Zhuhai United Laboratories Co. Ltd. 6/27/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-61

June 27, 2018

Ms. Shirley Cai
Chief Executive Officer
Zhuhai United Laboratories Co., Ltd.
No. 2428 Anji Road
Sanzao Town, Jinwan District
Zhuhai, Guangdong 519040
China

Dear Ms. Cai:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Zhuhai United Laboratories Co., Ltd., at No. 2428 Anji Road, Sanzao Town, Jinwan District, Zhuhai, from September 11 to 15, 2017.

This warning letter summarizes significant deviations from CGMP for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drugs 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 October 6, 2017, response in detail.

During our inspection, our investigators observed specific deviations including, but not limited to, the following.

1. Failure to adequately investigate and document out-of-specification results according to a procedure.

Our review of your out-of-specification (OOS) investigations found that you lacked adequate procedures for investigating, and scientific justification to invalidate, OOS results.

OOS Results for Assay
You initiated an investigation of an initial OOS assay result for **(b)(4)** batch **(b)(4)**, which was found to be significantly below specification (**(b)(4)**–**(b)(4)**%). You also initiated an investigation of an initial OOS assay result for **(b)(4)** batch **(b)(4)**, which also yielded a test result below specification (**(b)(4)**–**(b)(4)**%).

In both cases, your brief investigations found no anomalies and only stated that it was possible that the sample glassware was not thoroughly cleaned. Although you did not identify a laboratory error and lacked scientific justification, you invalidated the OOS results. Your firm released both batches based on passing retests.

Your acceptance of the passing results based on an assumed laboratory error was insufficient to invalidate the original failing result and conclude the investigation.

Re-analysis of the actual solutions, test units, and glassware is an integral part of an investigation to determine whether a laboratory error may have occurred. This assessment, in tandem with hypothesis testing if initial re-examinations do not reveal a root cause, is instrumental in determining whether there was a causative laboratory error. Whenever a laboratory investigation lacks conclusive evidence of laboratory error, it is essential that the investigation extends to a thorough investigation of potential manufacturing causes.

Your response acknowledged that there was “no scientific justification or studies performed to evaluate or prove this hypothetical root cause.”

Since our inspection, your indicated that you have shown that the API may degrade in the presence of residual detergent in glassware. However, your response did not include your study data.

OOS Results for Residual Solvent
You initiated investigation P201611001 for an initial OOS result of **(b)(4)** parts per million (ppm) in your **(b)(4)** residual solvent test (specification: not more than **(b)(4)** ppm) for **(b)(4)** API batch **(b)(4)**. The investigation did not reveal laboratory testing anomalies. You tested another sample preparation three times and obtained results very close to the specification upper limit (**(b)(4)**, and **(b)(4)** ppm). You invalidated the initial failing result, stating that your statistical analysis showed a significant difference between the original value and the retest results. Your investigation lacked further assessment of the root cause of the failing result.

You released the batch to use as an intermediate in your in-house production of **(b)(4)** batches of **(b)(4)** API (batches **(b)(4)**).

It is not appropriate to use an “outlier test” to invalidate your API test results. Such statistical treatments do not identify the cause of an extreme observation and are only of informational use. In this case, your investigation included multiple retests that were near the upper limit of **(b)(4)** ppm, similar to the original OOS result.

Furthermore, your OOS investigation procedure, Q0100012.001, was inadequate because it did not adequately address the need to retest the original sample and specify when a new sample should be tested.

We acknowledge receipt of your revised OOS investigation procedure. However, your response is inadequate because it does not meet CGMP. Your response stated that you can use an outlier test in determining whether to "waive the requirement for conducting appropriate laboratory investigation to determine definitive or potential root cause(s) for the atypical result(s)." It is inappropriate for your procedure to permit waiver of this requirement. Your OOS procedure should specify that outlier tests cannot be used for anything other than auxiliary, informational purposes.

Your response also indicated that your firm was retrospectively assessing effects of previously-reported OOS results on your products. However, your response did not provide related records to document your review or summarize findings. It is unclear whether the retrospective review included an evaluation of your use of the statistical outlier test to invalidate OOS results.

In response to this letter:

- Provide a retrospective review of all invalidated OOS results obtained for products on the U.S. market. Assess whether the scientific justification and evidence was conclusive. For investigations that established the laboratory root cause conclusively, determine the adequacy of the corrective action and preventive action (CAPA) plan and ensure the other laboratory methods vulnerable to the same root cause have been identified for remediation. For any OOS results that had an inconclusive or no root cause identified in the laboratory, include a thorough review of production, such as batch manufacturing records, adequacy of manufacturing steps, process capability, deviation history, and batch failure history. Provide a CAPA plan that identifies the potential manufacturing root causes for each such investigation. Include process improvements where appropriate.
- Evaluate all instances in which a statistical outlier test was used to invalidate OOS results. Determine the potential effect on drug quality.
- Assess your overall system for investigating OOS results. Provide a CAPA plan to improve the quality of OOS investigations. Your CAPA should ensure that your revised OOS investigations procedure includes improved quality unit oversight of laboratory investigations, identification of adverse laboratory control trends, and investigation of potential manufacturing causes when a laboratory cause cannot be conclusively identified.
- Comprehensive independent assessment of your overall system for investigations of deviations, discrepancies, complaints, OOS results, and failures. Your CAPA should include, but not be limited to, improvements in investigation competencies, root cause analysis, written procedures, and quality unit oversight. Also include your process for evaluating CAPA effectiveness.

