檔　　號：
保存年限：

衛生福利部食品藥物管理署　函

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受文者：中華民國西藥代理商業同業公會

裝

發文日期：中華民國105年12月8日
發文字號：FDA風字第1051106691號
速別：普通件
密等及解密條件或保密期限：
附件：原料藥廠違反GMP警訊乙份(A21020000I105110669101-1.pdf)

主旨：美國FDA發布日本原料藥廠「Sekisui Medical Co., Ltd.」（廠址：4-115 Matsuo, Hachimantai, Iwate, Japan）Warning Letter乙案，詳如說明段，請轉知所屬會員知照。

訂

說明：

一、美國衛生主管機關US Food and Drug Administration（FDA）查核旨揭原料藥廠，判定嚴重違反CGMP，並於105年11月8日正式發布Warning Letter（詳如附件）。

二、鑑於旨揭原料藥之製造品質無法符合GMP之要求，可能對藥品製造品質帶來影響與危害，請轉知所屬會員釐清相關輸台製劑產品是否使用旨揭原料藥廠所生產原料藥，並應依風險管理原則辦理相關後續處置。

線

正本：中華民國西藥商業同業公會全國聯合會、中華民國西藥代理商業同業公會、台北市西藥代理商業同業公會、中華民國開發性製藥研究協會、中華民國藥品行銷暨管理協會

副本：電2016-12-09 文2016-12-09 收01章

Sekisui Medical Co., Ltd. 11/8/16

Department of Health and Human Services

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

Via UPS
Return Receipt Requested

Warning Letter 320-17-04

November 8, 2016

Mr. Hideo Tagashira
President
Sekisui Medical Co., Ltd.
3-13-5, Nihombashi, Chuo-ku
Tokyo 103-0027
Japan

Dear Mr. Tagashira:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Sekisui Medical Co., Ltd., at 4-115 Matsuo, Hachimantai, Iwate, from June 13 to 17, 2016.

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 July 8, 2016, 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 compliance with established API specifications and standards.

Our investigator found that you failed to maintain complete data from all laboratory analyses, and that you relied on the incomplete information to determine whether your drugs met established specifications. For example:

a. Numerous data files were found in the recycle bin folder on the computer connected to gas chromatography instruments GC-4 and GC-6. Specifically, our investigator found deleted data for residual solvent testing for **(b)(4)**

lot **(b)(4)** in the recycle bin. Your records show that you retested the lot without documented justification or an investigation. You retained only the final test result.

b. During the inspection our investigator requested residual solvent release test data for two of your API, **(b)(4)** and **(b)(4)**. You were unable to retrieve this data.

Any data created as part of a CGMP record must be retained so that it can be evaluated by the quality unit as part of release criteria and maintained for CGMP purposes.

We acknowledge that you commit to revising your SOP for archiving data. Your response is inadequate because it does not explain your failure to maintain complete records prior to the inspection. You also did not address validation of the systems you use to archive your data.

2. Failure to prevent unauthorized access or changes to data, and failure to provide adequate controls to prevent omission of data.

Our investigator observed that your laboratory systems lacked controls to prevent deletion of and alterations to electronic raw data. You do not have adequate controls for seven of **(b)(4)** high performance liquid chromatography (HPLC) systems and one of **(b)(4)** gas chromatography systems. For example, the audit trail on HPLC 15 did not record the **(b)(4)** batch **(b)(4)** assay. Your records indicate that the assay was performed on March 3, 2014, but your audit trail shows no assays performed between February 28 and March 4, 2014. Moreover, your analyst demonstrated to our investigator that he could change the data, including injection time and date, without the changes being captured in the audit trail, prior to printing the results.

We acknowledge that you have committed to upgrading your analytical systems to be compliant with CGMP requirements. However, procuring new instruments, installing new and upgraded data acquisition software, and enabling various features on software are not sufficient alone. These steps will be effective only if you implement appropriate procedures and systems to ensure that your quality unit reviews all production and control data and associated audit trails as part of the batch release process.

3. Failure to ensure that your analytical methods used to test API are appropriately validated and verified.

Our investigator found that your microbiological test methods were not adequately verified and that stability test methods were inadequately validated. For example:

a. **(b)(4)** of your nonsterile API are intended for use in the manufacture of sterile finished dosage forms for U.S. distribution. You did not appropriately verify your test methods for total aerobic microbial count and total combined yeasts and molds. Specifically, you did not show that these methods are capable of recovering microorganisms in the presence of the API.

b. You did not demonstrate that your stability test methods are capable of detecting and resolving degradants from the main component as well as other **(b)(4)** components. Specifically, you did not perform forced degradation studies for the related-substance test methods for **(b)(4)**, **(b)(4)**, and **(b)(4)**.

We acknowledge that you have committed to verifying and validating your test methods, but you did not include a plan to evaluate API within expiry that were distributed to the United States.

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.

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 Sekisui Medical Co., Ltd. 4-115 Matsuo, Hachimantai, Iwate, 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:

Runa Musib, Interdisciplinary Scientist
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 3002806840.

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

More in 2016 (/ICECI/EnforcementActions/WarningLetters/2016/default.htm)