



Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Silver Spring MD 20993

Warning Letter

VIA FEDERAL EXPRESS MAIL

WL: 320 - 10 - 003

March 29, 2010

Mr. Jack M. Kay
President and COO
Apotex Inc.
150 Signet Drive
Toronto, Ontario, Canada M9L 1T9

Dear Mr. Kay:

During our July 27- August 14, 2009 inspection of your pharmaceutical manufacturing facility, Apotex Inc. located at 150 Signet Drive, Toronto, Ontario, Canada, investigators from the Food and Drug Administration (FDA) identified significant violations of the 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. In addition, our inspection revealed that you failed to submit NDA Field Alert Reports (FARs) to FDA as required by 21 C.F.R. § 314.81(b)(1) and section 505(k) of the Act [21 U.S.C. § 355(k)].

The July – August 2009 inspection uncovered several violations that are identical to those found during a December 10 – 19, 2008 inspection of your Etobicoke, Canada site that resulted in the issuance of a Warning Letter to the Etobicoke site in June 2009. These identical CGMP violations demonstrated a lack of adequate process controls and raised serious questions regarding your corporation's quality and production systems. This prompted the FDA to place both sites under import alert on August 28, 2009, whereby all finished drug products offered for entry into the United States and manufactured at the Etobicoke and Signet Drive, Ontario facilities are detained without physical

examination. Your firm has voluntarily recalled approximately 659 batches of different products manufactured at this site, and remains under Import Alert 66-40. However, this Warning Letter is being issued because of serious and repeat violations from the 2008 and 2009 inspections and because your response, dated September 3, 2009, and discussed below, is inadequate and lacks sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

CGMP VIOLATIONS

1. Your firm's quality control unit failed to follow the responsibilities and procedures applicable to release of the drug product [21 C.F.R. § 211.22(d)].

For example, **(b)(4)**, an Active Pharmaceutical Ingredient (API), batch #HY2470, was found to be contaminated with **(b)(4)** materials. You rejected part of this lot. However, you used a portion of this contaminated API to manufacture Cetirizine HCl Film Coated Tablets, 10 mg batches #HY2910 and #HY2912. These batches were released for distribution and shipped to the United States.

Additionally, Metformin HCl **(b)(4)** batch #HT2731 was found contaminated with **(b)(4)** particles identified as **(b)(4)** material, and charred material. This batch was not rejected. Instead, it was used to manufacture Metformin HCL **(b)(4)** tablets batch #HT2657, film coated into batch #HT2526, and packed into finished drug product batch #HR7670. Batch #HR7670 was subsequently released for distribution and shipped to the United States under batch #JC2151 on March 4, 2009.

The inspection also documented your practice of repackaging and assigning new batch numbers to products that failed the Acceptable Quality Level (AQL) test. Your firm lacks a scientific rationale and documentation to support this practice. For example, desiccant batch #HK8805 was used in approximately 76 different products, 11 of which failed the AQL desiccant leaking test. These 11 lots of contaminated Ranitidine Film Coated tablets 150 mg were initially rejected. However, 10 of these 11 lots were repackaged into 500 count bottles using a new lot of desiccant, and assigned a new batch number. These lots were then released for distribution without assessing the potential impact the leaking desiccant could have on product quality. You stated in your response that examination of retain samples for the 11 lots did not confirm the presence of leaky desiccant. However, it is possible that the absence of defective desiccant may be related to the limited number of retain samples examined. In your response to this letter please include a justification for

the sample size and the corrective actions you have implemented to prevent reoccurrence of these types of events.

Your response reports that for the period of July 2007 to August 2009 your firm had voluntarily recalled all products associated with: a) deviation reports, b) investigations of foreign components and material, and c) products included in opened Field Alert Reports. This corresponds to the immediate corrective action addressing this deficiency. However, your response does not address other unacceptable practices such as returning defective material back into inventory, or re-releasing failed material that was inadequately reprocessed or retested without a scientifically sound rationale and an assessment of potential impact to product quality.

Your corrective and preventive actions should include specific instructions for reprocessing and conditions under which failed material can be reprocessed and returned to inventory.

2. Your firm does not have adequate written procedures for production and process controls designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess [21 C.F.R. § 211.100(a)].

For example, three initial process validation batches (#HP0793, #HP0706, #HP0794) for Oxcarbazepine 300 mg tablets failed the dissolution test specification (Q=NLT **(b)(4)**% at 30 minutes) and the batches failed to meet the 30 minutes dissolution specification. Dissolution out of trend (OOT) results were also obtained for Oxcarbazepine 150 mg and 600 mg tablets. The same **(b)(4)** was used for the process validation of Oxcarbazepine 300 mg, 150 mg, and 600 mg tablets.

