Zhejiang Ludao Technology Co., Ltd. 2/23/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-37

February 23, 2018

Mr. Wang Xiaobing
General Manager
Zhejiang Ludao Technology Co., Ltd.
No. 5 Industry Road, Hairun Street, Sanmen County
Taizhou 317100
China

Dear Mr. Xiaobing:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Zhejiang Ludao Technology Co., Ltd., No. 5 Industry Road, Hairun Street, Sanmen County, Taizhou, from August 14 to 18, 2017.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products 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 September 11, 2017, response in detail and acknowledge receipt of subsequent correspondence.

During our inspection, our investigator observed specific violations including, but not limited to, the following.

1. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

Your firm lacks basic laboratory controls to prevent changes to paper and electronic records for your over-the-counter (OTC) drug products. You were not able to provide analytical test data for three batches of **(b)(4)** spray and one batch of **(b)(4)**. We found that you created certificates of analysis (COA) for these four batches before they were manufactured and tested.

When questioned, your firm acknowledged falsifying the analytical test results on the COA you used to support release and distribution of **(b)(4)** spray and **(b)(4)** drug products to the United States.

In addition, we found three electronic data files in the electronic recycle bin of the stand-alone HPLC system you used to test finished drug product **(b)(4)** spray. Because this instrument lacks back-up and audit trail capabilities, we could not determine how frequently test data obtained prior to "official" batch testing was discarded. You were unable to explain why these electronic files were deleted.

CGMP-related data must be retained by a laboratory to enable appropriate assessments and decisions by the quality unit regarding batch disposition and to demonstrate ongoing control.

In your response, you provided a revised procedure that requires retention of all test-related records and implements routine data review. Your response also committed to upgrading your analytical instrumentation to comply with CGMP requirements. However, your response was insufficient.

You did not perform a retrospective evaluation of the scope of poor data retention practices in other electronic data systems and assess the potential impact on your drug products. Your response also failed to provide details about the audit trail capability or adequately describe validation of the new HPLC system. See the Data Integrity Remediation section of this letter below.

2. Your firm failed to conduct at least one test to verify the identity of each component of a drug product. Your firm also failed to establish the reliability of component supplier analyses on which you rely in lieu of certain tests through appropriate validation of supplier's test results at appropriate intervals (21 CFR 211.84(d)(1) and (2).

You lacked identity testing of incoming lots of **(b)(4)** and **(b)(4)** active pharmaceutical ingredients (API) used to manufacture **(b)(4)** spray and **(b)(4)** OTC drug products. Your firm also failed to perform adequate testing to validate the reliability of your API suppliers' COA to ensure conformance with all appropriate written specifications for purity, strength, and quality.

In your response, you stated that a third-party lab will test each batch of API received for identity and that you will confirm the supplier's COA **(b)(4)**. Your response is inadequate. You did not sufficiently address your program for testing incoming components. You did not provide test results demonstrating that each of your incoming components was verified against your supplier's COA.

In response to this letter, provide the following for each of your API and other components:

- your current incoming lot release specifications for all components
- your procedures to assure that each incoming lot is tested for identity
- identity testing results for all component lots received since September 2017
- a summary of all studies done to validate the COA provided by each of your component suppliers.

3. Your firm failed to follow a written testing program designed to assess the stability characteristics of drug products and to use the results of such stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

You did not test **(b)(4)** spray stability batch **(b)(4)** and **(b)(4)** spray stability batch **(b)(4)** for assay and microbial attributes. Also, the assay methods were not stability indicating.

In your response, you stated that you will test all lots for stability attributes, including assay and microbial limits, and you provided your revised procedure. Your response is inadequate because you failed to provide data to demonstrate that batches currently on the market prior to your corrective actions meet all appropriate quality attributes throughout their shelf lives.

In your response to this letter, provide a full summary of stability data for **(b)(4)** and **(b)(4)** batches that shows whether batches currently in the market prior to the corrective actions meet all appropriate quality attributes. Also, provide the stability-indicating methods used to evaluate **(b)(4)** and **(b)(4)** batches currently in the market.

Sample Results

In September 2016, before FDA's inspection, FDA detained and tested samples of your OTC drug product, **(b)(4)** spray, batch **(b)(4)**. This batch was found to have nearly twice the active ingredient content claimed on the label. Subsequent batches detained and tested by FDA also yielded similar super-potent results.

On August 30, 2017, FDA held a teleconference with your firm regarding the test results, your drug product formulation, and your inadequate test methods. You committed to reformulate the **(b)(4)** spray and update your test methods as per the USP monograph.

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. We strongly recommend that you retain a qualified consultant to assist in your remediation.

In response to this letter, provide the following.

A. 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 data integrity deficiencies throughout your operation. We recommend that the qualified third party with specific expertise in the areas where potential breaches were identified evaluate all 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 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.

C. 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 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 already underway or completed.

CGMP Consultant Recommended

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant, qualified as set forth in 21 CFR 211.34, to assist your firm in meeting CGMP requirements. In addition to assisting with data integrity remediation, we request that the qualified consultant comprehensively audit your facilities, methods, controls, and quality systems to ensure they are in compliance with 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.

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations in your facility.

FDA placed your firm on Import Alert 66-40 on December 28, 2017.

Until you correct all violations 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 violations may also result in FDA continuing to refuse admission of articles manufactured at Zhejiang Ludao Technology Co. Ltd., No. 5 Industry Road, Hairun Street, Sanmen County, Taizhou, 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 violations 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:

Mr. W. DeVore Irick
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 3006460758.

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