Kyowa Hakko Bio Co., Ltd. 8/10/18

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter: 320-18-70

August 10, 2018

Mr. Yasuo Morita
Regulatory Office Manager
Kyowa Hakko Bio Co., Ltd.
1-1 Kyowa-cho, Hofu-shi
Yamaguchi, Japan 747-8522

Dear Mr. Morita:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Kyowa Hakko Bio Co., Ltd. at 1-1 Kyowa-cho, Hofu-shi, Yamaguchi, from September 4 to 8, 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 September 26, 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 of your quality unit to exercise its responsibility to ensure the API manufactured at your facility are in compliance with CGMP.

Your firm performed retesting or manipulated data after obtaining out-of-specification (OOS) or other unacceptable results. For example, investigation 2016-C-023 stated that the system suitability test (SST) was

nonconforming and that “some data were manipulated to meet SST specification” for the high-performance liquid chromatography (HPLC) analysis of your raw material **(b)(4)**. You attributed the root cause to your firm’s “lack of awareness of the seriousness” of CGMP deviations, and to an “environment where test data could be easily manipulated.” Your investigation stated that you reanalyzed the crude sample and concluded that it met the specification. You provided no further details on the root causes and on the effect of using a system that failed SST to test your raw material.

Your response stated that no product in distribution was found to be OOS, but you included no data to support this conclusion. Your response is inadequate. You identified additional data integrity issues, but failed to provide details regarding the corrective measures your firm has implemented.

In response to this letter, provide a thorough assessment of your overall system for investigating deviations, discrepancies, OOS results, complaints, and other failures. In addition, provide a retrospective review of all distributed lots within expiry to determine whether your firm released lots not conforming to established specifications or appropriate manufacturing standards.

For more information about handling failing, OOS, out-of-trend, or other unexpected results and documentation of your investigations, see FDA’s guidance document, *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*, at **https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf).**

2. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and failure to have adequate controls to prevent omission of data.

Your firm’s controls over your HPLC systems are inadequate. Some HPLC systems did not have audit trail capability or audit trails enabled. In addition, unique user names and passwords were not required to perform HPLC activities. You stated that you did not create unique usernames and passwords so that operators in different **(b)(4)** could continue what previous operators had initiated.

In your annual product reviews, you used unprotected Excel worksheets to perform calculations and statistical evaluations of production data, such as standard deviation and process capability. These electronic files were not secured to prevent unauthorized changes, and have no change history.

Your firm’s lack of data control calls the reliability of your data into question.

Your response stated that you stopped operating these HPLC systems without audit trail capability. Your response also stated that you will create a procedure for control of your electronic worksheets. Your response is inadequate because you have not assessed the effects of using data from uncontrolled HPLC systems or unsecured worksheets on your products.

In response to this letter, provide a comprehensive, independent review of controls and procedures for electronic data generated from all of your laboratory equipment. Based on this review, provide a detailed corrective action and preventive action (CAPA) plan to remediate laboratory systems, including but not limited to data creation, modification, maintenance, retention, and system security. Your plan should also include the process you will use to evaluate CAPA effectiveness.

Also see additional requests under the Data Integrity Remediation section below.

Repeat observations at multiple sites

In a previous warning letter (WL 320-10-009), FDA cited similar CGMP deviations related to your quality unit’s failure to thoroughly investigate and document OOS events. FDA also cited similar CGMP observations at your

Ube site during our September 2017 inspection. These repeated failures at multiple sites demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

Your executive management remains responsible for fully resolving all deficiencies, and ensuring ongoing CGMP compliance. You should immediately and comprehensively assess your company's global manufacturing operations to ensure that systems and processes, and ultimately, the products manufactured, conform to FDA requirements.

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 acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. Each third-party consultant used by your firm must be qualified for their specific assigned function, including data integrity 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 in all your facilities.

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 Kyowa Hakko Bio Co., Ltd. at 1-1 Kyowa-cho, Hofu-shi, Yamaguchi, 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:

Towanda Terrell
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 3002807424.

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

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