Inspections, Compliance, Enforcement, and Criminal Investigations

Yuki Gosei Kogyo Co., Ltd. 12/9/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

Via UPS Mail

WL: 320-11-04

December 9, 2010

Mr. Tsutomu Nakao
Director and General Manager
Yuki Gosei Kogyo Co., Ltd.
Ochial 788, Joban Nishigo-machi
Iwaki-shi, Fukushima
Japan, 972-8316

Dear Mr. Nakao:

During our July 16-21, 2010 inspection of your active pharmaceutical ingredient (API) manufacturing facility, Yuki Gosei Kogyo Co., Ltd., located at Ochial 788, Joban Nishigo-machi, Iwaki-shi, Fukushima, Japan, 972-8316, 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 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 August 6, 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 of your quality control unit/laboratory to ensure the analytical methods used within your laboratory are validated for their intended use.

For example, the release test methods your firm uses to test aerobic microbial count and endotoxin content of **(b)(4)** API are not validated. The testing for endotoxins and aerobic microbial counts are significant because your **(b)(4)** API is intended for use in the manufacture of a parenteral drug product **(b)(4)**.

Your response indicates that you will validate both the endotoxin content and aerobic microbial count methods. During the inspection, your QC Section Manager indicated to our investigators that these methods, among others, were on a schedule to be validated by the end of September 2010. All test methods should be validated prior to shipping APIs intended for the U.S. market. Include in your response to this letter the analytical method validation summaries for the endotoxin content and aerobic microbial determination for **(b)(4)**.

2. Failure of your quality control unit/laboratory to ensure your analytical methods used to evaluate the stability of your APIs are validated as well as stability indicating.

For example, the analytical test method entitled "Purity of **(b)(4)** by HPLC" your firm uses to release and support the stability of your **(b)(4)** API has not been validated or demonstrated to be stability indicating. Currently, the "Purity of **(b)(4)** by HPLC" test method only evaluates and reports the area percent for the four main peaks for **(b)(4)**. You have not demonstrated that this method is capable of detecting and quantifying impurities or degradants that may be present in your API.

You should establish an impurity profile describing the identified and unidentified impurities present in a typical batch for each API. This impurity profile should be established during development studies and should be evaluated (at appropriate intervals) over the product lifecycle to ensure continued comparability. Furthermore, API specifications should include control of significant impurities.

Once you validate your method and establish an impurity profile for **(b)(4)** API, we recommend you select and test a determined number of batches currently in distribution to confirm that the individual and total impurities are at acceptable levels.

In addition, your "Purity of **(b)(4)** by HPLC" test method does not include a scientifically sound or appropriate system suitability assessment. Currently, you only require **(b)(4)** injection of a standard to determine if the HPLC system is suitable for use. This **(b)(4)** injection of a standard is insufficient to determine that the system is suitable for its intended use.

Your response indicates you will validate your analytical method for "Purity of **(b)(4)** by HPLC," and that you will include a system suitability test. You also commit to revise your testing procedure and update your DMF accordingly. Please provide a copy of the method validation summary report. Additionally, provide the revised test method system suitability requirements.

3. Failure of your quality control unit/laboratory to ensure that analytical instrumentation and test equipment used to assure the quality of your APIs has been appropriately qualified and calibrated for their intended use.

Specifically, your firm has failed to conduct adequate qualifications of your analytical instruments and test equipment. For example, the residual solvent method used to test **(b)(4)** API has an initial starting gas chromatograph (GC) oven temperature of **(b)(4)**. Your firm's current qualification of the GC oven temperature does not include temperatures below 100°C. Additionally, the water bath you use in the assay determination of **(b)(4)** API is not qualified to maintain a bath temperature of **(b)(4)**, as required in your analytical method.

Your response indicates that you will perform instrument calibrations to include the operating ranges used to test **(b)(4)**, and that you will revise your calibration procedures to be able to confirm that the function of the instrument is the same as when the instrument's Operational Qualification (OQ) was performed. All laboratory instrumentation and equipment that you use to test material manufactured for the U.S. market should have an Operational Qualification (OQ) and should be calibrated to include applicable operating ranges.

General Comments:

Your firm does not adhere to the commitment indicated within your DMF **(b)(4)** for **(b)(4)** to test incoming **(b)(4)**, the starting material for your final **(b)(4)** API, for endotoxins. The **(b)(4)** starting material is not tested by your current supplier **(b)(4)** or by your firm for endotoxins to satisfy this DMF commitment. The testing of endotoxins is significant because your **(b)(4)** API is intended for use in the manufacture of **(b)(4)** Injection. Furthermore, there are no established specifications for the endotoxin content of the incoming starting material, **(b)(4)**. The DMF establishes that

the **(b)(4)** starting material will be tested, and the result of the endotoxin test recorded, but does not establish a specification.

Your response indicates that you will test all incoming lots of **(b)(4)** starting material for endotoxin once an analytical method is validated, and that you will establish endotoxin specifications for incoming **(b)(4)** starting material based on the endotoxin specification for the final **(b)(4)** API. Please include the timeframe of when you expect to have implemented the proposed corrective actions and notify us when the DMF has been revised.

In addition to the items listed above, the inspection uncovered additional deficiencies that increase our concerns regarding the quality of the API manufactured at your facility. These issues include, but are not limited, to:

- Testing of your process water for endotoxins only on a **(b)(4)** basis only
- Recording of "Pass" for the conducted endotoxin test on your issued COAs for **(b)(4)**; the quantitative number should be recorded

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 refusing admission of articles manufactured at Yuki Gosei Kogyo Co., Ltd., located at Ochial 788, Joban Nishigo-machi, Iwaki-shi, Fukushima, Japan, 972-8316 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 #3002808534.

If you have questions or concerns regarding this letter, contact Brian L. Belz (CDER), Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing and Product Quality
International Compliance Branch
White Oak, Building 51
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-4279

Sincerely,

/s/

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

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