Polydrug Laboratories Pvt. Ltd. 4/14/16

- **Warning Letter**

Via UPS

WL 320-16-10

April 14, 2016

Mr. Punit Thakrar, Managing Director
Polydrug Laboratories Pvt. Ltd. Corporate Office
A 201-202, Navbharat Estates, Zakaria Bonder Road
Sewri (W)
Mumbai – 400015
Maharashtra, India

Dear Mr. Thakrar:

From March 16-23, 2015, an investigator from the U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Polydrug Laboratories Pvt. Ltd., Plot N-37, Addl. Ambarnath Industrial Area, MIDC, Anand Nagar, Ambarnath (East), Maharashtra, Mumbai.

We identified significant deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (API).

These deviations cause your drugs to be 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), 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 reviewed your April 9, 2015, response in detail and acknowledge receipt of your subsequent response.

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

1. Failure to record and investigate all quality-related customer complaints according to an established procedure.

During the inspection our investigator found a torn sheet of paper titled “Product Quality Complaints” on the floor of your warehouse. We compared it to your firm’sofficial complaint log and discovered that only 2 of the 17 customer complaints on the torn sheet were recorded in your firm’s official complaint log. Further, your firm

indicated that there may be additional unlogged and/or uninvestigated complaints, but did not provide further explanation. Your firm had not investigated the complaints we found on the torn sheet. These uninvestigated complaints reported API that were either sub-potent or contained filth, including the following problems:

- low assay value for **(b)(4)** API
- particles and hairs in **(b)(4)** API
- an insect and dirt in **(b)(4)** API
- safety goggles in **(b)(4)** API
- **(b)(4)** scoop in **(b)(4)** API

Your response stated that you will initiate a corrective action and preventive action (CAPA) plan to include your quality unit's assessment of your current practices.

Your response is inadequate because it is silent on any retrospective investigations conducted for the 17 complaints that our investigator found on the sheet of paper on your warehouse floor. Your response also did not specify improvements to your complaint handling procedures and documentation practices or efforts to locate and investigate any other unlogged and/or uninvestigated complaints that your firm acknowledged could exist.

Although the 17 complaints in the unofficial log were not from U.S. customers, your firm uses shared equipment, personnel, and materials to manufacture products for multiple markets, including the United States. Your firm's poor complaint handling practices and your inability to prevent and detect product quality defects, such as filth, indicate significant lapses in your firm's quality system. You are responsible for ensuring that prior to release your API meet quality and safety requirements and for assuring that any subsequent quality defects are thoroughly investigated. You are also responsible for taking appropriate corrective actions and preventive actions.

In response to this letter, provide the following:

- a summary of your investigations of all complaints received since 2012, noting whether each complaint is logged in your official complaint log and including root cause determinations and CAPA
- your improved complaint handling procedure and details of any further controls implemented to ensure that all complaints are logged, documented, and promptly investigated

2. Failure to review and investigate all production deviations.

Our investigator found a torn page from a batch production record for lot **(b)(4)** of API **(b)(4)** in the trash. He noted discrepancies between the discarded page and the complete batch production record that your firm represented as the official record for that lot. Your firm did not investigate this deviation or the unacceptable practice of discarding a manufacturing record. You did not determine the root cause or assess its effect on drug quality prior to releasing lot **(b)(4)**.

Your response states that your quality unit is working on a system to record original data at the time it is generated. However, your response is inadequate because you failed to indicate whether you intend to retrospectively investigate the extent to which your firm's manufacturing records are unreliable, determine root causes, and take necessary corrective actions. Further, you did not note whether your quality unit will conduct a thorough review of all batch production records for accuracy and investigate any discrepancies.

In response to this letter, provide the following:

- a summary of your retrospective investigation of the duplicate batch production records for lot **(b)(4)**
- a retrospective review of all batch production records for lots within expiry, including an evaluation of the effect of any discrepancies on API batch quality
- your CAPA plan describing actions and controls to ensure accuracy and retention of all records including original batch production records
- documentation that your employees are adequately trained to complete batch production records contemporaneously and accurately, to investigate production record discrepancies, and to understand the connection between accurate recordkeeping and product quality

3. Failure of computerized systems to have sufficient controls to prevent unauthorized access or changes to data.

Your firm's computer system for entering test results and storing certificates of analysis (CoA), which document whether a drug meets specifications, does not have sufficient controls to prevent unauthorized changes to a CoA after quality unit approval.

During the inspection, our investigator reviewed **(b)(4)** CoA stored on computer #16, all of which were approved by the quality unit. A manager demonstrated for our investigator how results on an already finalized CoA could be manipulated after the formal quality unit approval. Also, the quality unit's electronic signatures on these CoA were uncontrolled images of signatures rather than certificate-based electronic signatures.

