Sato Yakuhin Kogyo Co., Ltd. 1/6/17

Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter: 320-17-15

January 6, 2017

Mr. Susumu Sato
President
Sato Yakuhin Kogyo Co., Ltd.
9-2, Kannonji-Cho, Kashihara City
Nara Prefecture
634-8567, Japan

Dear Mr. Susumu Sato:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Sato Kogyo Co., Ltd. at 9-2, Kannonji-Cho, Kashihara City, Nara Prefecture, from June 6 to 10, 2016.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products 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 June 27, 2016, response in detail and acknowledge receipt of your subsequent correspondence.

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

1. Your firm failed to ensure that laboratory records include complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)(4)).

Reliance on incomplete data
Our investigator reviewed the audit trails generated by your high performance liquid chromatography (HPLC) system for impurities testing that you conducted on **(b)(4)** (lots **(b)(4)**, **(b)(4)**, **(b)(4)**). The audit trail showed that you performed this testing in duplicate. The audit trail indicated that you conducted a chromatography sequence analyzing impurities on samples of these lots beginning at **(b)(4)** on April14, 2014. The audit trail showed that a new sequence was started approximately 24 hours later, at **(b)(4)** on April 15, 2014, for impurities testing that again included samples for lots **(b)(4)**, **(b)(4)**, and **(b)(4)**. None of the 19 chromatograms generated in the first sequence were maintained and available for review. Only the second set of chromatograms was maintained and relied upon in releasing lots **(b)(4)**, **(b)(4)**, and **(b)(4)** for use in the manufacture of products for the U.S. market. You could not provide any rationale for not maintaining the original data, and you failed to document a scientific justification for repeating the analysis.

Failure to appropriately maintain data
You do not maintain electronic data on your ultraviolet-visible spectrophotometer UV SP-502 which you use for content uniformity and identity testing of **(b)(4)** capsules, and it does not have an audit trail.

In your response, you acknowledged that your data integrity controls were deficient. You stated that the chromatography software version was upgraded and that you are retaining all electronic data as of June 1, 2016. You also committed to upgrade UV SP-502 and to appropriately control access to data for this instrument. In addition, you provided the revised procedure, *Procedure on Testing Records* (QC Standard 3-C-017), which stipulates, “All the data generated from any analytical devices should be kept as records.” However, your response is inadequate. You have not conducted a retrospective review to determine how your failure to maintain complete records affected the quality of your drugs. Moreover, you have not shown how your revised laboratory procedures prevent the deletion, manipulation, or exclusion of data from the records relied upon for batch release and other quality review decisions.

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

Your analysts told our investigator that, until June 1, 2016, they were permitted to perform repeat testing without scientific justification or documentation. They also told our investigator that they were not required to maintain the data from the original results when performing investigations of system suitability failures, suspected errors, or out-of-trend results. Our investigator reviewed records of your investigations for a two-year period and found that you recorded only two minor deviations in the production area and no out-of-specification investigations.

In your response you stated, “The analysts will not make the decision to perform re-analysis at their discretion and the investigation shall be conducted on the initial failure and the testing results shall be verified.” In addition, you stated that you will revise your procedure (*Procedure on Unexpected Testing Results (OOT),* QC Standard 3-C-006) to require that records be retained. However, you failed to describe the role of the quality unit in this procedure. Include this procedure as a part of your response to this letter.

For more information about handling failing, out-of-specification, out-of-trend, or other unexpected results and documentation of your investigations, please see two FDA guidance for industry documents:

- *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* available online at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf
- *Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance – Records and Reports* available online at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm.

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 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 of 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.

Request for additional information

In addition to the information requested above, provide the following with your response:

- All procedures referenced in your June 27, 2016, response to Form FDA 483 Observations 3, 4, and 7. Include accompanying documentation (e.g. change control and training records) demonstrating the quality unit has reviewed and approved the newly generated and revised procedures.
- Validation report for the validation of the microbiological test method you use for **(b)(4)** finished drug products.
- Validation report for the validation of the swabbing recovery method used during cleaning validation for **(b)(4)**.
- Clean hold study report for the clean hold time study of equipment used in **(b)(4)** manufacturing.
- Your plan for revalidating the **(b)(4)** system after you changed the flexible tank delivery lines to prevent **(b)(4)** when not in use, removed the dead legs, and began monitoring **(b)(4)**. When revalidation is completed, provide a validation report.
- Validation report for the revalidation of the manufacturing process for **(b)(4)**.

Conclusion

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

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 violations 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 violations may also result in FDA refusing admission of articles manufactured at Sato Yakuhin Kogyo Co., 9-2, Kannonji-Cho, Kashihara City, Nara Prefecture, 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 violations 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 or mail your reply to:

Metitia Gramby Sanders, Consumer Safety 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 3003183265.

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