U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Yunnan Hande Bio-Tech. Co. Ltd.

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-11-01

October 15, 2010

Ms. Huang Lei
Chairman
Yunnan Hande Bio-Tech Co., Ltd.
No. 3 Platform Jinding Tech-Zone
Kunming, People's Republic of China, 650033

Dear Ms. Lei:

During our May 17-21, 2010 inspection of your active pharmaceutical ingredient (API) manufacturing facility, Yunnan Hande Bio-Tech Co., Ltd., located at Jinding Tech-Zone, No. 3 Platform, Kunming, China, investigator(s) from the Food and Drug Administration (FDA) identified significant deviations from Current Good Manufacturing Practice (CGMP) for the manufacture of APIs. These deviations cause your API(s) 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 reviewed your firm's response of June 2, 2010, and note that it lacks sufficient corrective actions.

Specific deviations observed during the inspection include, but are not limited, to the following:

1. Failure to thoroughly investigate complaints for APIs batches that do not meet the United States Pharmacopeia (USP) compendial requirements that may have been associated with the specific failure or discrepancy. In addition, your investigation was not extended to other batches that may also be affected.

During the review of a customer complaint for lot **(b)(4)**, related to an out-of-specification in the optical rotation test, our inspection team noticed that the optical rotation test was conducted in a room with no temperature control during the sample analysis. Your firm does not monitor the temperature of the sample inside the polarimeter chamber as required by the USP chapter <781>. Your procedure DM No. 21-3, "Optical Rotation of **(b)(4)**," requires that a temperature correction factor be used when the reading is above or below 20°C; however you failed to apply the correction factor to any of the lots tested. Your quality unit confirmed this discrepancy during our inspection. You indicated that your firm monitors the sample temperature when conducting the optical rotation test by annotating the air condition thermostat reading of the room. However, our investigators found that the temperature of the Quality Control (QC) laboratory, where the optical rotation is conducted, is not controlled because there is no air conditioner in the room. Please clarify this discrepancy in your response to this letter.

Because your optical rotation testing was not conducted under the required environmental conditions, the test results generated may be inaccurate. In your response, you indicate that the temperature in the sampler (and in the room) will be maintained at 20 ± 0.5°C. However, USP <781> requires that the temperature of the sample be maintained at 25°C ± 0.5°C during the analysis. We recommend that you revise your procedures accordingly.

Although the above test is not conducted in accordance to the USP requirements, we are concerned that your Certificate of Analysis (COA) for **(b)(4)** API indicates that: "we hereby certify that the **(b)(4)** Drug Substance manufactured by Yunnan Hande Bio-Tech Co Ltd is meeting the quality specification of US Pharmacopeia." This is a repeat observation from our 2004 inspection where investigators found USP <61> was not followed.

In your response, please provide evidence that all lots of **(b)(4)** API manufactured and within expiration comply with the USP compendial requirements. Also, indicate whether you intend to issue new COAs to your customer(s) and what actions you intend to implement in those cases where the USP specification is not met. Your firm needs to implement adequate corrective and preventive actions to ensure that the QC personnel are qualified to conduct all analyses in your laboratory, and that those supervising laboratory operations are qualified to ensure scientifically rigorous operations.

2. Failure to have adequate procedures for the reprocessing of API batches and stability data to ensure that the API batches are not adversely affected by the formation of by products and over-reactive materials.

Your SOP 5018-9, "Leftover Products Processing Procedure," allows for the manufacture of **(b)(4)** API batches using reserved or retained samples, batch tails ends, and expired **(b)(4)** API. The reserved samples are **(b)(4)** under a new lot number. You fail to demonstrate that the quality of the new batch is not affected throughout the shelf life of the API. We are also concerned that you allow the reuse of retain and expired samples maintained for **(b)(4)** years (or up to **(b)(4)** years for lot distributed) without determining if the quality of the API has been adversely affected due to the formation of degradants or impurities. You also fail to have an evaluation of the individual batches prior to being **(b)(4)** into a new batch.