Your response states that your firm plans to implement an enterprise resource planning system. Your response is inadequate because you did not provide sufficient detail about how this system will prevent unauthorized access or data manipulation, nor did you indicate your timeframe for installing and validating the system. In addition, you failed to review and confirm authenticity of CoA data for products you have already released under the deficient conditions described above.

In response to this letter, provide the following:

- a CAPA plan for controlling access to computer systems for all laboratory and manufacturing records and equipment
- your firm's plan to establish, issue, and strictly control access to your manufacturing and laboratory systems
- a detailed summary of your steps to train personnel on the proper use of computerized systems

4. Failure to have appropriate test procedures to ensure that API conform to established standards of quality and/or purity.

Our investigator found numerous "invalid" moisture content results while reviewing data from the Karl Fischer Potentiometer (Tiamo 2.3 software). These results, generated from July 2012 to March 2015, indicate either a quality problem or an inadequate moisture content test method. Correctly measuring water content is especially important because excess moisture in your API can lead to quality defects such as chemical degradation and/or microbial growth.

During the inspection and in your written response, you referred to the invalid assay results as “out of specification” (OOS). You say that your staff failed to report the invalid results because they were not aware of the reporting and documentation requirements. You also say that you are revising your OOS procedure.

Your response is inadequate because, although you conducted a failure investigation, you did not provide us with sufficient detail about your investigation or its findings, such as whether your firm retrospectively investigated the “invalid” results or took necessary corrective actions. These problems have persisted for approximately three years without adequate resolution.

In response to this letter, provide the following:

- an evaluation of all laboratory methods to determine their suitabitily and copies of all validation reports for methods you will continue to use
- an action plan to replace any method found to be unsuitable for its intended use
- all original and retest results for moisture content for all API lots within expiry and distributed since 2012
- your actions to ensure all laboratory discrepancies, including any OOS or “invalid” results for any API lot within expiry, have been fully documented, investigated, and resolved
- your actions to ensure that any future laboratory discrepancies, including OOS or “invalid” results, will be adequately documented and resolved prior to API release for distribution

Conclusion

Deviations cited in this letter are not intended to be an all-inclusive list. You are responsible for investigating and determining the causes of the deviations identified above and for preventing their recurrence and the occurrence of other deviations.

Your quality system does not securely and reliably retain your manufacturing data and records. We acknowledge your ongoing work with your own subject matter experts to identify root causes of the deficiencies. In addition, we strongly recommend that you engage a third-party consultant with appropriate CGMP expertise to assess your firm’s facilities, procedures, processes, systems and data integrity to ensure the identity, strength, quality, and purity of the API you manufacture.

In addition to the specific items requested above, include the following in your response:

1. 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.

2. 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.

3. 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 your firm's data.
- A comprehensive description of the root causes of your data inaccuracies, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment.
- Interim measures describing the actions you have taken or will take to ensure the quality of your drugs, such as notifying your customers, conducting additional testing, recalling product, adding lots to your stability programs to assure stability, 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.

Additionally, you may wish to review FDA's guidance document entitled *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (ICH Q7), which describes CGMP for the manufacture of API. FDA considers the expectations outlined in ICH Q7, as well as alternatives intended to accomplish the same goals and provide an equivalent level of quality assurance, in determining whether a firm's API have been manufactured, processed, packed, and held according to CGMP under the FD&C Act. This guidance document is available on the FDA website at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073497.pdf.

If, as a result of receiving this warning letter, or for other reasons, you are considering a decision that could reduce the number of drugs produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Staff 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 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)(l), 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 you complete all corrections and FDA confirms your firm compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as drug manufacturer.

Due to our inspection findings, your firm was placed on Import Alert 66-40 on September 11, 2015.

If you fail to correct these deviations, FDA may continue to refuse admission of articles manufactured at Polydrug Laboratories Pvt. Ltd. Plot N-37, Addl. Ambarnath Industrial Area, MIDC, Anand Nagar, Ambarnath (East), Maharashtra, Mumbai, under Section 80l(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) as the manufacturing methods and controls 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).

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 detailed in this letter.

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

Jay Jariwala
Compliance Officer
U.S. Food and Drug Administration
White Oak 51 Room 4359
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
USA

Send your electronic reply to OC-OMQ-Communications@fda.hhs.gov

Please identify your response with FEI # 3007287078.

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

Cc:
Dr. Valerian D’Souza
Director of Operations
Polydrug Laboratories Pvt. Ltd.
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