WARNING LETTER

Jiangsu NHWA Pharmaceutical Co., Ltd.

MARCS-CMS 582511 — SEPTEMBER 10, 2019

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Sun Jia Quan

President and General Manager

Jiangsu NHWA Pharmaceutical Co., Ltd.

No. 6 Tianyong Road, Industrial Park
Xuzhou Shi Jiangsu Sheng, 221000
China

Issuing Office:

Center for Drug Evaluation and Research

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Warning Letter 320-19-42

September 10, 2019

Dear Mr. Sun Jia Quan:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Jiangsu NHWA Pharmaceutical Co., Ltd. (Jiawang site), FEI 3005619485, at No. 6 Tianyong Road, Industrial Park, Xuzhou, Jiangsu, from April 1 to 5, 2019.

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).

Additionally, your drug products, **(b)(4)** are adulterated under section 501(b) of the FD&C Act, 21 U.S.C. 351(b), for failure to conform to compendial standards for strength, quality, or purity.

We reviewed your April 26, 2019, response to our Form FDA 483 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 sampling plans and test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and purity.

You manufacture multiple API listed in the United States Pharmacopeia (USP) that were imported into the United States and supplied to compounding pharmacies. For **(b)(4)** API, the laboratory stability protocols used to support expiration dating of these API are based on methods and specifications in the 2015 Chinese Pharmacopeia. You were not able to demonstrate that the tests used are equivalent to or better than the current USP 42 compendial methods. FDA compared your test methods, based on the Chinese Pharmacopeia, to the current standard in the USP. We found multiple differences in specifications and test methods. We also found that required tests for quality attributes in the USP were not part of the Chinese Pharmacopeia or your stability protocols. Beyond a deviation from CGMP, this also causes your drugs to be adulterated within the meaning of 501(b) of the FD&C Act, 21 U.S.C. 351(b), in that their strength, quality, or purity falls below the standards set forth in an official compendium recognized in the FD&C Act.

Additionally, forced degradation studies were not validated for your USP-grade **(b)(4)**.

In your response, you stated that you would cease distribution until you have updated your methods, conducted a comparison of your test methods versus the current USP compendial methods, and tested reserve samples against the current USP standards. You stated that you would take appropriate action if you found quality issues with U.S. distributed product within expiry.

In response to this letter, provide:

- Your commitment to using current USP compendial methods until any alternative methods have been demonstrated to be equivalent or better than the USP methods.
- A comprehensive study that determines whether your test methods for your API are equivalent to, or better than, the USP method, if you are not using current USP compendial methods. Include all findings and deviations encountered in assessing whether your alternative method is equivalent or superior to the USP compendial method. For FDA's current thinking regarding analytical test method validation, see *Analytical Procedures and Methods Validation for Drugs and Biologics* at https://www.fda.gov/media/87801/download (https://www.fda.gov/media/87801/download).
- Updated test results using a validated test method (e.g., USP method) of all reserve samples for all drugs released to the U.S. market within expiry to ensure that your drug products conform to appropriate standards of identity, strength, quality, and purity.
- Your action plan to address any product quality or patient safety risks for your drug products in U.S. distribution, including potential customer notifications, recalls, or market withdrawals.
- Your procedure for documenting and investigating any deviations from laboratory control procedures.

2. Failure to adequately investigate and document out-of-specification results according to a procedure and implement appropriate corrective actions.

Our investigator discovered that **(b)(4)** batches of **(b)(4)** API failed finished release testing due to the discovery of foreign particles during color/clarity solution testing. The investigations, OOS-201607109 and OOS-201608130, failed to identify the root cause and source of the foreign materials.

Additionally, in October 2016, **(b)(4)** of **(b)(4)** API **(b)(4)** were returned to your firm due to the presence of **(b)(4)** of foreign particles (**(b)(4)** and **(b)(4)**).

In your response, you stated that you would reexamine your procedures for evaluating laboratory investigations, customer complaints, and deviations. You also committed to review all out-of-specification (OOS) results. Your response was inadequate in that you did not review the analytical test results you used to release drugs to the U.S. supply chain, using non-USP methods, to determine if any passing test results were, in fact, out of specification when compared to the USP standards.

In response to this letter, provide:

- A comparison of the test methods used to release API to the U.S. market versus the USP compendial standards. For any tests with differing specifications, investigate whether you released OOS material.
- A retrospective, independent review of all invalidated OOS (in-process and finished testing) results for products currently on the U.S. market within expiry. Assess whether the scientific justification and evidence for each invalidated OOS result was conclusive. For investigations that establish laboratory root cause, ensure that other laboratory methods vulnerable to the same root cause are identified for remediation.
- A thorough review of production (e.g., batch manufacturing records, adequacy of manufacturing steps, raw materials, process capability, deviation history, batch failure history) for any OOS results with inconclusive or no root cause identified.
- A corrective actions and preventive actions (CAPA) plan that identifies manufacturing root causes and specifies meaningful improvements.
- A review and remediation of your system for investigating OOS results. Provide a CAPA plan to improve OOS handling. Your CAPA plan should ensure that your revised OOS investigations procedure includes:
    - Enhanced quality unit oversight of laboratory investigations
    - Identification of adverse laboratory control trends
    - Resolution of causes of laboratory variation
    - Investigations of potential manufacturing causes when a laboratory cause cannot be conclusively identified

Drug Distribution Ceased Until Corrective Actions Implemented

We acknowledge your commitment to cease distribution of drugs manufactured at the Jiawang site to the U.S. market until you have completed your CAPA plan and confirmed its effectiveness.

In response to this letter, please confirm that you will not resume manufacturing drugs for the U.S. market until the FDA has verified the adequacy of your CAPA. When you have completed your corrective actions, notify this office in writing.

Conclusion

The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility. You are responsible for investigating and determining the causes of these deviations and for preventing their recurrence or the occurrence of other deviations.

Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

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:

Rokhsana Jazi

Compliance Officer
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 3005619485.

Sincerely,

/S/

Francis Godwin

Director

Office of Manufacturing Quality

Office of Compliance

Center for Drug Evaluation and Research

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