Yunnan Hande Bio-Tech. Co. Ltd. 4/6/15

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Silver Spring, MD 20993

Warning Letter

***via* UPS**

WL: 320-15-09

April 6, 2015

Ms. Huang Lei
Chairman of the Board
Yunnan Hande Bio-Tech. Co. Ltd.
No. 3 Platform Jinding Tech-Zone
Kunming, Yunnan Province 650033
P.R. China

Dear Ms. Lei:

During our April 14, 2014 through April 17, 2014 inspection of your manufacturing facility, Yunnan Hande Bio-Tech Co. Ltd., located at No. 3 Platform Jinding Tech-Zone, Kunming, Yunnan Province, China, investigators from the U.S. Food and Drug Administration (FDA) identified significant deviations from current good manufacturing practice (CGMP) regulations for the manufacture of active pharmaceutical ingredients (APIs). These deviations cause your APIs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 351(a)(2)(B), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding

do not conform to, or are not operated or administered in conformity with, CGMP.

We have conducted a detailed review of your firm's response dated May 1, 2014 and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated May 31, 2014, July 1, 2014, July 31, 2014, August 29, 2014, September 30, 2014, October 30, 2014, and November 28, 2014.

Our investigators observed specific deviations during the inspection, including, but not limited to, the following:

1. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.

You lacked controls to prevent the unauthorized manipulation of your laboratory's electronic raw data. Specifically, your infrared (IR) spectrometer did not have access controls to prevent deletion or alteration of raw data. Furthermore, the computer software for this equipment lacked active audit trail functions to record changes to data, including information on original results, the identity of the person making the change, and the date of the change. Audit trails that capture such critical data about the quality of your batch production should be reviewed as part of the batch review and release process.

We acknowledge your commitment to upgrade the IR software by adding full audit trail capabilities in compliance with CGMP. In your response, you also commit to obtain information about the **(b)(4)** archival of all data obtained on laboratory computerized systems, and to evaluate software upgrades to other instrumentation. However, your response is inadequate because you have not specified how you will ensure the integrity of raw analytical data or maintain data before you complete your planned corrective actions and preventive (CAPA) actions.

In response to this letter, provide your comprehensive CAPA plan for ensuring that electronic data generated in your manufacturing operations, including laboratory testing, cannot be deleted or altered. It essential that your firm implement controls that prevent the omission of data, and record information about changes to existing data, such as the date of the change, identity of person who made the change, and an explanation or reason for the change. Any such changes should be made in accordance with an established and appropriate procedure. Your response should address your laboratory equipment and any other manufacturing-related equipment that may be affected by the lack of adequate controls to prevent data manipulation.

2. Failure of your quality unit to ensure that materials are appropriately tested and the results are reported.

The inspection documented that an analyst at your firm failed to perform the IR

identity test for all lots of **(b)(4)**, API, as part of your quality control release. Instead, the analyst at your firm altered the file name in the spectrophotometer containing the sample identification information for **(b)(4)** API lot # **(b)(4)**, tested on April 2, 2014, to support the release of two previously manufactured lots, # **(b)(4)** and **(b)(4)**.

In your response dated May 1, 2014, you admit that an analyst altered the identity test result for lot # **(b)(4)** to approve and release lots # **(b)(4)** and # **(b)(4)**. This practice is unacceptable and raises serious concerns regarding the integrity and reliability of the laboratory analyses conducted by your firm. Laboratory control records must include accurate and truthful documentation of all raw data generated during each test, including graphs, charts and spectra from laboratory instrumentation. These records must be properly identified and maintained to demonstrate that each API lot was tested and met the release specification before the lot is released.

Your response is inadequate because you did not perform a comprehensive investigation and a retrospective review to ascertain the extent of this data alteration practice. A cursory review of records does not ensure that other personnel did not manipulate or inaccurately report test data. The review was also insufficient because you did not review data generated from other computerized systems such as high performance liquid chromatography or gas chromatography to determine if data generated by these systems were also manipulated or altered.

3. Failure of your quality unit to exercise its responsibility to ensure the APIs manufactured at your facility are in compliance with CGMP, and meet established specifications for quality and purity.

For example, your quality unit failed to detect that your laboratory altered IR raw data and misrepresented the results for approval and release of **(b)(4)**, API lots# **(b)(4)** and **(b)(4)**.

Your response indicates you revised your data review procedure to include the requirement for cross lot comparison review for batches tested during the same period. Additionally, you commit to strengthen work processes to prevent future data manipulation by ensuring the data is traceable and training the reviewers on data tracking.

Your response is inadequate in that it does not fully address the failure of your quality unit to detect and prevent the manipulation or alteration of laboratory documents. Additionally, your response is incomplete because you have not provided a comprehensive plan to ensure the integrity of all data used to assess the quality and purity of APIs manufactured at your facility.

SUMMARY

The above examples are serious CGMP deviations demonstrating that your quality system does not adequately ensure the accuracy and integrity of the data generated at your facility to support the safety, effectiveness, and quality of the drug products you manufacture. We strongly recommend that you hire a qualified third party auditor/consultant with experience in detecting data integrity problems to assist you with coming into compliance with CGMP requirements. However, it is your responsibility to ensure that any third party audit includes appropriate evaluation of sophisticated electronic systems and the vulnerability to data integrity manipulation of such systems.

In response to this letter, provide the following to the Agency:

1. A comprehensive evaluation of the extent of the inaccuracy of the reported data. As part of your comprehensive evaluation, provide a detailed action plan to investigate the extent of the deficient documentation practices noted above;

2. A risk assessment regarding the potential effect on the quality of drug products. As part of your risk assessment, determine the effects of your deficient documentation practices on the quality of the drug product released for distribution; and

3. A management strategy for your firm that includes the details of your corrective action and preventive action plan.

    a) As part of your corrective action and preventive action plan, describe the actions you have taken or will take, such as contacting your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, monitoring of complaints, and/or other steps to assure the quality of the product manufactured under the violative conditions discussed above.

    b) In addition, as part of your corrective action and preventive action plan, describe the actions you have taken or will take, such as revising procedures, implementing new controls, training or re-training personnel, or other steps to prevent the recurrence of CGMP violations, including breaches of data integrity.

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

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug

Shortages Program immediately, as you begin your internal discussions, at 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 Program 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 action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as an API manufacturer. In addition, your failure to correct these violations may result in FDA refusing admission of articles manufactured at Yunnan Hande Bio-Tech Co., Ltd, Kunming, China into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The articles may be subject to refusal of admission pursuant to Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3), 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 Act, 21 U.S.C. 351(a)(2)(B).

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct and prevent the recurrence of deviations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute the APIs at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3002808537.

Please send your reply to: Kevin Maguire, Compliance Officer; 10903 New Hampshire Avenue Building 51 Room 4237; Silver Spring, MD 20993.

Sincerely,
/S/
Thomas J. Cosgrove, J.D.
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

More in Compliance Actions and Activities

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U.S. Food and Drug Administration
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1-888-INFO-FDA (1-888-463-6332)

Contact FDA