During your second attempt to perform the process validation, three batches of Oxcarbazepine tablets 300 mg (lot #HT8606, #HT8607, and #HT8608) were made from one **(b)(4)** that failed to meet the 30 minutes dissolution specification. You released Oxcarbazepine 150 mg and 600 mg tablets that were manufactured from the same **(b)(4)** that was used to manufacture the 300 mg strength. Your investigation Q-note 200071071 concluded that the dissolution results were affected by the order in which the excipient **(b)(4)**, USP was added during the **(b)(4)** process. Appropriate process design studies were not conducted to scientifically establish the correct order of adding excipients, e.g., **(b)(4)**, during the **(b)(4)** operation to ensure proper dissolution of the drug product.

In addition, please explain your rationale for releasing different lots of product

(Oxcarbazepine 150 mg, 300 mg, and 600 mg) manufactured from the same defective **(b)(4)**.

3. Your firm fails to thoroughly investigate unexplained discrepancies or the 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 C.F.R. § 211.192].

For example, on March 31, 2008, during the preventive maintenance of the **(b)(4)**, yellow powder identified as residue of **(b)(4)** active materials and several excipients were found behind the **(b)(4)** seals. Subsequently, on May 12, 2008, a yellow contaminant was found during the production of Ranitidine HCL **(b)(4)** batch #HV9588 that led to the rejection of the batch. Your investigations of these incidents are inadequate because the investigations were not expanded to other lots manufactured in the same equipment prior to March 31, 2008.

The inspection revealed several other examples of inadequate investigations that did not extend to other batches of the same drug product, or other products that may have been associated with the failure or discrepancy. Specifically, investigation Q-note 200070632 involved the contamination of Metformin HCl API batch #HP8402 with particles identified as **(b)(4)** material, and charred material. You failed to assess all batches of finished product manufactured with this contaminated API. Metformin HCl tablets batch #HT2569, manufactured using the contaminated API, was released to the United States without an evaluation into the potential impact to product quality.

Furthermore, your investigation (Q-note 200068475) into the appearance failure of Lithium Carbonate 300 mg capsules (batch #HM6665) for missing imprint on the capsules, did not include an evaluation of related batches manufactured using the same batch of capsules lacking the imprint. In addition, the remaining empty capsules in your inventory were not evaluated for lack of imprint. Instead, they were used in the production of seven other batches of Lithium Carbonate capsules and distributed to the United States.

In addition, your product Metformin HCl **(b)(4)** lot #HL4695 was produced using **(b)(4)**, batch #HL8373. This batch of raw material was found to be contaminated with charred **(b)(4)** and **(b)(4)**.

It was used to produce 20 lots, including Metformin HCl 500 mg tablets and Gemfibrozil 600 mg tablets that were released for distribution to the United States. Your response lacks appropriate corrective actions to prevent the use of contaminated raw materials in product manufacturing. We are concerned with your organizational unit's lack of

appropriate oversight in assuring that procedures are followed during production and release, resulting in the use of contaminated raw materials in the manufacturing process.

FDA's inspection of your Etobicoke, Ontario, Canada manufacturing site during December 10 - 19, 2008 uncovered significant CGMP violations and the failure of your quality unit to carry out its responsibilities. This resulted in issuance of a Warning Letter on June 25, 2009. In your response to the FDA-483 you reported that your Etobicoke and Signet facilities are managed by the same quality unit. The violations found during the July – August 2009 inspection at Signet Drive, Ontario are an indication that your quality unit continues to fail to perform its responsibilities regarding control and review, and to release products that meet specifications. Your response to the FDA-483 is inadequate in that it does not address the inability of your quality unit to conduct adequate investigations, determine the root cause, or establish adequate preventive and corrective actions for the problems found. Please provide a corrective action plan that describes your procedures, corrective and preventive actions and controls to ensure product quality. This plan should also include a comprehensive retrospective review of your raw material suppliers, equipment adequacy, cleaning and maintenance procedures implemented to ensure that all products produced and released by your quality unit meet specifications.

4. Your firm fails to have an adequate equipment cleaning and maintenance procedure or program to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond other established requirements [21 C.F.R. § 211.67(a)].

