Sichuan Friendly Pharmaceutical Co., Ltd. 6/22/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-59

June 22, 2018

Mr. Shenyou Gong
President
Sichuan Friendly Pharmaceutical Co., Ltd.
No. 680 Hongpai Road
Dongxing District, Neijiang City
Sichuan Province
P.R.C. 641000

Dear Mr. Gong:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Sichuan Friendly Pharmaceutical Co., Ltd. at No. 680 Hongpai Road, Neijiang, Sichuan, from October 23 to 27, 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 November 17, 2017, 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 to ensure that all specifications and test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and purity.

Your firm failed to conduct residual solvent testing of your active pharmaceutical ingredient (API), **(b)(4)** USP, distributed to the United States.

For example, you did not test for residual solvent levels (e.g., **(b)(4)**) in your intermediate or finished **(b)(4)** API batches in order to determine whether results fell within acceptable levels.

You also manufacture this API on shared equipment. Multiple API are produced on this equipment and use other solvents, including **(b)(4)**, a class 2 solvent. Class 2 solvents must be limited because of their inherent toxicity and controlled to protect patients from potential adverse effects.

In your response, you committed to establish and validate an analytical method for residual solvents as per ICH guidelines, test for residual solvents in all batches of **(b)(4)** USP distributed in the United States, and provide the results to FDA. As of the date of this letter, you have yet to submit residual solvents test results for your drugs distributed to the United States.

In response to this letter, provide the following:

- A comprehensive risk assessment of all **(b)(4)** USP distributed within the United States that did not undergo residual solvent testing. Summarize your retention sample test results for the batches distributed to the U.S. Specify the actions you will take if any batch is found to contain residual solvent limits above appropriate specifications, including notifying customers or conducting recalls.
- A completed analytical method validation, and updated test methods and specifications in accordance with USP for your **(b)(4)** USP.
- A list of all residual solvents used in your facility and your risk-based plans to strictly limit (or discontinue use of) any class 1 or 2 solvents. Includes specification for all residual solvents used in API manufacturing and cleaning operations.

For more information on acceptable amounts for residual solvents in pharmaceuticals to ensure safety of patients, see FDA's guidance document, *Q3C Impurities: Residual Solvents* at **https://www.fda.gov/downloads/drugs/guidances/ucm073394.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm073394.pdf)**

2. Failure to adequately validate written procedures for the cleaning and maintenance of equipment.

You failed to conduct adequate cleaning validation studies to demonstrate that your cleaning procedures for non-dedicated production equipment are suitable to prevent cross-contamination.

You selected **(b)(4)**, one of **(b)(4)** API manufactured at your facility, as the only challenge product in your cleaning validation.

The **(b)(4)** API was manufactured on only 11 out of **(b)(4)** pieces of manufacturing equipment. You did not perform cleaning validation on the remaining **(b)(4)** pieces of shared equipment to ensure that cleaning procedures reproducibly prevent cross-contamination of different intermediates and APIs.

You also use multiple solvents, both class 2 and 3, in your manufacturing processes, but your validation did not address the potential carryover of residual solvents from one drug to another.

In your response, you committed to revise your cleaning procedures, reevaluate your cleaning validation program, and conduct additional studies.

Your response is inadequate. You did not include a comprehensive risk assessment to determine the potential cross contamination of various API, intermediates, and solvents into the API you distributed to the United States.

In response to this letter, provide the following:

- Your updated cleaning validation for all multi-use equipment at your facility. Include a summary report of cleaning validation with quantification of any drug carryover, residual solvents or other impurities detected; acceptable limits for each impurity; justification for the drugs you choose as worst-case candidates for the study; your rationale for selecting cleaning agents; and the effectiveness of your cleaning procedures.
- A comprehensive risk assessment to determine the impact of inadequate cleaning validation on batches of **(b)(4)** USP, within expiry released for distribution to the United States.

