WARNING LETTER

Dermameal Co., Ltd.
MARCS-CMS 582118 – SEPTEMBER 12, 2019

Delivery Method:
VIA UPS

Product:
Drugs

Recipient:
Mr. Kim Hong-Seop
President/Owner
Dermameal Co., Ltd.
5, Dangjeong-ro, 60beon-gil
Republic of Korea (South) Gunpo-si Gyeonggi-do 15847
South Korea

Issuing Office:
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Warning Letter 320-19-44

September 12, 2019

Dear Mr. Hong-Seop:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Dermameal Co., Ltd. at 5, Dangjeong-ro, 60beon-gil, Gunpo-si Gyeonggi-do, from March 25 to 29, 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).

We reviewed your April 19, 2019, response to our Form FDA 483 in detail.

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

1. **Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products. Your firm also failed to establish and follow adequate written responsibilities and procedures applicable to the quality control unit (21 CFR 211.22(a) & (d)).**

Your firm contract manufactures over-the-counter (OTC) drug products. Your quality unit (QU) failed to ensure every drug product batch is released only when satisfactory product quality testing is completed. Out of 41 lots reviewed, 26, over half, were distributed before microbial testing was completed. You stated during inspection that your customer was agreeable to this practice. Releasing drug products before completing all required testing is unacceptable and increases the risk that drug products that do not meet their quality attributes are distributed to consumers. It is important to note that some of your (b)(4) drug products are labeled for use on children.

In your response, you stated you are updating your procedures and having clients sign an “official document of cooperation.” Your response is inadequate. Your procedures already require you to hold drug products until all testing is complete. It is unclear how your proposed actions will prevent future release of drug products without complete data to demonstrate their quality. Furthermore, you failed to provide evidence that previous batches released prior to completion of testing met all quality attributes.

In response to this letter, provide:

- a retrospective review of all batches released to ensure all specifications have been met.

- a summary of test results obtained from testing retain samples of all drug products within expiry. You should test all appropriate quality attributes including, but not limited to, identity and strength of active ingredients and microbiological quality (total counts and identification of bioburden to detect any objectionable microbes). If your testing of any batch yields an out-of-specification result, indicate the corrective actions you will take, including notifying customers and initiating recalls.

- a comprehensive assessment with corrective and preventive actions (CAPA) to ensure your QU is given the authority and resources to effectively discharge its function. The assessment should also include, but not be limited to:
  - a determination of whether procedures used by your firm are robust and appropriate;
  - provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices; and
  - complete and final review of each batch and its related information before the QU disposition decision.
See FDA’s guidance document _Quality Systems Approach to Pharmaceutical CGMP Regulations_ for help implementing modern quality systems and risk management approaches to meet the requirements of CGMP regulations (21 CFR, parts 210 and 211) at [https://www.fda.gov/media/71023/download](https://www.fda.gov/media/71023/download).

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

The stability program is not adequate to demonstrate the quality of the drug products you manufacture throughout expiry. The stability program did not include assay testing of stability samples. The program must also verify that quantities of the active ingredient and other components of interest meet established specifications and all pre-determined quality criteria throughout the drug products’ shelf-life. In addition, your firm placed a single batch on stability for each drug product and did not have an ongoing stability program.

In your response, you stated that you will revise the stability procedure. You also committed to place three lots of each the (b)(4) drug products you manufacture on stability upon your next order from your client. You also stated you will perform stability testing using new unopened product samples for each testing interval.

Your response is inadequate. You have not adequately described the updated stability program, nor did you provide a timeline for execution.

In response to this letter, provide a comprehensive, independent assessment and CAPA to ensure the adequacy of the stability program. Your CAPA should include, but should not be limited to:

- a remediated standard operating procedure (SOP) describing the stability program;
- stability-indicating methods;
- stability studies to support each drug product in its container-closure system before distribution is permitted;
- an ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid; and
- specific attributes to be tested at each station.

3. **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 validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1) & (2)).**

Your firm failed to test incoming raw materials and active ingredients (e.g., (b)(4)) for identity. Instead, your firm relied on certificates of analysis (COA) from unqualified suppliers. Identity testing is required for each component lot prior to use in drug product manufacturing, and you can only rely on a COA for other component attributes through validation of supplier's test results at appropriate intervals.

In addition, (b)(4) is an ingredient in multiple drug products you manufacture. While your supplier’s COA shows evidence of (b)(4) limit testing for (b)(4), your firm failed to test all lots of all containers of (b)(4) to determine if (b)(4) or (b)(4) were present.

In your response, you stated that you will revise your procedures for supplier qualification and raw material testing. You also committed to performing identity testing of raw materials upon your client’s next order.

