檔　　號：
保存年限：

正本

衛生福利部食品藥物管理署　函

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受文者：中華民國西藥代理商業同業公會

發文日期：中華民國106年6月26日
發文字號：FDA風字第1061103904號
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附件：美國FDA Warning Letter 320-17-36影本1份

主旨：美國FDA發布中國原料藥廠「Qinhuangdao Zizhu Pharmaceutical Co., Ltd.」（廠址：No. 10 Longhai Avenue, Economic Development Zone, Qinhuangdao, Hebei, China）Warning Letter乙案，詳如說明段，請轉知所屬會員知照。

說明：

一、美國衛生主管機關US Food and Drug Administration（FDA）查核旨揭原料藥廠，判定違反CGMP，於106年3月8日列為Import Alert 66-40藥廠，並於106年4月24日正式發布Warning Letter（詳如附件）。

二、鑑於旨揭原料藥之製造品質恐無法符合GMP之要求，可能導致對藥品製造品質帶來影響與危害，請轉知所屬會員釐清相關輸台製劑產品是否使用旨揭原料藥廠所生產原料藥，並應依風險管理原則辦理相關後續處置。

正本：中華民國西藥商業同業公會全國聯合會、中華民國西藥代理商業同業公會、台北市西藥代理商業同業公會、中華民國開發性製藥研究協會、中華民國藥品行銷暨管理協會
副本：

署長吳秀梅

Qinhuangdao Zizhu Pharmaceutical, Co. 4/24/17

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS

Warning Letter 320-17-36

April 24, 2017

Mr. Jun Wu
Chairman
China Resources Zizhu Pharmaceutical Co., Ltd.
No. 27, Chaoyang North Road, Chaoyang District
Beijing 100024
China

Dear Mr. Wu:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Qinhuangdao Zizhu Pharmaceutical Co., Ltd. at No. 10 Longhai Avenue, Economic Development Zone, Qinhuangdao, Hebei from November 28 to December 1, 2016.

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 December 15, 2016, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific deviations including, but not limited to, the following.

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

Our inspection found your laboratory systems lacked controls to prevent deletion of and alterations to electronic raw data.

a. Our review of audit trail data revealed that your analysts manipulated the date/time settings on your high performance liquid chromatography (HPLC) systems. During the inspection your analysts admitted to setting the clock back and

repeating analyses for undocumented reasons. Initial sample results were overwritten or deleted, and unavailable for our investigators' review. Your firm reported only the passing results from repeat analyses. When test results are overwritten, the quality unit is presented with incomplete and inaccurate information about the quality of the drugs produced by your firm.

b. Your quality control analysts used a shared login account to access HPLC systems. This shared account allowed analysts, without traceability, to change the date/time settings of the computer, to modify file names, and to delete original HPLC data.

c. Seven out of **(b)(4)** of your firm's HPLC systems used for API testing had the audit trail feature disabled, although all **(b)(4)** had audit trail functionality.

In your response, you acknowledged that you lacked effective measures to control data within your computerized systems. You committed to revising procedures for computerized systems, locking date/time settings, and enabling audit trail functions. However, you noted that you do not expect audit trail functions for all quality control instruments to be completely activated until September 30, 2017. In the interim, you committed to control measures, including updated software and logbooks.

Your response is insufficient because it did not specify who holds administrative privileges on your computers, or address the significant pattern of data manipulation (e.g., deletions, date/time alterations) we observed at your facility.

In response to this letter:

- Clarify the specific user roles and detail the associated privileges for each laboratory system.
- Provide an assessment of the effectiveness of your interim system controls.
- Provide a commitment to conduct a similar future assessment of the effectiveness of all system controls expected to be in place by September 2017.
- Explain the oversight role of the quality unit in implementing these improvements and ensuring they remain effective.

2. Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.

Our investigators found that you failed to maintain complete data for all laboratory analyses, and you relied on incomplete information to determine whether your drugs met established specifications.

a. HPLC chromatograms were deleted and not available for our investigators' review. In your response, you acknowledged that in January 2016, "some data was deleted" while the network edition of the chromatographic operating system software was installed.

b. Our investigators found a recurring practice of re-testing samples until acceptable results were obtained. For example, our investigators found repeat HPLC testing for related substances of crude **(b)(4)**, batch **(b)(4)**. The initial test displayed an unknown peak in the chromatogram. A different analyst retested the batch five days later: this analysis did not display the unknown peak. Only the results of the second analysis were used for batch disposition, without documented justification or investigation.

Your response is inadequate because you did not include an assessment of the deleted data. Your response also lacked commitments to investigate the unknown peak in the chromatogram for crude **(b)(4)** batch **(b)(4)**, and to discontinue repeating tests without justification and investigation.

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

Our investigators found batch production records that contained blank or partially completed manufacturing data and lacked dates and signatures for verification. For example, in your **(b)(4)** plant, our investigators found a batch record for **(b)(4)** starting material, batch **(b)(4)**, with sticky notes from the quality assurance department directing operators to enter manufacturing data, such as missing weight and volume entries. Also, your quality unit did not approve this batch record before the material was used in further manufacturing.

All data in CGMP records must be complete and reliable so it can be evaluated by the quality unit during its batch review, as well as maintained for additional CGMP purposes.

Other documents—including cleaning records and equipment use logs—were also found to be partially completed, without dates and signatures for verification, or with pages or spaces intentionally left blank for documentation at a later time.

Your quality unit was aware of these unacceptable production department practices but did not ensure they were corrected.

Your response is inadequate because the investigation you documented under *Deviation No.: PC-002216-02* did not determine the impact of this missing manufacturing data on drug quality.

In response to this letter:

- Provide an update on your retrospective review of batch records for data integrity.
- Explain how your firm conducted this assessment, including your method(s) to determine if documentation was contemporaneous.
- Perform a comprehensive assessment of the sufficiency of the quality unit function at your facility.
- Provide a comprehensive assessment of your deviation and investigation systems, and a CAPA that remediates this significantly deficient part of your operation. Include specific measures you are taking to ensure all deviations and atypical events are immediately documented and fully investigated.

Our significant inspection findings indicate that your quality unit is not fully exercising its authority and/or responsibilities. You must provide your quality unit with appropriate authority and resources to carry out its responsibilities and consistently ensure drug quality.

Data Integrity Remediation. 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 strongly recommend you retain a qualified consultant to assist in your remediation.

In response to this letter, provide the following.

a. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- 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.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend these interviews be conducted by a qualified third party.
- 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. This includes a complete and comprehensive audit of all data from testing (including stability tests) used to support pending or approved applications.
- A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. We recommend a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

b. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

c. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:

- 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.

- 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.
- 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.
- 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.
- A status report for any of the above activities already underway or completed.

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.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA 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 or interruptions in your drug manufacture under 21 U.S.C. 356C(b) 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.

FDA placed your firm on Import Alert 66-40 on March 8, 2017.

Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these deviations may also result in FDA continuing to refuse admission of articles manufactured at Qinhuangdao Zizhu Pharmaceutical Co., Ltd., No. 10 Longhai Avenue, Economic Development Zone, Qinhuangdao, Hebei 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).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

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

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

Please identify your response with FEI 3009653722.

Sincerely,
/S/
Thomas J. Cosgrove, J.D.
Director
Office of Manufacturing Quality
Office of Compliance