Shanghai Desano Chemical Pharmaceutical Co., Ltd. 6/16/16

Department of Health and Human Services

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

Warning Letter: 320-16-18

Via UPS
Return Receipt Requested
June 16, 2016

Ms. Ying Kan
President
Shanghai Desano Chemical Pharmaceutical Co., Ltd.
1479 Zhangheng Road
Zhangjiang High-Tech Park
Shanghai 201203
China

Dear Ms. Kan:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Shanghai Desano Chemical Pharmaceuticals Co., Ltd. at No.417 Binhai Road, Laogang Town, Pudong District, Shanghai, from May 4–7, 2015.

This warning letter reviews 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 May 22, 2015, response in detail and acknowledge receipt of your subsequent responses.

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

1. Failure to have laboratory control records that include complete data derived from all tests conducted to ensure compliance with established specifications and standards.

Your laboratory personnel conducted "unofficial" testing without appropriate documentation, justification, and investigation.

The original, unofficial analyses were stored in a separate "Test" folder and were not part of the official quality control records. Our inspection found that your firm performed circa 8,400 of these unofficial chromatographic analyses between 2012 and 2014. According to your SOP-B-QC-022-01, *Instrument Use Standard Operating Procedure*, analysis of samples must be documented. The volume of data in these auxiliary "Test Folders" suggests that performing unofficial analyses is a common practice at your facility.

Your quality unit must review all pertinent analytical data when making batch release decisions in order to determine batch quality. During the inspection, a member of your staff told our investigator that you were now in the process of reviewing these unofficial analyses.

In your post-inspection response, you indicated that some of the analyses were related to out-of-specification (OOS) investigations, and you would review all of the approximately 8,400 injections by December, 2015. You also committed to continue reviewing all analytical data generated by your laboratory and to retrain employees.

Your response is inadequate because it lacks a comprehensive assessment of your laboratory practices and management oversight. Your response did not provide the extent of the unofficial analyses throughout your laboratory and the products affected.

2. Failure to ensure all production deviations are reported and evaluated, and that critical deviations are investigated and the conclusions are recorded.

Your firm failed to investigate and document a number of production deviations. During the inspection, our investigator found many electronic logs of production deviations in a folder titled "GMP Anomalies." Our investigator randomly selected folder 01/2014 from your electronic log, compared it to your firm's official deviation logbook for 2014, and found that the deviations in the "GMP Anomalies" folder were not investigated or reported in the official deviation logbook.

Production deviations included, but were not limited to:

- out-of-limit temperature readings for critical process parameters
- incomplete batch records
- batch records pre-filled before manufacturing
- failure to record temperature, humidity, and pressure
- failure to add portions of raw materials during manufacturing

In your response, you attribute the root cause of these failures to deficient procedures and operators' errors. You stated that you will conduct a retrospective review for all deviations made in the **(b)(4)** products "Production Coordination Log" from January 2014 through April 2015, to determine whether any CGMP deviations may have compromised product quality.

Your response is inadequate as your protocol did not include a thorough review of complaints to determine if undocumented deviations could be linked to product quality defects.

Conclusion

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

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 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. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

After you receive this letter, you have 15 business days to respond to this office in writing. Specify what you have done since our inspection to correct deviations and to prevent their recurrence.

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. In response to this letter, provide the following.

1. 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 all data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential batches were identified should evaluate all data integrity lapses.

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

3. 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 that are already underway or completed.

If you cannot complete corrective actions within 15 working days, state your completion date and reasons for delay.

Until you completely correct all deviations and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as an API manufacturer. Failure to correct these deviations may also result in FDA refusing admission of articles manufactured at Shanghai Desano Chemical Pharmaceutical Co., Ltd., Shanghai, China, 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).

Send your reply to:

Cesar E. Matto
Compliance Officer
U.S. Food and Drug Administration
White Oak, Building 51, Room 4359
10903 New Hampshire Ave
Silver Spring, MD 20993
USA

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov

Please identify your response with FEI 3006895951.

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

More in 2016 (/ICECI/EnforcementActions/WarningLetters/2016/default.htm)