# Keshava Organics Pvt. Ltd. 3/15/18


10903 New Hampshire Avenue
Silver Spring, MD 20993

**Via UPS**
**Return Receipt Requested**

**Warning Letter** 320-18-41

March 15, 2018

Mr. Dinkar K. Raut
Chief Executive Officer
Keshava Organics Pvt. Ltd.
T-97 & 100, MIDC-Tarapur
Dist. Thane, Maharashtra 401506
India

Dear Mr. Raut:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Keshava Organics Pvt. Ltd. at T-97 & 100, MIDC-Tarapur, Dist. Thane, Maharashtra, from May 25 to 31, 2017.

This warning letter summarizes significant deviations of 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 June 20, 2017, response in detail and acknowledge receipt of your subsequent correspondence.

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

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

Your investigations of out-of-specification (OOS) results were inadequate.

For example, in multiple instances, you disregarded the original failing result based on a retest, but you lacked a Phase 1 laboratory investigation to support invalidation of the result. You also often lacked Phase 2 investigations to evaluate your manufacturing operation for potential root causes.

Your response includes a retrospective review of OOS results. Your review shows a pattern of recurring, similar OOS results for which investigations were insufficient, including a lack of corrective actions and preventive actions (CAPA). Notably, your response adds that it was impossible to make reliable retrospective root cause determinations for the failing results and provide scientific rationales for decisions because considerable time had elapsed since the original OOS occurrences. Timely investigations are essential for providing credible information and scientific evidence for laboratory error hypotheses.

We also found that you investigated numerous OOS results between February 2015 and April 2017 as “incidents” and not as OOS results. Your “incident” procedure did not require a substantive investigation of OOS results. Your response acknowledges that this procedure was inadequate and that consequently your decisions regarding OOS results were not supported by sufficient inquiry and scientific rationale.

You also commit to not invalidate OOS results without appropriate scientific justification and to use your OOS procedure in the future.

For more information about handling failing, out-of-specification, out-of-trend, or other unexpected results and documentation of your investigations, see FDA’s guidance document, *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*, at **https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf)**.

In response to this letter, provide the following.

- A retrospective review of all invalidated OOS (in-process and finished testing) results obtained for products on the U.S. market. Assess whether the scientific justification and evidence was conclusive. For investigations that conclusively establish laboratory root cause, determine adequacy of the CAPA, and ensure that other laboratory methods vulnerable to the same root cause are identified for remediation. For any OOS with inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, raw materials, process capability, deviation history, batch failure history). Provide a CAPA plan that identifies the potential manufacturing root causes for each such investigation, and includes process improvements where appropriate.
- An independent assessment of your system for investigating OOS results. Include a CAPA to remediate OOS investigations at your facility. Elements of your CAPA should include, but not be limited to, immediate laboratory investigation of OOS results, enhanced quality assurance participation in investigations, identification of adverse laboratory control trends, and proper initiation of the Phase 2 manufacturing quality investigation stage.
- An independent assessment and CAPA of your overall investigation systems, including: investigating deviations, atypical events, OOS results, complaints, and failures. The CAPA should include but not be limited to, enhanced investigation competencies, improved procedures, and substantial improvements in quality unit oversight of investigations.

**2. Failure to maintain complete laboratory control records for test methods.**

In several instances, you failed to maintain complete data for API tested and distributed to the U.S. For example, we found test data sheets with missing sample weights for identity testing, batch/lot numbers for reference standards and reagents, equipment identification, and complete thin layer chromatography data for related compounds.

In response to this letter:

- Provide a comprehensive investigation into the inadequacies in data, records, and reporting. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. In addition, describe all parts of your facility's operations in which CGMP information is not recorded and maintained. Include a CAPA to remediate data recording and record retention practices throughout your operation.
- Provide a risk assessment summarizing the effect of incomplete data on assessing laboratory control and product quality.
- Provide a comprehensive corrective action plan, with a target date, to ensure that laboratory records are complete.

**Repeat observations at facility**

In previous inspections (May 15–17, 2011, and April 14–18, 2014), FDA cited similar CGMP deficiencies. You proposed specific corrections for these deficiencies in your responses. These recurring deviations demonstrate that your facility's oversight and control over the manufacture of drugs is inadequate.

**CGMP Consultant Recommended**

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations, and assist your firm in meeting CGMP requirements. The third-party review of your operation should comprehensively audit and assist with remediating your operations, including but limited to, investigations, laboratory controls, data management system, quality unit authorities and resources, and all other elements of your quality system.

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.

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 Keshava Organics Pvt. Ltd., T-97 & 100, MIDC-Tarapur, Dist. Thane, Maharashtra, 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 May 25–31, 2017, 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:

Christina Alemu-Cruickshank
Compliance 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 3003677831.

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

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