Inspections, Compliance, Enforcement, and Criminal Investigations

Asada Milling Co., Ltd. 3/22/13

Department of Health and Human Services

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

Warning Letter

VIA UPS MAIL

WL: 320-13-11

March 22, 2013

Masaji Kawauchi
Director
Asada Milling Co., Ltd
253 Obata
Kanra-machi, Kanra-Gun
Gunma, Japan 370-2202

Dear Masaji Kawauchi:

During our October 9-12, 2012, inspection of your active pharmaceutical ingredient (API) manufacturing facility, Asada Milling Co., Ltd, located at 253 Obata, Kanra-machi, Kanra-Gun, Gunma, Japan, investigators from the Food and Drug Administration (FDA) identified significant deviations from Current Good Manufacturing Practice (CGMP) for the manufacture of APIs. These deviations cause your API(s) 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.

Specific deviations observed during the inspection include, but are not limited, to the following:

1. Failure of the Quality Unit to perform quality-related activities in accordance to established written procedures.

Your firm's quality unit failed to review, release, or reject finished API products, and failed to perform annual product quality reviews. In addition, your quality unit also failed to have procedures in place to review process validation, change management documentation, release of raw materials, and to approve or reject batch records. Moreover, your firm failed to ensure the use of an effective system for calibrating critical manufacturing equipment and to provide employees with CGMP training.

We also note that your current Standard Operating Procedure (SOP), *Quality Control Regulation AM-2A50-01,* regarding the responsibilities of the quality unit is inadequate. For example, the written procedure fails to describe the firm officials who are authorized to release APIs; the approach used to properly investigate and resolve deviations; and the annual product quality review policy.

In response to this letter, please include a copy of your written procedures defining the responsibilities of the quality unit and the process by which the quality unit will execute quality related activities, including but not limited to the review of your API test results, annual product quality reviews, the review of process validation protocols and reports, the review of change control documentation, the system established for the release of raw materials, and the approval or rejection of batch records.

2. Failure to maintain and clean manufacturing equipment and facilities.

The inspection reported your manufacturing equipment as corroded, rusted, chipped of paint, and coated with an unidentified white powder. In addition, visible powder was observed on the equipment, floors, and walls of the mixing, **(b)(4)** rooms of the facility. Two types of APIs are manufactured at your facility. One product group contains **(b)(4)** and the other product group contains **(b)(4)**. The visible powder, observed throughout the manufacturing area of your facility, could lead to a cross-contamination of manufactured products.

Your firm also failed to have written procedures and established schedules for facility sanitation and manufacturing equipment maintenance. The FDA investigator observed hundreds of insects in the **(b)(4)** insect catchers located in the processing areas of your facility. For example, one such insect catcher was located in close proximity to the **(b)(4)**, which your firm discharged into **(b)(4)** covers. This observational finding is subsequent to your firm's pest control report spanning September 3-18, 2012, concluded two weeks prior to the FDA inspection. This pest control report also noted an excessive number of insects in the **(b)(4)** insect catcher located in the processing areas of the facility.

In response to this letter, include a copy of your written procedures that specify how your firm plans to maintain and clean the facility and manufacturing equipment. Describe how the cleaning procedures will prevent cross-contamination between materials manufactured using the same equipment. In addition, submit established cleaning schedules for both facility and manufacturing equipment, and describe the process by which these records are captured, maintained, and approved. Please also submit revised pest control procedures designed to ensure that insects and other pests do not enter the processing areas.

3. Failure to establish written procedures pertaining to handling of raw materials used in API production, and failure to establish specifications for finished API release.

Your firm failed to perform identity testing on incoming raw materials to be used for API manufacturing and to verify the reliability of certificates of analysis for these raw materials at appropriate intervals. There are no established procedures that describe the receipt, identification, quarantine, or storage of raw materials. In addition, your firm has established specifications for neither raw materials nor finished APIs. During the FDA inspection, the investigator noted that your firm was unable to determine from its records if **(b)(4)**, in finished API **(b)(4)**, was released in accordance to finished API specifications.

