Pan Drugs Limited 8/25/16

Department of Health and Human Services

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

Warning Letter 320-16-29

Via UPS
Return Receipt Requested

August 25, 2016

Mr. Kamal Pandya
Managing Director and Chairman
Pan Drugs Limited
192 G I D C Makarpura Industrial Estate
M I Estate, Vadodara 390001
India

Dear Mr. Pandya:

The U.S. Food and Drug Administration (FDA) inspected your pharmaceutical manufacturing facility, Pan Drugs Limited, 192 G I D C Makarpura Industrial Estate, M I Estate, Vadodara, from November 30 to December 3, 2015.

This warning letter reviews significant violations of current good manufacturing practice (CGMP) 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 firm's December 17, 2015, response in detail.

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

1. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products (21 CFR 211.22(a)).

Your firm's quality unit allowed the use of adulterated **(b)(4)** USP API, dated May 25–31, 2015, manufactured at the Pan Drugs Ltd. Nandesari facility. The Pan Drugs Ltd. Nandesari facility was placed on FDA import alert 66-40 on May 5, 2015, for egregious CGMP deviations. Your firm used this API for the manufacture of **(b)(4)**, which were then shipped to the U.S. market from October 7 to November 23, 2015.

Additionally, your quality unit approved certificates of analysis (COA) for **(b)(4)** and **(b)(4)** API, as well as finished products, prior to conducting all quality control and release testing. Your production manager falsified the documents by signing and dating the "Prepared By" and "Checked By" sections of the COA.

Furthermore, your quality unit failed to identify data integrity issues in 11 batch production records reviewed by our investigator. Your production manager admitted that he falsified the signatures of other employees in the "Prepared By," "Reviewed By," "Approved By," and "Authorized By" sections.

According to your response, you recognized that these practices were not adequate. You intended to implement a signature list and revise your SOPs to address these failures. However, these actions do not address the quality unit failures observed.

2. Your firm failed to maintain the buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition and to keep them free of infestation by rodents, birds, insects, and other vermin (21 CFR 211.56(a)).

For example, our investigators observed mold-like substances on the walls of your drug processing area, and accumulations of **(b)(4)** powder throughout your facility.

Our investigators also observed gaps and holes in the walls of your facility around piping and air ducts. These gaps and holes were open to the surrounding environment and allowed pests to enter your facility. During the inspection, we observed a lizard exiting one of the holes, and evidence of other pest activity. For example, our investigators observed what appeared to be rodent droppings within three feet of **(b)(4)** bags purported to hold **(b)(4)** drug product.

3. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements (21 CFR 211.67(a)).

For example, our investigators observed rust, dirt, and lubrication leaks on and around your shared drug manufacturing equipment. Your processing **(b)(4)** for the production of **(b)(4)** and **(b)(4)** had non-food-grade oil on and around the equipment. We also observed black particles in the **(b)(4)** used in manufacturing drug products.

You told our investigator that your firm had no cleaning procedure for the equipment or facility.

Your equipment was observed to be in poor operating condition. For example, we observed a warped lid on your "**(b)(4)**" that prevented proper closure.

In response to this letter, provide details of the plan you stated you will develop for facility upgrades and corrections, including photographic evidence that demonstrates 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.

4. 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)).

For example, the computer in your quality unit area did not have controls to restrict access and prevent unauthorized changes to data files and folders. All employees had access to your Annual Product Review (APR) spreadsheet. The desktop computer containing the APR was not locked.

In your response, you committed to "reassessing the GMP" requirements for computer-based systems; you stated the systems would be "evaluated, checked and validated." You did not include a timeline or specify a plan to review released batches and determine the impact of the deficiency.

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential batches were identified evaluate all data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include *analyses* of the risks to

patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related data at your firm.
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
- A status report for any of the above activities already underway or completed.

Access to Information during Inspection

Your firm attempted to delay the start of the inspection, and some records we requested during the inspection were not provided.

On November 30, 2015, our investigator observed your warehouse supervisor tearing out pages from your firm's annual report and placing the pages into his pocket. Eventually, the supervisor provided the pages to our investigator.

On December 1, 2015, our investigator requested printed chromatograms from you HPLC and GC. You failed to provide them.

When an owner, operator, or agent delays, denies, limits, or refuses an inspection, the drugs may be adulterated under section 501(j) of the FD&C Act. We recommend that you review FDA's guidance for industry, *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection* at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf

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.

FDA placed your firm on Import Alert 66-40 on December 8, 2015.

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 product manufacturer.

Failure to correct these violations may also result in FDA continuing to refuse admission of articles manufactured at Pan Drugs Limited, 192 G I D C Makarpura Industrial Estate, M I Estate, Vadodara 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 completion date and reasons for delay.

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

Carla Norris
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 3010532174.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research