Hubei Danao Pharmaceutical Co., Ltd. 11/6/17

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS **Warning Letter 320-18-07**

November 6, 2017

Mr. Cui Lixin
General Manager
Hubei Danjiangkou Danao Pharmaceutical Co., Ltd.
Fandan Road
Danjiangkou, Hubei Province, 442600 China

Dear Mr. Lixin:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Hubei Danjiangkou Danao Pharmaceutical Co., Ltd. at Fandan Road, Danjiangkou, Hubei Province, from July 31 to August 4, 2017.

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 response dated August 25, 2017, and received on September 29, 2017, in detail. However, your response is inadequate and did not provide sufficient evidence of corrective actions to bring your operations into compliance with CGMP.

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

1. Failure to demonstrate that your manufacturing process can reproducibly manufacture an API meeting its predetermined quality attributes.

You did not validate the processes used to manufacture numerous batches of **(b)(4)** API prior to commercial distribution. You did not perform process qualification studies

and lacked an ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality. You provided our investigator with a validation protocol that was approved on May 22, 2017, and the subsequent validation report that was approved on July 25, 2017, shortly before we inspected your facility.

Your batch records also lacked defined process parameters that you identified as critical for the manufacture of **(b)(4)** API such as blending **(b)(4)** and **(b)(4)**.

Your firm does not have an adequate ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality. See FDA's guidance document, *Process Validation: General Principles and Practices*, for general principles and elements of process validation at **http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070336.pdf (http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070336.pdf)**.

2. Failure of your quality unit to approve changes that potentially impact API quality.

You failed to follow your change management program. Our investigator found numerous changes that were not adequately documented, and implemented without quality unit evaluation and approval per your procedure, *Change Control*. These changes included, but were not limited to, product specifications, test methods, analytical equipment, and cleaning procedures for the manufacturing of **(b)(4)** API. An effective change management program is essential to ensure adequate quality unit oversight of changes that may impact the quality of your **(b)(4)** API.

FDA considers the expectations outlined in ICH Q7 in determining whether API are manufactured in conformance with CGMP. See FDA's guidance document, *Q7 Good Manufacturing Pracitce Guidance for Active Pharmaceutical Ingredients*, for guidance regarding CGMP for the manufacture of API, at **https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pd (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pd** Specifically, refer to section XIII, Change Control.

3. Failure to ensure that all test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and purity.

You failed to establish adequate test procedures. For example, your analyst manually integrated a high performance liquid chromatography test for **(b)(4)** API despite the fact that the chromatogram lacked peak resolution. When a chromatogram lacks peak resolution, detailed methods and appropriate oversight are essential to ensure test results, considered by the quality unit in batch release decisions, are scientifically valid. You lacked an approved protocol for manual integration or quality oversight of the practice.

CGMP consultant recommended

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations, and to assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

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 November 1, 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 Hubei Danjiangkou Danao Pharmaceutical Co., Ltd., at Fandan Road, Danjiangkou, Hubei 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 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 3004881534.

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

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