WARNING LETTER

Hubei Kangzheng Pharmaceutical Co., Ltd.

MARCS-CMS 616581 — NOVEMBER 23, 2021

Delivery Method:

Email

Product:

Drugs

Recipient:

Mr. Chen Tianzhong

CEO/General Manager

Hubei Kangzheng Pharmaceutical Co., Ltd.

No. 88 Hexi Jinquan Road
Anlu City Hubei Sheng, 432600
China

Issuing Office:

Center for Drug Evaluation and Research | CDER

United States

Warning Letter 320-22-05

November 23, 2021

Dear Mr. Chen:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Hubei Kangzheng Pharmaceutical Co., Ltd., FEI 3010580682, located at No. 88 Hexi Jinquan Road, Anlu City, Hubei Province, China, from June 16 to 24, 2021.

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).

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).

In addition, pi yen chin is an unapproved new drug in violation of section 505(a) of the FD&C Act, 21 U.S.C. 355(a), and is misbranded under sections 502(x) and (ee) of the FD&C Act, 21 U.S.C. 352(x) and (ee). Introduction or delivery for introduction of such products into interstate commerce is prohibited under

sections 301(d) and (a) of the FD&C Act, 21 U.S.C. 331(d) and (a). These violations are described in more detail below.

We reviewed your June 28, 2021, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

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

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

You failed to demonstrate that your manufacturing process is capable of preventing microbial contamination of your over-the-counter (OTC) drug product, pi yen chin ophthalmic redness reliever drops, containing naphazoline hydrochloride (HCl) 0.1%. For example,

- You manufactured pi yen chin as a non-sterile drug product in a Grade D clean area without appropriate controls to prevent microbial contamination.
- You failed to establish and validate a process that is suitable for the manufacture of a sterile drug product.
- You failed to establish and follow appropriate written procedures for sterilizing equipment used for manufacturing your ophthalmic drug product.
- You failed to establish an adequate system for monitoring environmental conditions to ensure the suitability of the areas used to manufacture your ophthalmic drug product.
- You distributed batches of pi yen chin to the U.S. market without conducting sterility testing or testing for particulate and foreign matter prior to release.

In your response, you stated that because you manufactured and released pi yen chin as non-sterile nasal drops, the requirements for producing a sterile drug product do not apply. You also stated that sterility testing and visual inspection for particulate and foreign matter are not needed. In addition, you stated that environmental monitoring (EM) in the manufacturing area should be conducted **(b)(4)**.

Your response is inadequate. Your drug product is labeled as an ophthalmic and includes the instruction to apply into eyes. Therefore, your interpretation that this drug product is not required to be sterile is incorrect. See 21 CFR 200.50(a)(1).

See FDA's guidance document *Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice* to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing at https://www.fda.gov/media/71026/download (https://www.fda.gov/media/71026/download).

We acknowledge that your firm initiated a voluntary recall for all the batches distributed in the U.S. market within expiry.

In response to this letter, provide:

• A comprehensive risk assessment of all contamination hazards with respect to your aseptic processes, equipment, and facilities, including an independent assessment that includes, but is not limited to:
  o All human interactions within the ISO 5 area
  o Equipment placement and ergonomics
  o Air quality in the ISO 5 area and surrounding room
  o Facility layout
  o Personnel Flows and Material Flows (throughout all rooms used to conduct and support sterile operations)

• A detailed remediation plan with timelines to address the findings of the contamination hazards risk assessment. Describe specific tangible improvements to be made to aseptic processing operation design and control.

• A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle for your **(b)(4)** drug product, along with associated procedures. Describe your program for process performance qualification, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.

• A timeline for performing process performance qualification for your marketed drug product.

• Include your process performance protocol(s), and written procedures for qualification and sterilization of equipment.

• A comprehensive summary of your media fill program that ensures an appropriate simulation of the worst-case conditions of commercial manufacturing. In addition, describe in detail how you examine units for presence of growth and how you perform batch yield reconciliation. Include all related standard operating procedures.

• Smoke studies conducted under static and dynamic conditions to fully evaluate air flow patterns on the aseptic processing line. Provide an independent assessment of the smoke studies.

