WARNING LETTER

Haw Par Healthcare Limited

MARCS-CMS 578581 — AUGUST 19, 2019

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Wee Ee Lim

Chief Executive Officer

Haw Par Healthcare Limited

401 Commonwealth Drive
#03-03 Haw Par Technocentre
SINGAPORE 149598
Singapore

Issuing Office:

Center for Drug Evaluation and Research

10903 New Hampshire Avenue,
Silver Spring, MD 20993
United States

Warning Letter 320-19-37

AMENDED

(This letter replaces Warning Letter No. 320-19-37 dated August 14, 2019)

August 19, 2019

Dear Mr. Lim:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Haw Par Healthcare Limited at 2 Chia Ping Road, #09-03, Haw Par TIGER BALM Building, Singapore, from February 25 to March 1, 2019.

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).

In addition, your firm manufactures "TIGER BALM LINIMENT." The product is misbranded under section 502(f)(2) of the FD&C Act, 21 U.S.C. 352(f)(2). Introduction or delivery for introduction of such products into interstate commerce is prohibited under section 301(a) of the FD&C Act, 21 U.S.C. 331(a).

We reviewed your March 22, 2019, response in detail and acknowledge receipt of your subsequent correspondence.

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

CGMP Violations

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

You invalidated out-of-specification (OOS) test results for assay for **(b)(4)**, active pharmaceutical ingredient (API) (batches **(b)(4)** and **(b)(4)**) without scientific justification. Batch **(b)(4)** of this API was subsequently used to manufacture multiple batches of your **(b)(4)** Patch over-the-counter (OTC) drug product. Several batches of OTC drug product made from these OOS API lots also had OOS results for **(b)(4)** assay. In addition, your API supplier informed you of the potential for **(b)(4)** to separate and have changes in viscosity. The supplier recommended performing additional processing steps before use in manufacturing.

During your initial investigation you determined adequate raw material mixing had not occurred. Even though all sub lots of drug product were made using API from a deficient mixing process, you only rejected portions of the drug product batches that were found to be OOS. You also invalidated an assay OOS result for **(b)(4)**, a **(b)(4)** active ingredient, in **(b)(4)** Patch without adequately investigating the root cause and released the drug product for distribution. Moreover, for the same drug product, you did not adequately investigate a customer complaint reported for a lack of drug effect. You failed to test the returned sample to confirm the amount of active ingredient in the product.

In your response, you acknowledge inadequate mixing of **(b)(4)** API led to the OOS drug product results. You also provided sampling data on one batch of **(b)(4)** from two containers as evidence that your mixing process can achieve homogeneity.

Your response is inadequate because your mixing study did not evaluate multiple batches from your suppliers to determine if your process can consistently achieve homogeneity with varying levels of raw material quality. You have not provided an adequate investigation of the additional mixing parameters required for your API to achieve homogeneity. Your approach to demonstrate that your manufacturing process is validated should be scientifically based.

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/media/71001/download (https://www.fda.gov/media/71001/download).

In response to this letter, provide:

- A retrospective review of all invalidated OOS (in-process and release testing for raw materials and finished drug products) results obtained for products on the U.S. market and within expiry/retest date. Assess whether the scientific justification and evidence was conclusive. For investigations that conclusively establish laboratory root cause, determine adequacy of the corrective and preventive

action (CAPA), and ensure that other laboratory methods vulnerable to the same root cause are identified for remediation. For any OOS with inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, raw materials, process capability, deviation history, batch failure history).

- A CAPA plan that identifies the potential manufacturing root causes for each such investigation and includes process improvements where appropriate. Your CAPA plan should also include, but not be limited to, improvements in investigation competencies, root cause analysis, written procedures, quality unit oversight, and a process for evaluating CAPA effectiveness.

- An independent assessment and CAPA of your overall investigation systems, including investigating deviations, atypical events, OOS results, complaints, and failures. The CAPA should include, but not be limited to, enhanced investigation competencies, improved procedures, and substantial improvements in quality unit oversight of investigations.

2. Your firm failed to establish 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(b)).

Your firm completed forced degradation studies for your OTC drug products but did not use the data to scientifically establish stability acceptance criteria. For example, degradation chromatographic peaks of less than **(b)(4)**% of the API were determined to be insignificant. In addition, there is no assurance that the analytical test methods that you used were capable of quantifying all drug product impurities resulting from the forced degradation studies you performed.

For example, the main peak area of your API **(b)(4)** for **(b)(4)** Patch decreased by approximately 12% after the oxidative degradation study, yet your chromatographic report did not include a record of impurities resulting from the API degradation. You did not establish associated specifications or monitor your drug products for potential impurities or degradation products you identified during your degradation studies.

In your response, you stated that you will “re-study your forced degradation approach,” complete a protocol that includes acceptance criteria, and establish test procedures with specifications for monitoring impurities.

Your response is inadequate because you have not provided an interim plan of action to ensure that the products released to the market are of appropriate purity.

In response to this letter, provide:

- The drug product specifications established for monitoring impurities. Your acceptance criteria and study design should be scientifically justified.
- The drug product degradation protocol and report, which should include but not be limited to the impurities that will be monitored throughout the product life cycle.
- Your studies demonstrating that your analytical test methods, established to monitor impurities in each finished drug product manufactured for the U.S. market are stability indicating. Also include the validation protocol and report completed for these test methods.
- An independent assessment of all test methods and data review procedures used by your firm to ensure they have appropriate instructions, method suitability criteria, and validation to determine whether they are fit for intended purposes.