Your response is inadequate. You did not provide the updated procedures or detail how you will qualify suppliers and verify your suppliers’ COA.
In response to this letter:

- Describe how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any testing results on your supplier’s COA in lieu of testing each component lot for purity, strength, and quality, specify how you will first establish the reliability and consistency of your supplier’s test results for these attributes through initial validation, followed by periodic re-validation. In addition, commit to conduct at least one specific ID test for incoming components and provide testing methods.

- Summarize test results obtained from full testing of all components to evaluate the reliability of the COA from each component manufacturer. Include your SOP that describes this COA validation program.

- Test retain samples of all glycerin lots for (b)(4). Indicate whether (b)(4) is present in any of the (b)(4) lots. If your testing of any batch yields an out-of-specification result, indicate the corrective actions you will take, including notifying customers and initiating recalls.

See FDA’s guidance document Testing of (b)(4) to help you meet the CGMP requirements when manufacturing drugs containing (b)(4) at (b)(4).

4. Your firm failed to establish 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)).

Your firm has not validated your manufacturing process for OTC (b)(4) drug products.

Process validation establishes scientific evidence that a process is capable of consistently delivering quality product. Sampling and testing of in-process materials and drug product requires control procedures to monitor output and validate performance of manufacturing processes that may cause variability in drug product characteristics. Samples must be representative of the batch, provide appropriate statistical confidence, and meet predetermined specifications.

In your response, you stated that you will establish a validation management procedure in accordance with 21 CFR parts 210 and 211. You committed to performing process validation upon your client’s next order of (b)(4) products.

Your response is inadequate because you failed to provide sufficient details for an overall program for assuring maintenance of a validated process throughout the product lifecycle. In addition, you did not provide a detailed timeline to execute the validation.

In response to this letter, provide:

- A detailed validation plan, include your process performance protocol(s) and your written procedures for qualification of equipment and facilities.


5. Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).

Your firm did not validate your cleaning processes used for cleaning non-dedicated manufacturing equipment, such as your tube filling and sealing machine. Inadequate removal of residues from the product contact surfaces of manufacturing equipment during cleaning can contaminate drug products subsequently manufactured on non-dedicated equipment.

Your firm also failed to adequately document when equipment cleaning activities were performed.
In your response, you stated that you will review and update your equipment cleaning procedures and incorporate the use of equipment logbooks to document equipment cleaning activities. You also committed to conduct cleaning validation of your manufacturing equipment.

Your response is inadequate. You did not adequately describe how updating your procedures will ensure the appropriate cleaning of your non-dedicated equipment. You also failed to provide sufficient details of your cleaning validation program along with timeline for completion.

In response to this letter, provide:

- A comprehensive plan to evaluate the adequacy of cleaning procedures, practices, and validation studies for each piece of manufacturing equipment used to manufacture more than one product.

- Scientific rationale for your cleaning validation strategy to ensure the efficacy of your cleaning procedures is adequately assessed.

- A summary of updates to your cleaning validation protocol to better incorporate conditions identified as worst case. This should include but not be limited to evaluating drugs that are of highest toxicity, drugs that are lowest solubility in their cleaning solvents, drugs that have characteristics that make them difficult to clean, and swabbing of various equipment locations that are most difficult to clean.

- A summary of SOPs that have been updated to ensure an appropriate program for verification and validation of cleaning procedures for new products, processes, and equipment.

- A scientific rationale for the frequency of microbial testing of production equipment.

**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.

**Responsibilities as a Contractor**

Drugs must be manufactured in conformance with CGMP. FDA is aware that many drug manufacturers use independent contractors such as production facilities, testing laboratories, packagers, and labelers. FDA regards contractors as extensions of the manufacturer.

You and your customer, (b)(4) have a quality agreement regarding the manufacture of drug product(s). You are responsible for the quality of drugs you produce as a contract facility regardless of agreements in place with product owners. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act for safety, identity, strength, quality, and purity. See FDA’s guidance document *Contract Manufacturing Arrangements for Drugs: Quality Agreements* at [https://www.fda.gov/media/86193/download](https://www.fda.gov/media/86193/download).

**Conclusion**

The violations cited in this letter are not intended as an all-inclusive statement of violations that exist at your facility. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations.

FDA placed your firm on Import Alert 66-40 on July 19, 2019.

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 the FDA continuing to refuse admission of articles manufactured at Dermameal Co., Ltd. at 5, Dangjeong-ro, 60beon-gil, Gunpo-si Gyeonggi-do 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:

DeVore Irick
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4235
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3013144674.

Sincerely,

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

Cc: (b)(6)

President

(b)(4)