Unimark Remedies Ltd. 9/28/15

Department of Health and Human Services

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

Warning Letter

VIA UPS

WL: 320-15-17

September 28, 2015

Mr. Mehul J. Parekh
Managing Director
Unimark Remedies Ltd.
Enterprise Centre, 1st Floor
Off. Nehru Road
Vile Parle (E), Mumbai 400 099
India

FEI# 3005202703

Dear Mr. Parekh:

During our March 18-21, 2014 inspection of your pharmaceutical manufacturing facility, Unimark Remedies Ltd., located at 337 Kerala Nalsarovar Road, Kerala Village, Bavla, Ahmedabad District, India, an investigator 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 (FD&C Act), 21 U.S.C. 351(a)(2)(B). 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 acknowledge receipt of your responses dated April 8, 2014, June 5, 2014, September 16, 2014, and November 28, 2014. We note that they lack sufficient corrective actions.

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

1. Failure to document production and analytical testing activities at the time they are performed.

During our inspection, we found that test results and other entries in the production records were not entered while batches were in production. For example,

a. The investigator observed **(b)(4)** batch **(b)(4)** production on March 18, 2014. The start and stop times and **(b)(4)** for Step #**(b)(4)** were not recorded or signed in the batch record contemporaneously.

b. For your **(b)(4)** products returned due to the presence of extraneous threads, the investigator found many inconsistencies in your reprocessing batch records. Specifically, operators signed batch records for periods when they were not in your facility, indicating these activities were documented by personnel who did not perform them. During the inspection, and in your written responses, your managers admitted that the batch records were created after the manufacturing process.

c. Water testing records for sampling point **(b)(4)** on March 19, 2014, were incomplete. Specifically, the analyst did not record observations at the time they were made on March 18, 2014. Your microbiology records did not identify who prepared the samples, when they began incubation, who read the samples, or when the samples were read.

According to your responses to these FDA 483 observations, your manufacturing staff did not exhibit acceptable documentation practices, and your chemist or microbiologist each neglected his work. However, your management is responsible for routine oversight of manufacturing and testing operations, including the activities of operators and other personnel, and your responses do not address the failure of management and the flaws in your overall quality system.

In response to this letter, conduct and provide the results of a comprehensive investigation into your poor documentation practices. Your investigation should address the flaws in your quality systems and management oversight that led to these serious deficiencies. Provide your plans to revise your procedures so that all CGMP operations are documented at the time they occur. Also provide your plans to revise your procedures so that you preserve original or true copies of data in the batch records. Also provide your procedures for addressing deviations from acceptable documentation practices, including training and oversight of personnel whose duties require preparation and review of API records.

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. During the inspection, we noted that you had no unique usernames, passwords, or user access levels for analysts on multiple laboratory systems. All laboratory employees were granted full privileges to the computer systems. They could delete or alter chromatograms, methods, integration parameters, and data acquisition date and time stamps. You used data generated by these unprotected and uncontrolled systems to evaluate API quality.

b. Multiple instruments had no audit trail functions to record data changes.

We acknowledge your commitment to take corrective actions and preventive actions to ensure that your laboratory instruments and systems are fully compliant by January 15, 2015. In response to this letter, provide a copy of your system qualification to demonstrate that your electronic data systems prevent deletion and alteration of electronic data. Describe steps you will take (e.g., installing better systems or software) if your qualification efforts determine that the current system infrastructure does not assure adequate data integrity. Explain the archival process your firm has implemented to address these issues and how you will evaluate the effectiveness of these corrections. Provide a detailed summary of the steps taken to train your personnel on the proper use of computerized systems.

3. Failure to maintain complete data derived from all testing, and to ensure compliance with established specifications and standards.

Because you discarded necessary chromatographic information such as integration parameters and injection sequences from test records, you relied on incomplete records to evaluate the quality of your APIs and to determine whether your APIs conformed with established specifications and standards. For example:

a. During the inspection, the investigator found no procedures for manual integration or review of electronic and printed analytical data for **(b)(4)** stability samples. Electronic integration parameters were not saved or recorded manually. When the next samples were analyzed, the previous parameters were overwritten during the subsequent analyses.

b. We found that some analytical testing data was inadequately maintained and reviewed.

i. Your HPLC 14 computer files included raw data for undocumented **(b)(4)** stability samples analyzed on December 30, 2013, but no indication of where these samples came from and why they were tested.
ii. In a data file folder created on May 22, 2013, 23 chromatograms were identified as stability samples for **(b)(4)** lots **(b)(4)**, and **(b)(4)**. Results were not documented. More importantly, the acquisition date was July 7, 2013, more than six weeks after the samples were run.
iii. **(b)(4)** lots **(b)(4)** and **(b)(4)** were not in your stability study records at the time of inspection. Additionally, there were no log notes of any samples from the three lots removed from the stability chamber.

You responded that “the probable reason for this inconsistency in data acquisition was due to some malfunction in the computer system at the time of data acquisition.” Your response is inadequate because you have provided neither evidence to support this conclusion, nor a retrospective review of the effects your incomplete analytical data records may have had on your evaluation of API quality.

In response to this letter, provide your revised procedures and describe steps you have taken to retrain employees to ensure retention of complete electronic raw data for all laboratory instrumentation and equipment. Also, provide a detailed description of the responsibilities of your quality control laboratory management, and quality assurance unit for performing analytical data review and assuring integrity (including reconcilability) of all data generated by your laboratory.

4. Failure to properly maintain buildings and facilities used in the manufacture of intermediates and APIs in a clean condition.

We saw evidence of pests in your facility. For example, when we inspected your **(b)(4)** block, the **(b)(4)** manufacturing building was not sealed against pests. There were significant gaps in the **(b)(4)** level, where piping entered from outside. The investigator observed what appeared to be a bird's nest near the ceiling. On March 18, 2014, the investigator saw bird feces on a rack and on a bag of **(b)(4)** in the general raw material warehouse #2. On the same day, the investigator saw a lizard in the general raw material warehouse #1.

Your firm did not have written procedures for pest control. According to your responses, you performed corrective actions on the facility. However, you did not include any assessment of potential damage to your products.

Proper building design and maintenance, including operator training in prescribed cleaning and maintenance procedures are required elements of your facility's operations. In response to this letter, provide details of your pest prevention and control program and provide the results of your review of the effects of the presence of pests in your facility on API quality.

Summary

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.

We strongly recommend that you hire a qualified third-party auditor/consultant with experience in detecting data integrity problems to help you comply with CGMP requirements. However, it is 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:

1. A complete 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 comprehensive investigation into root causes of the data integrity problems, including but not limited to independent interviews of current and former employees.

3. A risk assessment of the effects of these deviations on data submitted in any pending drug applications.

4. A comprehensive management strategy to address these serious issues, including the details of your corrective action and preventive action plans.

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

b) Alsoinclude in your corrective action and preventive action plan, a section describing the actions you have taken or will take to prevent the recurrence of CGMP deviations, including breaches of data integrity. Revising procedures, implementing new systems and controls, and training or re-training personnel may be among the steps.

The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility. You are responsible for 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 letter or for other reasons, you are considering a decision that could reduce the number or volume 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 manufacturing 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 the 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.

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.

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 dates and reasons you ceased production. Please identify your response with FEI # 3005202703.

Send your reply to:

Xiaohui Shen
Consumer Safety Officer
c/o Division of Drug Quality
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research
White Oak, Building 51, RM 4223
10903 New Hampshire Ave
Silver Spring, MD 20993

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

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10903 New Hampshire Avenue
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