Inspections, Compliance, Enforcement, and Criminal Investigations

Zhejiang Jiuzhou Pharmaceutical Co., Ltd. 7/9/14

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: 320-14-12

July 9, 2014

Ms. Hua Lirong
CEO
Zhejiang Jiuzhou Pharmaceutical Co., Ltd.
No. 99 Waisha Road, Jiaojiang
Taizhou, Zhejiang Province, 318000
P. R. China

Dear Ms. Hua Lirong:

During our October 21-24, 2013 inspection of your active pharmaceutical ingredient manufacturing facility, Zhejiang Jiuzhou Pharmaceutical Co., Ltd., and your import/export company Zhejiang Zonebanner Jiuzhou Imp. & Exp. Co., Ltd., both located at No. 99 Waisha Road, Taizhou, Zhejiang Province, China, an investigator from the U.S. Food and Drug Administration (FDA) identified deviations from 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 acknowledge receipt of your firm's correspondences dated November 14, 2013, and January 14, 2014.

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

CGMP VIOLATIONS

Zhejiang Zonebanner Jiuzhou Imp. & Exp. Co., Ltd. (FEI 3010365339)

1. Failure to implement an effective system of managing quality and failure to transfer all quality or regulatory information received from the API manufacturer to your customers.

Your trading company, hereafter referred to as Zonebanner, purchased APIs from an outside supplier and relabeled them without the oversight of a quality unit. The information from the original certificate of analysis, generated by the actual manufacturer, was transferred to a new certificate of analysis on Zhejiang Jiuzhou Pharmaceutical Co. letterhead with no information about the original manufacturer or analytical laboratory performing the analyses. In addition, a new label identifying Zhejiang Jiuzhou Pharmaceutical Co. as the manufacturer was added to drums. In doing so, your firm essentially obscured the supply chain of these APIs.

Zonebanner had no quality system in place for the relabeling operations. In addition, we note that in at least one instance of a lot of gabapentin shipped to the U.S., the retest date from the original manufacturer's certificate of analysis (November 2013) was changed to an expiration date listed as eleven months later (October 2014) on the new certificate of analysis.

In your response, your firm states that Zonebanner exists as a separate legal entity under Chinese law. However, the FDA considers this entity to be under your control. During the inspection, your employees stated that Zonebanner is a group within Zhejiang Jiuzhou Pharmaceutical Co. Ltd. and provided organizational charts showing that Zonebanner management reports to you as CEO. Zonebanner is located at the same physical address as the inspected manufacturing facility, and the Zonebanner personnel work in the same office space. Moreover, API shipments from Zonebanner are accompanied by a letter stating that Zhejiang Zonebanner and Zhejiang Jiuzhou Pharmaceutical Co. Ltd. are in one group. Despite this close relationship, however, your management has allowed the Zonebanner group to continue to operate outside of your firm's quality system.

In response to this letter, provide details of the proposed quality system to be implemented at Zonebanner. Describe procedures and provide examples that demonstrate that traceability is maintained for currently distributed APIs and that information sent to customers includes an accurate representation of the manufacturer and analytical testing laboratory. In addition, provide your rationale for the expiry extension of the gabapentin lot described above. If this or other similar extensions were unsupported, then describe your intended actions for the lot(s) in question.

Zhejiang Jiuzhou Pharmaceutical (FEI 3003744377)

2. Failure of the quality unit to review batch production records prior to distribution of an API batch.

Our investigator discovered that your firm shipped finished lots without reviewing the batch records for these lots. Although your firm has procedures requiring the review of batch records prior to their release and distribution, on several occasions your quality unit authorized the shipment of lots prior to their release. Several of your firm's employees were aware of this practice but took no measures to prevent it.

During the inspection, your firm's personnel conducted an internal review and found three additional lots that were distributed prior to release by the quality unit. However, we are concerned that your internal review would be unable to detect every instance for which your firm shipped materials whose batch records had not yet been reviewed based on your poor documentation practices described below under #3. We remind you that the quality unit's approval of batch records should not merely serve as a paperwork exercise but should include a thorough review of all deviations which occurred and any unexpected results which were obtained during the manufacture of the lot being reviewed.

Quality unit review of batch records is a clear expectation of CGMP. Responsible management should ensure that the quality unit performs its assigned functions. In response to this letter, please provide a full accounting of this practice and describe all actions taken to prevent its recurrence. Describe any improvements to ensure that your internal auditing program will detect and correct similar instances in the future.

