Reine Lifescience 5/9/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-50

May 9, 2018

Mr. Amish Shah
Managing Partner
Reine Lifescience
Plot No. 5901, B H Sajjan India Limited
GIDC Industrial Estate
Ankleshwar, Gujurat 393002 India

Dear Mr. Shah:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Reine Lifescience, at Plot No. 5901, B H Sajjan India Limited, GIDC Industrial Estate, Ankleshwar, Gujurat, from October 30 to November 3, 2017.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API 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 November 23, 2017, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigator observed specific deviations including, but not limited to, the following.

1. Failure to validate and verify the suitability of analytical methods.

You lacked documentation of method validation or verification of your analytical methods.

Our investigator also observed analytical data in a folder named “PD Trial.” While the folder was normally intended for product development, the folder contained batch data for API, and results appeared to differ significantly from recorded test results.

In your response, you committed to completing method validation and performing an “impact assessment” for commercially distributed batches by February 2018.

Your response is inadequate because you did not provide updated procedures that will implement use of only validated (or verified, if compendium is used) methods for testing future batches of API intended for the U.S. supply chain. Also, you have not provided any updates on your method verification/validation or impact assessment.

In response to this letter, provide:

- a summary of method validation and verification studies for all analytical methods used for product release;
- a summary of the impact assessment for released batches;
- improved procedures regarding validation/verification requirements and updated analytical methods;
- a comprehensive, independent review of your laboratory practices, methods, equipment, and analyst competencies. Based on this review, provide a detailed corrective action and preventive action (CAPA) plan to fully remediate your laboratory system.
- a global CAPA plan as requested below under “Data Integrity Remediation.”

2. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and failure to have adequate controls to prevent omission of data.

Our investigator observed that the audit trail feature was disabled on instruments you use for quality control testing of your API, including your high performance liquid chromatography system. Your analytical systems also lacked controls to prevent users from deleting or altering electronic data. For example, your quality assurance executive, who also performed your analytical tests, had administrator access to each system.

In your response, you committed to validating all computerized systems with incorporation of audit trails, restrictions on data, and user-access controls by March 31, 2018.

Your response is insufficient because it does not include interim control measures and procedural changes for the control and review of analytical data. You also do not specify who will have administrator privileges on your analytical instrument systems used for CGMP quality control testing.

In response to this letter:

- provide a summary of your interim controls to prevent deletion and modification of data;
- define the roles and responsibilities of personnel who have access to analytical instruments and data;

- provide a standard operating procedure (SOP) that ensures that all quality control tests are performed by an analyst and receive second-tier review (e.g., by a manager) from a separate individual;
- detail the associated user privileges for each analytical system;
- provide a detailed summary of your procedural updates and associated training for user role assignment and controls; and
- provide detailed procedures for your review of audit trail data.

3. Failure to adequately validate written procedures for the cleaning and maintenance of equipment.

You released and shipped API to the U.S. market that were manufactured using multi-product equipment before completing equipment cleaning validation. You also provided a cleaning validation report, completed after release and shipment of API for the United States that did not include evaluation of cleaning methods for the product identified as worst case. Without proper cleaning validation, you cannot assure that you prevent cross-contamination with other API that you manufacture with the same equipment.

In your response, you stated that your post-cleaning rinse water samples and your finished API samples were within specifications. You also stated that you will perform cleaning validation through your approved cleaning validation protocol before shipping to the U.S. market in the future.

Your response is inadequate because it does not provide documentation and rationale for the limited sampling strategy initially used by your firm at the time of product release. You also did not address whether you evaluated cleaning methods for the API identified as representing worst case conditions, and you did not include detailed corrective actions and preventive actions.

In response to this letter, provide a comprehensive CAPA plan for your cleaning validation and cleaning procedures including:

- scientific rationale for API, rinse, and swab sample specifications prior to performing cleaning validation;
- a summary of updates to your cleaning validation protocol to better incorporate conditions identified as worst case. This should include evaluating drugs that are of highest toxicity, drugs that are lowest solubility in their cleaning solvents, and swabbing of various equipment locations that are most difficult to clean.
- a summary of SOP that have been updated to ensure an appropriate program for verification and validation of cleaning procedures for new products, processes, and equipment.

CGMP Consultant Recommended

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations and assist your firm in meeting CGMP requirements. This consultant should also evaluate any proposed CAPA before your firm pursues compliance status resolution. Your use of a consultant does not relieve your firm’s obligation to comply with CGMP. Your firm’s executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

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. In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting.

B. A current risk assessment of the potential effects of the observed poor practices 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.

Additional API CGMP guidance
FDA considers the expectations outlined in ICH Q7 in determining whether API are manufactured in conformance with CGMP. See FDA's guidance document, *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients,* for guidance regarding CGMP for the manufacture of API at https://www.fda.gov/downloads/Drugs/.../Guidances/ucm073497.pdf.

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

FDA placed your firm on Import Alert 66-40 on March 30, 2018.

Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these deviations may also result in FDA continuing to refuse admission of articles manufactured at Reine Lifescience, Plot No. 5901, B H Sajjan India Limited, GIDC Industrial Estate, Ankleshwar, Gujurat, 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 deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

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

Marisa Heayn
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 3011543431.

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