For more information about handling failing, out-of-specification, out-of-trend, or other unexpected results and documentation of your investigations, see FDA's guidance document, *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*, at **https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf)**.

2. Failure of your quality unit to ensure that critical deviations are investigated and resolved.

You did not adequately investigate findings from your February 2015 retrospective review of analytical chromatography data irregularities (e.g., data deletion, sample trial injections, and missing audit trails). You did not sufficiently expand the scope of your limited review to a larger data set when you found significant data integrity lapses. Your investigation was also insufficient because your corrective actions failed to prevent recurrence of major data integrity deviations. For example, our investigators found that your firm deleted the initial chromatographic injection of **(b)(4)** API, batch **(b)(4)**, during batch release testing performed several months after the retrospective investigation.

Your response stated that you performed a further retrospective review (protocol SD-Q0100011.000) of analytical chromatographic data and found further residual solvents results with inappropriate integration, system suitability testing data showing non-consecutive injections of the reference solution, and repeat injections. Your response was inadequate because you did not include sufficient details to demonstrate that you confirmed the validity of initial test results. Such detail would include retest sample testing dates and results, comparison of retest data to original data, and your "comprehensive review records" for the batches included in the assessment. Your response also lacked an assessment of the root cause of data integrity breaches and corrective actions for any products that failed to meet specifications.

In response to this letter, provide:

- a copy of the deviation investigation, GOV-2017001, initiated in response to our inspectional findings;
- completed reports for all review stages in your retrospective review (protocol SD-Q0100011.000) including related annex documents; and
- the additional information requested in the Data Integrity Remediation section of this letter.

Additional Concerns Related to Aseptic Processing
Our investigators found additional examples of incomplete data relating to the sterile manufacturing operations evaluated as part of our pre-approval inspection. For instance, your firm failed to maintain electronic data documenting decontamination cycles for the grade A area of workshop **(b)(4)** where you aseptically manufacture sterile powders. Your firm overwrote the electronic data and kept only a cursory written record.

You also did not assure reliability of electronic data for monitoring non-viable particles in your manufacturing areas. Our investigators observed that you disabled the electronic audit trail function for your non-viable particle monitoring system for grade A and B areas of workshops **(b)(4)** and **(b)(4)** on at least two days in August 2017 when sterile API was manufactured. Also, data files containing particle counts had been modified with no indication of who made the changes or what was modified.

In your response, you provided a review of these findings. Your firm committed to assess the effects on your products of any additional insufficient non-viable particulate monitoring records since the last FDA inspection in March 2015. Your response was inadequate because you did not provide sufficient data to support your conclusions, or commit to a more comprehensive CAPA to assess data systems integrity.

Our inspection also revealed poor aseptic processing operation behaviors. In response to this letter, provide:

- Your plan to assure appropriate aseptic practices and cleanroom behavior during production. Include specific steps to ensure routine supervisory oversight for all production batches. Also describe the frequency of quality assurance oversight during aseptic processing and other operations.
- Comprehensive identification of all contamination hazards with respect to your aseptic processes, equipment, and facilities. Provide a risk assessment that covers all human interactions with the ISO 5 area, equipment placement and ergonomics, air quality in the ISO 5 area and surrounding room, facility layout, personnel flow, and material flow. Also include a detailed CAPA plan, with timelines, to address the findings of the contamination hazards risk assessment.

Also, see FDA's guidance document, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing, at **https://www.fda.gov/downloads/Drugs/Guidances/ucm070342.pdf (https://www.fda.gov/downloads/Drugs/Guidances/ucm070342.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. In response to this letter, provide:
A. A comprehensive investigation into the extent of the inaccuracies in data, records and reporting, including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your 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. The detailed CAPA plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm, including all laboratory data, manufacturing records, and all data submitted to FDA. Part of this CAPA plan should be focused on remediating vulnerabilities in the design and controls (con-figurations, administrative rights, oversight, etc.) of your computer systems.

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 to assist your firm in meeting CGMP requirements. We also recommend that the qualified third party perform a comprehensive systems audit of your entire operation for CGMP compliance (including data integrity), and evaluate the completion and effectiveness of your corrective actions and preventive actions.

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.

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.

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 refusing admission of articles manufactured at Zhuhai United Laboratories Co., Ltd., at No. 2428 Anji Road, Sanzao Town, Jinwan District, Zhuhai, 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 (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)** or mail your reply to:

Ms. Carrie Ann Plucinski
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 3006531950.

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

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