Chongqing Lummy Pharmaceutical Co. Ltd. 6/21/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS

Warning Letter 320-16-19

Return Receipt Requested

June 21, 2016

Mr. An Lin
General Manager
Chongqing Lummy Pharmaceutical Co., Ltd.
No. 2 the 4th Branch Road, Hua'nan Road
Changshou District
Chongqing, 401221
China

Dear Mr. An Lin:

The U.S. Food and Drug Administration (FDA) inspected your Chongqing Lummy Pharmaceutical Co., Ltd. facilities, Chayuan at No. 8 Rose Road, Nan'an District Chongqing, and Changshou at No. 2 the 4th Branch Road Hua'nan Road, Chongqing, from March 14–16, 2016.

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 March 31, 2016, response in detail and acknowledge receipt of your subsequent responses.

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

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

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

Our investigator found that your firm failed to prevent data manipulation on multiple computerized analytical systems. Your firm re-tested samples without justification and deleted raw analytical data from computerized systems. You are responsible for determining the causes of these deviations, for preventing their recurrence, and for preventing other deviations from CGMP.

a. Our investigator's review of the audit trail for the residual solvent stability testing indicated that an analyst manipulated your computerized gas chromatography (GC) system to falsify residual solvent stability results for multiple batches of **(b)(4)** API distributed to the U.S.

For example, on March 4, 2016, your analyst set the GC personal computer (PC) clock back to make it appear as if testing had been done seven months earlier – on August 3, 2015. The analyst then performed five different injections to produce falsified results for long term stability 25C/65% RH 12 month time-point residual solvent testing for finished API lot **(b)(4)**. The analyst deleted the first four backdated results and reported only the results of the fifth and final injection as passing in the quality control data package. Your quality unit relied on this incomplete data package to evaluate the quality of this lot of API and determine whether it was within specification. Our investigator observed that long-term stability results for at least five other lots of **(b)(4)** API were falsified using this technique of setting back the clock on the GC personal computer and then performing multiple injections until favorable results were obtained. Your firm failed to prevent analysts' access to manipulate and delete laboratory data. In addition, your laboratory equipment lacked software controls to assure data integrity.

b. Our investigator's review of the audit trails for the high performance liquid chromatography (HPLC) system indicated that, just prior to the completion of certain stability analyses for **(b)(4)** API, analysts routinely aborted the ongoing tests to prevent your HPLC system from recording some assay and impurities test data.

Your HPLC system, controlled by Chemstation software, was configured to automatically delete the results if a test was aborted prior to completion. Our investigator's review of the system's limited audit trails indicated that when an analyst aborted assay and impurities tests, the partial results from the aborted tests were automatically deleted from your computerized HPLC system's records.

For example, our investigator reviewed a data file audit trail that showed that during impurities analysis of an 18-month stability sample of **(b)(4)** crude batch **(b)(4)**, your analyst aborted the injection before the test was complete, set the HPLC PC clock back, and then repeated the injection. Your analyst only reported the results of the second injection in the quality control data package. This test, for which your computerized system did not retain original data about the quality of your **(b)(4)** crude, had been performed as part of a stability study your firm executed in response to FDA's previous inspection in July, 2013. Our investigator observed the same technique for data manipulation and deletion in multiple other impurities analyses for **(b)(4)**.

When our investigator asked your staff about these instances of falsification and manipulation, your quality control manager stated that your firm "forgot" to perform stability testing and therefore created falsified results for each missed time point by manipulating the controlling PC clock.

In your response to the FDA-483, you stated that you would upgrade your GC and HPLC software, and revise standard operating procedures (SOPs) for handling analytical data and train your staff on these revised SOPs. You also indicated that you would retrospectively review analytical data, and if data manipulation was identified, conduct a risk assessment to determine whether "re-testing actions are required."

Your response is inadequate because you have not demonstrated how the software upgrades, SOP revisions, and training will correct the broad data manipulation and deletion problems observed at your facility and to prevent their recurrence. Your quality unit must review all pertinent analytical data when making decisions about the quality of your drugs and when evaluating their conformance to established specifications. When your electronic systems permit the falsification and manipulation of data to obscure or delete test results, the quality unit is presented with incomplete and inaccurate information about the quality of your drugs. Your response does not demonstrate how your proposed software upgrades, revised procedures, or training will prevent the deletion of data or how your quality unit ensures that the records relied upon for batch release and other quality review decisions are complete and accurate

2. Failure to document manufacturing operations at the time they are performed.

During the inspection, our investigator reviewed 20 executed batch manufacturing records and found that most of them contained similar or identical entries that could not be adequately explained. For example, our investigator examined batch records for **(b)(4)** different batches of **(b)(4)** API manufactured between January and February 2015. All **(b)(4)** batch records indicated that certain process steps or measurements had transpired at exactly the same time for each different batch. When our investigator asked your production supervisor to explain why the time stamps were identical on these records, the production supervisor stated that the full manufacturing process takes **(b)(4)** to complete, and that all batch records are kept in the production area until **(b)(4)** lots are completed. The production supervisor stated

that the operators most likely did not record the actions at the time they were performed but rather completed batch records in groups.

In your response to the FDA-483, you indicated that you would not release any new **(b)(4)** API to the U.S. market until "FDA deems our facility acceptable." You also indicated that you had reviewed all manufacturing data and found "some batches have the same falsification" and committed to revising your batch manufacturing record template and SOPs, and retraining your staff.

Your response was inadequate. Neither revised templates and procedures nor retraining your staff alone can prevent operators from continuing to falsify batch manufacturing records.

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 in all your facilities.

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.

After you receive this letter, you have 15 working days to respond to this office in writing. Specify what you have done since our inspection to correct your 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 your firm's March 31, 2016, response, you admitted that personnel were not properly trained and that you planned to hire a consultant to perform comprehensive CGMP training. You committed to recall your API in your April 29, 2016, correspondence to the Agency. We have since received confirmation from your **(b)(4)** sales agent that you did initiate a voluntarily recall of **(b)(4)** of **(b)(4)** API from your U.S. customers. We strongly recommend that you retain a qualified consultant to assist in your remediation. 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 the testing and manufacturing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential lapses 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.

Because of the findings of the FDA inspection described in this letter, your firm was placed on Import Alert 66-40 on April 19, 2016.

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 continuing to refuse admission of articles manufactured at Chongqing Lummy Pharmaceutical Co., Ltd. facilities, Chayuan at No. 8 Rose Road, Nan'an District, Chongqing, and Changshou at No. 2 the 4th Branch Road Hua'nan Road, Chongqing, 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:

Towanda Terrell
Consumer Safety Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

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

Please identify your response with FEI 3006560479 and 3011957289.

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