• Updated EM procedures that include appropriate:
  o Frequency, location, and duration of sampling; sample size; specific sampling equipment and techniques
  o Action and alert limits for each location, and a description of its function and ISO classification
  o Instructions regarding investigation of out-of-limit EM results
  o Identification of microorganisms detected in EM samples

• Appropriate microbiological batch release specifications (i.e., total counts, identification of bioburden to detect objectionable microbes) for your ophthalmic drug product.

• All chemical, physical, and microbial test methods used to analyze your ophthalmic drug products.

2. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

During the inspection, you acknowledged that you do not have a written stability program for your pi yen chin drug product, and were unable to provide data to demonstrate that its chemical, physical, and microbiological properties, including sterility, will remain acceptable throughout the labeled three-year expiry period.

In your response, you stated that you have established a stability protocol to support a three-year expiration date for future drug product batches.

Your response is inadequate. You did not provide the stability protocol and details, including all relevant quality attributes, acceptance criteria, and stability indicating methods.

In response to this letter, provide:

• A comprehensive, independent assessment and corrective action and preventive action (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)

• All procedures that describe these and other elements of your remediated stability program.

3. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

Your firm failed to thoroughly investigate unexplained discrepancies and out-of-specification (OOS) results. For example,

• You did not initiate an investigation when the infrared (IR) spectrum of naphazoline HCl active pharmaceutical ingredient (API) lot **(b)(4)** was found to be different from the standard. You used this API lot to manufacture pi yen chin drug product batches **(b)(4)**, which were distributed to the U.S. market.

• You did not perform an investigation when unknown peaks were detected during release assay testing for batches **(b)(4)**.

In your response, you stated that a new external laboratory IR test result for naphazoline HCl API lot **(b)(4)** conformed to the standard. You also stated that you contacted a qualified laboratory to characterize the unknown peaks for the finished drug product batches.

Your response is inadequate. We acknowledge that you recently initiated a deviation for the IR test result discrepancy involving your API sample. However, you have not provided any scientific justification to invalidate the original OOS result. In addition, you did not initiate an investigation to determine a root cause for the unknown peaks that were detected in your finished drug product batches and implement a CAPA to prevent reoccurrence.

For more information about handling failing, OOS, out-of-trend, or other unexpected results and documentation of your investigations, see FDA's guidance document *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* at https://www.fda.gov/media/71001/download (https://www.fda.gov/media/71001/download).

In response to this letter, provide:

• A retrospective, independent review of all invalidated OOS (including in-process and release/stability testing) results for U.S. product and a report summarizing the findings of the analysis, including the following for each OOS:
o Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error.
o For investigations that conclusively establish laboratory root cause, provide rationale and ensure that all other laboratory methods vulnerable to the same or similar root cause are identified for remediation.
o For all OOS results found by the retrospective review to have an inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, suitability of equipment/facilities, variability of raw materials, process capability, deviation history, complaint history, batch failure history). Provide a summary of potential manufacturing root causes for each investigation, and any manufacturing operation improvements.

4. 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)).

Your cleaning validation and verification program for manufacturing equipment is inadequate to prevent cross contamination. For example,

• Your cleaning validation lacked the study of a **(b)(4)** agent for the equipment train used in the manufacturing of your ophthalmic drug product.

• You used reusable, non-sterile wipes for cleaning equipment used for manufacturing your ophthalmic drug product.

• Apparent rust was observed in the **(b)(4)** that attaches from the **(b)(4)** tank (F-219-01-001) to the filling line (**(b)(4)**), which comes into direct contact with your ophthalmic drug product. In addition, fraying of a conveyor belt on the filling line was observed.

In your response, you stated that you removed the rust from the **(b)(4)** and repaired the fraying parts of the conveyor belt. You also stated that you manufactured pi yen chin as nasal drops, therefore, a study of a **(b)(4)** agent is not required for cleaning validation. In addition, you stated that there is no need to use sterile wipes for equipment cleaning.

Your response is inadequate. You failed to provide a comprehensive CAPA plan to address the deficiencies and prevent recurrence. As previously noted, your pi ye chin drug product is intended for ophthalmic use and must be manufactured accordingly.

In response to this letter, provide:

• Your 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.

Unapproved New Drug and Misbranding Violations

Pi yen chin is a "drug" as defined by section 201(g)(1)(B) of the FD&C Act, 21 U.S.C. 321(g)(1)(B), because it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and/or under section 201(g)(1)(C) of the FD&C Act, 21 U.S.C. 321(g)(1)(C), because it is intended to affect the structure or any function of the body. Specifically, this product is intended for use as an ophthalmic vasoconstrictor (redness reliever).

