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

發文日期：中華民國105年12月8日
發文字號：FDA風字第1051106692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(A21020000I105110669201-1.pdf)

主旨：美國FDA發布印度原料藥廠「Srikem Laboratories Pvt. Ltd.」（廠址：Plot No. 17/24, MIDC Taloja, Navi Mumbai, India）Warning Letter乙案，詳如說明段，請轉知所屬會員知照。

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。

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 交09:52:52章

# Srikem Laboratories Pvt. 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: 320-17-05**

November 8, 2016

Mr. Srinivasan Subramaniam
Managing Director
Srikem Laboratories Pvt. Ltd.
Plot No. 17/24, MIDC Taloja
Navi Mumbai, MH 410208
India

Dear Mr. Subramaniam:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Srikem Laboratories Pvt. Ltd., Plot No. 17/24, MIDC Taloja, Navi Mumbai, from December 14 to 18, 2015.

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 January 12, 2016, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific deviations, including, but not limited to, the following.

**1. Failure to have laboratory control records that include complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.**

The audit trail for High Performance Liquid Chromatography (HPLC) instrument QCIEQPI40 showed multiple integrations conducted on the 18-month stability tests for unknown impurity content for **(b)(4)**, USP lots **(b)(4)**, without appropriate documentation, justification, and investigation.

Your quality assurance manager agreed that these integrations were inappropriate. When our investigator asked you to reprocess the chromatograms using appropriate integration parameters, the results were out-of-specification for unknown impurity content. Your quality unit must review all pertinent analytical data when making batch release decisions in order to determine batch quality.

In your response, you provided passing 24-month stability results for **(b)(4)** lots **(b)(4)**, and committed to use the auto integration function. Your response is inadequate because it does not address the failing 18-month stability results for these lots and does not demonstrate how you will ensure that you retain complete and accurate records of all tests.

**2. Failure to follow and document laboratory controls at the time of performance.**

Our investigator observed inconsistently-dated laboratory records. For example, your executed protocol records show that a 24-month time-point stability testing sample of **(b)(4)**, USP batch **(b)(4)**, entered the laboratory on February 14, 2015. Our investigator requested the HPLC data. You provided our investigator HPLC chromatogram printouts showing that the sample was tested on February 12 and 13, 2015: one or two days before your protocol shows that the samples even entered the lab. You were unable to find any raw data corresponding to these tests. The use-log of the HPLC does not contain entries for these runs.

In another example, a printed chromatogram from related substance analysis performed by gas chromatography for **(b)(4)**, batch **(b)(4)**, was dated August 26, 2014. The data saved to your computer system from this analysis was dated December 28, 2013: nearly eight months before the date on the printed chromatogram.

In your response, you attributed data discrepancies to software malfunctions, power outages, and personnel shift changes. Your response is inadequate because you have not sufficiently explained how you are improving controls, notwithstanding these claimed sources of discrepancies, to ensure the reliability and accuracy of the data you rely on to evaluate the quality of your drugs.

**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 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 analyses of the risks to patients caused by the release of drugs affected by a lapse in data integrity, and risks posed by ongoing operations.

C. A management strategy 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 the FDA.
- A comprehensive description of the root cause 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.

FDA placed your firm on Import Alert 66-40 on July 6, 2016.

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 Srikem Laboratories Pvt. Ltd. Plot No. 17/24, MIDC Taloja, Navi Mumbai, MH 410208, 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:

Carlos Gonzalez, Compliance Officer
U.S. Food and Drug Administration
White Oak, Building 51 Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993