Inspections, Compliance, Enforcement, and Criminal Investigations

Sumitomo Chemical Co., Ltd.

hhsbluebirdDepartment of Health and Human Services

Public Health Service
Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Manufacturing and Product Quality
International Compliance Branch
While Oak. Building 51
10903 New Hampshire Avenue
Silver Spring, MD 20993

Warning Letter

VIA FEDERAL EXPRESS MAIL

WL: 320- 09-11

August 24, 2009

Mr. Shinji Kawamura
General Manager, Gifu Plant
Sumitomo Chemical Company Limited
3750 Juhachicho
Maid, Anpachi-Cho, Anpachi-Gun
Gifu Prefecture, Japan 503-0125

Dear Mr. Kawamura:

This is regarding an April 6-9, 2009, inspection of your active pharmaceutical ingredient (API) manufacturing facility, Sumitomo Chemical Company Limited, located at 3750 Juhachicho, Maid, Anpachi-Cho, Anpachi-Gun, Gifu Prefecture, Japan, conducted by Investigator, Jose R. Hernandez and Chemist, Javier O. Vega. The inspection revealed significant violations from U.S. current good manufacturing practice (CGMP) in the manufacture of APIs. The CGMP violations were listed on an Inspectional Observations (FDA-483) form issued to you at the close of the inspection.

These violations cause the APIs manufactured by your firm to be adulterated within the meaning of Section 50 I(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 USC § 351(a)(2)(B)]. Section 501 (a)(2)(B) of the Act requires that all drugs, as defined in the Act, be manufactured, processed, packed, and held according to CGMP.

We have received your firm's responses of May 14 and August 12,2009, and note that they lack sufficient corrective actions.

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

1. Your firm does not assure that suitable processing (b)(4) is used for the (b)(4) step of the Hydralazine HCl manufacturing process. This API is intended for use in parenteral drug products. Your firm currently uses (b)(4) and does not test this (b)(4) for endotoxins and total microbial

count. [FDA-483 Observation 8]

Your written response states that you do not intend to conduct endotoxin testing for **(b)(4)** or sanitize your **(b)(4)** system. It is essential that non-sterile APIs intended for use in parenteral drug products are manufactured using **(b)(4)** that is suitable for the process stage and that routine monitoring is performed to ensure ongoing **(b)(4)** system control. Our inspection found that your firm uses **(b)(4)** at the **(b)(4)** and **(b)(4)** stage, and failed to test for total microbial count and endotoxins.

Please refer to ICH Q7A Guidance for Industry for guidance regarding" quality of active pharmaceutical ingredients intended for use in parenteral drug products.

2. Your firm's (b)(4) system is not designed to minimize the risk of microbial contamination. [FDA-483 Observation 8]

Your written response states that you are in the process of re lacin the distribution pipes, connections, and flexible hoses. However, your **(b)(4)** tank #**(b)(4)** cannot be drained and has been in use since 1990. Your **(b)(4)**, approximately 100-meter, distribution pipe contains numerous threaded connectors, at least two flexible hoses, and has no mechanism for **(b)(4)**. This design is not conducive for controlling the **(b)(4)** system's microbial and endotoxin levels. We continue to have serious concerns about the impact of your **(b)(4)** system's design on endotoxin and microbial load.

Please provide us with a corrective action plan for how you will address these concerns.

3. The new method validation for bicalutamide API did not include sensitivity (limit of quantitation), linearity, accuracy, or an appropriate precision determination. [FDA-483 Observation 1]

The establishment inspection report indicates that the new method has not been validated for the aforementioned validation elements, and the precision was conducted with only three injections. Your response states that you have revised your method validation protocol, but does not indicate whether your protocol includes the elements, or if you have performed the method validation. Please provide us with your revised stability and method validation protocols, and method validation report.

Please note that an analytical method should be adequate for its intended use. The extent of the analytical method validation studies will depend on the purpose of the analysis and the complexity of the manufacturing process. Adequate analytical performance elements should be considered in the validation to establish that the method meets proper standards of accuracy and reliability, as well as the requirements for the intended analytical procedures. For example, the validation of the assay method of a component may include performance elements such as accuracy, precision, specificity, linearity, and range. For a method used to determine impurities, additional elements such as quantitation limit and detection limit will be required.

The violations cited above, or on the FDA-483 issued to your firm, are not an all inclusive list of the CGMP violations that may exist at your facility. FDA inspections are audits that are not intended to address all deficiencies from CGMP, or violations that may exist at a firm. 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 violations, and your firm's compliance with CGMPs, this office may recommend withholding approval of any new applications or supplements listing your firm as an API manufacturer. In addition, failure to correct these violations may result in FDA denying entry of articles manufactured at Sumitomo Chemical Company Limited, Gifu Prefecture, Japan, into the United States. The articles could 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 current good manufacturing practice within the meaning of Section 501 (a)(2)(B) of the Act [21 U.S.C

§ 351 (a)(2)(B)].

Please respond to this letter within thirty days of receipt and identify your response with FEI #3002808125. If you have questions or concerns regarding this letter, contact Karen Takahashi, Compliance Officer, at the below address and telephone number.

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Sincerely,
/S/

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