Tai Heng Industry Co., Ltd. 5/12/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20963

Via UPS
Return Receipt Requested

Warning Letter: 320-16-11

May 12, 2016

Mr. Yusheng Fang, CEO & President
Tai Heng Industry Co., Ltd.
2715 Long Wu Road, Building 2
Shanghai Juke Biotech Park
Shanghai, China, 200231

Dear Mr. Fang:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Tai Heng Industry Co., Ltd., 2715 Long Wu Road, Building 2, Shanghai Juke Biotech Park, Shanghai, China from May 4–11, 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 Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your firm's May 28, 2015, response in detail and acknowledge receipt of your subsequent responses.

Our investigator observed specific deviations during the inspection, including, but not limited to, the following.

1. Failure to adequately investigate out-of-specification results and implement appropriate corrective actions.

The investigator found that batch samples were routinely retested following failing or atypical results until acceptable results were obtained. Failing or atypical results were not investigated or included in official laboratory control records.

2. Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent manipulation and omission of data.

During the inspection, an FDA investigator discovered a lack of basic laboratory controls to prevent changes to your firm's electronically stored data and paper records. Your firm relied on incomplete records to evaluate the quality of your drugs and to determine whether your drugs conformed with established specifications and standards.

Our investigator found that your firm routinely re-tested samples without justification, and deleted analytical data. We observed systemic data manipulation across your facility, including actions taken by multiple analysts and on multiple pieces of testing equipment.

Specifically, your Quality Control (QC) analysts used administrator privileges and passwords to manipulate your high performance liquid chromatography (HPLC) computer clock to alter the recorded chronology of laboratory testing events.

3. Failure to record activities at the time they are performed, and destruction of raw data.

Your employees did not complete batch production and control records immediately after activities were performed. Your operators used "mock" sheets (copies of the uncontrolled copy of the master production records) to capture critical manufacturing data. Your employees then completed and backdated batch production records days after operations ended.

Our investigator noted discrepancies between the "mock" sheets and the complete batch production record that your firm represented as the official record for that lot. Because of your uncontrolled documentation practices, you could not produce evidence that your batch production records were accurate.

Batch production records must be generated contemporaneously and include complete and accurate information on the production and control of each batch. The practice of using unbound, uncontrolled loose paper, in conjunction with backdating records, raises additional concerns about the integrity, authenticity, and reliability of all your data, and the quality of your API.

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 from CGMP.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of drugs produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Staff immediately at **drugshortages@fda.hhs.gov (mailto:drugshortages@fda.hhs.gov)** so that we 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 in the manufacture of your drug under 21 U.S.C. 356C(a)(1), 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. In appropriate cases, you may be able to take corrective actions without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

After you receive this letter, you have 15 working days to respond to this office in writing. Specify what you have done since our inspection to correct your deviations and to prevent their recurrence.

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 your commitment to hire a third party to perform **(b)(4)** audits of your quality system, but we feel that an **(b)(4)** audit is inadequate. We recommend more frequent reviews of your quality system for more timely oversight and compliance with CGMP. We also recommend your third party audit include appropriate evaluation of sophisticated electronic systems and the possibility of data integrity manipulation of such systems.

In your response to this letter, provide the following.

1. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:
   - o 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.
   - o 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.
   - o 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.
   - o A comprehensive retrospective evaluation of the nature of all data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential batches were identified should evaluate all data integrity lapses.

2. 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.

3. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:
   - o 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.
   - o 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.
   - o 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.
   - o 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.
   - o A status report for any of the above activities that are already underway or completed.

If you cannot complete corrective actions within 15 working days, state your completion date and reasons for delay.

Until you completely correct all deviations and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as an API manufacturer. Failure to correct these deviations may also result in FDA refusing admission of articles manufactured at Tai Heng Industry Co., Ltd., 2715 Long Wu Road, Building 2, Shanghai Juke Biotech Park, Shanghai, China 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).

Send your reply to:

Kevin Maguire
Compliance Officer
U.S. Food and Drug Administration
White Oak, Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Send your electronic reply to **CDER-OC-OMQ-Communications@fda.hhs.gov (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)**

Please identify your response with FEI 3006986091.

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

More in 2016 (/ICECI/EnforcementActions/WarningLetters/2016/default.htm)