In response to this letter, provide a retrospective evaluation of the lots that have been manufactured using the above practice. Include evidence that your decision to manufacture **(b)(4)** using expired and retain samples, **(b)(4)** tails ends batches is preceded by a careful evaluation to ensure that the quality of the API is not adversely affected due to the potential formation of byproduct and over-reacted material. Note your firm should ensure that the manual process used to produce these batches is validated and adequately described in the approved DMF.

3. Failure to have an adequate performance qualification (calibration) program for the QC laboratory instruments.

Your HPLC calibration lacks a carry over test (sample injection residual test), sample energy (intensity of light source), and lamp use hours determination. You fail to challenge the analytical balances for minimum weight, measurement for uncertainty, and drift value. In addition, you do not calibrate the Karl Fisher syringe used during **(b)(4)** API water content analysis.

Your firm also fails to maintain raw data associated with the re-qualification and calibration of your laboratory instruments. During the inspection the investigators were informed that the annual re-qualification and calibration of your laboratory equipment (e.g., HPLC, GC, polarimeter, and analytical balance) is performed by the **(b)(4)**. However, you were unable to provide raw data or documentation regarding the qualification and calibration of your instruments and data to demonstrate that your quality unit reviewed and approved the work performed by your contractor.

During our inspection, our investigators learned that the calibration program does not include parameters to challenge the precision and accuracy of the laboratory instruments. Your firm acknowledged that your firm lacks a written procedure describing the qualification and calibration of the laboratory equipment.

We are concerned that the inspection of 2004 reported similar deficiencies related to the qualification of your laboratory equipment. In your response, please provide information to show that the above deficiencies have not adversely affected the accuracy of the analytical results used to release your APIs.

4. Failure to have adequate analytical procedures designed to assure that your APIs conform to appropriate specification. For example,

a. The FTIR assay does not include a **(b)(4)** USP standard during the performance of the identification analysis nor are the critical analytical parameters documented.

Your firm does not concurrently analyze the FTIR samples with a **(b)(4)** reference standard. Instead, you analyze the sample against a spectrum stored in the memory of the FTIR. During our inspection, you were unable to provide data to show when and how you prepared and qualified the FTIR spectrum standard.

Additionally, the investigators found that the FTIR parameter (e.g. number of samples scanned, resolution, and bean slitter) are not documented in your laboratory record. Moreover, the expiration date of **(b)(4)** reagent lot **(b)(4)**, used during the sample preparation is unknown. Also SOP DM No. 02-04 does not include instructions to **(b)(4)** the **(b)(4)** reagent under a **(b)(4)**, which is an activity conducted by the QC technicians.

b. The suitability of your testing method for your residual solvent determination has not been demonstrated and verified. Additionally, your acceptance criteria are different to the established by the USP.

Your system suitability test requires that **(b)(4)** injections of standard be performed and that a Relative Standard Deviation (RSD) of **(b)(4)**% be met in order for the test to be acceptable. This acceptance criterion is contrary to the USP requirement chapter <621>. During our inspection, you were unable to provide validation data to support your current RSD criteria. Your response is inadequate in that you failed to provide scientific rationale to justify the change in your analytical method for system suitability requirements. In response to this letter, please provide a valid % RSD and the analytical data to support it.

The deviations detailed in this letter are not intended to be an all-inclusive statement 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 you wish to continue to ship APIs to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

Until all corrections have been completed and FDA has confirmed corrections of the deviations 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, failure to correct these deviations may result in FDA refusing admission of articles manufactured at Yunnan Hande Bio-Tech Co., Ltd., Kunming, People's Republic of China, 650033 into the United States. The articles are 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 Current Good Manufacturing Practice 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 deviations. Include an explanation of each step being taken to prevent the recurrence of deviations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture or distribute **(b)(4)** API, and provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 2002808537.

If you have questions or concerns regarding this letter, contact Rafael Arroyo, Compliance Officer, at the below address and telephone number.

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Sincerely,
/S/
Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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