Daito Kasei Kogyo Co Ltd 1/18/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-26

January 18, 2018

Mr. Kazumasa Koyama
Plant Manager
Daito Kasei Kogyo Co., LTD., Okayama Factory
441 Kadani, Bizen
Okayama, 705-0035
Japan

Dear Mr. Koyama:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Daito Kasei Kogyo Co., LTD., at 441 Kadani, Bizen, Okayama, from July 18 to 21, 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 August 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 ensure that, for each batch of API, appropriate laboratory tests are conducted to determine conformance to specifications.

You released numerous drugs without completing all required testing. You claimed that the drugs were tested for identity and assay, and met required specifications for these attributes. However, these tests were never conducted, so you had no assurance that the drugs conformed to specification. Your actions may have put consumers at risk in at least two ways: first, through use of potentially ineffective **(b)(4)**, and second, through possible exposure to toxic impurities such as **(b)(4)** and **(b)(4)**.

In your response, you said that the former quality control manager decided that identification tests would not be required if "… identification tests of raw materials were confirmed with COA provided by the raw material manufacturers" and that "The QC manager at the time approved the product without testing…" Your revised SOP for issuing COA requires confirmation of raw data.

Your response was inadequate because you have not shown how you intend to confirm such data, who is responsible for conducting tests, and how you intend to ensure the integrity of this data. You also failed to conduct a risk assessment on the effects of the lack of release testing on the quality of drugs you distributed.

In response to this letter, provide:

- A detailed description of how you plan to test each component for conformity with all appropriate written specifications for identity, purity, strength and quality.
- A detailed description of how you plan to test bulk API to determine conformance to specifications.
- A detailed explanation of who will conduct raw material and finished API testing and how you plan to assure the suitability of test methods and the reliability of test results.

- A risk assessment for any API within the re-test date and distributed within the United States that were released with inaccurate COA.

2. Failure to completely report test results on certificates of analysis.

During the inspection, we reviewed certificates of analysis (COA) for batches of **(b)(4)** API that you manufactured and released between June 2011 and February 2016. Your quality control unit signed these COA, which indicated that all required tests had been conducted on these batches. However, you told our investigator during the inspection that you signed these COA without having conducted all the tests for which you reported results on these COA. For example, your COA reported the results of identity and impurities tests that you never conducted.

You falsified the COA you issued to your customers. Regulators and customers rely on COA for accurate information about the quality and sourcing of drugs and their components. Falsifying information about the quality of your drugs on COA compromises supply chain accountability and traceability, and may put consumers at risk.

We acknowledge that, due to our inspection, your firm conducted a voluntary recall of all lots of **(b)(4)** API that you produced between June 2011 and February 2016.

In your response to the inspection, you said you had no standard operating procedure (SOP) that required you to check the raw data before issuing COA, and that the quality control manager decided identity tests could be assessed by COA of raw materials. In addition, you said the quality control manager deleted columns for the results of these tests from your Product Analysis Data Sheet, and that although "…subsequent personnel involved in quality control had recognized this deviation, it continued without being corrected."

Your response was inadequate. You did not identify the extent of falsification at your facility, or provide details of your plans to correct the conditions that led to falsification of your COA.

CGMP consultant recommended

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations and assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

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.

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.

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.

FDA placed your firm on Import Alert 66-40 on October 25, 2017.

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 continuing to refuse admission of articles manufactured at Daito Kasei Kogyo Co., LTD., Okayama Factory, 441 Kadani, Bizen, Okayama, 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:

LT Matthew Schnupp, PharmD.
Consumer Safety Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359

10903 New Hampshire Avenue
Silver Spring, MD 20993
US

Please identify your response with FEI 1000223178.

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

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