WARNING LETTER

Wuhu Nuowei Chemistry Co., Ltd.

MARCS-CMS 697727 — FEBRUARY 04, 2025

Delivery Method:

Via Electronic Mail Return Confirmation Requested

Reference #:

320-25-38

Product:

Drugs

Recipient:

Ms. Hongwei Xu
General Manager
Wuhu Nuowei Chemistry Co., Ltd.
Chuangxin Road, Economic Development Zone
Jiujiang Qu Wuhu Shi Anhui Sheng, 241000
China

Issuing Office:

Center for Drug Evaluation and Research (CDER)
United States

Warning Letter 320-25-38

February 4, 2025

Dear Ms. Xu:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Wuhu Nuowei Chemistry Co., Ltd., FEI 3014438694, at Xuancheng 323 Provincial Road, Pang, Jingde, Xuancheng, from September 2 to 6, 2024.

This warning letter summarizes significant deviations from Current Good Manufacturing Practice (CGMP) for active pharmaceutical ingredients (APIs).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your APIs 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 **(b)(4)** is 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 September 24, 2024 response to our Form FDA 483 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 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.

You manufacture **(b)(4)** API that was imported into the United States and supplied to **(b)(4)**. This drug is commonly used **(b)(4)**. You failed to establish that your test methods for testing **(b)(4)** are scientifically sound, and that your specifications for **(b)(4)** are appropriate.

Your test method for impurities analysis for **(b)(4)** is based on methods and specifications in the Chinese Pharmacopeia. However, you failed to establish that these test methods are equivalent to or better than the current United States Pharmacopeia (USP) compendial methods.

You also failed to establish appropriate impurity specifications for **(b)(4)**. Specifically, your specification limits for any single impurity (**(b)(4)**%) and for total impurities (**(b)(4)**%) exceed the USP specification limits of **(b)(4)**% and **(b)(4)**%, respectively. We note that a shipment to the United States of a **(b)(4)** lot, manufactured at your facility, Lot **(b)(4)**, exceeded the USP monograph specification for any single impurity. Beyond a deviation from CGMP, this also causes your drug to be adulterated within the meaning of section 501(b) of the FD&C Act, 21 U.S.C. 351(b), in that its strength, quality, or purity falls below the standards set forth in an official compendium recognized in the FD&C Act. Further, your release testing did not include the related compound **(b)(4)** and **(b)(4)**, as required by the USP.

In your response, you provided an updated method verification report and supporting data for the impurity testing of **(b)(4)**. Your response is inadequate because it did not provide any information to demonstrate that your method is equivalent to or better than the USP compendial method. Your response also did not characterize the impurity profile of **(b)(4)** manufactured at your facility to demonstrate that your API does not pose a potential safety risk to patients.

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 APIs 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 APIs released to the U.S. market within expiry to ensure that your APIs conform to appropriate standards of identity, strength, quality, and purity.
- Your action plan to address any product quality or patient safety risks for your APIs 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 of your quality unit to exercise its responsibility to ensure the API manufactured at your facility is in compliance with CGMP.

You lack adequate quality unit (QU) oversight for the manufacture of your API. Your QU failed to ensure that there was adequate stability data to support retest or expiration dates of API manufactured at your facility.

You have inadequate stability data to support the **(b)(4)** retest date for **(b)(4)**. While you provided stability data tables for **(b)(4)** lots **(b)(4)** and **(b)(4)**, you were unable to provide any records of raw data pertaining to these batches.

In your response, you provided the stability test data for **(b)(4)** lot **(b)(4)** that was shipped to the United States. Your response is inadequate. You did not provide the analytical testing data for lots **(b)(4)** and **(b)(4)** that was used to support your **(b)(4)** retest date, nor any other data to support your retest dates.

In response to this letter, provide:

- A comprehensive, independent assessment and corrective action and preventive plan to ensure the adequacy of your stability program. Your remediated program should include, but not be limited to:
  o Stability-indicating methods.
  o Stability studies for each API in its marketed container-closure system before distribution is permitted.
  o An ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid.
  o Detailed definition of the specific attributes to be tested at each station (timepoint).
- All procedures that describe these and other elements of your remediated stability program.

