Zhejiang Huahai Pharmaceutical 11/29/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter: 320-19-04

November 29, 2018

Mr. Jun Du
Executive Vice President
Zhejiang Huahai Pharmaceutical Co., Ltd.
Coastal Industrial Zone, Chuannan No. 1 Branch No. 9
Donghai Fifth Avenue, Linhai, Taizhou Zhejiang 317016
CHINA

Dear Mr. Du:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Zhejiang Huahai Pharmaceutical Co., Ltd., located at Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai Fifth Avenue, Linhai, Taizhou Zhejiang, from July 23 to August 3, 2018.

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 August 26, 2018, response 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 of your quality unit to ensure that quality-related complaints are investigated and resolved.

Valsartan API

Your firm received a complaint from a customer on June 6, 2018, after an unknown peak was detected during residual solvents testing for valsartan API manufactured at your facility. The unknown peak was identified as the probable human carcinogen N-nitrosodimethylamine (NDMA). Your investigation (DCE-18001) determined that the presence of NDMA was caused by the convergence of three process-related factors, one factor being the use of the solvent **(b)(4)**). Your investigation concluded that only one valsartan manufacturing process (referred to as the **(b)(4)** process in your investigation) was impacted by the presence of NDMA.

However, FDA analyses of samples of your API, and finished drug product manufactured with your API, identified NDMA in multiple batches manufactured with a different process, namely the **(b)(4)** process, which did not use the solvent **(b)(4)**. These data demonstrate that your investigation was inadequate and failed to resolve the control and presence of NDMA in valsartan API distributed to customers. Your investigation also failed:

• To include other factors that may have contributed to the presence of NDMA. For example, your investigation lacked a comprehensive evaluation of all raw materials used during manufacturing, including **(b)(4)**.

• To assess factors that could put your API at risk for NDMA cross-contamination, including batch blending, solvent recovery and re-use, shared production lines, and cleaning procedures.

• To evaluate the potential for other mutagenic impurities to form in your products.

Our investigators also noted other examples of your firm's inadequate investigation of unknown peaks observed in chromatograms. For example, valsartan intermediates **(b)(4)** and **(b)(4)** failed testing for an unknown impurity (specification ≤ **(b)(4)**%) with results of **(b)(4)**% for both batches. Your action plan indicated that the impurity would be identified as part of the investigation; however, you failed to do this. In addition, no root cause was determined for the presence of the unknown impurity. You stated that you reprocessed the batches and released them for further production.

Your response states that NDMA was difficult to detect. However, if you had investigated further, you may have found indicators in your residual solvent chromatograms alerting you to the presence of NDMA. For example, you told our investigators you were aware of a peak that eluted after the **(b)(4)** peak in valsartan API residual solvent chromatograms where the presence of NDMA was suspected to elute. At the time of testing, you considered this unidentified peak to be noise and investigated no further. Additionally, residual solvent chromatograms for valsartan API validation batches manufactured using your **(b)(4)** process, with **(b)(4)** in 2012 ((**b)(4)**, and **(b)(4)**) show at least one unidentified peak eluting after the **(b)(4)** peak in the area where the presence of NDMA was suspected to elute.

Your response also states that you were not the only firm to identify NDMA in valsartan API. In your case, FDA analyses of samples identified amounts of NDMA in valsartan API manufactured at your firm that were significantly higher than the NDMA levels in valsartan API manufactured by other firms. FDA has grave concerns about the potential presence of mutagenic impurities in all intermediates and API manufactured at your facility, both because of the data indicating the presence of impurities in API manufactured by multiple processes, and because of the significant inadequacies in your investigation.

In response to this letter:

• Submit risk assessments for all APIs and intermediates manufactured at your facility for the potential presence of mutagenic impurities.

• Provide an update on investigations and CAPA plans initiated to address the presence of NDMA and other potential mutagenic impurities in all APIs manufactured at your firm.

• Provide a thorough, independent assessment of your overall system for investigating deviations, discrepancies, out-of-specification (OOS) results, complaints, and other failures. In addition, provide a retrospective review of all distributed batches within expiry to determine if your firm released batches that did not conform to established specifications or appropriate manufacturing standards.

• Provide test results for all **(b)(4)** and intermediates for the presence of NDMA, N-Nitrosodiethylamine (NDEA), and other potentially mutagenic impurities.

