Lijiang Yinghua Biochemical and Pharmaceutical Co., Ltd. 4/19/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-47

April 19, 2018

Mr. Yinghua Liu
President
Lijiang Yinghua Biochemical and Pharmaceutical Co., Ltd.
Nankou Industrial Park
Lijiang, Yunnan, 674100
China

Dear Mr. Liu:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Lijiang Yinghua Biochemical and Pharmaceutical Co., Ltd. at Nankou Industrial Park, Lijiang, Yunnan, from October 16 to 20, 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 3, 2017, response in detail.

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

1. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data.

Laboratory equipment used to generate analytical data for batch release purposes by your quality unit lacked restricted access. For example, the high-performance chromatography (HPLC) and gas chromatography systems each had a single username with administrator rights. All users could delete or modify files, and there was no mechanism to trace individuals who may have created, modified, or deleted data generated by computerized systems.

In your response to a previous FDA inspection conducted March 30 to April 3, 2015, you committed to:

- enabling the audit trail function on laboratory electronic instruments;
- assigning unique user names and passwords for each staff member; and
- authorizing **(b)(4)** levels of accessibility to prevent electronic data from being deleted, removed, transferred, renamed or altered.

In the October 2017 inspection, our investigator observed that you had not implemented any of these promised corrective actions.

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

Your firm performed HPLC assay testing for **(b)(4)** API release to the United States, along with stability and intermediate testing, on your Waters HPLC system between September 25, 2011, and May 5, 2017. Official quality control data packages presented to the quality unit for batch disposition decisions reported the results of testing performed during this timeframe on this equipment. During our inspection, when we sought to reconcile assay results reported in the quality control data package for a released batch with the underlying electronic data, you responded that you could not provide the electronic data from laboratory analyses on this equipment for the above period of several years. You explained that the electronic data in question had been deleted by accident and was no longer available.

In your response, you stated that the electronic data had been downloaded to a “mobile hard disk for backup” and that you would be able to recover the data after you have upgraded your HPLC software. However, you did not include evidence to support recovery of deleted electronic data or demonstrate how you will prevent such deletions from recurring in the future.

3. Failure to document, explain, and investigate any deviation from established procedures.

During the inspection, our investigator reviewed the electronic HPLC injection history for **(b)(4)** intermediate stability sample, batch **(b)(4)**. The history indicated that the same vial was injected twice on June 14, 2017. The first injection was not included in the final data packet provided to the quality unit for batch review, and the intermediate batch was ultimately cleared for and used in manufacturing a finished lot of **(b)(4)** API, batch **(b)(4)**.

According to your quality control analyst, the first injection appeared abnormal because it did not show a peak at the expected retention time. The second injection, within specification, was used to release the batch. There was no documentation, explanation, or investigation of the abnormal result of the first injection.

Our investigator also observed similar instances in which abnormal injections were disregarded without investigation.

In your response, you stated that you conducted a deviation investigation of batch **(b)(4)** on October 21, 2017, and you started retesting retention samples of related batches at that time. Your response is inadequate because it lacks details of this deviation investigation. It also lacks a comprehensive assessment and remediation of your overall system for investigations of deviations, atypical events, complaints, out-of-specification results, and failures.

4. Failure of your quality unit to review and approve all appropriate quality-related documents.

Your quality unit approved the certificate of analysis (COA) for release of an API batch to your customer before testing was complete and available for review.

During the inspection, our investigator reviewed the COA for **(b)(4)** API batch **(b)(4)**. Your quality unit reviewed and approved this COA on May 29, 2015. However, the test for related substances on this batch was not performed until May 30, 2015. During the inspection, your quality control manager explained that this specific COA had been released early to the quality unit because it was urgent and needed to be provided to your customer.

In your response, you summarized your standard operating procedures for testing, reviewing, and approving COA. Your response did not explain the reasons for this failure or indicate how your proposed revision to the reporting structure and approval procedures will prevent recurrence.

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 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.

Repeat Deviations at Facility

In a previous FDA inspection of March 30 to April 3, 2015, FDA cited numerous similar CGMP deviations. You proposed specific remediation for these deviations in your response. Our current inspection identified multiple failures to implement your specific corrective actions. These repeated failures demonstrate that your facility's oversight and control over the manufacture of drug products is inadequate. Explain how you intend to assure your commitments are fulfilled and corrective actions are 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 February 8, 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 Lijiang Yinghua Biochemical and Pharmaceutical Co., Ltd. at Nankou Industrial Park, Lijiang, Yunnan, 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:

Joseph Lambert, Pharm.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 3005742706.

Sincerely,

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

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