Yuki Gosei Kogyo Co., Ltd. 7/17/18

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-63

July 17, 2018

Mr. Masaru Matsui
President and CEO
Yuki Gosei Kogyo Co., Ltd.
10-4, Nihonbashi-Ningyocho 3-Chome
Chuo-Ku, Tokyo 103-0013
Japan

Dear Mr. Matsui:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Yuki Gosei Kogyo Co., Ltd. at Ochiai 788, Joban Nishigo-machi, Jobannishigo-Machi Iwaki, Fukushima, from November 13 to 17, 2017.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your December 8, 2017, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigator observed specific deviations including, but not limited to, the following.

1. **Failure to maintain complete data derived from all laboratory tests conducted to ensure your API complies with established specifications and standards.**

Your firm does not ensure that complete data from testing of your API are included in the official batch record and reviewed by your quality unit. For example, you reported passing results for related substances testing of **(b)(4)** lot #**(b)(4)** analyzed starting at **(b)(4)** on July 28, 2015. However, our investigator found unreported analyses including out-of-specification (OOS) results for the same lot acquired earlier on the same date, and on the next day as the reported results. You failed to include this data to be reviewed by your quality unit prior to the release of the lot. Our investigator documented the same pattern with other products not intended for the U.S. market.

In your response, you explained that this “trial analysis” was performed on the sample solution for conditioning the high-performance liquid chromatography (HPLC) column. However, your explanation did not address why the “trial analysis” was performed using a sample solution instead of a standard solution, or why you ran this extra analysis in addition to the system suitability test, which verifies that a chromatographic system is adequate as set forth in USP <621>.

You also acknowledged that a retrospective review conducted after the inspection found additional instances of unreported electronic data in original batch records. Your review only assessed laboratory data and did not assess all parts of your facility’s operation where CGMP information is generated and maintained. In addition, you failed to provide details of your review criteria and methodology.

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation.

In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility’s operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the testing, manufacturing and other data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate, including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
- A status report for any of the above activities already underway or completed.

Conclusion

Deviations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these deviations, for determining the causes, for preventing their recurrence, and for preventing other deviations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) 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 you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these deviations may also result in FDA refusing admission of articles manufactured at Yuki Gosei Kogyo Co. Ltd., at Ochiai 788, Joban Nishigo-machi, Jobannishigo-Machi Iwaki, Fukushima into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, 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 FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to **CDER-OC-OMQ-Communications@fda.hhs.gov (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)** or mail your reply to:

Rebecca Parrilla
Compliance Officer
U.S. Food and Drug Administration

White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3002808534.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

cc:
Mr. Nobuyoshi Miyata, General Manager Joban Factory
Yuki Gosei Kogyo Co., Ltd.
788, Ochiai, Joban Nishigo-machi
Iwaki-shi, Fukushima, 972-8316 Japan

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