3. Failure to establish adequate written procedures for cleaning equipment and its release for use in manufacture of API.

Your cleaning validation for your shared manufacturing equipment for **(b)(4)** APIs is inadequate.

You provided a protocol for cleaning the **(b)(4)** tank used to manufacture **(b)(4)**, which does not include acceptance criteria for carryover residues. Instead, you relied on visual inspection to determine cleanliness of your equipment and could not provide any analytical or microbiological data to support the efficacy of your cleaning procedures.

In your response, you provided an updated cleaning protocol and report for your **(b)(4)** tank with supporting microbiological data. Your response is inadequate because you did not consider performing analytical testing of potential carryover residues to demonstrate that your cleaning procedure is effective. You also did not provide cleaning procedures for the other equipment used in the manufacture of your APIs.

In response to this letter, provide:

- Appropriate improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. This should include, but not be limited to, identification and evaluation of all worst-case:
  o Drugs with higher toxicities
  o Drugs with higher drug potencies
  o Drugs of lower solubility in their cleaning solvents
  o Drugs with characteristics that make them difficult to clean
  o Swabbing locations for areas that are most difficult to clean
  o Maximum hold times before cleaning

In addition, describe the steps that must be taken in your change management system before introduction of new manufacturing equipment or a new product.

- A summary of updated standard operating procedures that ensure an appropriate program is in place for verification and validation of cleaning procedures for products, processes, and equipment.
- A risk evaluation of potential cross-contamination due to inadequate cleaning for APIs within expiry in distribution in the United States.

Ineffective Quality System

Significant findings in this letter demonstrate that your firm does not operate an effective quality system in accord with CGMP. In addition to the lack of effective management oversight of your production and laboratory operations, we found your QU is not enabled to exercise proper authority and/or has insufficiently implemented its responsibilities. Executive management should immediately and comprehensively assess your company's global manufacturing operations to ensure that your systems, processes, and products conform to FDA requirements.

Imported Drug Labeled for "R&D only"

You indicated that you do not distribute your products to the United States, and that one of your customers, **(b)(4)**, ships your products to the United States. Prior to distributing to **(b)(4)**, you label the **(b)(4)** with labels provided to you by **(b)(4)** that state, in English, "For R&D only. Not for commercial." We note, however, the quantity of API (recently as much as **(b)**

(4) in one shipment) shipped into the United States is inconsistent with quantities typically used for research and development.

Drug Production Ceased

We acknowledge your commitment to cease production of drugs for the U.S. market and that you deregistered your facility as a drug manufacturer. In response to this letter, clarify whether you intend to resume manufacturing drugs for the U.S. market at this facility in the future and whether you intend to notify your customers that your drugs are not intended for the U.S. market.

If you plan to resume any manufacturing operations regulated under the FD&C Act, notify this office before resuming your drug manufacturing operations. If your firm intends to resume manufacturing drugs for the U.S. market, you should engage a consultant qualified to evaluate your operations 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 resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

FDA considers the expectations outlined in ICH Q7 when 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/regulatory-information/search-fda-guidance-documents/guidance-industry-q7a-good-manufacturing-practice-guidance-active-pharmaceutical-ingredients.

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 any deviations and for preventing their recurrence or the occurrence of other deviations.

FDA placed products offered for import into the United States from your firm on Import Alert 66-40 on January 24, 2025.

Correct any deviations promptly. FDA may withhold approval of new applications or supplements listing your firm as a drug manufacturer until any deviations are completely addressed and we confirm your compliance with CGMP. We may re-inspect to verify that you have completed corrective actions to any deviations.

Failure to address any deviations may also result in the FDA continuing to refuse admission of articles manufactured at Wuhu Nuowei Chemistry Co., Ltd., at Jiujiang, Chuangxin Road, Economic Development Zone, Wuhu, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority that appear to be adulterated may be detained or refused 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).

This letter notifies you of our findings and provides you an opportunity to address the above deficiencies. After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done to address any deviations and to prevent their recurrence. In response to this letter, you may provide additional information for our consideration as we continue to assess your activities and practices. 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. Identify your response with FEI 3014438694 and ATTN: Christopher Keating.

Sincerely,
/S/

Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

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