Pan Drugs Ltd. 9/2/15

Department of Health and Human Services

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

Warning Letter

WL: 320-15-15

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

September 2, 2015

Mr. Kamal Pandya
Managing Director and Chairman
Pan Drugs Limited
167-168, GIDC Nandesari Industrial Estate
Baroda-397340
Gujarat, India

Dear Mr. Pandya:

During our July 14-18, 2014, inspection of your pharmaceutical manufacturing facility, Pan Drugs Limited, 167-168, GIDC Nandesari Industrial Estate, Nandesari, Vadodara, India, an investigator 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 FD&C 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 reviewed your firm's response dated August 4, 2014. It lacks sufficient corrective actions.

CGMP Violations

Our investigator observed specific violations during the inspection, including, but not limited to, the following.

1. Failure to properly maintain, repair, and keep clean buildings used in the manufacture of APIs in a manner that prevents contamination where open equipment is used. For example,

a) Our investigator observed holes in the walls and roof which allowed pigeons access near production equipment in multiple manufacturing areas.

b) Gaps and holes in outside walls for piping and air ducts which allow contaminants to enter the building.

2. Failure to properly maintain equipment used in the manufacture of APIs and minimize the risk of contamination, where open equipment is used. For example,

a) Our investigator observed rust, dirt, lubrication leaks, and exposed insulation material on and around open drug manufacturing equipment.

We note that you continued to manufacture product intended for the U.S. market even after you recognized that your facility and equipment were in disrepair and not compliant with CGMP requirements. Your June 6, 2014, change control (CC14/001) stated, "Warehouse and Facility to be upgraded to achieve GMP standards." However, in July 2014, you manufactured **(b)(4)** API batches **(b)(4)**.

In your response, you state, "we have decided to divert the referred batches" to the domestic (India) market.

We acknowledge that you ceased manufacturing operations, on July 12, 2014, upon notice of FDA to inspect your facility. We also acknowledge that you have committed to complete various repair and renovation activities within 60 to 90 days, with the intention to assure a suitable facility. However, your facility was also under renovation during the previous FDA inspection in May 2011, when you made similar statements about ongoing renovations.

In response to this violation, provide photographic evidence that you have fulfilled your commitment to fully renovate the facility, and demonstrate that the entire facility meets CGMP requirements. Your response should also include your plan to ensure your facility and equipment will be proactively maintained in such a way that your product is continually manufactured under CGMP conditions.

3. Failure to maintain complete data derived from all testing and to ensure conformance with established specifications and standards.

For **(b)(4)** USP, lot number **(b)(4)**, manufactured in June of 2012, the "ANALYTICAL TESTING PROTOCOL" used to record the results of testing contained fillable sections for heavy metals analysis, residual solvent analysis, the names of analysts performing those tests, and the names of a second person to review the results. The document provided to the investigator for the lot indicated that:

a. No heavy metals analysis was performed
b. The name of the analyst who performed the residual solvents analysis was not included

c. No second person reviewed the documents for accuracy, completeness, and compliance with established standards

In your response, you provided subsequent test results on lot number **(b)(4)**, and stated that you are retraining personnel involved in analytical testing. You also stated that you "will check all analytical records till current batch and take corrective action for all such types of oversight errors." Your response failed to specify whether any lots were released that lacked complete analytical testing information, either because the test was not performed or the data was not recorded. You also did not indicate if any lot was released without a secondary review of results to ensure compliance with established standards.

In response to this letter, please provide a list of all lots distributed to the U.S., within expiry. For each lot, indicate whether the lot was released without complete testing information or secondary review. If, in compiling this data, you find any discrepancies that show material was released that did not comply with established standards, please provide your plan of action for that material.

Because of continuing CGMP issues at your firm, we recommend that you engage a third party consultant with appropriate CGMP expertise to comprehensively assess your firm's entire operation, including facility conditions, procedures, processes, laboratory controls, and quality management systems. Your executive management is responsible for the ongoing acceptability of your operation, and for affording proper daily oversight to assure the identity, strength, quality, and purity of the drugs you manufacture.

Until we receive adequate confirmation that you have made global corrections, we will not schedule a follow-up FDA inspection and your firm will remain on Import Alert 66-40.

Deviations cited in this letter are not intended as an all-inclusive list. You are responsible for determining the causes of these deviations, for preventing their recurrence, and for preventing other deviations.

For guidance on current good manufacturing practice for APIs, consult "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" from the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. This ICH Q7 CGMP guidance helps ensure that all APIs meet international standards for quality and purity. You may download this guidance from FDA's website at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf

FDA considers ICH Q7 in determining if APIs have been manufactured, processed, packed, and held according to current good manufacturing practice under section 501(a)(2)(B) [21 U.S.C 351(a)(2)(B)] of the Act.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Staff immediately 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 Staff 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 an API manufacturer. In addition, your failure to correct these violations may result in FDA continuing to refuse admission of articles manufactured at 167-168, GIDC Nandesari Industrial Estate, Baroda-397340, Gujarat, India into the United States under Section 801(a)(3) of the FD&C 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 FD&C Act, 21 U.S.C. 351(a)(2)(B).

Disparity in Information Provided During the Inspection vs. US Import Records
During the July 2014 inspection, you stated that **(b)(4)** API is the only product your facility manufactures and distributes to the U.S. market. Accordingly, the FDA investigator focused solely on **(b)(4)** manufacturing operations.

However, after reviewing import entries, we found that you have been manufacturing and shipping significant quantities of **(b)(4)** other APIs to the United States. The import documents detail shipments directly from your facility both before and after the inspection of **(b)(4)**, and **(b)(4)**.

In your response to this letter, please provide an explanation as to the disparity between the statement you made to the investigator and the importation records for drugs you have shipped to the United States.

Please be reminded that the Food and Drug Administration Safety and Innovation Act § 707 also deems drugs to be adulterated if they have been manufactured, processed, packed, or held in an establishment by an owner or operator who has delayed, denied, or limited an inspection. We recommend that you review FDA's guidance for industry *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection*. To obtain this guidance document for your reference, please refer to the following page of FDA's website: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf.

Within 15 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. If you cannot complete corrective actions within 15 working days, state the reasons for the delay and the date by which you will have completed the corrections. If you no longer manufacture or distribute the APIs at issue, provide the date(s) and reason(s) you ceased production. Send your reply to:

Celestina Arowosegbe, Compliance Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research

Office of Compliance
Office of Manufacturing Quality
Division of Drug Quality II
White Oak, Building 51, RM 4369
10903 New Hampshire Ave
Silver Spring, MD 20993

Please identify your response with FEI # 3003263118.

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