Inspections, Compliance, Enforcement, and Criminal Investigations

Tianjin Zhongan Pharmaceutical Co., Ltd. 6/10/14

Department of Health and Human Services

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

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-14-09

June 10, 2014

Mr. Li Zhengen
General Manager
Tianjin Zhongan Pharmaceutical Co. Ltd.
No. 188 Fukang Road
Xiqing District
Tianjin 300384
China

Dear Mr. Li Zhengen:

During our September 23-27, 2013 inspection of your pharmaceutical manufacturing facility, Tianjin Zhongan Pharmaceutical Co. Ltd., located at No. 188 Fukang Road, Xiqing District, Tianjin, China, an investigator from the U.S. Food and Drug Administration (FDA) identified significant deviations of current good manufacturing practice (CGMP) 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 and note that it lacks sufficient corrective actions.

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

1. Failure to adequately complete and follow written procedures for cleaning equipment and its release for use in API manufacture, and to maintain adequate records of major equipment usage.

Your firm failed to ensure that employees adequately cleaned **(b)(4)** after use. Your **(b)(4)** equipment cleaning standard operating procedures (SOP-HE 063-02 - instruction 4.2.2.1, SOP-HE 064-02 – instruction 4.3.4.3, and SOP-HE 055-02 – instruction 4.2.1.1), require that employees visually inspect equipment after the cleaning process. Our inspection found **(b)(4)** in the manufacturing workshop for **(b)(4)** with various levels of contamination and foreign

objects inside, including what looked like the remains of a pen in one of the **(b)(4)**. Your employees had labeled this equipment as clean. These **(b)(4)** are used for the manufacture of multiple APIs.

In addition, your firm's production system did not maintain equipment logs or other documents that adequately record manufacturing operations performed on individual pieces of equipment.

We note that your production operation supervisors and Quality Unit (QU) failed to detect and correct these deficient cleaning practices.

Your response is inadequate because it does not address the extent of these deficient practices throughout your facility, or the impact on the quality of your active ingredients. Additionally, you do not commit to maintain equipment logs or other documents that record all of the manufacturing operations performed on individual pieces of equipment.

In response to this letter, you should prepare and implement a corrective action plan sufficient to address and prevent the recurrence of these deficiencies. The corrective action plan should detail the systemic improvements to be made, including, but not limited to, improved management oversight of cleaning operations, commitment to maintain individual equipment records (e.g., equipment logs), and training all relevant personnel in cleaning procedures. You should also demonstrate the sufficiency and effectiveness of this corrective action plan.

2. Failure to conduct adequate change control to evaluate all changes that could affect the production and control of intermediates or APIs.

a. Your firm failed to identify, document, evaluate, and approve several changes in production. Specifically, the equipment referenced in the flow chart in Drug Master File (DMF) **(b)(4)** for the manufacture of **(b)(4)** API differed from the equipment actually used. The DMF **(b)(4)** flow chart contains a step for **(b)(4)** that follows the **(b)(4)** step. Firm officials stated that your firm no longer conducted the **(b)(4)** during the manufacture of this API. You did not evaluate whether this change was appropriate based on its impact on product quality, or validate the effectiveness of change implementation. In addition, you failed to conduct a change control investigation or document the significant changes in your manufacturing process as required by your change control SOP SMP-QA 009-08.

b. Your firm failed to conduct a change control investigation or document the significant changes in **(b)(4)** systems as required by your change control procedure SMP-QA 009-08. In the **(b)(4)** system used for the manufacture of **(b)(4)** APIs, you connected an **(b)(4)** device via **(b)(4)** hose to a port on the **(b)(4)** system piping (**(b)(4)**) at the entrance to holding tank #V20129. Furthermore, in the **(b)(4)** system used for the manufacturing of **(b)(4)** USP, you relocated the **(b)(4)** tank; you extensively altered the piping system throughout the facility; and you added an **(b)(4)** unit. Also, the drawings for both systems were not current.

In your response, you state that you revised and implemented procedure SMP-QA-009-08 "SMP for Changes Control" on June 20, 2012. Although you had previously trained your employees in this procedure, the examples described above show that they failed to comply with it. Your response does not contain significant detail on how you will ensure compliance with procedure SMP-QA-009-08. In addition, the revised procedure indicates that it does not apply retroactively to existing equipment for which critical changes have been made without adequate change control.

In response to this letter, you should conduct a retrospective assessment of all changes you have made to equipment and procedures used in the manufacture of all **(b)(4)** and **(b)(4)** APIs. Provide the report of this assessment and the impact of these changes on product quality. Also, describe how your firm will correct the deficient change management system and ensure full implementation and compliance in the future.

