**WARNING LETTER**

# Tianjin Darentang Jingwanhong Pharmaceutical Co., Ltd.

**MARCS-CMS 683619 — OCTOBER 30, 2024**

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**Delivery Method:**

Via Email

**Product:**

Drugs

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**Recipient:**

Mr. Xiangqi Zhang

Vice General Manager

Tianjin Darentang Jingwanhong Pharmaceutical Co., Ltd.

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China

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**Issuing Office:**

Center for Drug Evaluation and Research (CDER)

United States

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**Warning Letter** 320-25-08

October 30, 2024

Dear Mr. Zhang:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Tianjin Darentang Jingwanhong Pharmaceutical Co., Ltd., (also known as Tianjin Pharmaceutical Da Ren Tang Group Jing Wan Hong Co., Ltd.), FEI 3006283468, at No. 20 Daming Street, Xiqing, Tianjin, Tianjin, China, from March 18 to 22, 2024.

This warning letter summarizes significant violations of Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

Our investigators documented your firm limited and/or refused an FDA inspection. Under section 501(j) of the FD&C Act, 21 U.S.C. 351(j), your drugs are adulterated in that they have been manufactured, processed, packed, or held in an establishment where the owner or operator has limited inspection and/or refused inspection.

Additionally, because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug product is 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 April 15, 2024, response to our Form FDA 483 in detail.

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

**Limiting the Inspection**

Your firm limited and refused to permit the FDA inspection as follows:

*Limiting Access to Records*

Your firm limited access to manufacturing records that our inspection team was entitled to inspect. For example, during the inspection, FDA investigators requested the process validation report for your over-the-counter (OTC) drug product "**(b)(4)**" and the manufacturing production batch record for Batch **(b)(4)**. Although you translated the documents line by line to the FDA investigators, translated copies provided were unreasonably redacted for the total net weights of components in the production batch record and processing parameters in the process validation report, respectively. In addition, records of equipment qualification for the following units were also redacted: **(b)(4)** tank ID 447, **(b)(4)** tank ID 344, and **(b)(4)** tank ID 264. Redactions included all critical process parameters, such as **(b)(4)**, and corresponding acceptable and recorded ranges.

Your firm provided redacted copies because you stated that you are required by the firm's top management to protect the information included in batch records, process validation studies, and equipment parameters. Your firm's actions during this inspection significantly hindered FDA from fully assessing your compliance with CGMP. When our inspection team explained that your failure to provide the requested records would be documented as a refusal, you acknowledged the refusal.

Our inspection team documented other instances in which your firm limited the inspection by providing some, but not all, of the records requested that FDA had authority to inspect. For example, the inspection team requested the list of corrective actions and preventive actions (CAPAs) initiated from 2016 to 2024; however, you limited the inspection by providing the list of CAPAs issued in 2024 only.

*Limiting Photography*

During the inspection, our inspection team attempted to take photos of the filling machines ID-192, and ID-197, which were observed to be dirty and in an apparent state of disrepair, despite the equipment status being identified as clean. This equipment is currently used to manufacture a drug intended for U.S. distribution. Your management stated that the investigators were not allowed to take photographs of the equipment as part of the inspection. When our inspection team explained that failure to allow photography would be documented as a refusal, you acknowledged the refusal.

*Limiting Access to Areas*

Your management did not permit our inspection team to access the manufacturing room where **(b)(4)** and **(b)(4)** are performed. When our inspection team explained that failure to allow FDA to access and evaluate manufacturing equipment and operations would be documented as a refusal, you acknowledged the refusal.

**Delaying, Denying, Limiting, or Refusing a Drug Inspection**

When an owner, operator, or agent delays, denies, limits, or refuses an inspection, the drugs may be deemed adulterated under section 501(j) of the FD&C Act. See FDA's guidance document: *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug or Device Inspection (June 2024)* at https://www.fda.gov/media/86328/download.

**GMP Violations**

**1. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements (21 CFR 211.67(a)).**

You failed to demonstrate that your cleaning practices are adequate to remove contaminants from equipment used to manufacture your topical drug product, "**(b)(4)**." On March 19, 2024, our investigators observed residues on filling machines ID-192 and ID-197, despite both being identified as clean.

In addition, your filling machines were not adequately maintained and were observed to be in a state of disrepair. For example, the filling machine ID-192 had several missing screws and a broken motor housing panel, and filling machine ID-197 lacked a cover for the **(b)(4)** bowl and was observed with degraded and cracked **(b)(4)** bands apparently holding the equipment together. As such, your equipment was not suitable for their intended use.

