Jilin Shulan Synthetic Pharmaceutical Co. Ltd. 5/14/18

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov (http://www.fda.gov)

Warning Letter 320-18-51

Via UPS
Return Receipt Requested

May 14, 2018

Mr. Daqian Li
General Manager
Jilin Shulan Synthetic Pharmaceutical Co., Ltd.
No. 2066 People's Main Road
Shulan City, Jilin Province, 132600
China

Dear Mr. Li:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Jilin Shulan Synthetic Pharmaceutical Co., Ltd., at No. 2066 People's Main Road, Shulan City, Jilin Province, from November 7 to 10, 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 November 27, 2017, response in detail.

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

1. Failure to document known deviations and out-of-specification results and conduct a thorough investigation.

Undocumented manufacturing deviation
You failed to ensure that manufacturing process deviations are documented, and any critical process deviations are investigated, and resolved. Specifically, the **(b)(4)**. Our investigator found a note in your batch record stating that the **(b)(4)**(which violated the process) and the operator was to be fined 50 yuan. There was no formal deviation report documented. You failed to investigate the effects of this deviation on product quality, nor did you evaluate the criticality of this process parameter.

In your response, you said the operator violated your procedure for **(b)(4)**. Your response was inadequate because you did not explain why the operator did not follow the procedure. Also, you did not explain how you will ensure all deviations are documented and critical deviations are investigated as required.

Dual sets of laboratory records and uninvestigated OOS results
Our investigator also found that you failed to document, investigate, and resolve out-of-specification (OOS) results in your laboratory. The investigator identified two sets of laboratory testing records for four **(b)(4)** batches and five **(b)(4)** batches: one set of records included OOS results; the second set included results within specifications. You could not provide evidence to support the passing results. You also failed to conduct investigations for the OOS results. Your quality department acknowledged this practice during the inspection.

In your response, you stated that the failure to investigate these deviations was due to the staff's lack of CGMP knowledge. You provided retest results and your updated "*Out-Of-Trend (OOT) Manage Procedure*." Your response was inadequate because you addressed OOT results instead of OOS results; you did not provide your investigations into the original OOT/OOS results. You also failed to identify the root causes of the OOS results.

For more information about handling failing, OOS, OOT, 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.

Our investigator found that audit trails in your standalone instruments (**(b)(4)** high-performance liquid chromatography systems, **(b)(4)** gas chromatography systems, and **(b)(4)** infrared radiation system) were not enabled. You also did not have other mechanisms for recording and monitoring any changes to data generated on these instruments. Your firm backed up electronic data from these instruments to a portable drive **(b)(4)**. However, the drive was not password-protected, and it was stored in an unlocked drawer in an unlocked office.

Our investigator also found that operators had full system permissions, including the ability to modify and delete files. For example, our investigator found files related to system suitability tests for **(b)(4)** in the recycle bin folder on the computer connected to high performance liquid chromatography system.

In your response, you committed to upgrading your chromatography computer systems to a software version with audit trails. Your response was inadequate because you did not provide appropriate procedures or details on your updated computer systems to demonstrate how you will restrict access or changes to your data.

3. Failure to record activities at the time they are performed.

Our investigator found numerous examples of your failure to record manufacturing operations contemporaneously with their performance. For example, our investigator discovered blank batch production records that were pre-signed by your operator, partially-completed batch records, and batch records with data

changes in pencil without any justification. Our investigator also identified two process batch records for the same operation for **(b)(4)** batch **(b)(4)**; one record was partially filled out by one operator and the second record was completed by a different operator.

In your response, you indicated that these deficiencies were due to the lack of oversight by your quality assurance department. Your response was inadequate because you did not explain why your quality unit did not ensure contemporaneous documentation or exercise adequate oversight.

Data Integrity Remediation

Significant findings in this letter indicate that your quality unit is not able to fully exercise its authority and/or responsibilities. Your firm must provide the quality unit with the appropriate authority, sufficient resources, and qualified staff to carry out its responsibilities and consistently ensure drug quality. 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, 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 analyses of 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.

FDA placed your firm on Import Alert 66-40 on March 1, 2018.

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 Jilin Shulan Synthetic Pharmaceutical Co., Ltd., at No. 2066 People's Main Road, Shulan City, Jilin Province, 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:

Mr. Lixin (Leo) Xu
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4212
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3003091092.

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

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