3. Failure to design a documented, on-going stability testing program to monitor the stability characteristics of API and to use the results to confirm appropriate storage conditions and retest or expiry dates.

During the inspection, you were unable to provide data to support your **(b)(4)** API's **(b)(4)** shelf-life labelled to meet the United States Pharmacopeia.

In your response, you indicated that you tested retain samples using a different pharmacopeia, and stated that data indicates your drug is stable. However, you also observed that your methods may differ from the USP and "maybe that the test results are not the same." You committed to test the retention samples of **(b)(4)** batches according to the USP monograph to confirm that the API meet specifications after storage for more than **(b)(4)**.

Your response is inadequate because you did not commit to develop a complete stability program for your API or to demonstrate that your methods meet the USP label claim, and did not demonstrate that your test methods are stability-indicating.

In response to this letter, provide the following:

- An updated stability program, including stability-indicating methods, and methods that detect changes in the physical appearance of the API which could indicate degradation.
- Retention sample test data for all batches of **(b)(4)** distributed to the U. S. market within expiry using stability-indicating methods.

4. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and to have adequate controls to prevent omission of data.

You used a non-validated Excel spreadsheet to calculate assay results for **(b)(4)** USP for product release and stability testing. Our investigator found that this spreadsheet lacked password protection and contained unlocked calculation formulas which were incorrect.

During the inspection, your QC manager acknowledged that the formula in the spreadsheet used to calculate assay results was incorrect. Because of these incorrect formulas, multiple certificates of analysis (COA) contained inaccurate data.

In your response, you identified multiple batches with incorrectly calculated release assay results, including instances of stability results that your spreadsheet calculated as in specification, but were in fact out-of-specification (OOS).

Your response is inadequate because you did not adequately address these OOS results, and you failed to address the deficient data review process by your Quality Unit. Although you committed to validate your Excel spreadsheets, you failed to specify which spreadsheet controls will prevent unauthorized access, modifications, or deletion of data. Your response also lacked a comprehensive assessment and retrospective review of all data generated from all computerized laboratory systems used in CGMP operations.

In response to this letter, provide the following:

- A comprehensive assessment of your data review system used throughout your manufacturing and laboratory operations to determine where else it is deficient. Include a detailed corrective action and preventive action (CAPA) plan with systemic remediation to address deficient data review, including quality unit oversight. The CAPA should include, but not be limited to, revised procedures, training, and systemic actions implemented to assure the integrity of all CGMP records.
- An assessment of all Excel spreadsheets used to support CGMP operations to identify and investigate the extent of inaccuracies, such as incorrect formulas and other deficiencies. Include a detailed CAPA plan to address the noted deficiencies and to prevent recurrence.
- A retrospective review and risk assessment of all test data for API within expiry and distributed in the United States using computerized systems that lack sufficient control to prevent modifications and deletions. If you obtain OOS results based on this assessment, indicate your action plan, such as notifying customers and/or initiating recalls.
- A comprehensive independent assessment of your overall system for investigations of deviations, atypical events, complaints, OOS results, and failures. Your CAPA should include, but not be limited to, improvements in investigation competencies, root cause analysis, written procedures, and quality unit oversight.

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 assist your firm in meeting CGMP requirements. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance, and evaluate the completion and effectiveness of any corrective actions and preventive actions you have implemented before you pursue resolution of your firm's compliance status with FDA.

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.

FDA placed your firm on Import Alert on March 22, 2018.

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 Sichuan Friendly Pharmaceutical Co., Ltd., No. 680 Hongpai Road
Dongxing District, Neijiang City, Sichuan, 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 maybe subject to refusal 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 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 or mail your reply to:

Cesar E. Matto, M.S.
Senior Policy Advisor
U.S. Food and Drug Administration
White Oak Building 51, Room 4235
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3012903349.

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

More in Warning Letters (/ICECI/EnforcementActions/WarningLetters/default.htm)