3. Failure to adequately review and investigate product deviations.

During our inspection, the investigator observed that the **(b)(4)** manufacturing workshop **(b)(4)**, used for **(b)(4)** steps, contained significant particulate material, **(b)(4)** fluid, and a plastic tube (apparently from a pen) in the bottom of the various **(b)(4)**. These **(b)(4)** were labeled as clean. The samples collected of the residues were insufficient to allow for an adequate investigation. You did not initiate an investigation prior to the investigator's observation. Your investigation consisted of a high performance liquid chromatography (HPLC) assay test for **(b)(4)**, the last API manufactured in that **(b)(4)**, even though the sample was a complex mixture of **(b)(4)** phases. You conducted no further testing, and disposed of the sample after the HPLC analysis.

In your response, you state that you revised procedure SMP-QA-007-03 "SMP of Deviation" to address these issues. Your response in insufficient because it does not describe or address the extent of these problems, or their impact on the quality of your APIs.

In response to this letter, you should provide an assessment of your deviations system. Provide a corrective action plan to ensure adequate investigations are conducted for all deviations. This includes, but is not limited to, hiring qualified personnel to perform investigations, improving the training program, maintaining a sufficient number of staff, conducting timely remediation, and improving deviation investigation procedures.

We also note that you did not adequately control your Certificates of Analysis (COAs). Your employees in the Foreign Trade Office generated and issued COAs for your products, and your Quality Unit did not control, or retain records of all such COAs. For example, the **(b)(4)** USP API, batch #**(b)(4)**, was imported into the U.S. with a different COA than the one you retained on record for that batch. You should investigate this significant recordkeeping deficiency, and ensure control of all of the COAs you issue for your products. It is your responsibility to ensure that all of your documents are properly controlled and maintained in compliance with CGMPs.

Your firm's inadequate qualification of critical production equipment is also a concern. Specifically, you did not maintain current technical drawings of any **(b)(4)**, or the **(b)(4)** production equipment used in manufacturing of **(b)(4)**, and **(b)(4)** APIs. In addition, the qualification documents for these **(b)(4)** did not include important installation verification parameters such as material of construction, the volume capacity, **(b)(4)**, configuration/location of **(b)(4)**, or material of **(b)(4)**. You should ensure that the contact surfaces of your production equipment are not reactive, additive, or absorptive so as to prevent impact on the quality of your products beyond appropriate limits.

Executive management has the responsibility to ensure the quality, safety, and integrity of the products manufactured at your facility. A fundamental part of this responsibility is ensuring timely investigation and resolution of issues to prevent the distribution of defective products. FDA strongly recommends that your executive management immediately undertake a comprehensive evaluation of global manufacturing operations to ensure compliance with CGMP regulations. As part of these efforts, it is imperative that you build a robust quality system, and assure proper management oversight of operations and quality. Your inability to detect and prevent the above deficient practices, as well as other deficiencies found during the inspection, indicate that your current quality system is ineffective at achieving overall compliance with CGMP.

Due to continuing CGMP issues at your firm, we recommend you engage a third party consultant with appropriate CGMP expertise to assess your firm's facility, procedures, processes, and systems to ensure that the APIs you manufacture have the appropriate identity, strength, quality, and purity.

Please note that a guidance document entitled "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" (ICH CGMP guidance), prepared under the auspices of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, describes current good manufacturing practice (CGMP) for the manufacture of APIs. The guidance is intended to help ensure that all APIs meet the standards for quality and purity they purport or are represented to possess. FDA considers the

expectations outlined in ICH Q7, as well as alternatives intended to accomplish the same goals and provide an equivalent level of quality assurance, in determining whether a firm's APIs have been manufactured, processed, packed, and held according to current good manufacturing practice under section 501(a)(2)(B) [21 USC 351(a)(2)(B)] of the Act. To obtain the ICH CGMP guidance document for your reference, please refer to the following page of FDA's website: http://www.fda.gov/cder/guidance/4286fnl.htm[1].

Furthermore, we remind you that you are required to submit any addition, deletion, or other change to the information in your Drug Master File (DMF) to the FDA under 21 CFR 314.420. Additionally, you are required to notify each person authorized to reference the information in your DMF of the pertinent changes.

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 finished drug products or 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.

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, your failure to correct these deviations may result in FDA refusing admission of articles manufactured at Tianjin Zhongan Pharmaceutical Company Limited located at 188 Fukang Road, Xiqing District, Tianjin, 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 dates and reasons you ceased production. Please identify your response with FEI # 3003671775.

Please send your reply to:

Joseph Duran
Compliance Officer
FDA/CDER/OC/OMPQ/DIDQ
10903 New Hampshire Ave
White Oak Building 51, Room 4237
Silver Spring, MD 20993

Sincerely,
/S/
Thomas Cosgrove, J.D.

Acting Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

Page Last Updated: 06/16/2014
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

Links on this page:

1. http://www.fda.gov/cder/guidance/4286fnl.htm