Zhejiang Hisun Pharmaceutical Co., Ltd. 12/31/15

Department of Health and Human Services

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

Warning Letter: 320-16-06

Via UPS

December 31, 2015

Mr. Hua Bai, CEO
Zhejiang Hisun Pharmaceutical Co., Ltd.
46 Waisha Road
Jiaojiang District
Taizhou City, Zhejiang Province
China 318000

Dear Mr. Bai:

From March 2-7, 2015, investigators from the U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Zhejiang Hisun Pharmaceutical Co., Ltd., 46 Waisha Road, Jiaojiang District, Taizhou City, Zhejiang Province.

We identified significant deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (API).

These deviations cause your drugs to be 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 that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have reviewed your March 27, 2015 response in detail and acknowledge receipt of subsequent responses.

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

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

During the inspection, FDA investigators discovered a lack of basic laboratory controls to prevent changes to your firm's electronically stored data and paper records. Your firm relied on incomplete records to evaluate the quality of your drugs and to determine whether your drugs conformed with established specifications and standards.

Our investigators found that your firm routinely re-tested samples without justification and deleted analytical data. We observed systemic data manipulation across your facility, including actions taken by multiple analysts, on multiple pieces of testing equipment, and for multiple drugs. You are responsible for determining the causes of these deviations, for preventing recurrence, and for preventing other deviations from CGMP.

a. During the inspection, we reviewed the electronic log for high performance liquid chromatography (HPLC) system #36 and determined that the audit trail was disabled on February 6, 2014. One of your analysts executed 80 HPLC injections for assay and impurity tests of validation stability batches **(b)(4)** of **(b)(4)** API.

Because the audit trail was disabled, neither your quality unit nor your laboratory staff could demonstrate that records for these batches included complete and unaltered data. All supporting raw data was discarded, including sample solution dilutions and balance weight printouts. Sample analyses were not recorded in the instrument use logbook. Test results were deleted from the hard drive and all supporting chromatograms were discarded. Audit trail functions were re-enabled on February 8, 2014, and the same analyses were repeated. You submitted the February 8th test results to the FDA in March 2014 in support of Drug Master File (DMF) **(b)(4)**.

During the inspection, we asked the analyst who generated the data submitted to the FDA whether audit trails could be disabled. The analyst stated that another employee, who was no longer with the company, had disabled the audit trails. Your firm could not explain why the audit trail was disabled or why the original data was deleted, nor could you demonstrate whether the original results were within specification.

In your response, you assumed that the original raw data was deleted because a system suitability failure invalidated the data. You acknowledged that the data should not have been invalidated without an investigation of the laboratory event. However, your response is inadequate. There is no evidence to support invalidation of the original data on the grounds of a system suitability failure because your firm deleted all of the original records associated with these analyses.

b. While reviewing the electronic log for HPLC system #28, we determined that two of your analysts deleted portions of HPLC sample sequence 20140221 during assay, impurities, and identity testing for **(b)(4)** API batches **(b)(4)**, and **(b)(4)**.

During the inspection, the investigator reviewed the data package that your firm used for batch release decisions for this drug. This data package included results from 44 HPLC injections. However, the electronic audit trail from the instrument used to generate these results showed that there were a total of 61 injections. Raw data for 17 of the 61 injections was deleted from the reported sequence as if the injections

had never been performed. The investigator later discovered the missing data in a backup folder.

You stated in your response that these specific API batches “were sold to [the] Chinese market” and that you planned to retest batches **(b)(4)** to determine whether they are within specification.

You also stated in your response that the missing portions of the sample sequence were actually injections conducted for training, so product quality was not affected by the deletions. This response is inadequate, because, regardless of the reason for conducting the injections, your laboratory records must retain all original raw data.

c. While reviewing the audit trail on HPLC system #28, we determined that one of your analysts performed trial HPLC injections during assay and impurities testing for batches of **(b)(4)** API (**(b)(4)** and **(b)(4)**). These trial injections were performed on May 4-6, 2014. The data for the sample set was deleted from the system. Testing was not recorded in the instrument use logbook. All supporting electronic raw data was discarded. Testing results for these batches were then recorded on May 7, 2014, when the analyses were repeated using HPLC system #32.

During our inspection, one of your analysts provided the original analyses worksheets to review. According to this analyst, tests were repeated because of poor column efficiency. The analyst neither initiated an investigation of the laboratory event nor documented the original analyses in the instrument use logbook. The analyst did not respond when we asked why the initial chromatograms were deleted.

However, in your written response, you claimed that this analyst later recalled deleting the data (chromatogram) because column inefficiency may have invalidated the data. Your quality unit must review all pertinent analytical data when making batch release decisions. When analysts delete nonconforming test results, the quality unit is presented with incomplete and inaccurate information about the quality of the products. Your response does not demonstrate how your laboratory procedures prevent the deletion of data or how the quality unit ensures that the records relied upon for batch release and other quality review decisions are complete and accurate.

Our concerns about deletion of data are heightened by the significant number of customer complaints for subpotency and out-of-specification (OOS) impurity levels from 2012-2014. We observed data deletion in your laboratory related to assay and impurity levels during this time period. During the inspection, we asked to review your lab’s raw analytical data of the lots associated with four of the 61 complaints. However, you were unable to provide the raw data because it had been deleted. Without raw test data for the lots associated with these complaints, your firm could not adequately investigate the complaints, nor could you expand your investigation to determine whether other lots were affected by the same problems or take corrective actions, such as recalling drugs if appropriate.

