檔　　號：
保存年限：

衛生福利部食品藥物管理署　函

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受文者：中華民國西藥代理商業同業公會

發文日期：中華民國105年8月2日
發文字號：FDA風字第1051103733B號
速別：普通件
密等及解密條件或保密期限：
附件：原料藥廠違反GMP警訊乙份(A2102000I105110373302-1.pdf)

主旨：美國FDA發布印度原料藥廠「Megafine Pharma Limited」（廠址：No.201, Village Lakhmapur, Dindori, Nashik , India）Warning Letter乙案，詳如說明段，請轉知所屬會員知照。

說明：

一、美國衛生主管機關US Food and Drug Administration（FDA）查核旨揭原料藥廠，判定嚴重違反cGMP，並於105年5月19日正式發布Warning Letter（詳如附件）。

二、鑒於旨揭原料藥廠之製造品質無法符合GMP之要求，可能對藥品製造品質帶來影響與危害，請轉知所屬會員釐清相關輸台製劑產品是否使用旨揭原料藥廠所生產原料藥，並應依風險管理原則辦理相關後續處置。

正本：中華民國西藥商業同業公會全國聯合會、中華民國西藥代理商業同業公會、台北市西藥代理商業同業公會、中華民國開發性製藥研究協會、中華民國藥品行銷暨管理協會

副本：電2016-08-02 交11:47:47章

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Megafine Pharma Limited 5/19/16

Department of Health and Human Services

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

Via UPS
Return Receipt Requested

Warning Letter: 320-16-13

May 19, 2016

Mr. Hasmukh Gandhi, Director
Megafine Pharma Limited
Sethna, 4th Floor
55 Maharshi Karve Road
Marine Lines, Mumbai
India 400002

Dear Mr. Gandhi:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Megafine Pharma Limited at No. 201, Village Lakhmapur, Dindori, Nashik, from May 11-15, 2015.

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 firm's June 3, 2015, response in detail and acknowledge receipt of subsequent responses.

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

1. Failure to ensure that, for each batch of intermediate and API, appropriate laboratory tests are conducted to determine conformance to specifications.

One of your analysts acknowledged falsifying test data for **(b)(4)** stability batch **(b)(4)** in August 2012. The analyst substituted a reference standard chromatogram in place of the 12-month stability interval

chromatogram. You also submitted this data to FDA in support of drug master file (DMF) **(b)(4)**.

In your response, you stated that laboratory management did not discover the discrepancy until the 24-month stability interval. You also stated that the batch quality is unaffected because subsequent test results met specifications at the 24-month and 36-month stability intervals.

Your response is inadequate because it does not address the extent of the data falsification that could exist in your laboratory. You have not provided the results of any investigation to determine the accuracy of the test data for other batches of drugs and the corrective actions that should be implemented to ensure the quality of the drugs intended for U.S. distribution.

In response to this letter, conduct a complete review of all data submitted to the agency in support of DMF **(b)(4)** and provide a detailed assessment of any discrepancies found. Also provide a review of all test results for any **(b)(4)** batch released for U.S. distribution within expiry.

2. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent manipulation and omission of data.

Multiple analysts, testing multiple drugs, deleted unknown peaks without justification. These manipulations made the drugs appear to meet their specifications. Of concern, one of these unknown peaks was for a residual solvent known to be a **(b)(4)** impurity.

In response to this letter, provide the residual solvent results performed by an independent laboratory for all lots of drugs distributed to the United States.

3. Inadequate investigation of critical deviations or a failure of a batch to meet its specifications or quality standards.

Your quality unit released **(b)(4)** batch **(b)(4)** for distribution despite its failure to meet the specification for **(b)(4)**, a **(b)(4)** and **(b)(4)** impurity. Your impurity specification is not more than **(b)(4)** parts per million (ppm). However, the batch had a result of **(b)(4)** ppm.

In your response, you indicated that the batch had been reprocessed and yielded a result of **(b)(4)** ppm for the impurity. However, the chromatograms that you provided as evidence of passing results were dated April 28, 2014, almost **(b)(4)** after the batch was distributed.

In response to this letter, retain an independent laboratory to conduct testing for all known **(b)(4)** and/or **(b)(4)** impurities that may be present in your drugs distributed to the United States. Provide a summary of the lab's findings and actions you take in response to any out-of-specification (OOS) results.

For more information about the proper handling of out-of-specification results and documentation of your investigations, please refer to *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* at **http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf (http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf)**

Data Integrity Remediation

Your quality system does not adequately ensure the adequacy and integrity of data to support the safety, effectiveness, and quality of 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:

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.
- A comprehensive retrospective evaluation of the nature of the data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential lapses were identified should evaluate all data integrity lapses.

2. A current risk assessment of the potential effect 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 in data integrity, and risks posed by ongoing operations.

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

- The 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 the 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 or drug application 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 that are already underway or completed.

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, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of dugs 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. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

Because of the findings of the FDA inspection described in this letter, your firm was placed on Import Alert 66-40 on October 14, 2015.

Until you completely correct all deviations and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as an API manufacturer. Failure to correct these violations may also result in FDA continuing to refuse admission of articles manufactured at Megafine Pharma Limited at No. 201, Village Lakhmapur, Dindori, Nashik, 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, you have 15 working days to respond to this office in writing. 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 days, state your completion date and reasons for delay.

Send your reply to:

Tracie H. Sharp
Compliance Officer
U.S. Food and Drug Administration
White Oak, Building 51 Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

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

Please identify your response with FEI 3005694111.

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

More in 2016
(/ICECI/EnforcementActions/WarningLetters/2016/default.htm)