Yicheng Goto Pharmaceuticals Co., Ltd 7/26/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter: 320-18-65

July 26, 2018

Mr. Michael Zou
Chief Marketing Officer
Yicheng Goto Pharmaceuticals Co., Ltd.
5th Floor, East Gate of Building #2
Servo Industrial Park, 1st Qilin Road
Xiangyang
Hubei Province, 441021
China

Dear Mr. Zou:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Yicheng Goto Pharmaceuticals Co., Ltd. at Group 1 Gaokeng, Xiaohe Town, Yicheng City, Hubei Province, from September 11 to 14, 2017.

This warning letter summarizes significant deviations of 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 received on October 13, 2017, in detail and acknowledge receipt of your subsequent correspondence.

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

1. Failure to adequately validate the process for cleaning and maintenance of equipment.

You have not conducted cleaning validation studies to demonstrate that your cleaning procedures for non-dedicated production equipment are adequate to prevent potential cross-contamination between your API (e.g., **(b)(4)**), which include **(b)(4)** drugs. Your firm also processes intermediates on this equipment.

More specifically, you failed to conduct cleaning validation for the majority of the critical non-dedicated production equipment you use to manufacture **(b)(4)** intermediates and API.

Reactors, **(b)(4)** are examples of critical multi-use equipment used by your firm.

During the inspection, your staff alsostated that it was not required to document equipment cleaning between manufacturing runs. For example, for **(b)(4)** batch **(b)(4)**, your firm was able to provide a cleaning record for only one piece of equipment (a **(b)(4)**) to demonstrate that cleaning was performed prior to batch manufacture.

In your response, you state that you will conduct cleaning validation for your non-dedicated equipment. However, you failed to provide your plan to ensure that your equipment is adequately cleaned in the interim.

In response to this letter, provide:

- Your updated cleaning validationprotocol and report for all equipment you use to manufacture drugs including all results and established acceptance criteria. Also, include updated procedures for equipment cleaning and maintenance, with provisions including but not limited to documentation of all cleaning operations.
- A risk assessment to determine the effect of inadequate cleaning practices on all potentially affected lots of intermediates and API distributed to the U.S. market. This assessment should include but not be limited to an analysis of retains of all lots at risk for potential cross-contamination.
- Your proposed market action plan including customer notifications, retain testing protocol, enhanced complaint monitoring, and recalls, if appropriate, to address all potentially affected lots of intermediates and API in the U.S. supply chain at risk for potential cross-contamination.
- Provide your interim action plan to ensure adequate cleaning before you complete your validation studies, including but not limited to performing cleaning verification testing before change-over to a different API or intermediate to ensure cleaning effectiveness. Also include your acceptance criteria for each API and intermediate.
- A comprehensive, independent review to identify risks of cross-contamination between drugs (API and intermediates) manufactured at your facility. Assess the suitability of your facility and process design to prevent cross-contamination, and include an evaluation of your equipment, material, personnel, and waste flows. Include a detailed corrective action and preventive action (CAPA) plan with systemic remediation and timelines.

2. 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 perform adequate analytical tests for **(b)(4)** API. For example, you conducted assay, related substance, and residual solvent testing without performing system suitability tests and use of standards. In addition, your analysts performed manual integration on chromatograms without a written procedure.

In your response, you state that you have established procedures that require your analysts to use standards, perform system suitability tests, and employ appropriate practices for chromatographic integration. However, you did not provide your procedures on the use of standards and system suitability. Your response also lacked a retrospective assessment of the effect of manual integration on data generated prior to implementing your new procedure.

In response to this letter, provide:

- An assessment of all test methods used by your firm to ensure they have appropriate instructions, method suitability criteria, and have been appropriately validated to determine whether they are fit for purpose.
- A reanalysis plan for all batches within retest date that were analyzed using methods lacking system suitability or standards.
- A comprehensive review of all instances of chromatographic manual integration. Provide scientific justification for the manual integration parameters you used for analysis. For integrations that lacked scientific justification, provide your plan for reintegration with appropriate reintegration parameters. Assess whether reintegration results comply with your established API acceptance criteria. If you identify out-of-specification (OOS) results, describe actions, such as customer notification and recalls, you have taken or will take to ensure the quality of marketed products and to protect patients.
- Provide a comprehensive, independent review of your laboratory practices, methods, equipment, and analyst competencies. Based on this review, provide a detailed CAPA plan to fully remediate your laboratory system. Elements of your CAPA should include, but not be limited to, measures you will take to strengthen quality assurance oversight of review and approval of method validation and test results. Your plan should also include your process for evaluating the effectiveness of the implemented CAPA.

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

For example, you do not have stability data to support the **(b)(4)** retest date assigned to your **(b)(4)** API. You also have not performed ongoing annual stability monitoring of API.

In your response, you state that you plan to initiate stability monitoring of **(b)(4)** API during their next manufacturing campaign.You failed to provide justification for the **(b)(4)** retest date in the interim.

In response to this letter, provide your plan of action with timelines to develop and implement a complete drug stability program for API manufactured for the U.S. market. Your program should be designed to support all assigned retest dates and process hold times for each API. Assess the stability of all API currently distributed to the U.S. market.

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

Your firm failed to conduct process performance qualification for several API. For other API, you conducted partial process performance qualification as you did not adequately evaluate significant variables (e.g., parameters) in your manufacturing processes for those API. In addition, you do not have an on-going 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 approaches that FDA considers appropriate elements of process validation, at **http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070336.pdf (http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070336.pdf)**.

In your response, you state that you will complete process validation for your API. However, your response is inadequate because you failed to specify how you will ensure that your API are manufactured reproducibly. You also did not provide a retrospective review of your manufacturing processes to identify whether drug quality was adversely affected.

In response to this letter, provide your validation protocols and reports. Also provide an update on the status of process performance qualification for your manufacturing processes for all API distributed to the U.S. market and your program for ensuring an ongoing state of control of your manufacturing processes.

Repeat Observations at Facility

FDA cited similar CGMP observations during inspections we conducted from September 12 to 15, 2011; and September 1 to 4, 2014. You proposed specific remediation for these observations in your responses. These repeated failures demonstrate that your management's oversight and control over the manufacture of intermediates and API is inadequate.

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. We also recommend that the third party perform a comprehensive audit of your entire operation for CGMP compliance and, 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 66-40 on January 10, 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 Yicheng Goto Pharmaceuticals Co., Ltd., Group 1 Gaokeng, Xiaohe Town, Yicheng City, 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:

Ms. Christina Alemu-Cruickshank
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4212
10903 New Hampshire Avenue
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USA

Please identify your response with FEI 3004459466.

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

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