Mahendra Chemicals 7/13/15

Department of Health and Human Services

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

Warning Letter

WL: [320-15-12]

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

July 13, 2015

Mr. Rajnibhai Patel
Technical Director
Mahendra Chemicals
B-1, 217 & 218/2, G.I.D.C. Estate
Naroda, Ahmedabad, Gujarat 382330
India

Dear Mr. Patel:

During our May 19, 2014 through May 24, 2014 inspection of your pharmaceutical manufacturing facility, Mahendra Chemicals, B-17, 217 & 218/2, G.I.D.C. Estate, Naroda, Ahmedabad, Gujarat, India, investigators from the U.S. Food and Drug Administration (FDA) identified significant deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (APIs).

These deviations cause your APIs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic 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 reviewed your firm's response dated June 16, 2014, in detail. It lacks sufficient corrective actions.

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

1. Failure to record activities at the time they are performed and destruction of original records.

Specifically, your employees completed batch production records entries days after operations had ended, released lots before the proper approvals, and failed to maintain original manufacturing data for critical steps in the batch production records. For example,

a) Our investigators found that some of your operators used “rough notes” (unbound, uncontrolled loose paper) to capture critical manufacturing data and then destroyed these original records after transcription into the batch production records. For example, the **(b)(4)** chemist recorded original manufacturing data as rough notes and left these rough notes for the **(b)(4)** chemist to transcribe into the batch production records. The next morning, the **(b)(4)** chemist signed the batch production records and destroyed the original rough notes. We interviewed employees during the inspection who confirmed your firm’s practice of transcribing data to batch records and destroying original records.

b) Additionally, our investigators found backdated batch production records dated February 10 to February 25, 2014, signed by your Production Manager and Technical Director in the “Batch Manufacturing Record Reviwed [*sic*] by” section. The Technical Director stated that he was not in the facility on these dates and was “countersigning” for another person who allegedly performed these review activities. However, these records did not contain signatures (contemporaneous or otherwise) of the alternate reviewer who purportedly conducted the review. Furthermore, the Technical Director backdated his own signature to the date the quality unit (QU) reviewed and released your drug product. His backdated signatures are on **(b)(4)** batch records for lots **(b)(4)**; and **(b)(4)** batch records for lots **(b)(4)**. You released these batches before the Technical Director returned to the facility and backdated his signatures. The batch records, therefore, do not demonstrate that you completed your required review before releasing your products. You did not distribute these lots to the United States. However, your failure to assure proper review of production and control records before product release raises questions about the authenticity and reliability of your data and the quality of the APIs you producefor the U.S. market.

Your response does not explain your use of rough notes for documenting CGMP data. This practice, in conjunction with backdating records, raises additional concerns about the integrity, authenticity, and reliability of all your data, and the quality of your APIs. Batch production records must include complete and accurate information on the production and control of each batch. Employees responsible for supervising or checking significant steps in manufacturing operations must do so and appropriately document their review of critical steps (for example, records must not be backdated and signatures must be authentic).

In your response to this letter, describe how systems and procedures will be changed to assure that all CGMP operations are documented at the time they occur and that original records are preserved in the batch records. Explain how you will determine that all personnel involved with the preparation and review of API records adhere to your procedures. Also, provide your plans to ensure QU review of completed batch production and laboratory records before API release.

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

Your laboratory systems lacked access controls to prevent raw data from being deleted or altered. For example,

a) There is no assurance that you maintain complete electronic raw data for your Gas Chromatography (GC) instrument. FDA investigators observed multiple copies of raw data files in the recycle bin connected to the GC instrument QC-04 even in the presence of “Do Not Delete Any Data” notes posted on two laboratory workstation computer monitors.

b) Employees were allowed uncontrolled access to operating systems and data acquisition software tracking residual solvent, and test and moisture content. Our investigators noted that there was no password functionality to log into the operating system or the data acquisition software for the GC, the High Performance Liquid Chromatography (HPLC) instrument QC-17, or the Karl Fischer (KF) Titrator QC-13.

c) HPLC SpinChrome and GC Lab Station data acquisition software lacked active audit trail functions to record changes in data, including original results, who made changes, and when.

In your response, you state that your laboratory GC, HPLC and KF systems are now password-protected and that you have begun drafting analytical software password procedures for the GC, HPLC and KF laboratory instruments. However, your response does not state whether every analyst will have their own user identification and password. You also mention plans to install a validated computer system. However, you did not provide a detailed corrective action and preventive action (CAPA) plan or conduct a review of the reliability of your historical data to ensure the quality of your products distributed to the U.S. market.

