Inspections, Compliance, Enforcement, and Criminal Investigations

Smruthi Organics Limited 3/6/14

Department of Health and Human Services

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

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-14-005

March 6, 2014

Mr. Eaga Purushotham
Chairman and Managing Director
Smruthi Organics Ltd
165-A, Balaji Bhavan,
1st Floor, Railway Lines,
Solapur, 413 001 India

Dear Mr. Purushotham:

During our October 15, 16, 17 & 18, 2013 inspection of your pharmaceutical manufacturing facility, Smruthi Organics Ltd located at Plot No. A-27, MIDC, Chincholi Village, Taluka Mohol, Solapur, India, investigators from the U.S. Food and Drug Administration (FDA) identified 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 (the 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 have conducted a detailed review of your firm's November 4, 2013 response and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated December 17, 2013.

1. Failure to maintain complete and accurate laboratory test data generated in the course of establishing compliance of your APIs to established specifications and standards.

a. There was no written explanation for deletion events observed on audit trails for your standalone HPLC units. Your standard operating procedures (SOPs) did not include instructions for the retention of electronic raw data. In response to this letter, provide your procedures describing requirements to maintain complete data.

b. Your laboratory test data did not include records of the integration parameters used for any HPLC analyses.

c. There was incomplete raw data to support the test method validation/verification activities for the test methods used for your APIs. Your response should include new test

method validation/verification data for the **(b)(4)** residual solvents testing that was requested during the inspection.

d. Our investigators identified the practice of performing trial injections for HPLC analyses prior to running the release and stability tests that are then reported. There was no justification for the practice of the trial preparations and injections.

Your response indicates that the practice has been stopped. Provide a comprehensive retrospective review and address any trial sample injections performed. Also provide an action plan that details how you plan to implement reliable laboratory controls to prevent the misuse or misidentification of test sample injections.

e. Our investigators identified calibration and media preparation records that were not authentic in that the persons that signed each record as having performed the activity were not at work on the day the work was accomplished.

Audit and identify the extent of this activity in your laboratory and manufacturing operations and provide an update to your investigation into this matter.

2. Failure to maintain and make available for inspectional review production and control records for currently marketed APIs.

A February, 2013, European Directorate for the Quality of Medicines (EDQM) inspection found that your firm was blending out-of-specification (OOS) API batches with other API batches. Your Head of Quality Assurance and Regulatory Affairs stated to our investigator that the relevant records had been destroyed. However, your written response states that there was a miscommunication during our inspection and that in fact these records have not been destroyed.

In your response, describe the control of records relating to these blended batches that we requested, why they were not provided to the investigator during the inspection, and where they were located. Also provide copies of these records in your response.

Also, provide a full accounting of all API batches blended with another API batch after obtaining an out-of-specification result. During the current FDA inspection, you informed our investigator that you had not conducted a written investigation into the blended OOS batches that EDQM had identified in February 2013. Your response indicates that a preliminary investigation has begun. Provide an update on this investigation, which should be extended to all batches that contained an OOS result for your API and were blended to obtain a passing API result. Provide the Certificates of Analyses (CoAs) and shipment information (customer, date, batch, and amount) for these batches.

3. Inadequate investigations of critical deviations or a failure of a batch to meet its specifications or quality standards.

Your investigations into the June 7 and 18, 2012 complaints that cited particulate matter found in nine of your **(b)(4)** API batches were incomplete and inconclusive. Your response states that additional investigations are ongoing, and that preventive and corrective actions will be taken in response to your findings. Provide the investigations and the preventive and corrective actions taken. Provide records of the returned API and the disposition of each returned batch. Discuss the expansion of your investigation to other batches that might be affected by particulate contamination.

In addition to the above findings, provide information about the following deficiencies:

- Our investigator found a chemist assigned to create a duplicate logbook ("general inward register"). There was no record made describing the reason for the replacement of the original logbook. Explain why the pages in the current logbook were different from pages with the same number that were kept from the old logbook. Provide complete copies of the original logbook and the current logbook in your response. Also address our concern that

your employee was required to perform such an activity, and explain how frequently such transcription activities occur at your plant.

- Your firm states that, while you have some original source data for HPLC runs, you are unable to recover the integration parameters used for API assay and impurity tests. Include in your response tests of the retained samples for all batches of APIs (**(b)(4)** and **(b)(4)**) used in US products, and describe the integration parameters used. Provide the results of these analyses, as well as any differences in the chromatography from the originally performed release tests for these batches. Provide the conclusions to this additional testing as a part of your response and determine the acceptability of all API batches used for US products.
- Reassess your analytical test method validation and verification activities and identify those methods which do not have complete supporting data (e.g. chromatographic data) and describe your remediation plan.

You are responsible not only for having controls to prevent omissions in data, but also for recording any changes made to existing data, which should include the date of change, identity of person who made the change, and an explanation or reason for the change. Your response should address your laboratory equipment and any other process-related equipment that may be affected by the lack of adequate controls to prevent data manipulation. All changes to existing data should be made in accordance with an established procedure. You are also responsible for maintaining complete analytical testing data.

Please provide your corrective action plan that describes your commitment, procedures, actions, and controls to ensure data integrity. This plan should include the corrective actions implemented to ensure that all managers, supervisors, and quality unit personnel are properly trained in detecting data integrity and manipulation. The investigation should provide detailed descriptions of other incidents where your quality unit failed to ensure proper testing of materials and include a comprehensive retrospective review of all test results generated by your laboratory personnel. The integrity of records in other part of your operation, including manufacturing, should also be carefully audited. If other instances of non-existent, inaccurate, or unreliable tests results are found, your investigation should assess the impact of these discrepancies on the quality of the APIs manufactured at your facility. Provide the documentation of specific training offered to all employees regarding the importance of following CGMP and ensuring that all required tests are performed.

We highly recommend that you hire a third party auditor, with experience in detecting data integrity problems, to assist you with this evaluation and your overall compliance with CGMP. It is your responsibility to ensure that data generated during operations is accurate and that the results reported are a true representation of the quality of your APIs. Provide a list of all the lots of APIs shipped to the U.S. where release relied upon non-existent, inaccurate, or unreliable test data.

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 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, you are considering a decision that could reduce the number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, 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 Program also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), 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 all corrections have been completed and FDA has confirmed corrections of the violations

and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as an API manufacturer. In addition, your failure to correct these violations may result in FDA continuing to refuse admission of articles manufactured at Smruthi Organics Ltd located at Plot No. A-27, MIDC, Chincholi Village, Taluka Mohol, Solapur, India, into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The 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 fifteen 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, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute the APIs at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3004896392.

Please send your reply to: Regina T. Brown, Senior Policy Advisor, CDER/OC/OMPQ/DIDQ, Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993.

Sincerely,
/S/
Steven Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

Page Last Updated: 04/01/2014
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