3. Failure to document manufacturing operations at the time they are performed.

When reviewing the entries in your **(b)(4)** use, cleaning, and maintenance logbook for the days immediately prior to the inspection, our investigator found missing entries. Your operators stated that lines were left blank to later add information about cleaning events that may have occurred during a previous shift. During the inspection, our investigator found other similar instances of missing data or belated data entry in your manufacturing records. These practices are not consistent with CGMP. Operators acknowledged that there is no system in place to report these lapses in the documentation system; documentation errors of this type did not require deviation investigations or notification to the Quality Unit.

In addition, during the inspection, one of your quality unit employees presented the investigator with a batch record containing his signature, stating that he had performed the review of this batch record. The employee later admitted that he had falsified this CGMP record and stated that he in fact had not performed the review, despite having signed the batch record as the QA reviewer and having released the batch. This data falsification and the record-keeping deficiencies described above raise doubt regarding the validity of your firm's records.

In response to this letter, provide a comprehensive investigation into your personnel's data falsification practices. In addition, provide your procedures governing the timing of data entry with respect to actions being recorded and describe how you ensure that these procedures are followed. Also provide your procedures describing the filing of deviation notifications when your firm's documentation practices are not followed. Provide your specific corrective actions to avoid instances of data falsification and/or alteration by your personnel.

4. Failure to adequately maintain equipment in a state appropriate for its intended use in the manufacture of APIs.

Our investigator noted a leak in the purified water (PW) system during the current inspection; this is noteworthy given our previous inspection's similar findings of leaks in the same PW system. Your preventive measures described in your previous response were not sufficient to allow your staff to detect and repair leaks in the PW system; we therefore question whether the current measures will be effective. In your response to this letter, describe why the previous measures failed, what new measures have been taken, and why these measures will be effective.

The current inspection also found other pieces of manufacturing equipment in need of repair. The effectiveness of your revised preventive maintenance program will be reviewed in more detail during a future inspection.

In your response to this letter, provide a comprehensive corrective action plan to address data integrity practices at your firm. We highly recommend that you hire a third party auditor with experience in detecting data integrity problems, who may assist you in evaluating your overall compliance with CGMP.

During the inspection, your Quality Unit's personnel indicated that the unit's workload was too large for its current staffing levels. Our review of the significance of current findings indicates that your quality unit is not able to fully exercise its responsibilities. For instance, at the time of the inspection, your chief operating officer informed our investigator that your quality unit had not yet had time to review batch records for any products manufactured that month. It is your responsibility to ensure that adequate and appropriate resources are available to the quality unit to allow it to carry out its responsibilities.

MISBRANDING VIOLATIONS

In addition to violating CGMP, your firm shipped a misbranded active pharmaceutical ingredient to the U.S. As described above, according to our inspection, your firm prepared a certificate of analysis (COA) for gabapentin on your firm's letterhead, indicating that the product was manufactured by your firm, Zhejiang Jiuzhou Pharmaceutical Co., Ltd, when in fact it was not. The gabapentin was manufactured by **(b)(4)**. In addition, the expiration date on your firm's COA is not one supported by the COA from the original manufacturer, **(b)(4)**.

Moreover, your firm relabeled gabapentin and included on the label an official stamp that identifies your firm, Zhejiang Jiuzhou Pharmaceutical Co., Ltd, as the manufacturer of the product, rather than the actual manufacturer, **(b)(4)**. Based on our findings, the active pharmaceutical ingredient, gabapentin, is misbranded within the meaning of Section 502(a) of the Act [21 U.S.C. 352(a)] in that its labeling is false or misleading in any particular. See also 21 CFR 201.1(h)(2).

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 continuing to refuse admission of articles manufactured at Zhejiang Jiuzhou Pharmaceutical Co., in Zhejiang, 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 numbers 3003744377 and 3010365339.

Please send your reply to: Mary E. Farbman, Ph.D., Compliance Officer; 10903 New Hampshire Avenue Building 51 Room 4234; Silver Spring, MD 20993.

Sincerely,
/S/
Thomas Cosgrove
Acting Director
Office of Manufacturing and Product Quality
Center for Drug Evaluation and Research

/S/
Eric Nelson
Director
Division of Compliance
Office of Surveillance and Compliance
Center for Veterinary Medicine

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