Malladi Drugs & Pharmaceuticals Ltd. 3/9/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-40

March 09, 2018

V.N. Gopalkrishnan, CEO
Malladi Drugs & Pharmaceuticals Limited
No 9, G.S.T. Road
St. Thomas Mount
Chennai 600 016
India

Dear V.N. Gopalkrishnan:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Malladi Drugs & Pharmaceuticals Limited, Unit 1, at 67 SIPCOT Industrial Complex, Ranipet, Vellore District, Tamil Nadu, from September 4 to 8, 2017.

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 September 2017 response in detail.

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

1. Failure to use appropriate precautions to minimize the risk of API contamination where open equipment is used.

Parts of your facility in which API production is conducted are open to the outdoors. Our investigator observed vermin, such as birds and insects, in the facility near open

equipment used for drug manufacturing. Their presence puts your drugs at risk of contamination. You failed to take adequate precautions to prevent the risk of contamination while producing drugs using open equipment.

You committed to corrective and preventive actions (CAPA), but your response is inadequate because you failed to address the potential risk to product quality and safety.

In response to this letter, provide a risk assessment for all drugs within their re-test date manufactured and distributed within the United States. Include an evaluation of all **(b)(4)**, drug intermediates, and drugs potentially contaminated by vermin.

2. Failure to have equipment of the appropriate design and suitability for its intended use and cleaning for the manufacture of API.

You use **(b)(4)** vessels in the **(b)(4)** and **(b)(4)** stages of your production process. In your response, you indicate that **(b)(4)** water is used for cleaning the **(b)(4)** vessels. However, your cleaning processes are insufficient. You lack justification that you can prevent contamination from foreign matter and other impurities that may seep from the **(b)(4)**. Further, your equipment is difficult to reproducibly clean.

Your response also states that the **(b)(4)** is kept partially full with water for up to **(b)(4)** because the **(b)(4)** when it is fully dry. Using vessels made of **(b)(4)** and partially filled with standing water may increase the risk of drug contamination. In addition, equipment surfaces should be easily cleanable, and constructed to prevent additive, absorptive, or reactive characteristics.

In response to this letter:

- Commit to replacing your unacceptable **(b)(4)** equipment with equipment composed of materials that are suitable for their intended use.
- Provide a risk assessment for any drugs within their re-test date manufactured using inappropriate equipment and distributed within the United States. Determine whether any of your equipment surfaces are reactive, absorptive, or additive so that drug quality, purity, or safety may be affected.

3. Failure to demonstrate that your manufacturing process can reproducibly manufacture an API meeting its predetermined quality attributes.

During our inspection, you acknowledged that you failed to adequately validate your **(b)(4)** API drug manufacturing process. In addition, our inspection found that your process lacked adequate control during the **(b)(4)** step. Twenty-four batches yielded out-of-specification test results for an unspecified impurity over approximately two years. Your firm rejected these nonconforming batches and reprocessed some of them.

Prior to the manufacture of process qualification batches, a manufacturer should identify all significant sources of variability and develop robust controls throughout the operation. Your process validation program failed to sufficiently address process parameters and other variables in the commercial manufacturing operation to support process reproducibility. It is essential that your process validation program provide substantial information and data to determine if the process can consistently produce acceptable quality products under commercial manufacturing conditions.

In your response, you also acknowledged that your investigations and timeliness of response to the batch failures was inadequate, and that process changes were initiated without formal change management. You also provided data from many batches that met specifications for impurity and identity. However, this data is not a replacement for adequate process design, control, CAPA and change management, and does not sufficiently support your claim that your process is robust.

Your firm does not have an adequate ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality. See FDA's guidance document, *Process Validation: General Principles and Practices*, for general principles and elements of process validation at **http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070336.pdf (http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070336.pdf)**.

In response to this letter, provide:

- A data-driven and scientifically sound process validation program that identifies all sources of variability, establishes robust design and controls, and ensures oversight of intra-batch and inter-batch variation on an ongoing basis throughout the product lifecycle. Also, include your process qualification protocol and results from your recent validation study.
- The results from your stability study of validation batches.
- A comprehensive, independent evaluation and remediation of your change management system. The evaluation should include, but not be limited to, assuring changes are appropriately justified, approved by your quality unit, and evaluated for effectiveness. Also, include a retrospective assessment of all changes executed outside an appropriate change management process since September 1, 2015, and the effect on product quality.
- A comprehensive, independent evaluation and remediation of your CAPA system. The evaluation should include but not be limited to a retrospective analysis of the effectiveness of all CAPAs since September 1, 2015.
- An assessment of drug quality risk and toxicity of the **(b)(4)** impurity. Also, provide an updated investigation into the impurity, including the specification established for it and verification that your process improvements (including automation) have been effective.

CGMP consultant recommended

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations and assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

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.

FDA placed your firm on Import Alert 66-40 on December 13, 2017.

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 continuing to refuse admission of articles manufactured at Malladi Drugs & Pharmaceuticals Limited, Unit 1, at 67 SIPCOT Industrial Complex, Ranipet, Vellore District, Tamil Nadu, 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:

LT Matthew Schnupp, Pharm.D.
Consumer Safety 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 3005115135.

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

CC:
R. Ravichandran, Vice President–Manufacturing
Malladi Drugs & Pharmaceuticals Limited, Unit-1
67, SIPCOT Industrial Complex
Ranipet, Vellore District
Tamil Nadu, India 632403

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