U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Macco Organiques 12/10/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-11-005

December 10, 2010

Mr. Kendrick Martin
General Manager
Macco Organiques, Inc.
100 McArthur
Valleyfield, Quebec
Canada J6S 4M5

Dear Mr. Martin:

During our April 20-23, 2010 inspection of your active pharmaceutical ingredient (API) manufacturing facility, Macco Organiques, Inc. located at 100, Rue McArthur, Salaberry-De-Valleyfield, Canada, an investigator 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 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 reviewed your firm's response of April 30, 2010, and note that it lacks sufficient corrective actions.

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

1. Failure to have adequate laboratory controls and maintain adequate records. For example,

   a) You do not maintain original raw data pertaining to the testing of drug products manufactured at your facility. Instead, your firm discards the original raw data of analytical tests after the information is transferred to a Summary Result book.

   b) The analytical notebooks you use at your facility are deficient because they lack the information regarding the sample preparation.

   c) You have no documentation to demonstrate the analysts are following the analytical methods as instructed in the USP. In addition, there were no USP methods readily available for analysts performing testing in the laboratory.

   d) You do not confirm analytical tests results through a second person for accuracy, completeness and compliance with the established standards.

Your response fails to address these deviations. Provide the appropriate commitments and documentation to demonstrate that your laboratory control records include complete data derived from all tests conducted to ensure compliance with established specifications and standards.

2. Failure of your quality unit to exercise its responsibility to ensure the APIs manufactured are in compliance with CGMP, and meet established specifications for quality and purity.
For example,

Your quality unit fails to adequately review and investigate production deviations. The inspection documented that your firm released and shipped **(b)(4)** FCC/USP batch# **(b)(4)** to a customer for hemodialysis, while it was still under investigation for black particles. Your non-conformance investigation found that there was a feed interruption that leads your product to be in direct contact with hot areas of the **(b)(4)**, and as a result your product is charred or burned.

Your response is inadequate because it fails to provide the documentation and final investigation of this non-conformance. Please provide supporting data regarding the identity of the particles, root cause analysis, conclusion, and your rationale for releasing this batch. Also explain the corrective and preventive action implemented for this non-conformance, and other similar incidents.

In your response you indicate that your products will no longer have a United States Pharmacopeia (USP) claim on the label and that, therefore, you do not need to comply with the USP. We disagree with your response. These three APIs are all the subject of monographs in the USP, which is an official compendium recognized in section 201(j) of the Act [21 U.S.C. § 321(j)]. According to section 501(b) of the Act [21 U.S.C. § 351(b)], a drug is adulterated "[i]f it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium…" Removing the designation "USP" from your product labels does not eliminate the statutory requirement that your firm comply with the USP requirements. If your product fails to meet the standards of strength, quality, or purity in the USP, you may state on the label how your drug differs from these compendial standards. Either failing to comply with the USP compendial requirements or to state on the label how your drug differs from the compendial standards renders your drug adulterated under the Act.

Provide a copy of all letters or other communications with your distributors on how to address lots with this defect, and a list of all distributors and known drug manufacturers.

3. Failure of your quality unit to provide confidence that API manufacturing processes will consistently yield a product meeting its intended specifications. Your firm manufactures USP products at your facility without applying the appropriate controls and GMPs. For example,

   a) Our inspection of your facility revealed that your firm failed to perform process validation for three USP products: **(b)(4)**. This is a repeat observation. The June 2001 FDA inspection reported that your firm failed to conduct process validation studies for **(b)(4) ,** a USP product manufactured at your facility.

   b) Your firm failed to perform stability studies for **(b)(4)** to support the **(b)(4)** year expiration date currently assigned. This is a repeat observation. The June 2001 FDA inspection documented your failure to perform stability studies on **(b)(4)**, a USP product

manufactured at your facility.

c) Your firm failed to perform cleaning validation studies to support the use of "city water" to clean all your equipment. Your firm lacks data to support the use of city water for the cleaning operation. Also, the inspection documented that **(b)(4)** #2 and **(b)(4)** #4 are non-dedicated pieces of equipment, and that they can be used for various USP products. The potential for product carry-over between batches or manufacturing campaigns underscores the importance of a robust cleaning procedure.

Your response lacks the appropriate documentation corrections to these deviations regarding process validation, stability studies, and cleaning validation for all drug products manufactured at your facility, intended for the U.S. market.

4. The buildings and facilities used in the manufacture of USP products are not designed and constructed to facilitate cleaning, maintenance, and operations as appropriate to the stage of manufacture. Additionally, facilities are not designed to minimize potential contamination. For example,

During the inspection, the investigator observed the following in Building **(b)(4)**:

a) Live flying insects in a large opened bag of **(b)(4)** lot #**(b)(4)**, located next to production equipment.

b) Dust and debris covering products. Some of the products were stored in drums, however, there were numerous lids missing.

Your firm response indicates that the company will improve practices and have procedures to control insects, housekeeping, and raw materials. Your response is inadequate because it lacks a specific corrective and prevention action plan to ensure that you maintain and clean the warehouse and production areas to prevent contamination. The facilities you use in the manufacture of intermediates and APIs should be appropriately maintained, and remain in a clean condition. Please include in your response a copy of the procedures implemented to address this deviation.

The deviations identified on the FDA 483 for this inspection are the same types of deviations noted on the previous FDA 483 issued in June 2001. We appreciate the scope of your corrective action plan submitted in your April 30, 2010 correspondence and believe it is critical for CGMP

compliance. The Agency takes repeat deviations very seriously. We note that many of the repeat deviations resulted from poor supervision or a failure of quality assurance oversight. Please refer to November 2000 International Conference on Harmonization ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, which states in part 2.2., "The quality unit(s) should review and approve all appropriate quality-related documents." It is the responsibility of the quality units to comply with CGMPs, approve or reject products manufactured and conduct adequate investigations for deviation from established procedures.

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.

Additionally, your firm is neither registered nor has it listed every API in commercial distribution in the United States with FDA, as required by 21 C.F.R. § 207.40 and section 510(i) of the Act [21 U.S.C. § 360(i)]. The FDA investigator discussed this issue with you during the inspection. Your response did not address this issue. Information on how to register and list is available at the following internet website:
http://www.fda.gov/cder/drls/registration_listing.htm [1]. You must complete the required registration and listing and provide evidence that you have fulfilled these requirements in your response to this letter.

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 refusing admission of articles manufactured at Macco Organiques, Inc. located at 100, Rue McArthur, Salaberry-De-Valleyfield, Canada 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)].

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. Please identify your response with FEI # 3002807518.

If you have questions or concerns regarding this letter, contact Maan Abduldayem, Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
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Division of Manufacturing and Product Quality
International Compliance Branch
White Oak, Building 51
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-3916
Fax: (301) 847-8741

Sincerely,

/s/

/Richard L. Friedman/
Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

Links on this page:

1. http://www.fda.gov/cder/drls/registration_listing.htm