We acknowledge your commitment to hire a third-party consultant, set up user access restrictions, and upgrade computerized systems with audit trails. However, simply activating audit trail functions and instituting password controls are insufficient

to correct the broad data manipulation and deletion problems observed at your facility and to prevent their recurrence.

Your management is responsible for the assuring that the scope and extent of the third party audit is adequate, including a full evaluation of sophisticated electronic systems and their potential for manipulation. Your management is also responsible for fully documenting and preserving records.

For more information about handling OOS results and documentation of your investigations, please refer to *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf and *Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance—Records and Reports* at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm

In your response to this letter, provide the following:

- A comprehensive investigation and evaluation. Describe your methodology. Results should include conclusions about the extent of data integrity deficiencies and their root causes, which may involve record control, contemporaneous recording, deletion of data, and other data integrity deficiencies.
- A risk assessment of how the observed deficiencies may affect the reliability and completeness of quality information available for your drugs. Also determine the consequences of your deficient documentation practices on the quality of drugs released for distribution.
- A management strategy that includes a detailed global corrective action and preventive action plan.

Describe the actions you will take, such as contacting your customers, recalling drugs, conducting additional testing and/or adding lots to your stability programs, or other steps to assure the quality of your drugs manufactured under the deficient conditions discussed above.

Describe the actions you will take, such as revising procedures, implementing new controls, training or re-training personnel, or other steps to prevent the recurrence of CGMP deviations, including breaches of data integrity.

2. Failure to conduct appropriate microbiological testing on API batches where microbial quality is specified.

On March 2, 2015, we observed that all 14 culture media plates in incubator #6 were dried out and cracked, which compromised microbial growth promotion and accurate enumeration. These plates were used to test multiple API batches of **(b)(4)** and **(b)(4)** and **(b)(4)**).

Your investigation concluded that deformed glass plates caused the media to crack. In your response, you claimed that the issue was isolated to the 14 culture media plates and that you retested these **(b)(4)** batches.

Your response is inadequate because your investigation did not evaluate the **(b)(4)** other associated batches tested with culture media plates from the same lot

containing deformed glass plates. In addition, we disagree with your claim that these dried culture media plates were isolated to the 14 plates we observed on March 2, 2015. On March 5, 2015, we observed two additional culture media plates in incubator SPX-150, Series No. 061103-811-0003, which also showed signs of drying out.

From 2012 to 2014, several of your customers complained that microbial results were OOS when they tested your API upon receipt. In your response, you concluded that the percentage of customer complaints reporting OOS microbial test results was insignificant. You attributed the customers' OOS microbial results to test methods that differ from your own.

Your response lacks your findings and corrective actions from your recent investigation of dried out and cracked culture media plates. For example, you did not retest the batches that received OOS microbial complaints, even after we pointed out this deficiency. You lack scientific justification to conclude that your customers' OOS findings are inaccurate or insignificant.

In your response to this letter, provide the following:

- An accelerated timeline for completing retroactive microbial testing of all potentially-compromised batches via an independent laboratory, and a commitment to respond with all results promptly.
- Your review of all microbial test methods to ensure they are suitable for their intended use.
- A detailed update on whether your firm has implemented any further risk mitigations, such as purchasing prepared culture plates from qualified outside vendors.
- Your improved deviation and corrective action and preventive action management procedure.
- Documentation of all changes implemented as a result of your review and remediation of these issues.

Access to information during inspection

We note that some records we requested during the inspection were not provided in a timely manner.

During the inspection, an analyst removed a USB thumb drive from a computer controlling an HPLC. When asked to provide the drive, the analyst instead exited the room with the thumb drive. After approximately 15 minutes, management provided our investigator with what they asserted was the USB thumb drive in question. It is impossible to know whether management provided the same USB thumb drive that the analyst had removed.

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

Conclusion

Deviations cited in this letter are not intended as an all-inclusive list. Although we acknowledge and appreciate your significant efforts to implement corrective actions to date, FDA will conduct a follow-up inspection following the complete implementation of global corrective actions.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of drugs produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov so that we 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 in the manufacture of your drug under 21 U.S.C. 356C(a)(1), 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 complete all corrections and FDA confirms your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Because of the findings of the FDA inspection described herein, your firm was placed on Import Alert 66-40 on September 9, 2015. If you fail to correct these deviations, FDA may continue to refuse admission of articles manufactured at Zhejiang Hisun Pharmaceutical Co., Ltd., 46 Waisha Road, Jiaojiang District, Taizhou City, Zhejiang Province, under Section 80l(a)(3) of the FD&C Act, 21 U.S.C. 38l(a)(3) as the manufacturing methods and controls 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).

Within 15 working days of receipt of this letter, please notify this office, in writing, of the specific steps that you have taken to correct and prevent the recurrence of deviations detailed in this letter.

If you cannot complete corrective actions within 15 working days, state your reasons for the delay and the date by which you will have completed the corrections. If you no longer manufacture or distribute the drugs at issue, provide the date(s) and reason(s) you ceased production. Send 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

Please identify your response with FEI 3007719313.

Sincerely,
/S/
Thomas J. Cosgrove, J.D.

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