Sato Pharmaceutical Co., Ltd. 2/2/17

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-17-22

February 2, 2017

Mr. Yoshinori Ito
Factory Director
Sato Pharmaceutical Co., Ltd.
1468 Hazamamachi
Hachioji, Tokyo 193-0941
Japan

Dear Mr. Ito:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Sato Pharmaceutical Co., Ltd. at 1468 Hazamamachi, Hachioji, Tokyo, from February 8 to 12, 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 product is 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 February 26, 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 establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

During the inspection we noted that your firm did not perform routine personnel monitoring during sterile manufacturing operations prior to your renovations. Although you have drafted a new standard operating procedure, *Common Hygiene Standard-015: Monitoring of Adherent Microorganism for the Filling Operator of* ***(b)(4)*** *Drugs Production*, this SOP lacks clear instructions. For example, it does not sufficiently address the appropriate response to take when personnel monitoring yields results outside of action and alert limits. In addition, it is unclear if the action and alert limits are supported by an appropriate scientific rationale.

Additionally, during the inspection we found that you did not perform routine surface sampling of cleanroom environments. You also lack data on the air quality within your **(b)(4)**. Although we acknowledge your revised SOPs, *C011: Measurement Location and its Frequency for Environmental Monitoring* and *Common Hygiene Standard-014: Manufacturing Facility Surface Sampling (Aseptic Production Area: White Zone),* your environmental monitoring frequencies and locations remain deficient.

In response to this letter, provide a reassessment and CAPA (Corrective Action and Preventive Action) of your environmental monitoring program to ensure it supports robust environmental control, including but not limited to:

- justifying sampling locations, and associated action and alert limits
- ensuring all locations are sampled at appropriate frequencies, with special emphasis on implementing routine sampling of aseptic processing room surfaces
- defining circumstances under which investigation of an adverse trend or out-of-limit result is triggered, as well as appropriate responses to such occurrences in order to promptly address contamination hazards

2. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

You did not perform smoke studies under “at rest” and “dynamic” conditions to evaluate air flow characteristics of your open Restricted Access Barrier System (RABS). You subsequently released the sterile **(b)(4)** products manufactured on this aseptic processing line without studies to demonstrate unidirectional airflow over the exposed sterile product during processing.

Your firm has since renovated your RABS to use a closed design and conducted validation studies. However, your response is deficient in that it does not address your release of **(b)(4)** products currently on the U.S. market using the original open RABS design.

In response to this letter, provide a risk assessment describing process failure modes, full sterility history (e.g., sterility testing, media fills), and all actions taken to evaluate and address the acceptability of **(b)(4)** produced on the open RABS that were distributed to the U.S. market.

CGMP consultant recommended

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant, qualified as set forth in 21 CFR 211.34, to 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 for ensuring ongoing CGMP compliance.

Additional guidance on aseptic processing

See FDA's guidance document, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, to help you meet CGMP requirements when manufacturing sterile drugs using aseptic processing, at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070342.pdf.

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 Pharmaceutical Co., Ltd. at 1468 Hazamamachi, Hachioji, Tokyo, 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:

Rokhsana Safaai-Jazi
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 3004055563.

Sincerely,
/S/
Thomas J. Cosgrove
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research