***(b)(4)** API*

Your firm received a customer complaint on September 13, 2016, concerning **(b)(4)** API batches (**(b)(4)** and **(b)(4)**) that exceeded the specification for **(b)(4)** (≤ **(b)(4)**ppm). **(b)(4)** has been classified as a probable human carcinogen. Your customer's test results conflicted with your **(b)(4)** test results, which showed the two batches meeting the specification upon release. Your complaint investigation (CC-16008) identified no clear laboratory error, and no anomalies were detected during the production of the batches. Your investigation failed to evaluate other **(b)(4)** API batches to determine if the presence of excess **(b)(4)** was an adverse trend. For example, **(b)(4)** batches **(b)(4)**, and **(b)(4)** were OOS for **(b)(4)** because of production errors; however, they were not discussed in your complaint investigation.

Your response states that **(b)(4)** API batches **(b)(4)** and **(b)(4)** were returned, reprocessed, and released to customers in non-U.S. markets.

Your response also states that in August 2017 you implemented a new **(b)(4)** test method that uses a **(b)(4)** LC-MS/MS method, to replace the **(b)(4)** LC-MS method that was prone to erroneous OOS results. You failed to verify the reliability of the **(b)(4)** results for all **(b)(4)** API batches (including **(b)(4)** batch **(b)(4)**) originally released using your **(b)(4)** LC-MS method, which you indicated was inferior to your updated method.

In response to this letter, provide:

• A risk assessment for all **(b)(4)** API batches manufactured within expiry.

• A revised complaint handling procedure and details of any further controls your facility has implemented to ensure that all complaints are adequately documented and thoroughly investigated.

• Procedures for accepting and reprocessing returned drugs.

• Results of **(b)(4)** testing of all **(b)(4)** API batches released to the U.S. market using your updated **(b)(4)** LC-MS/MS **(b)(4)** test method.

2. Failure to evaluate the potential effect that changes in the manufacturing process may have on the quality of your API.

In November 2011 you approved a valsartan API process change (PCRC - 11025) that included the use of the solvent **(b)(4)**. Your intention was to improve the manufacturing process, increase product yield, and lower production costs. However, you failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process. Specifically, you did not consider the potential for mutagenic or other toxic impurities to form from **(b)(4)** degradants, including the primary **(b)(4)** degradant, **(b)(4)**. According to your ongoing investigation, **(b)(4)** is required for the probable human carcinogen NDMA to form during the valsartan API manufacturing process. NDMA was identified in valsartan API manufactured at your facility.

You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change. You are responsible for developing and using suitable methods to detect impurities when developing, and making changes to, your manufacturing processes. If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients.

Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and that that your process development study was adequate. We disagree. We remind you that common industry practice may not always be consistent with CGMP requirements and that you are responsible for the quality of drugs you produce.

Your response does not describe sufficient corrective actions to ensure that your firm has adequate change management procedures in place: (1) to thoroughly evaluate your API manufacturing processes, including changes to those processes; and (2) to detect any unsafe impurities, including potentially mutagenic impurities. For FDA's current thinking on control of potentially mutagenic impurities, see FDA's guidance document M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk for approaches that FDA considers appropriate for evaluating mutagenic impurities, at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf.

In response to this letter, provide:

• Detailed revised change management procedures describing how your firm will assess and control all impurities, including mutagenic impurities, in API and intermediates manufactured at your facility.

• Detailed procedures describing how your firm establishes impurity profiles for products manufactured at your firm. These procedures should contain instructions for comparing at appropriate intervals against the impurity profile in the regulatory submission, or for comparing against historical data, to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.

• A retrospective analysis of other API and intermediates manufactured at your firm to determine if they were adequately evaluated for anticipated and unanticipated impurities, including potentially mutagenic impurities.

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 and 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 fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Quality Systems Guidance

Your firm's quality systems are inadequate. For guidance on establishing and following CGMP compliant quality systems, see FDA's guidances: *Q8(R2) Pharmaceutical Development*, at https://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf; *Q9 Quality Risk Management*, at https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf; and *Q10 Pharmaceutical Quality System*, at https://www.fda.gov/downloads/drugs/guidances/ucm073517.pdf.

Additional API CGMP guidance

FDA considers the expectations outlined in ICH Q7 in 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/downloads/Drugs/.../Guidances/ucm073497.pdf.

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.

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.

FDA placed your firm on Import Alert 66-40 on September 28, 2018.

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 Huahai Pharmaceutical Co., Ltd., located at Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai Fifth Avenue, Linhai, Taizhou Zhejiang, 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:

Rory K. Geyer
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4235
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3003885745.

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