In your response, you acknowledge the incomplete cleaning of filling machine ID-192 and state that the equipment's cleaning procedure is revised. You also state that the conditions identified above filling machine ID-197 are repaired.

Your response is inadequate because you did not implement sufficient corrective actions related to the status and cleaning of all equipment used in the manufacture of drugs intended for the U.S. market. You also failed to evaluate the potential impact of your filling machines' condition and inadequate cleaning on the quality of your distributed drug batches.

In response to this letter, provide:

• A CAPA plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of equipment/facilities performance issues, effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing management review.

• A comprehensive, independent retrospective assessment of your cleaning effectiveness to evaluate the scope of cross-contamination hazards. Include the identity of residues, other manufacturing equipment that may have been improperly cleaned, and an assessment whether cross-contaminated products may have been released for distribution. The assessment should identify any inadequacies of cleaning procedures and practices and encompass each piece of manufacturing equipment used to manufacture more than one product.

• A CAPA plan, based on the retrospective assessment of your cleaning program, that includes appropriate remediations to your cleaning processes and practices, and timelines for completion. Provide a detailed summary of vulnerabilities in your process for lifecycle management of equipment cleaning. Describe improvements to your cleaning program, including enhancements to cleaning effectiveness; improved ongoing verification of proper cleaning execution for all products and equipment; and all other needed remediations.

**2. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).**

Based on the limitation of the inspection described above, you failed to provide data to demonstrate that you adequately validated your manufacturing processes used to manufacture your OTC drug product and to demonstrate that your processes are reproducible and controlled to consistently yield drugs of uniform character and quality.

Although you state your manufacturing process is validated and equipment is qualified, you do not submit supporting information.

In response to this letter, provide:

• A complete and unredacted process validation protocol and report for your drug product "**(b)(4)**."

• A complete and unredacted batch record for the most recent batch of "**(b)(4)**" released and shipped to the United States for each drug product configuration (i.e., **(b)(4)**g, **(b)(4)**g, and **(b)(4)**g).

• A complete and unredacted qualification report for the following manufacturing equipment: **(b)(4)** tank ID-447, **(b)(4)** tank ID-344, and **(b)(4)** tank ID-264.

**3. You firm failed to establish required laboratory control mechanisms (21 CFR 211.160(a)), including those related to stability studies (21 CFR 211.166).**

The analytical method used for the release and stability testing of your drug product "**(b)(4)**" is not stability indicating.

Also, your firm has not performed forced degradation studies to identify degradants that may be present in sufficient quantities to require testing during stability studies.

In your response, you commit to conduct an "impact factor" and accelerated test to assess the impact of different factors on your drug product stability. You also committed to test three batches per production schedule.

Your response is inadequate because you did not provide details of your "impact factor" and accelerated test plan and how they relate to the lack of degradation studies. Your plan also fails to include a retrospective evaluation of batches that have been released and are currently within expiry in the U.S. market.

In response to this letter provide:

• A report for the "impact factor" and accelerated tests for the analytical method for U.S. drug product. Include details of any changes implemented and how the results may impact previously analyzed batches.

• A comprehensive assessment and CAPA 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 drug product 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)
  o all procedures that describe these and other elements of your remediated stability program.

• A list of chemical and microbial specifications, including test methods, used to analyze each batch of your drug products before a disposition decision.
  o An action plan and timelines for conducting full chemical and microbiological testing of retain samples to determine the quality of all batches of drug product distributed to the United States that are within expiry as of the date of this letter.
  o A summary of all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug products, take rapid corrective actions, such as notifying customers and product recalls.

**Conclusion**

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of any violations and for preventing their recurrence or the occurrence of other violations.
FDA placed products offered for import into the U.S. from your firm on Import Alert 66-40 on August 20, 2024.

Until FDA is permitted to inspect your facility and confirms compliance with CGMP, we may withhold approval of any new applications or supplements listing your firm as a drug manufacturer. In addition, shipments of articles manufactured at Tianjin Darentang Jingwanhong Pharmaceutical Co., Ltd., No. 20 Daming Street, Xiqing, Tianjin into the United States that appear to be adulterated or misbranded are subject to being detained or refused admission pursuant to section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3).

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

Failure to address any violations may also result in the FDA continuing to refuse admission of articles manufactured at Tianjin Darentang Jingwanhong Pharmaceutical Co., Ltd., No. 20 Daming Street, Xiqing, Tianjin, 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 violations 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 3006283468 and ATTN: Vilmary Negron Rodriguez.

Sincerely,
/S/

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

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