Zhejiang Hisoar Pharmaceutical Co. Ltd. 8/11/16

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
SIlver Spring, MD 20993

Warning Letter: 320-16-26

Via UPS
Return Receipt Requested

August 11, 2016

Mr. Siwei Yang, President
Zhejiang Hisoar Pharmaceutical Co., Ltd.
100 Waisha Road
Jiaojiang District
Taizhou City, Zhejiang Province
China 318000

Dear Mr. Yang:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Zhejiang Hisoar Pharmaceutical Co. at 100 Waisha Road, Jiaojiang District, Taizhou City, Zhejiang Province, from August 10 to 13, 2015.

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 firm's September 3, 2015, response in detail and acknowledge receipt of your subsequent responses.

Our investigators observed specific deviations including, but not limited to, the following.

1. Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.

During the inspection, FDA investigators discovered a lack of basic laboratory controls to prevent changes to your electronically-stored data and paper records. When you encountered suspect and out-of-specification (OOS) results, you retested samples until you obtained desirable results. You did not investigate, review, or report original results. You relied on incomplete records to evaluate the quality of your drugs and to determine whether your drugs conformed to established specifications and standards.

For example, during the inspection, we reviewed electronic data from your high performance liquid chromatography (HPLC) system. An unknown impurity peak was present when the original three-month stability sample of **(b)(4)** batch **(b)(4)** was run on October 9, 2014. This unknown peak was OOS and would have caused the sample to fail for unknown impurities, but it was not included in the official record for this stability test. Instead, an analyst ran a new sample to obtain a passing result on October 10, 2014, and only the passing result from the second sample was reported in the official record.

In your response, you stated that the analyst thought that the unreported OOS value was related to the reference solution and not the sample being tested. You said the analyst was afraid of making mistakes, and invalidated the data without notifying management. You acknowledged that the data should not have been invalidated without an OOS investigation and committed to revise procedures.

2. Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent manipulation and omission of data.

During the inspection, we observed that your laboratory systems lacked access controls to prevent deletions or alterations to raw data. For example, our investigator reviewed the electronic folder containing data files generated when your firm tested **(b)(4)** batches of **(b)(4)** API for residual solvents by gas chromatography (GC). The investigator compared the file names in the folder with the metadata generated by the Chemstation software you used to operate your GC system, and found that two chromatograms had been deleted from the system. Because there were no controls restricting operators' or supervisors' abilities to alter or manipulate the data, an analyst had completed two runs and deleted the results, and then changed the subsequent file names in the folder where reported data was stored to make it appear that the deleted runs never occurred.

In your response, you stated that two injections were deleted from the system because the analyst believed that an unstable baseline made retaining the files unnecessary. You also confirmed that your software had no access controls and that your analysts had authorization to delete data.

3. Failure to record activities at the time they are performed.

During the inspection, we observed that you did not have worksheets for recording microbial test results and that you failed to contemporaneously document microbial limits test results for **(b)(4)** API batch **(b)(4)**.

In your response, you stated that tests for microbial limits were not routine for **(b)(4)**. The microbiologist documented test methods and results "when she had time," and "there was a possibility that our QC microbiologist documents results by memory instead of document (sic) at time of operation." Your response did not demonstrate the reliability of any data recorded and reported in the past.

In your response to this letter, provide:

- microbial limits retest data of all **(b)(4)** API batches within expiry
- your review of all microbial test methods to verify suitability for intended use

Delay producing records during inspection

Some records that our investigators requested during the inspection were not available for review.

For example, during the inspection of the microbiology laboratory, our investigators requested the completed microbial QC worksheet for **(b)(4)** API batch **(b)(4)**. Your laboratory staff led our investigators out of the lab to another room where, according to your staff, the completed document was located. After approximately 30 minutes outside of the laboratory without being provided the completed worksheet, our investigators reentered the microbiology lab and observed a microbiologist with a partially-completed QC worksheet for the batch in question.

Later, a member of your laboratory staff told our investigators that, contrary to initial statements, the "original" completed QC worksheet never existed.

When an owner, operator, or agent delays, denies, limits, or refuses an inspection, the drugs may be adulterated under section 501(j) of the FD&C Act. We recommend that you review FDA's guidance for industry *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection* at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.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. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.

- A comprehensive retrospective evaluation of the nature of the data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
- A status report for any of the above activities already underway or completed.

Conclusion

Deviations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these deviations, for determining the causes, for preventing their recurrence, and for preventing other deviations.

FDA placed your firm on Import Alert 66-40 on January 20, 2016.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer. Failure to correct these deviations may also result in FDA continuing to refuse admission of articles manufactured at Zhejiang Hisoar Pharmaceutical Co. Ltd., 100 Waisha Road, Jiaojiang District, Taizhou City, Zhejiang Province, into the United States under Section 801(a)(3) of the FD&C Act, 21 U.S.C.

381(a)(3). Under the same authority, articles may be subject to refusal of 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).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your deviations and to prevent their recurrence. 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 or mail your reply to:
Tracie H. Sharp
Compliance Officer
U.S. Food and Drug Administration
White Oak, Building 51 Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3003735151.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research