microbial plate that was confirmed as containing microbial growth raises concerns about the accurate reporting of results in your records. Accurate and reliable microbial data management is essential to support the reliability of your aseptic manufacturing of finished drug products intended for distribution in the United States.

B. Apotex, Inc., 380 Elgin Mills Road East, Richmond Hill, Ontario, Canada

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).

For example, **(b)(4)** Injection **(b)(4)** lot #**(b)(4)** failed its sterility test on April 19, 2012. Your firm rejected all manufactured batches of **(b)(4)** Injection **(b)(4)** up to the resumption of commercial production on June 28, 2012. However, you did not recall the lots of **(b)(4)**, manufactured on the same filling line, and still within expiry. In your response of November 16, 2012, you indicated that one of the probable root causes was the lubricant used on a **(b)(4)** for the **(b)(4)** filling line. In addition, you indicated that the last shipment of **(b)(4)** was January 21, 2011, and that all distributed batches but that one had expired. Your response was inadequate because it did not address all products within expiry as of the date of the sterility failure.

2. 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)).

For example, your firm failed to record the incubation dates of the microbiological plates in the validation study of the **(b)(4)** of **(b)(4)** for **(b)(4)** Solution, **(b)(4)** Solution, **(b)(4)** Solution, and **(b)(4)** Spray. Your procedure for the validation study requires the incubation of the **(b)(4)** plates to be **(b)(4)** to **(b)(4)** and the incubation of the **(b)(4)** plates to be **(b)(4)** to **(b)(4)**. You indicate in your response that you have revised procedures, conducted a risk assessment, and will re-execute the validation of the **(b)(4)** of **(b)(4)**. Your response is inadequate because the risk assessment did not assess the impact of your failure to document the incubation period on the released batches.

In addition, your firm failed to record and maintain the raw data to support your conclusions regarding the effectiveness of the **(b)(4)** used in **(b)(4)** Solution, **(b)(4)** Solution, **(b)(4)** Solution, and **(b)(4)** Spray. Your firm recorded the **(b)(4)** test results from **(b)(4)** plates for each time point rather than recording the actual observed colony count for each plate. In your response, you indicated that you will revise procedures, conduct a risk assessment, and re-execute **(b)(4)** effectiveness testing. However, you failed to include an assessment as to how the lack of raw data supporting **(b)(4)** effectiveness affects batches that you released to the market.

We note that some of the CGMP violations cited above are repeat violations; that is, we cited Apotex in previous warning letters for violating the same regulations, often in very similar ways. For example, in WL #320-09-06, dated June 25, 2009, we cited violative practices at your Etobicoke, Ontario, Canada facility, including a charge for inadequate investigations under 21 CFR Part 211.192. In WL #320-10-003, dated March 29, 2010, we cited violative practices at your Signet, Toronto, Canada facility, again including a 21 CFR Part 211.192 charge for inadequate investigations. In the March 29, 2010 warning letter, we also identified violations similar to those cited here and indicative of your firm's failure to have an overall quality management system (QMS) (e.g., a citation for violation to 21 CFR Part 211.22, supported by documented instances of unjustified release by your quality control unit of contaminated batches, noting your practice of repackaging, reassigning batch numbers, and releasing products for distribution notwithstanding their failure of the acceptable quality level (AQL) test).

The evidence suggests that Apotex has failed to implement adequate global and sustainable corrective and preventive actions, and that it continues to manufacture and distribute pharmaceutical product without upholding its legal obligation to comply with CGMP. FDA's inspections continue to find repeated deficiencies in your quality systems. We highly recommend that appropriate resources be used to conduct a thorough retrospective evaluation of past deficiencies and that appropriate permanent changes be implemented to ensure that your corporation manufactures pharmaceutical products using a sustainable quality platform in all your facilities. Fundamental to this responsibility is your assurance of timely investigation and resolution of the issues, prevention of distribution of defective product, and implementation of an effective quality management system across all facets of your pharmaceutical manufacturing operations.

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facilities. 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.

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.

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 refusing the admission of articles manufactured at Apotex, Inc., located at 150 Signet Drive, Toronto, Canada; and Apotex, Inc., located at 380 Elgin Mills Road East, Richmond Hill, Ontario, Canada 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 product(s) at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3002906944 for the Signet facility, and FEI # 3001617666 for the Richmond Hill facility.

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
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-3916
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Sincerely,
/Michael Smedley/
Michael Smedley
Acting Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

Department of Health and Human Services

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

ADDENDUM to Warning Letter

Re: WL 320-13-09

Date: March 19, 2013
Subject: Warning Letter 320-13-09 from the Food and Drug Administration

Warning Letter (WL: 320-13-09) was issued on February 21, 2013 with the incorrect date of February 21, 2012. The Warning Letter was amended to reflect the correct issuance date of February 21, 2013.

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