WARNING LETTER

Sichuan Deebio Pharmaceutical Co. Ltd.

MARCS-CMS 669808 — FEBRUARY 14, 2024

Delivery Method:

VIA EMAIL WITH READ RECEIPT

Reference #:

320-24-21

Product:

Drugs

Recipient:

Mr. Zhang Ge

Chairman

Sichuan Deebio Pharmaceutical Co. Ltd.

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Issuing Office:

Center for Drug Evaluation and Research | CDER

United States

United States

Warning Letter 320-24-21

February 14, 2024

Dear Mr. Ge:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Sichuan Deebio Pharmaceutical Co. Ltd., FEI 3011139911, at 15 Gaocaocun, Xiaohanzhen, Guanghan, Deyang, Sichuan, from September 4 to September 8, 2023.

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 September 28, 2023 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 follow and document laboratory controls at the time of performance, and failure to document and explain any departures from laboratory procedures.

You failed to ensure the integrity of data generated by your Quality Control (QC) microbiology laboratory. Specifically, our investigators observed that numerous microbiological plates supporting **(b)(4)**, USP API production operations were not read and recorded contemporaneously. After investigators found microbiological plates in a waste bin, QC personnel provided conflicting information as to whether results had been read and recorded on laboratory worksheets following established procedures. The following day, your firm interviewed QC personnel about the plates and the investigation confirmed that test results were not contemporaneously documented. The investigation revealed that QC personnel admitted to not having written down the test results and relying on their memory, indicating, "I haven't written it yet" and "It's in my head."

CGMP activities must be documented at the time of performance. Non-contemporaneous documentation on laboratory worksheet records raises concerns about the validity and integrity of your firm's laboratory testing records.

In your response, you acknowledge the employee autoclaved and disposed of the test plates prior to recording test results. You commit to process improvements, retraining, and an independent verification of compliance prior to distribution to the United States.

Your response is inadequate as you fail to provide details of a retrospective review of all your documentation practices and data records supporting **(b)(4)**, USP API distributed to the U.S. market.

In response to this letter, provide:

- A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed corrective action and preventive action (CAPA) plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.
- A comprehensive investigation into the extent of the inaccuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.
- A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.
- A management strategy for your firm that includes the details of your global CAPA plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

2. Failure of your quality unit to exercise its responsibility to ensure the API and intermediates manufactured at your facility are in compliance with CGMP.

Your firm's quality unit (QU) failed to perform routine QU functions to ensure **(b)(4)**, USP API manufacturing operations were adequate. For example, your QU failed to:

- Confirm deviations in testing methods were investigated and resolved.
- Ensure adequate document control and retention of printouts and electronic records for all **(b)(4)**, USP API testing.
- Extend product quality complaint investigations to other batches or APIs potentially associated with the root cause, failure, or deviation.

In your response, you acknowledge deficiencies in your investigations and document control. You commit to process improvements, retraining personnel, and adding third-party oversight.

Your response is inadequate as you fail to perform a sufficient retrospective review of investigations and data retention deficiencies.

In response to this letter, provide the following:

- A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should include, but should not be limited to:

o A determination of whether procedures used by your firm are robust and appropriate.
o Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices.
o A complete and final review of each batch and its related information before the QU disposition decision
o Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products. Also describe how top management supports quality assurance and reliable operations, including but not limited to timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing state of control.

Quality Systems

Your firm's quality systems are inadequate. See FDA's guidance document *Quality Systems Approach to Pharmaceutical CGMP Regulations* for help implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and 211 at https://www.fda.gov/media/71023/download.

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/files/drugs/published/Q7-Good-Manufacturing-Practice-Guidance-for-Active-Pharmaceutical-Ingredients-Guidance-for-Industry.pdf.

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document

Data Integrity and Compliance with Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/119267/download.

Drug Production Suspended

We acknowledge your commitment to suspend production of **(b)(4)**, USP API for the U.S. market. In response to this letter, clarify whether you intend to resume manufacturing drugs for the U.S. market at this facility in the future.

If you plan to resume any manufacturing operations regulated under the FD&C Act, notify this office before resuming your drug manufacturing operations. You are responsible for resolving all deficiencies and systemic flaws to ensure your firm is capable of ongoing CGMP compliance. In your notification to the Agency, provide a summary of your remediations to demonstrate that you have appropriately completed all CAPA.

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 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.

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.

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 refusing admission of articles manufactured at Sichuan Deebio Pharmaceutical Co. Ltd. at 15 Gaocaocun, Xiaohanzhen, Guanghan, Deyang, Sichuan 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 3011139911 and ATTN: Joseph Lambert, Pharm.D.

Sincerely,
/S/

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