U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Via Email
Return Receipt Requested

October 17, 2024

Mr. Zhang Liguo
General Manager
Shandong Boyuan Pharmaceutical Co., Ltd.
No. 169 Huiyu South Road
Yucheng High-Tech Development Zone
Dezhou, Shandong 251200
China
registration@boyuanpharm.com

Dear Mr. Liguo:

Your facility is registered with the United States Food and Drug Administration (FDA) as a manufacturer of active pharmaceutical ingredients (API). FDA has reviewed the records you submitted in response to our February 8, 2023 initial request for records and information, as well as subsequent requests, pursuant to section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for your facility, Shandong Boyuan Pharmaceutical Co., Ltd., FEI 3008915591, at No. 169 Huiyu South Road, Yucheng High-Tech Development Zone, Dezhou, Shandong.

This letter summarizes deviations from Current Good Manufacturing Practice (CGMP) for (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).

Following the review of records and other information provided pursuant to section 704(a)(4) of the FD&C Act, deviations were observed including, but not limited to, the following:

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

Your response to our request for records indicates that you manufactured (b) (4) without validating the manufacturing processes, and therefore would not be able to provide any documents. This product was imported and distributed to the United States (U.S.) market.

Without process validation documentation, you cannot demonstrate that your manufacturing process can consistently produce API that meet predetermined quality attributes.

FDA's guidance document *Process Validation: General Principles and Practices* for general principles and approaches that FDA considers appropriate elements of process validation at https://www.fda.gov/media/71021/download.

2. Failure of your quality unit to ensure that there is stability data to support retest or expiry dates and storage conditions of API.

In the records and information you provided, you state that stability studies have not been performed for (b) (4)

Without performing adequate stability studies, you are unable to ensure that the API you manufacture and store in the container-closer systems retain their identity, strength, purity, and quality through the assigned shelf-life.

3. 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.

In the records and information you provided, you state (b) (4) analytical test methods have not been validated.

Without performing comprehensive validation of your test methods, you are unable to demonstrate that the method is suitable for its intended purpose. There is no assurance that the methods you use are able to adequately assess the quality attributes of the API you manufacture.

Additional API CGMP Guidance

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/media/71518/download.

CGMP Consultant Recommended

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified. The qualified consultant should also perform a comprehensive six-system audit of your entire operation for CGMP compliance and evaluate the completion and efficacy of your corrective actions and preventive actions (CAPAs) 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 resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

Additional Considerations

In your response dated March 20, 2023, you stated that your API were not intended for the U.S. market and were imported to the U.S. market without your knowledge. You also stated that these

API were in research and development stage. We acknowledge your efforts to identify the entity that imported these API.

In a subsequent response dated April 8, 2024, you state that your intentions are to distribute drugs to the U.S. market in the future. During a teleconference meeting held with your firm on September 12, 2024, you were informed that your API were previously imported with an intended use for human pharmacy compounding. Before distribution to the U.S. market, you need to correct the CGMP deficiencies, including but not limited to, those referenced in this letter. Your firm will remain on import alert until FDA verifies corrective actions and that you are compliant with CGMP.

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 all drugs manufactured by your firm on Import Alert 66-40 on July 15, 2024.

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 30 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 30 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 3008915591 and ATTN: Christina Alemu-Cruickshank.

Sincerely,

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

CC: Liu Xujing
International Drug Registration Manager
Shandong Boyuan Pharmaceutical Co., Ltd.
Email: registration@boyuanpharm.com