Inadequate controls of your computerized analytical systems raise questions about the authenticity and reliability of your data and the quality of your APIs. It is essential that your firm implements controls to prevent data omissions or alterations. It is critical that these controls record changes to existing data, such as the individuals making changes, the dates, and the reason for changes.

In response to this letter, provide your comprehensive CAPA plan for ensuring that electronic data generated in your manufacturing operations, including laboratory testing, cannot be deleted or altered. Also identify your quality control laboratory equipment and any other manufacturing-related equipment that may be affected by inadequate controls to prevent data manipulation.

3. Failure to train employees on their particular operations and related CGMP practices.

a) In interviews, multiple employees stated that they had not received on-the-job training for their production operations.

b) There was no record of training for the GC analyst testing for residual solvent release in final API.

c) According to your "**(b)(4)** Training Program" procedure, a report is generated for each training with the names of trainer and trainees, subjects covered, evaluation sheets, etc. However, you were not able to provide any training reports to our investigators.

In your response, you state that, per your standard operating procedure (SOP) from 2013, your firm has trained all employees by contracting a consultant. However, as noted in item 3c, our inspection revealed that your firm is not following this procedure.

In response to this letter, provide a corrective action plan for investigating the extent of this deficiency. Address why manufacturing and quality management failed to detect these training deficiencies. Include updated procedures and proper quality oversight to ensure that employees are adequately trained to perform all of their responsibilities for consistent manufacturing and laboratory operations. Explain how you will determine the effectiveness of your new consultant trainer, as your previous consultant was permitted to ignore your training procedures.

The examples in this letter are serious CGMP deviations. Your quality system does not adequately ensure the accuracy and integrity of data generated at your facility to support the safety, effectiveness, and quality of the drug products you manufacture. Our current significant findings also indicate that your quality unit is not able to fully exercise its responsibilities. It is essential to give your quality unit appropriate authority and staff to carry out its responsibilities.

We strongly recommend hiring a qualified third-party auditor/consultant with experience in detecting data integrity problems to help you comply with CGMP requirements. Note that it remains your responsibility to ensure that any third-party audit evaluates your sophisticated electronic systems and their vulnerability to data integrity manipulation.

In response to this letter, provide the Agency:

1. A comprehensive evaluation of the extent of inaccuracies in your reported data. Include a detailed action plan to investigate the extent of your deficient documentation practices noted above.

2. A risk assessment of potential effects on drug product quality. Determine the effects of your deficient documentation practices on drug products released for distribution.

3. A management strategy for your firm, including the details of your corrective action and preventive action plans.

a) As part of your corrective action and preventive action plan, describe the actions you have taken or will take to assure product quality. Contacting your customers, recalling product, conducting additional tests, adding extra lots to your stability programs, and monitoring complaints may be among the steps.

b) In another part of your corrective action and preventive action plan, describe the actions you have taken or will take to prevent the recurrence of CGMP violations, including breaches of data integrity. Revising procedures, implementing new controls, and training or re-training personnel may be among the initial steps toward a comprehensive remediation.

For guidance on current good manufacturing practice for APIs, consult "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" from the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. This ICH Q7 CGMP guidance helps ensure that all APIs meet international standards for quality and purity. You may download this guidance from FDA's website at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf

FDA considers ICH Q7 and equivalent alternatives in determining if APIs have been manufactured, processed, packed, and held according to current good manufacturing practice under section 501(a)(2)(B) [21 U.S.C 351(a)(2)(B)] of the Act.

The deviations cited in this letter are not intended to be an all-inclusive list of deviations at your facility. 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.

If, as a result of receiving this warning letter or for other reasons, are you are considering a decision that could reduce the number of active pharmaceutical ingredients 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 your drug manufacture under 21 U.S.C. 356C(a)(1). FDA must consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect 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.

Until you complete all corrections and FDA confirms that your firm complies 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 refusing admission of articles manufactured at Mahendra Chemicals, Gujarat, India, into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). Articles may be subject to refusal of admission pursuant to Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3), 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 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. Provide copies of supporting documentation. 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 APIs at issue, provide the date(s) and reason(s) you ceased production.

Send your reply to:

Mary D. Davis-López, Compliance Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Manufacturing Quality, Division of Drug Quality II
White Oak Building 51 Room 4312
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Please identify your response with FEI # 3003802404.

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