Hanlim Pharm Co., Ltd. 10/3/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-19-01

October 3, 2018

Mr. Jung Jin Kim
President
Hanlim Pharm Co., Ltd.
Seocho-Daero, 52-Gil 42
Seocho-Dong, 137-881, South Korea

Dear Mr. Kim:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Hanlim Pharm Co., located at 2-27 Yeongmun-ro, Yonginsi Ceoin-gu, Gyeonggi-do, from January 29 to February 6, 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 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 February 21, 2018, 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.

1. Your firm failed to follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and

sterilization processes (21 CFR 211.113(b)).

Your operators' poor aseptic practices during set-up and filling operations for your sterile **(b)(4)** solution posed a significant risk of microbial contamination. During filling set-up, an operator touched the **(b)(4)** between an ISO-7 and ISO-5 area. The operator then continued equipment set-up activities in the ISO-5 zone without disinfecting his hands, which could transfer microorganisms from the ISO-7 area to the surfaces and components in the ISO-5 aseptic filling zone. Also, on Jan. 30, during filling of an **(b)(4)** solution on Line **(b)(4)**, our investigator observed operators stopping the lines and opening the **(b)(4)** to clear bottle jams more than 10 times in a 90-minute period. On several occasions, operators leaned their heads and torsos inside the **(b)(4)** over open bottles. They restarted the line without clearing open bottles that may have been contaminated by their interventions.

In your response, you stated that you will make changes to the filling line and will train operators on movement in filling rooms. Your response was inadequate because you did not sufficiently assess the adequacy of your aseptic filling line design. You did not provide a detailed plan for qualifying changes to your filling line by conducting media fills and smoke studies. You also did not provide any details on operator training.

Furthermore, FDA cited a similar CGMP violation regarding inadequate design of your aseptic line in an April 2014 inspection.

In response to this letter, provide:

- Your plan to assure strict adherence to appropriate aseptic practices and cleanroom behaviors. Specify how your firm will ensure routine and effective supervisory oversight during manufacture of each batch. Also, describe the frequency of quality assurance oversight, such as audits, during aseptic processing and other operations.
- A thorough risk assessment that evaluates how poor aseptic technique and cleanroom behavior such as that observed during the inspection may have affected quality and sterility of your drugs.
- Comprehensive, independent identification of all contamination hazards specific to your aseptic processes, equipment, and facilities. Provide an independent risk assessment that covers, among other things, 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.
- A detailed corrective action and preventive action (CAPA) plan, with timelines, to address the findings of the contamination hazards risk assessment. Describe how you will significantly improve aseptic processing operation design, control, maintenance, and personnel qualification.

2. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

Your firm did not perform routine monitoring of viable organisms in the filling area inside the **(b)(4)** barrier on Line **(b)(4)**. Our investigator observed operators spraying **(b)(4)**, which can inhibit microbial growth, next to your environmental monitoring plates. Additionally, you did not conduct personnel monitoring of the individual performing set-up for sterile manufacturing. Poor environmental monitoring practices may underestimate the true microbiological contamination levels in your facility.

In your response, you stated that you would add two settling plates inside the Line **(b)(4)** barrier and train your operators on how to "spray **(b)(4)**." You also stated you will conduct personnel monitoring of the operators who perform aseptic processing equipment setup. Although you stated in your response that you added monitoring locations, you failed to include the revised procedure for this change. You also did not fully evaluate the sufficiency of your overall environmental monitoring program (including personnel monitoring) to promptly identify potential routes of contamination and enable corrections before product contamination occurs.

In response to this letter, provide a comprehensive assessment and CAPA plan for your environmental monitoring program (including personnel monitoring) to ensure it supports robust environmental control of your aseptic processing facility. Your assessment should include justification of sampling locations, frequency of sampling, alert and action limits, the adequacy of your sampling techniques, and trending program.

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 ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf.***

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3. 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)).

Our investigator observed a quality control analyst and laboratory team leader signing and backdating a test record. In the microbiology laboratory, we also observed an analyst recording microbiological test results from environmental monitoring settling plates before reading the plates, as well as recording results for a previous day. Upon questioning by our investigator, the analyst stated the plate count data had been mistakenly omitted. CGMP activities must be documented at the time of performance.

Your response acknowledged that your analysts lacked awareness of "Good Documentation Practice" and stated that you would perform self-audits and hire a consultant to perform related training. Your response is inadequate because you did not include a detailed CAPA plan with supporting documentation. In response to this letter, provide your CAPA plan as requested in the Data Integrity Remediation section of this letter below.

4. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

Three of your quality control team leaders had administrator privileges within your HPLC computerized laboratory software system. Because they review and approve CGMP data, their access level should preclude file deletion or modification. In addition, two of your laboratory software systems had unlocked time and date functions, which allowed users to change the recorded dates and times of analyses.

FDA cited a similar CGMP violation regarding inadequate controls over your computerized laboratory systems in our July 2016 inspection.

In your response, you stated you would grant administrator privileges to only an information technology employee not involved in laboratory testing. You also stated that you locked the time and date setting function for the system. Your response is inadequate because you did not evaluate whether CGMP data were improperly modified or deleted, and you did not include supporting documentation for your proposed CAPA plan.

In response to this letter, provide a comprehensive, independent review of controls and procedures for electronic data generated from all of your laboratory equipment. Based on this review, provide a detailed CAPA plan to remediate laboratory systems, including but not limited to data creation, modification, maintenance, retention, and system security. Your plan should also include the process you will use to evaluate CAPA effectiveness.

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 acknowledge that you are using a consultant to audit

your operation and assist you in meeting FDA requirements. 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 that ensures all laboratory equipment and systems are covered by the assessment. Also describe all other parts of your manufacturing operation that will be assessed for data integrity and documentation practices and justify any exclusion.
- 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. Interview employees to identify the nature, scope, and root cause of data inaccuracies.

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 CAPA plan. Your strategy should include:

- A comprehensive description of the root causes of your data integrity lapses.
- A detailed corrective action plan that describes how you will ensure the reliability and completeness of all data you generate, including analytical data, manufacturing records, and all data submitted to FDA.
- 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

We note that you have retained a CGMP consultant. Based upon the nature of the violations we identified at your firm and because you failed to adequately correct repeat violations, we strongly recommend that your consultant is qualified as set forth in 21 CFR section 211.34, to assist your firm in meeting CGMP requirements. We also recommend that a qualified third party perform a comprehensive audit of your entire operation for CGMP compliance, and evaluate the sufficiency, and effectiveness of corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

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.

FDA placed your firm on Import Alert 66-40 on May 3, 2018.

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 Hanlim Pharm Co., Ltd, 2-27 Yeongmun-ro, Yonginsi Ceoin-gu, 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:

Marie Mathews
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 3004886113.

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

More in Warning Letters (/ICECI/EnforcementActions/WarningLetters/default.htm)