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WARNING LETTER

Dong Yuan Technology Co., Ltd.

MARCS-CMS 568292 — 18/03/2019

Product: Drugs

Recipient:

Mr. Buru Wang

General Manager and Owner

Dong Yuan Technology Co., Ltd.

No. 12 Volvo Road
Economic and Technical Development Zone
Linyi Shi Shandong Sheng, 276023
China

Issuing Office:

Center for Drug Evaluation and Research

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Via UPS **Warning Letter 320-19-16**

Return Receipt Requested

March 18, 2019

Mr. Buru Wang

General Manager and Owner

Dong Yuan Technology Co., Ltd.

No. 12 Volvo Road

Economic and Technical Development Zone

Linyi, Shandong Province 276023

People's Republic of China

Dear Mr. Wang:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Dong Yuan Technology Co., Ltd. at No. 12 Volvo Road, Economic and Technical Development Zone Linyi, Shandong Province, from September 24 to 28, 2018.

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 product is 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).

You did not respond to the Form FDA 483 within 15 business days of the inspection. FDA acknowledges receipt of your subsequent correspondence.

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

1. Your firm failed to establish and follow laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160 (a) and (b)).

Inadequate Laboratory Controls

Your laboratory assay methods for **(b)(4)** Spray over-the-counter (OTC) drug product have not been shown to be equivalent to or better than United States Pharmacopeia (USP) 41 compendial methods. For example, the preparation of your reference standards, the calculation of the relative standard deviation for injections, and the calculation for the resolution between the peak and the internal standard have not been shown to be equivalent to the USP 41 compendial method.

Failure to Follow Laboratory Procedures

You did not test the number of samples required by your SOP-LAB-002. For example, **(b)(4)** cans of lot **(b)(4)** Spray were sampled but only **(b)(4)** cans were tested. According to your procedure, all **(b)(4)** cans should have been tested. You did not record or justify deviating from this procedure. Further, your SOP-LAB-002 refers to the MIL-STD-105E empty can test procedure, which was cancelled more than ten years ago.

In response to this letter, provide:

- Your commitment to using current USP compendial methods until any alternative methods have been qualified.
- Your comprehensive study that determines whether your assay test methods for **(b)(4)** Spray are equivalent to, or better than, the USP method. Include all findings and deviations encountered in assessing whether your alternative method is equivalent or superior to the USP compendial method.
- Your procedure for documenting and investigating any deviations from laboratory control procedures.
- Your test results using a validated test method (e.g., USP method) of all retain samples for all drugs released to the U.S. market within expiry to ensure that your drug products conform to appropriate standards of identity, strength, quality, and purity.

2. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

You validated your manufacturing process for **(b)(4)** Spray OTC drug product for batches up to **(b)(4)** units even though you released **(b)(4)** batches up to more than **(b)(4)** times the validated batch size in 2018. Additionally, these **(b)(4)** batches included a **(b)(4)** bulk liquid hold time during manufacturing that you did not evaluate during your process validation.

Your process validation program is inadequate. Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed to assure the quality of raw material inputs, in-process materials, and finished drugs. Process qualification studies determine whether an initial state of control has been established by sound process design. Successful process qualification studies are necessary prior to commercial distribution. Thereafter, ongoing vigilant oversight of process performance and product quality is necessary to ensure that you maintain a stable manufacturing operation throughout the product lifecycle.

In response to this letter, provide the following:

- A validation plan for ensuring a state of control throughout the product lifecycle. Include a timeline for performing appropriate process performance qualification for each of your drug products. Describe your program for monitoring batch-to-batch variation to ensure an ongoing state of control.
- The actions you have taken to determine the quality of your distributed drug products in the U.S. market within expiry, which were manufactured without a validated manufacturing process.

See FDA's guidance document, *Process Validation: General Principles and Practices*, for general principles and approaches that FDA considers appropriate elements of process validation, at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf).

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

You do not retain laboratory data generated by your analysts. During our inspection, your staff told our investigator that your firm's laboratory worksheets contain only final laboratory results. You do not retain records of sample weights written on paper. The papers are discarded after your staff performs calculations.

Due to your failure to retain laboratory data, our investigator was unable to confirm the validity of your results. You could not provide any rationale for failing to maintain the complete data. Your staff further stated to our investigator that if a sample preparation is not good, it is thrown away and restarted. The staff does not retain that data.

In response to this letter, provide a comprehensive review of your laboratory practices, procedures, methods, equipment, and analyst competencies. Based on this review, provide a detailed corrective action and preventive action (CAPA) plan to remediate your laboratory system. Include the process you will use to evaluate the effectiveness of its implementation.

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. See FDA's guidance document Data Integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/downloads/drugs/guidances/ucm495891.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm495891.pdf).

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 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 analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the 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 corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

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 all your facilities.

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 refusing admission of articles manufactured at Dong Yuan Technology Co., Ltd., No. 12 Volvo Road, Economic and Technical Development Zone Linyi, Shandong Province 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 (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov) or mail your reply to:

Rokhsana Safaai-Jazi

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 3011780163.

Sincerely,

/S/

Francis Godwin

Director

Office of Manufacturing Quality

Office of Compliance

Center for Drug Evaluation and Research

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