In response to this letter, include a copy of your written procedures by which you plan to handle, identify, and approve or reject raw materials. Clearly describe your finished API release process, including use of finished API release test results. Include your firm's established release specifications for each finished API manufactured at your facility.

4. Failure to prepare adequate batch production records and failure to identify produced batches with a unique batch identification number.

Batch Record **(b)(4)** Lot **(b)(4)**, reviewed during inspection, was not controlled or reviewed by your firm prior to the release of API for distribution. Your firm failed to ensure that batch records were completed in their entirety or that they specified the equipment used during API manufacturing. At least one executed batch record was observed to have no associated lot number.

We also noted that your firm has no written procedure for assigning lot numbers to API

products and failed to ensure that lot numbers were unique identifiers. While firm officials stated that certain unwritten rules are followed in creating batch numbers, application of these rules appeared to be inconsistent. For example, while firm officials stated that the **(b)(4)** signify the date of manufacture, our inspection found that lot number **(b)(4)** was actually manufactured on March 9, 2011.

In response to this letter, please include a copy of your written procedures for the preparation and review of master production instructions and the issuance, review, approval or rejection, and archiving of executed batch records. Also include your written procedure for unique lot number assignment. During the review of your documents, obtained from the FDA inspection, we observed your firm's inconsistent use of terms such as batch, batch record, and lot. Please include definitions of these terms within your submitted procedures.

5. Failure to have an API stability program to monitor stability characteristics of your firm's APIs, and failure to set an expiry or retest date for APIs based on the evaluation of data derived from stability studies.

The inspection documented that the label for API **(b)(4)**, lot number **(b)(4)**, provided a **(b)(4)** expiration date. Your firm failed to provide stability data to support the expiration date provided on the label for this product. Furthermore, representatives from your firm stated that the firm has no stability program for any of the API products manufactured at your facility.

In response to this letter, include a copy of your stability data to support any assigned expiry or retest dates. In addition, provide a copy of the written procedures by which you plan to monitor the stability of your APIs on an ongoing basis. Provide a summary of the validation of the analytical methods used in your stability program and describe how you have demonstrated that these methods are stability-indicating.

6. Failure to perform process validation for critical manufacturing parameters of all manufactured API products.

Your firm failed to perform process validation for the manufacturing of its API products including **(b)(4)**. During the inspection your firm prepared and presented a document entitled "How to Determine Process Conditions," briefly describing your firm's experience with parameters such as mixing duration, speed, and temperature; **(b)(4)** conditions; and **(b)(4)** temperature and duration. This document is an inadequate replacement for executing process validation as it fails to demonstrate a robust state of control with data obtained from the API production process. In addition, it is not clear which of your many API manufacturing processes this document describes.

In response to this letter, please include a copy of your process validation protocols for all API products. These validation protocols should, for example, describe the processes by which you identify your manufacturing parameters, acceptance criteria for these parameters and for any in-process and finished product tests, and identification of personnel responsible for protocol execution, review, and approval. Provide a timeline for execution of these protocols. In addition, describe your continued process verification program to be implemented that will verify that your API manufacturing processes remain in an ongoing state of control.

The deviations detailed in this letter are not intended to be an all-inclusive statement 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 you wish to continue to ship APIs to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

Until all corrections have been completed and FDA has confirmed corrections of the deviations 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, failure to correct these deviations may result in FDA continuing to refuse admission of articles manufactured at Asada Milling Co., Ltd, located at 253 Obata, Kanra-machi, Kanra-Gun, Gunma, Japan, into the United

States. The articles are 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 Current Good Manufacturing Practice within the meaning of section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)].

If, as a result of receiving this warning letter or in general, you are considering making a decision that will result in a decreased 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 in order to ensure that your action(s) does not adversely affect the public health.

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 deviations. Include an explanation of each step being taken to prevent the recurrence of deviations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture or distribute the APIs manufactured at this facility, and provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3006415943.

If you have questions or concerns regarding this letter, contact Christina Alemu-Cruickshank, Compliance Officer, at the below address and telephone number.

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Sincerely,
/S/
Michael D. Smedley
Acting Director
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Office of Compliance
Center for Drug Evaluation and Research

Page Last Updated: 04/02/2013
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