Megafine Pharma (P) Limited 2/24/17

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter: 320-17-26

February 24, 2017

Mr. Shailesh Sanghvi
Business Development Director
Megafine Pharma (P) Ltd.
Sethna, 4th Floor
55 Maharshi Karve Road
Marine Lines, Mumbai 400002
India

Dear Mr. Sanghvi:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Megafine Pharma (P) Ltd. at Plot No. 911 & 912, GIDC, Phase III, Vapi, Gujarat State, from September 19–23, 2016.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for drugs.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drugs 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 October 14, 2016, response in detail and acknowledge receipt of your subsequent correspondence.

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

1. Failure of your quality unit to exercise its responsibility to ensure the drugs manufactured are in compliance with CGMP, and meet established specifications for quality and purity.

Your facility manufactures active pharmaceutical ingredient (API) intermediates. Your quality unit approved the use of adulterated materials to manufacture drugs.

Our investigators found that you sourced material from a facility on FDA Import Alert 66-40 for failure to meet CGMP requirements. Specifically, you obtained and used material for the manufacture of **(b)(4)**, an API intermediate for the **(b)(4)** drug **(b)(4)**, from **(b)(4)** facility at **(b)(4)**. The **(b)(4)** facility has been on FDA Import Alert 66-40 since **(b)(4)**, and was issued Warning Letter **(b)(4)** stating that **(b)(4)** API are adulterated within the meaning of section 501(a)(2)(B) of the FD&C Act. In addition, you used the **(b)(4)** site to store and test stability samples.

Your response is inadequate. You did not perform a sufficient risk assessment for use and release of drugs manufactured using in-process material from **(b)(4)** facility.

In response to this letter, provide the following:

- an action plan to ensure the quality of your drugs, i.e., by notifying customers about adulterated material in your drug manufacturing process and recalling any adulterated drugs for U.S. distribution still within expiry;
- stability testing and analysis from an independent laboratory for all lots of drugs within expiry for U.S. distribution;
- a summary report of any corrective actions that you have implemented or plan to implement based on your consultant's review of stability studies.

2. Failure to establish and follow adequate written procedures for cleaning equipment and its release for use in API manufacture, and to maintain adequate records of major equipment usage.

Our investigators found that the interior surfaces of your drug manufacturing equipment (**(b)(4)**, **(b)(4)** apparatus, and **(b)(4)**) were not clean as required by your procedures. For example, our investigators observed **(b)(4)** residue and **(b)(4)** discoloration at the bottom of **(b)(4)** apparatus BSR-04, although the machine was labeled "clean."

Your response failed to address the adequacy of preventive maintenance to ensure that your equipment is in a good state of repair and will not contaminate your drugs with material accumulated on surfaces that come in contact with your drugs.

In response to this letter, provide chemical identification of the observed residue and a risk assessment to determine the impact of the **(b)(4)** residue on drugs within expiry in the U.S. supply chain. Also provide a complete assessment of your equipment preventive maintenance program including necessary procedure revisions to ensure it is suitable for use in drug manufacturing.

3. Failure to ensure all specifications and test procedures are scientifically sound and appropriate to ensure that your drugs conform to established standards of quality and/or purity.

Your test methods were not capable of demonstrating the purity of your drugs. Specifically, **(b)(4)** batches **(b)(4)** and **(b)(4)** displayed an unidentified peak, or shoulder, overlapping the principal peak. You neither integrated nor investigated this potential impurity. In addition, analysts reprocessed data up to 12 times, and only included the final result in the report for review by Quality Assurance. Your Deputy Manager, Quality Control stated that it is common practice to "play with parameters" to get the proper integration.

Your firm reviewed **(b)(4)** batches and determined they all had a similar shoulder, which you concluded was a distortion of the principal peak. However, you did not provide sufficient data to support this determination.

In response to this letter, identify the unknown peak(s), with data to support your identification including mass spectrometry results and a risk assessment for the impact on drugs in the U.S. market.

4. Failure to control the issuance, revision, superseding, and withdrawal of all documents by maintaining revision histories.

Your quality assurance unit provides analysts with blank controlled document forms that have already been approved and signed. Investigators observed torn, partially complete QA-signed calibration records in the trash and observed QA staff shredding documents without recording the identity or the reason for shredding the documents.

In your response, you acknowledged the importance of maintaining complete reconciliation details for document control and revised your document control procedures. However, your response is inadequate as you did not provide a risk assessment for the impact on drugs in the U.S. market.

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 failures on the quality of your drugs. Your assessment should include analysesof 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.

Reference Megafine Nashik Warning Letter 320-16-13 for additional details to provide on data integrity remediation.

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 in all your facilities.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA 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 or interruptions in your drug manufacture under 21 U.S.C. 356C(a) 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 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 refusing admission of articles manufactured at Megafine Pharma (P) Ltd., Plot No. 911 & 912, GIDC, Phase III, Vapi, Gujarat State 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 (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)** or mail your reply to:

Tamara Rosbury, Ph.D.
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 3006688078.

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

More in 2017 (/ICECI/EnforcementActions/WarningLetters/2017/default.htm)