WARNING LETTER

Henan Lihua Pharmaceutical Co., Ltd.

MARCS-CMS 548089 — JUNE 12, 2018

Recipient:

Mr. Liu Dongxue

Henan Lihua Pharmaceutical Co., Ltd.

Middle of Huanghe Street
Anyang, Henan 455000
China

Issuing Office:

Center for Drug Evaluation and Research

United States

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-58

June 12, 2018

Mr. Liu Dongxue
General Manager
Henan Lihua Pharmaceutical Co. Ltd.
Middle of Huanghe Street
Anyang, Henan, 455000
China

Dear Mr. Liu Dongxue:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facilities, Henan Lihua Pharmaceutical Co. Ltd. at Middle of Huanghe Street, Anyang, Henan, and at Qilidian North Part of Antang Road, Longan District, Anyang, Henan, from December 11 to 14, 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 January 4, 2018, 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 of your quality unit to review and approve all appropriate quality-related documents.

Our investigator observed numerous blank batch manufacturing records in an open cabinet in your manufacturing workshop office. Among these were multiple blank, product release forms marked with a red quality assurance release stamp as "Permitted to Leave [the] Factory." Our investigator also observed two record issuance stamps for batch and page number in the open cabinet.

These blank records and stamps were uncontrolled, although your standard operating procedure states that your quality unit is responsible for release of blank CGMP records. Your quality unit failed to control these records to assure that information entered on these forms is accurate and reliable. The use of uncontrolled records without quality unit review and approval poses a risk to data integrity and adequate assurance of product quality. FDA recommends that, if used, blank forms be controlled by the quality unit or by another document control method.

In your response, you said the product release form was "stamped in advance for convenience of release and warehousing of products" from your facility. You also said the quality unit record controller "did not realize the risk of the damaged lock" on the cabinet containing the records and stamps.

We note you revised your standard operating procedures and re-trained your quality personnel. Your response is inadequate because it does not provide assurance that your employees are adequately qualified and trained to perform their duties.

2. Failure to maintain complete data derived from all laboratory tests conducted to ensure your API complies with established specifications and standards.

You used a **(b)(4)** instrument (FK03011) for stability testing for multiple API, including **(b)(4)** and **(b)(4)**. You subsequently used the same instrument and software to perform in-process analytical testing. Our investigator reviewed the audit trail on this instrument and observed that the software was configured to permit continuous use of the "preview run" function and routine overwriting of previous runs. Only the final "preview run" **(b)(4)** in each project folder was retained.

Our review of the audit trail demonstrated that multiple distinct **(b)(4)** were performed and that the length of each **(b)(4)** was consistent with the time required to perform blank, sample, and standard **(b)(4)**. It is essential to retain raw data to ensure the ability to reconstruct CGMP activities and to review raw data, as necessary, for CGMP control testing.

In your response, you stated the software did not allow retrieval of "non-data acquisition **(b)(4)**," and you did not realize that you needed to retain the preview run data. We acknowledge that you intend to replace the affected **(b)(4)** instruments. 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 you retain data as required so that your quality unit can review production and control data and associated audit trails as part of evaluating whether your API complies with all established criteria for in-process and stability testing.

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 acknowledge that you committed to using a consultant to assist in meeting FDA requirements. 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 and manufacturing 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 in all of your facilities.

FDA placed your firm on Import Alert 66-40 on March 29, 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 continuing to refuse admission of articles manufactured at Henan Lihua Pharmaceutical Co. Ltd. at Middle of Huanghe Street, Anyang, Henan, and at Qilidian North Part of Antang Road, Longan District, Anyang, Henan, 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:

Lynnsey Renn, Ph.D.
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 3001164052.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality

Office of Compliance
Center for Drug Evaluation and Research

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)