Examples of claims observed on the pi yen chin product label and labeling that provide evidence of the intended use (as defined in 21 CFR 201.128) of the product include, but may not be limited to, the following:

"Ophthalmic Redness Reliever Drops . . . Drug Facts ...**Uses** Temporarily relieves redness due to minor irritation of eyes."

This ophthalmic vasoconstrictor product is a "new drug" within the meaning of section 201(p) of the FD&C Act, 21 U.S.C. 321(p), because it is not generally recognized as safe and effective (GRASE) for use under the conditions prescribed, recommended, or suggested in its labeling. New drugs may not be introduced or delivered for introduction into interstate commerce without prior approval from FDA, as described in section

505(a) of the FD&C Act, 21 U.S.C. 355(a), unless they are lawfully marketed under section 505G of the FD&C Act (which is not the case for this product, as further described below), or under other exceptions not applicable here. No FDA-approved application pursuant to section 505 of the FD&C Act, 21 U.S.C. 355, is in effect for this drug product, nor are we aware of any adequate and well-controlled clinical studies in the published literature that support a determination that your pi yen chin drug product is GRASE for use under the conditions suggested, recommended, or prescribed in its labeling. Accordingly, this product is an unapproved new drug marketed in violation of sections 505(a) and 301(d) of the FD&C Act, 21 U.S.C 355(a) and 331(d).

Section 505G of the FD&C Act addresses nonprescription drugs marketed without an approved application. Under section 505G(a)(1) of the FD&C Act, 21 U.S.C. 355h(a)(1), category I drugs that were subject to a final monograph (FM) issued under 21 CFR Part 330 are deemed to be GRASE and not "new drugs," as long as they are in conformity with the relevant conditions of use outlined in the applicable FM and comply with all other applicable requirements. We note that OTC ophthalmic products were addressed in the FM for Ophthalmic Drug Products for OTC Use (ophthalmic final monograph), see 21 CFR Part 349.

Under 505G(b)(8) of the FD&C Act, 21 U.S.C. 355h(b)(8), the FM for Ophthalmic Drug Products for OTC Use is deemed to be a final administrative order. However, your pi yen chin product does not conform to the final administrative order, because it is inconsistent with the applicable FM or any other applicable TFM or proposed rule, and it accordingly does not meet the conditions under section 505G(a)(1) of the FD&C Act for marketing without an approved application under section 505.

Specifically, your product's labeled concentration for the active ingredient naphazoline HCl exceeds the allowable concentration for this active ingredient as specified in the ophthalmic FM. Pi yen chin is labeled to contain naphazoline HCl 0.1% and the ophthalmic FM requires that naphazoline HCl be present at 0.01% to 0.03%, per 21 CFR Part 349.18(b). Thus, such a product formulated and labeled as pi yen chin does not conform with the ophthalmic FM described above.

In addition, pi yen chin is misbranded under section 502(x) of the FD&C Act, 21 U.S.C. 352(x), because the product label fails to disclose a complete domestic address or domestic telephone number through which the responsible person may receive a report of a serious adverse event with such drug.

Lastly, this product is misbranded under section 502(ee) of the FD&C Act, 21 U.S.C. 352(ee), because pi yen chin is a nonprescription drug subject to section 505G of the FD&C Act, 21 U.S.C. 355h, but does not comply with the requirements for marketing under that section and is not the subject of an application approved under section 505 of the FD&C Act, 21 U.S.C. 355.

The introduction or delivery for introduction of a misbranded drug into interstate commerce is prohibited under section 301(a) of the FD&C Act, 21 U.S.C. 331(a).

Drug Production Ceased

We acknowledge your commitment to cease production of drugs 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 manufacturing drugs for the U.S. market, notify this office before resuming your operations.

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 your firm on Import Alert 66-40 on November 4, 2021.

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 Hubei Kangzheng Pharmaceutical Co., Ltd., at No. 88 Hexi Jinquan Road, Anlu City 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 or misbranded 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) and are misbranded under section 502 of the FD&C Act, respectively.

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 3010580682 and ATTN: Qin Xu.

Please identify your response with FEI 3010580682.

Sincerely,
/S/

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

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