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)).

The computer systems you use to control the operations of your analytical instrumentation do not have audit trail capabilities, including Gas Chromatography (GC) instruments used for drug product stability analyses and Fourier Transform Infrared Spectroscopy (FTIR) and Ultraviolet (UV) spectroscopy instruments used for raw material release testing.

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/media/119267/download (https://www.fda.gov/media/119267/download).

In your response, you stated that you moved GC testing to other instruments with audit trail functionality, and you will update your FTIR and UV instrumentation with audit trails in 2020. In the interim you will initiate a program to protect raw data from deletion.

Your response is inadequate because you did not provide sufficient details of how you plan to ensure the integrity of the electronic data you generate until implementation of your updated instrumentation controls.

In response to this letter, provide:

- A comprehensive independent review of your entire data system and investigation into the inadequacies in data, records, and reporting. Describe all parts of your facility's operations in which CGMP information is not recorded and maintained.

- Your detailed CAPA plan to remediate data recording and record retention practices throughout your operation. Your CAPA plan should include, but not be limited to, appropriate controls to maintain and prevent the deletion and alteration of raw data files.
- Provide a risk assessment summarizing the effect of incomplete data on assessing laboratory results and product quality.

4. Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR 211.63).

Your **(b)(4)** system used to generate **(b)(4)** for the manufacture of your drug product has "dead legs." This inadequate system design could foster the development of biofilms and lead to contamination of **(b)(4)** used in drug manufacturing. In addition, your practice of flushing the system at the manufacturing sampling points before sample collection for **(b)(4)** analysis is not consistent with how you use these **(b)(4)** points of use in production. This inconsistent sampling practice could potentially lead to inaccurate microbial results for **(b)(4)** analysis.

In your response, you stated that you have re-designed your **(b)(4)** circulation line.
Your response is inadequate because you have not provided your data and evaluation of all **(b)(4)** sampling points, with consistent sampling procedures, used for manufacturing to ensure that your microbial results comply with specifications.
In response to this letter, provide:

- Your **(b)(4)** system validation protocol and report and a summary of improvements made to your **(b)(4)** system design.
- Your current procedures for routine monitoring of the redesigned **(b)(4)** system as well as system controls and maintenance. This should include, but not be limited to, test methods, appropriate microbial limits (total count, objectionable organisms), and **(b)(4)** analysis frequency and locations of sampling points.
- Justification that the frequency of sanitization and **(b)(4)** analysis of your **(b)(4)** system is adequate for ensuring that no biofilm exists in your **(b)(4)** system.
- Data demonstrating appropriate microbial total count to ensure this system produces **(b)(4)** suitable for the intended uses of each of your drug products.
- A detailed risk assessment addressing the potential effects of **(b)(4)** system failures on the quality of all drug product lots currently in U.S. distribution and within expiry. Specify actions that you will take in response to the risk assessment, such as customer notifications and product recalls.

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.

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

Misbranding Charge

"TIGER BALM LINIMENT"

"TIGER BALM LINIMENT" is a "drug" as defined by section 201(g)(1)(B) of the FD&C Act, 21 U.S.C. 321(g)(1)(B), because it is intended for the diagnosis, cure, mitigation, treatment, or prevention of disease and/or under section 201(g)(1)(C) of the FD&C Act, 21 U.S.C. 321(g)(1)(C), because it is intended to affect the structure or any function of the body. Specifically, this product is intended as an external analgesic. Examples of claims observed on the product label that establish the intended uses, as defined in 21 CFR 201.128, of the product include, but may not be limited to, the following:

"For temporary relief of minor aches and pains of muscles and joints associated with simple backache, arthritis, bruises, sprains and strains."

The labeling for such drugs, like all OTC drugs, must comply with all of the requirements of section 502 of the FD&C Act and all pertinent regulations found in Title 21 of the Code of Federal Regulations (21 CFR). However, your product does not meet these requirements for the reason described below.

"TIGER BALM LINIMENT" is misbranded under section 502(f)(2) of the FD&C Act, 21 U.S.C. 352(f)(2), because the product label fails to include a warning required under 21 CFR 201.303(b). Under 21 CFR 201.303, specific warning language is required for drug preparations that contain significant proportions (5% or higher) of wintergreen oil. Wintergreen oil is also known as methyl salicylate, and "TIGER BALM LINIMENT" contains methyl salicylate 28%. As required in 201.303(b), the labeling must specifically warn that use otherwise than as directed therein may be dangerous and that the article should be kept out of reach of children to prevent accidental poisoning. The labeling of "TIGER BALM LINIMENT" fails to bear such warnings.

The introduction or delivery for introduction of a misbranded drug into interstate commerce is prohibited under section 301(a) of the FD&C Act, 21 U.S.C. 331(a). Therefore, the marketing of "TIGER BALM LINIMENT" violates this provision of the FD&C Act.

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.

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 Haw Par Healthcare Limited at 2 Chia Ping Road, #09-03, Haw Par TIGER BALM Bldg., Singapore, 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:

Christina Alemu-Cruickshank
Compliance Officer
U.S. Food and Drug Administration
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10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI No. 3001432470.

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

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