# Jinan Jinda Pharmaceutical Chemistry Co., Ltd. 2/24/17

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

**Via UPS**
**Return Receipt Requested**

**Warning Letter 320-17-25**

February 24, 2017

Mr. Yu Shui Cheng, General Manager
Jinan Jinda Pharmaceutical Chemistry Co., Ltd.
No. 6121 Longquan Road
Zhangqiu City (Jinan), Shandong Province, 250200
China

Dear Mr. Cheng:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Jinan Jinda Pharmaceutical Chemistry Co., Ltd. at No. 6121 Longquan Road, Zhangqiu City (Jinan), Shandong Province, from May 30 to June 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 June 22, 2016, response in detail and acknowledge receipt of your subsequent correspondence.

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

**1. 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.**

Your quality control laboratory disregarded multiple out-of-specification (OOS) impurity results without justification. For example, on September 22, 2015, you encountered an OOS unknown impurity peak during high performance liquid chromatography (HPLC) testing of **(b)(4)** 36-month stability batch **(b)(4)**. You terminated the analysis. Testing of a new sample also showed the OOS impurity peak. The chromatogram was then manually rescaled, which hid the presence of this peak. Your laboratory set the integration parameters to omit this peak from integration. Because the peak was omitted, the quality unit was not provided with full information to evaluate whether the stability batch, and potentially other marketed batches, continued to meet quality standards.

In addition, your audit trail showed that from July 1 to 2, 2015, you performed seven sample injections of **(b)(4)** 60-month stability batch **(b)(4)** to test for impurities using HPLC. You permanently deleted the first five sample injections. You then renamed the last two injections and reported that they met specifications. Your quality unit failed to identify and address these serious data manipulations.

We acknowledge your commitment to hire a third-party consultant to rebuild your quality system by July 2018. However, your response is inadequate. You lack a detailed interim plan to mitigate risk while you work to resolve deficiencies and implement a robust quality system by mid-2018.

**2. Failure to adequately investigate out-of-specification results.**

Your firm did not initiate investigations into failing results as required by your standard operating procedure (SOP) ZL/SOP/ZK/00405. On October 5, 2015, when you encountered an OOS value for an unknown impurity peak through HPLC testing of **(b)(4)** API 12-month stability batch **(b)(4)**, you prepared and tested new aliquots. You did not investigate the failing result.

We acknowledge your commitment to hire a third-party consultant to identify and evaluate all batches compromised by data integrity lapses. However, you failed to perform a comprehensive retrospective evaluation to determine whether appropriate corrective actions and preventive actions were identified and implemented for each OOS result obtained. Also, your retrospective review does not appear to address whether data integrity breaches occurred when using laboratory methods and systems that do not generate electronic data.

For more information about handling OOS results and documentation of your investigations, please refer to the FDA guidance for industry publication *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* available online at **http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf (http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf)**.

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

Our investigator observed that your laboratory systems lacked controls to prevent your staff from altering or deleting electronic data. Analysts manipulated and deleted audit trails. You lacked adequate controls for all HPLC, gas chromatography, and ultra-violet systems.

For example, an analyst deleted audit trails in your gas chromatography equipment #YQ-07-10 from September 15, 2015, through April 24, 2016, and permanently deleted audit trails from November 6 to 13, 2015. In addition, our investigator observed that your quality control manager and quality control deputy manager had full administrative rights on all of your computerized systems, which allows them to manipulate data and turn off audit trails.

We acknowledge that you commit to upgrading your analytical systems to be compliant with CGMP requirements. However, procuring new instruments, installing new and upgraded data acquisition software, and enabling various software features are insufficient to achieve CGMP compliance. These steps will be effective only if you implement appropriate procedures and systems to ensure that your quality unit reviews all production and control data and associated audit trails as part of the batch release process.

Your response states that your SOP for electronic data management specifies that only information technology staff will have full administrator rights. However, you did not specify which information technology personnel will have these administrator rights. In addition, this SOP became effective on May 9, 2016, prior to the FDA inspection. However, your quality control management still had full administrative rights to all computerized systems during our inspection from May 30 to June 1, 2016.

**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 acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements.

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 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 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 in your facility.

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.

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.

FDA placed your firm on Import Alert 66-40 on November 25, 2015.

Failure to correct these deviations may also result in FDA continuing to refuse admission of articles manufactured at Jinan Jinda Pharmaceutical Chemistry Co., Ltd. at No. 6121 Longquan Road, Zhangqiu City (Jinan), Shandong Province, 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:

Bryce A. Hammer
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 3004002973.

Sincerely,
/S/
Thomas J. Cosgrove
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

**More in 2017 (/ICECI/EnforcementActions/WarningLetters/2017/default.htm)**