WARNING LETTER

Yibin Lihao Bio-technical Co., Ltd.

MARCS-CMS 592503 — FEBRUARY 13, 2020

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Xiuguo Tuo

Owner & General Manager

Yibin Lihao Bio-technical Co., Ltd.

Number 5 Binjiang Road, Luolong Industrial Central Park
Yibin Shi Sichuan Sheng, 644104
China

Issuing Office:

Center for Drug Evaluation and Research | CDER

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

February 13, 2020

Warning Letter 320-20-24

Dear Mr. Tuo:

The U.S. Food and Drug Administration (FDA) conducted an inspection at Yibin Lihao Biotechnical Co., Ltd, FET 3008846564, at Number 5 Binjiang Road, Luolong Industrial Central Park. Yibin, Sichuan, from July 31 to August 6, 2019.

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 August 26, 2019, response to our Form FDA 483 in detail.

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

1. Failure to prepare and use production and control records for each intermediate and APT

batch.

Your site produces crude heparin for purification into finished API. During a pre-inspectional call on July 10, 2019, your firm stated to FDA that you had not manufactured any materials for months. At the start of the FDA inspection on July 31, 2019, your firm stated to the investigator that you were not manufacturing crude heparin and were only per forming equipment testing.

During a walkthrough of your warehouse, the investigator observed a warehouse employee leaving the warehouse with a fiber drum and inquired about the contents of the drum. Your firm stated that the drum contained **(b)(4)** bags. However. inspection of the drum revealed two batches of crude heparin manufactured just a few days before the FDA inspection (CU190726, **(b)(4)**, manufacturing date July 26, 2019, and CU 190727, **(b)(4)**, manufacturing date July 27, 2019). When asked about manufacturing and testing records pertaining to these two crude heparin batches, your firm told us that you do not have records for the two crude heparin batches.

In your response, you acknowledged the failure to provide timely and complete records for crude heparin batches CU190726 and CU190727 due to deficiencies in your record keeping practices. Additionally, your response indicated that your firm is providing training to warehouse employees and your firm would not sell to European or U.S. markets before "official approval". However, you did not adequately address how you would remediate your documentation practices, nor did you assess the impact of poor documentation practices for distributed drugs.

In response to this letter, you should provide:

• A complete reconciliation of all drugs, including crude heparin, distributed from your facility. Include in the reconciliation:
o Batch number
o Batch quantity
o Name of drug
o Date of release
o Date of shipment
o Destination of shipment
o Destination market

• A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed corrective action and preventive action (CAP A) plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.

2. Failure to establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

During the inspection, the investigator observed your firm did not adequately control critical documentation pertinent to the traceability of crude heparin manufactured at your facility. During the walkthrough on July 31, 2019, our investigator observed numerous records on the floor, desks, and cabinets of the Quality Assurance (QA) Office on the third floor of the office building. Some of these records included batch production records for heparin.

During the inspection, one of your employees stated that these records were generated to support an application for government funding, but the crude heparin batches specified in the records had not actually been manufactured. However, later during the inspection, on August 2, 2019, your firm stated that all the records in the QA Office were in fact associated with genuine crude heparin batches.

Additionally, even though your *Crude Heparin Sodium Inventory and Distribution Record* indicated your firm manufactured **(b)(4)** batches of crude heparin (CU190601 to CU190730) from June 1, 2019, to July 30, 2019, your firm was only able to provide complete batch records for two batches, CU190728 and CU190730.

Traceability of crude heparin is a critical part of managing quality. You must ensure that a complete contemporaneous record of each batch of drug manufactured is retained for CGMP purposes. Your system for managing quality is inadequate and calls into question the traceability of all drugs, including crude heparin. manufactured at your facility.

For further reference regarding heparin. see the guidance for industry *Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality* available online at http://www.fda.gov/downloads/Drugs/GuidanceComplianccRegulatorylnformation/Guidances/UCM291390.pdf (http://www.fda.gov/downloads/Drugs/GuidanceComplianccRegulatorylnformation/Guidances/UCM291390.pdf).

Your response is inadequate because it does not holistically address systemic Quality Unit (QU) deficiencies.

In response to this letter, you should provide a comprehensive assessment and remediation plan to ensure your firm will establish, document, implement, and maintain a robust system for managing quaIity involving the active participation of management and appropriate manufacturing personnel. The assessment should also include, but not be limited to:

• A determination of whether procedures used by your firm are robust and appropriate.

• Provisions for oversight throughout your operations to evaluate adherence to appropriate practices.

• A complete and final review of each batch and its related in formation before the QU disposition decision.

• Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products.

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. See FDA's guidance document *Data lntegrily and Compliance with Drug CGMP* for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/97005/download (https://www.fda.gov/media/97005/download).

We strongly recommend that you retain a qualified consultant to assist in your remediation.

In response to this letter, you should provide the following:

• A comprehensive investigation into the extent of inaccuracies in data records and reporting, including results of the data review for drugs distributed to the United States. Describe the scope and root causes of your data integrity lapses in detail.

• 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 analyses of the risks posed by ongoing operations.

• A management strategy for your firm that includes the details of your global CAPA plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm, including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

Conclusion

The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility/in connection with your products. You are responsible for investigating and determining the causes of these deviations and for preventing their recurrence or the occurrence of other deviations.

FDA placed your firm on Import Alert 66-40 and 55-03 on January 15, 2020.

Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

Failure to correct these deviations may also result in the FDA continuing to refuse admission of articles manufactured at Yibin Lihao Bio-technical Co., Ltd at Number 5 Binjiang Road, Luolong Industrial Central Park, Yibin, Sichuan, into the United States under section 801 (a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under this 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 or mail your reply to:

Rokhsana Jazi
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4235
10903 New Hampshire A venue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3008846564.

Sincerely,

/S/

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

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