Yicheng Chemical Corp. 1/2/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-23

January 2, 2018

Ms. Yan Chen
General Manager
Yicheng Chemical Corporation
Fuchen Garden, Suite 1-402, Xinbei District
Changzhou, Jiangsu, 213001
China

Dear Ms. Chen:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Yicheng Chemical Corporation at Fuchen Garden, Suite 1-402, Xinbei District, Changzhou, Jiangsu, from July 17 to 21, 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 August 4, 2017, response in detail. It lacks sufficient corrective actions.

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

1. Failure to package (b)(4) drugs (including (b)(4) and (b)(4)) and other drugs under appropriate conditions to avoid potential cross-contamination.

Your firm failed to use separate facilities to manufacture **(b)(4)** and **(b)(4)** API. Your management stated that you weighed and repackaged **(b)(4)** (for example, **(b)(4)** USP and **(b)(4)** EP) and **(b)(4)** API, in the same room using non-dedicated equipment.

In your response, you stated that you would continue to use non-dedicated facilities, and will designate a time to handle, repack, and relabel **(b)(4)** in an area which would be cleaned before and after such operations.

Your response was inadequate. Cleaning cannot substitute for proper segregation. Cross-contamination with your **(b)(4)** can initiate life-threatening allergic reactions or other drug-induced **(b)(4)** reactions. Your current practices demonstrate an unacceptably high risk of **(b)(4)** API cross-contamination into other API repackaged at your facility. You should conduct all **(b)(4)** manufacturing activities in dedicated, segregated facilities with separate air handling systems and production equipment.

No safe level of **(b)(4)** contamination has been determined. Susceptible patients exposed to extremely low levels of **(b)(4)** and other **(b)(4)** may suffer severe allergic responses. Such low levels are difficult to detect with current analytical methods.

We recommend that you retrospectively assess whether any **(b)(4)** API packaged by your firm were contaminated with **(b)(4)**. However, be mindful that any test intended to detect **(b)(4)** contamination provides only limited confidence, because of method limitations and sample size. This low detectability, the severe risk to patients, and the limitations of production controls to preclude cross-contamination underscore the importance of meeting the minimum standard of manufacture in completely separate facilities.

For additional information, please refer to our guidance for industry, **(b)(4)**

If you continue to repackage **(b)(4)** products, indicate how you will assure that drugs manufactured at your facility will be free from **(b)(4)** contamination. In your response to this letter include your plans for decontaminating, renovating, and requalifying your facility. Include decontamination agent(s), your analytical methodology for environmental testing, your acceptance criteria, and the studies you used to support your decontamination plan.

If you continue to repackage any **(b)(4)** products, submit your comprehensive plan for complete segregation of these products from **(b)(4)**. Furthermore, include your proposed action plan to address the hazards posed by any drugs with potential **(b)(4)** contamination.

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

Your firm failed to have repackaging batch records. Furthermore, your quality unit lacked written procedures for API repackaging batch review, approval, and release prior to distribution.

In response to this letter, provide your repackaging batch review and release procedure which ensures that API repackaged at your facility are in compliance with CGMP.

3. Failure to maintain complete traceability of API in commercial distribution.

Your firm lacked documentation or procedures to ensure that each batch can be traced from your API suppliers, through your repackaging operations, and into commercial distribution.

In response to this letter, provide your procedure to ensure the integrity, traceability, and transparency of your API supply chain.

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 management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Additional API CGMP guidance

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 Practice Guidance for Active Pharmaceutical Ingredients,* for guidance regarding CGMP for the manufacture of API, at **https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf)**.

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.

FDA placed your firm on Import Alert 66-40 on August 11, 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 Yicheng Chemical Corporation at Fuchen Garden, Suite 1-402, Xinbei District Changzhou, Jiangsu 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:

Joseph Lambert, Pharm.D.
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 3004102971.

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

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