Hebei Yuxing Bio-Engineering Co Ltd 9/6/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-16-31

September 6, 2016

Mr. Wang Yufeng
Chairman of the Board
Hebei Yuxing Bio-Engineering Co. Ltd.
Xicheng District, Ningjin County
Hebei 055550
China

Dear Mr. Wang:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Hebei Yuxing Bio-Engineering Co. Ltd. at Xicheng District, Ningjin County, Hebei, from August 17 to 21, 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 Cosmetics Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your firm's September 9, 2015, response and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigator 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.

Your quality control laboratory failed to record and maintain complete data from analyses of your **(b)(4)** (**(b)(4)**) API. For example:

- Prior to conducting official analyses,your quality control laboratory performed “experimental” analyses on product batches to assess whether your API met specifications, but failed to document these “experimental” tests in official laboratory records or to justify their exclusion. Our investigator found the results of 2,404 high performance liquid chromatography (HPLC) injections in a folder titled “Experimental” on instrument SZG-002-006l. Your quality unit indicated that these “experimental” injections were being conducted in all **(b)(4)** chromatographic units in your quality control laboratory. Your management provided different explanations in an attempt to justify the practice, including “fear” that the sample results would not pass.
- Our review of the audit trails of chromatographic systems SZG-002-009, -010, -011, and -012 documented that your laboratory analysts deleted raw chromatographic data on multiple occasions. Your firm indicated that analysts may have been testing the system and may have deleted associated files. You also indicated that the deleted files may represent aborted analyses. However, we documented that some audit trail entries of deleted raw data files contained batch numbers for actual batch samples being tested. There is no assurance that laboratory records and raw data are accurate and valid.

We acknowledge your decision to revise your current procedure for the testing of **(b)(4)**. In response to this letter, provide a summary of how your chromatography procedures will conform to U.S. Pharmacopeia requirements, including those for the establishment of system suitability.

In addition to deciding to revise your **(b)(4)** testing procedure, in your response you commit to acquiring additional chromatographic instruments, restricting certain chromatographic instruments to specific analyses, installing a new data control system, upgrading instrument software, and enabling data integrity features included in the laboratory software.

Your response is inadequate. None of your explanations justify your failure to maintain complete records, nor do they support your practice of substituting repeat tests after failing results. Acquiring new instruments, installing new and upgraded software, and enabling various features on software are only effective if you have implemented appropriate procedures and systems to ensure that your quality unit reviews all production and control data and associated audit trails as part of the batch release process.

2. Failure to follow and document laboratory controls at the time of performance, and failure to document and explain any departures from laboratory procedures.

During the inspection, your firm provided our investigator a chromatogram for an assay analysis of **(b)(4)** batch **(b)(4)** dated August 30, 2014, at 9:46:39 a.m. Your firm later submitted to FDA a different chromatogram corresponding to the same analysis, instrument, date, time, and batch. The second chromatogram appears exactly the same as the one provided during the inspection, but it includes a different method file name, column type and serial number, and system temperature. Both versions of these documents cannot represent the actual assay analysis that you conducted for batch **(b)(4)** on August 30, 2014, at 9:46:39 a.m.

3. Failure of the quality unit to ensure that all critical deviations are investigated and resolved.

At the time of the inspection, your firm had documented 67 deviations regarding microbiological contamination found or related to the **(b)(4)** step for **(b)(4)**. These deviations occurred between January 1 and August 20, 2015, but our investigation documented that microbiological contamination has been a persistent and unresolved problem at your firm since 2013. Over time, your firm has identified four potential causes:

- contaminated **(b)(4)** supply due to inadequate **(b)(4)** controls
- failing **(b)(4)** of the **(b)(4)** in the **(b)(4)** tank **(b)(4)** systems
- production operator errors
- inadequate sterilization of the supplement tanks used to store materials before they are discharged into the **(b)(4)** tanks

However, you have not definitively identified the specific root causes(s) of your microbiological contamination problems, nor have you taken appropriate corrective actions and preventive actions.

In response to this letter, provide the report of your thorough investigation to identify the root cause(s) and your corrective action and preventive action plan.

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 testing 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.

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 8, 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 Hebei Yuxing Bio-Engineering Co. Ltd., Xicheng District, Ningjin County, Hebei, 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:

Jason F. Chancey, Consumer Safety 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 3008996626.

Sincerely,
/S/
Francis Godwin