For example, a field alert report (FAR) involving Eplerenone Tables (ANDA 78-482) reported the presence of powder residues during a preventive maintenance check of the **(b)(4)** (asset #5001-PR31-**(b)(4)**). Based on your investigation, the root cause was determined to be an inadequate cleaning procedure because the procedure did not provide for complete disassembly of the **(b)(4)** lines, as well as use of the clean-in-place system. Your investigation also concluded that your preventive maintenance program was not robust enough to detect the potential contamination. In December 2009, two other FARs were reported regarding the same situation. Although the first notification about cross-contamination was in September 2009, it was not until December 2009 that other equipment and products were implicated because of cross-contamination. As part of this investigation, you used placebo batches (instead of product) in a study to determine if the cleaning procedure was adequate and the product was fit for release. This study is inadequate in that it did not reproduce the scenario and conditions that specifically lead to the problem nor predict the level of the contamination that may exist. Your cleaning procedure should be robust enough to ensure that no residue from previous lots remains in the manufacturing equipment.

Furthermore, a FAR investigation initiated on October 2, 2009, for Diltiazem capsules

manufactured in (b)(4), indicated that a powder residue was present on some of the (b)(4) units used in your facility. The (b)(4) piping, connected to the (b)(4) to provide (b)(4) to the units, came in contact with the product. Your investigation is inadequate because it does not provide assurance that the powder particles in (b)(4) did not contaminate the product manufactured in this equipment. Your actions did not include a global approach of corrective actions in that all (b)(4) were not examined for powder residue.

Additionally, an investigation into a FAR initiated on December 8, 2009, for Clonazepam tablets (0.5 mg, 1 mg, and 2 mg) in 100 and 500 bottles, revealed that foreign materials were found in the (b)(4) (asset #750) above the (b)(4) of the (b)(4) (asset #5001-PR25-KE209). Your investigation indicated that the presence of the foreign material was due to incorrect sizing of the (b)(4) and seal during equipment modification. Also, you indicated that the contaminated products were Clonazepam tablets and (b)(4) capsules. This investigation is inadequate because it did not include when the modification occurred, or identify all the lots manufactured with the (b)(4) since the modification. The investigation report also fails to include whether the modification occurred in other (b)(4) used in your facility, or if the other (b)(4) were examined for similar issues. The FAR only included Clonazepam tablets lots. It did not list the lots related to (b)(4) capsules.

We are concerned about your inadequate preventive maintenance and cleaning procedures and your failure to conduct a timely investigation into all equipment and products potentially affected by the deviations.

FIELD ALERT REPORTING VIOLATIONS

The NDA/ANDA Field Alert reporting requirements in 21 C.F.R. § 314.81(b)(1)(i) and (ii), effective since May 23, 1985, require holders of NDAs and ANDAs to submit certain information about distributed drug products to the appropriate FDA district office within three working days of receipt by the applicant. The intent of the 21 C.F.R. § 314.81(b)(1) regulation is to establish an early warning system so that significant problems are brought to the Agency's attention by applicant holders in order to prevent potential safety hazards from drug products already in distribution and also to prevent potential safety hazards with drug products manufactured in the future. Field Alert Reports must be submitted for confirmed and unconfirmed problems meeting the definition of the regulation within three working days of becoming aware of the problem.

In addition to the aforementioned CGMP violations, your firm is in violation of the Field Alert reporting requirements set forth in 21 C.F.R. § 314.81(b)(1)(i) and (ii). For example, during November and December 2009, your firm submitted two FARs due to contamination found in your manufacturing equipment. Your quality unit was notified of

one of the two FARs that pertains to Eplerenone tablets (ANDA 78-482) on September 16, 2009. However, the FAR was not submitted to FDA until November 20, 2009. The second FAR, pertaining to the (b)(4) (asset #5001-PR29-(b)(4)) equipment used in manufacturing room (b)(4), was submitted to FDA on December 7, 2009. However, your quality unit was aware of this information on November 26, 2009.

We remain concerned with the continuing CGMP violations demonstrated at your facilities and failure to report FAR related events within three days of becoming aware of a problem. Please include in your written response the corrective action you plan to take regarding distributed products manufactured at these facilities that may be affected by the violations.

The violations cited in this letter are not intended to be an all-inclusive statement 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. If you wish to resume shipping products to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, this office will recommend withholding approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, failure to correct these violations will result in FDA continuing to deny entry of articles manufactured at Apotex Inc., Toronto, Canada into the United States. Because your firm is currently under Import Alert, the articles are 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 Current Good Manufacturing Practice 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 violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Please identify your response with FEI #3002906944.

If you have questions or concerns regarding this letter, contact Maan Abduldayerem, Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing and Product Quality
International Compliance Branch
White Oak, Building 51
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-3916
Fax: (301) 847-8741

Sincerely,
Teddi Lopez for
/Richard L. Friedman/
Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research