檔　　號：
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# 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105年8月29日
發文字號：FDA風字第1051104895號
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密等及解密條件或保密期限：
附件：原料藥廠違反GMP警訊乙份(A21020000I105110489500-1.pdf)

主旨：美國FDA發布中國原料藥廠「Zhejiang Medicine Co., Ltd., Xinchang Pharmaceutical Factory」（廠址：98 East Xinchang Dadao Road, Xinchang, Zhejiang, 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，判定嚴重違反CGMP，並於105年8月4日正式發布Warning Letter（詳如附件）。

二、鑒於旨揭原料藥之製造品質無法符合GMP之要求，可能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

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**U.S. Food and Drug Administration**
Protecting and Promoting *Your* Health

# Zhejiang Medicine Co. Ltd. Xinchang Pharmaceutical Factory 8/4/16

**Department of Health and Human Services**

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

**Warning Letter 320-16-24**

Via UPS
Return Receipt Requested

August 4, 2016

Mr. Jiang Xiao Yue
CEO
Zhejiang Medicine Co. Ltd.
Xinchang Pharmaceutical Factory
Floor 3, Building A Kechuangyuan
398 Mahuan Road, Binhaixincheng
Shaoxing, Zhejiang 312366
China

Dear Mr. Yue:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Zhejiang Medicine Co., Ltd., Xinchang Pharmaceutical Factory, at 98 East Xinchang Dadao Road, Xinchang, Zhejiang, from June 15–18, 2015.

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 Cosmetics Act (the FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your firm's July 8, 2015, response in detail and acknowledge receipt of your subsequent responses.

Our investigators observed specific deviations including, but not limited to, the following.

**1. Failure to have laboratory control records that include complete data derived from all tests conducted to ensure compliance with established specifications and standards.**

Your laboratory personnel conducted unofficial testing without appropriate documentation, justification, and investigation.

Our inspection found that analysts performed multiple gas chromatography (GC) analyses of **(b)(4)** samples for residual solvents. Analysts performed these unofficial analyses and recorded them in separate "R&D" folders before conducting the officially reported sample analyses. The original, unofficial analyses stored in separate R&D folders were not part of the official quality control records for your API, and your firm did not consider the results of these unofficial analyses to evaluate the quality of your API or make batch release decisions for numerous batches of API.

Our investigator reviewed chromatograms found in the R&D folders and noted that some displayed large unknown peaks that were not reported in the official records for the same samples. The presence of such peaks in the chromatograms may indicate the presence of unknown and uncharacterized impurities (including potential contaminants) in your drugs.

In your response, you stated that from April to July 2013 you performed "pre-trial" sample analyses for residual solvent testing of **(b)(4)** batches to check system suitability. You also stated you were not testing into compliance and attempted to attribute the unknown peaks found in your "pre-trial" sample analyses to operator error. FDA considers the use of an actual sample in test, prep, or equilibration runs as a means of disguising testing into compliance, a violation of CGMP.

**2. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and failure to provide adequate controls to prevent omission of data.**

Our investigator found that your GC system used to test for residual solvents in **(b)(4)** lacked controls to prevent manipulation, data deletion, and unauthorized access. For example, operators responsible for generating CGMP records had full administrator rights to access the computers containing temporary data prior to routine transfer of the data to a server. All analysts shared a common login ID and password. Your use of universal administrator privileges and a single common login/password meant that actions could not be traced to specific individuals. Additionally, because the audit trail feature on the system's software was not configured to create a file history for all activities executed by the user during analysis, your electronic data was exposed to manipulation and/or deletion without traceability.

**3. Failure to record activities at the time they are performed.**

During the inspection, our investigators observed **(b)(4)** different analysts pre-dating or backdating results in your API quality control laboratory. Analysts were observed using pre-dated laboratory worksheets to document system suitability testing for high performance liquid chromatography (HPLC) analyses for **(b)(4)** purity testing. The worksheets were dated five days before the tests that they purported to document were actually carried out. Our investigators also observed analysts signing and dating microbiological testing laboratory worksheets five days before the test results would be available and backdating laboratory worksheets for impurities and content testing by four days.

**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 that 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 that 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.
- A comprehensive retrospective evaluation of the nature of the analytical testing data integrity deficiencies. We recommend that 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 *analyses* of 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 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.

After you receive this letter, you have 15 working days to respond to this office in writing. 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 days, state your completion date and reasons for delay.

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

deviations may also result in FDA refusing admission of articles manufactured at Zhejiang Medicine Co., Ltd., Xinchang Pharmaceutical Factory, at 98 East Xinchang Dadao Road, Xinchang, Zhejiang, 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).

**Send your reply to:**

Christina Alemu-Cruickshank
Consumer Safety Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

**Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov.**

Please identify your response with FEI 3003631275.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

Cc: Mr. Zhang Ding Feng
Site Head
Zhejiang Medicine Co. Ltd. Xinchang Pharmaceutical Factory
98 East Xinchang Dadao Road
Xinchang, Zhejiang 312500
China

**More in 2016 (/ICECI/EnforcementActions/WarningLetters/2016/default.htm)**