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

Unimark Remedies Limited 8/12/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-16-27

August 12, 2016

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

Dear Mr. Parekh:

The U.S. Food and Drug Administration (FDA) inspected your manufacturing facilities: Vapi, Plot 41/42, Phase 1 – GIDC District Valsad Pardi, from May 18-22, 2015; and Belva, 300 Village Kerala, Bavla, Kerala Nalsarovar Road, Ahmedabad District, from August 3-14, 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 drugs are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic (FD&C) Act, 21 U.S.C. 351(a)(2)(B).
We reviewed your firm's June 12, 2015, and August 30, 2015, responses (for Vapi and Bavla, respectively) in detail and acknowledge receipt of your subsequent correspondence.

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

Vapi Facility (FEI: 3004414652)

1. Failure to adequately investigate and document out-of-specification results and implement appropriate corrective actions.

Our investigator found that you failed to adequately investigate impurity specification failures for **(b)(4)** API batches # **(b)(4)** and #**(b)(4)**.

For example, for batch #**(b)(4)**, you concluded that the root cause of the failing impurity test results was an **(b)(4)** during manufacturing, even though your own records indicated that this batch was manufactured at the same **(b)(4)** as other batches that had passing results and were released. Similarly, for batch #**(b)(4)**, you attributed the failing test result to a **(b)(4)** step, even though your own investigation report lacked evidence to demonstrate that this was the assignable cause for the failure.

Your response acknowledges that your investigations into these and other out-of-specification (OOS) results are deficient, and indicates steps you have taken to improve your investigations. However, you have not provided a corrective action and preventive action plan (CAPA) that adequately resolves the specific OOS results discussed above, nor have you demonstrated how your broader investigation procedure improvements will address similar root cause analysis deficiencies in the future.

For more information about the proper handling of out-of-specification results and documentation of your investigations, please refer to *FDA Guidance for Industry: 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)**.

2. Failure to evaluate the potential effect that changes in the manufacturing process may have on the quality of your API.

Our inspection documented that you modified the manufacturing process multiple times for **(b)(4)** API. Your quality unit did not approve these changes, nor did you document themthrough a change control review process. Furthermore, you did not place samples from any of the batches produced through modified processes in your stability monitoring program to assess the effects of these changes on the quality of your API throughout the expiry period.

In your response you referenced stability data from batches not manufactured using the modified processes discussed above. Your response is inadequate because you do not have stability data to demonstrate that your API meets specifications throughout its expiry period.

Bavla Facility (FEI: 3008117347)

1. Failure to adequately investigate and document out-of-specification results and implement appropriate corrective actions.

Your firm routinely re-tested samples without documented justification and deleted analytical data. Our inspection found that you did not adequately investigate failing or atypical results. Although you obtained failing results in 2014, you did not initiate and document investigations for those failing results until July 2015. In addition, the conclusions of your investigations lacked supporting data.

Your firm's response attributed all unauthorized retesting of API batches to the lack of adequate training of your analysts.

2. Failure to ensure that test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and/or purity.

During the inspection, our investigator reviewed your growth promotion test procedures and on August 6, 2015, observed a growth promotion test failure of the **(b)(4)** tested on August 4, 2015. The test recovered *Pseudomonas aeruginosa* at **(b)(4)** percent, however, the acceptance criteria is **(b)(4)** to **(b)(4)** percent.

In your response, you indicated that the incubation times in your SOP for growth promotion tests were incorrect for **(b)(4)** and **(b)(4)** media. Your laboratory personnel, supervisors included, and your quality unit were not aware of this discrepancy. Your response fails to address the root cause of the growth promotion test failure.

3. Failure to maintain training records of employees involved in the manufacture of intermediates or API.

Our investigator found that your employees' CGMP training records contained numerous discrepancies that raise doubts regarding their authenticity. For example, the inspection documented that 10 of 11 training records contained identical handwritten responses. Our investigator also found incomplete training assessment forms for two employees. The forms indicated that the employees had not been evaluated as required in your procedures, yet the employees' training files stated that they had been evaluated as "very good" for the skills in question.

In response to this letter, provide a corrective action and preventive action plan to address your poor documentation practices and oversight of training activities. Include an updated training plan describing how you will ensure that all employees are adequately qualified to perform their assigned responsibilities in the manufacturing and laboratory operations.

4. Failure to properly keep buildings and facilities used in the manufacture of API in a clean condition.

Among other observations, our investigator found that the walls of your manufacturing area had open holes that could permit ingress of insects, birds, lizards, rodents, or other animals to the manufacturing space. During the inspection, the investigator observed dirt and birds in the manufacturing area as well as a lizard in the controlled **(b)(4)** processing area. Your response states that this area of your facility was **(b)(4)** and that the **(b)(4)** had **(b)(4)**. Nonetheless, our investigators found a batch record inside this area demonstrating that you had been conducting manufacturing operations in this space as recently as August 2, 2015 — one day prior to the beginning of the inspection.

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(b) 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 Unimark's Vapi and Balva facilities 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:

Rafael Arroyo, Compliance Officer
Rebecca Parilla, Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Ave.
Silver Spring, MD 20993
USA

Please identify your response with FEI 3004414652 (Vapi) and 3008117347 (Bavla).

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)