**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 10903 New Hampshire Ave,Bldg 51,Rm 4225<br>Silver Springs, MD 20993<br>(301)796-3334 Fax:(301)847-8738 | 1/29/2018-2/6/2018*<br>FEI NUMBER<br>3004886113 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Jong-Hyeon Ryu, Quality Division/Executive Director

| FIRM NAME | STREET ADDRESS |
|---|---|
| Hanlim Pharm Co., Ltd. | 2-27 Yeongmun-ro |
| CITY, STATE, ZIP CODE, COUNTRY<br>Yonginsi Ceoin-gu, Gyeonggi-do, 17040<br>Korea (the Republic of) | TYPE ESTABLISHMENT INSPECTED<br>Sterile OTC Drug Manufacturer |

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

**DURING AN INSPECTION OF YOUR FIRM I OBSERVED:**
Production System

## OBSERVATION 1

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not followed.

Specifically, on 1/30/18 during filling of (b) (4) Solution Lot (b) (4) on Line (b) (4) the following was observed:

- Operators repeatedly reached over open empty bottles to operate the filling line's HMI control panel for up to a minute at a time. The control panel is located above and behind the filling line prior to the bottles entering the Restricted Access Barrier (RABS).

- Operators entered and exited the Grade A filling area through a (b) (4) located next to the bottle (b) (4) multiple times during filling. The (b) (4) is adjacent to a Grade B corridor which leads to a Grade B supply room containing bags of bottles, (b) (4), and caps used for filling. Operators must leave the Grade A filling area to retrieve these supplies, which are then individually brought back into the Grade A area by hand. Approximately (b) (4) bags of bottles, (b) (4) bags of (b) (4) and (b) (4) bags of caps were used during filling of (b) (4) Solution Lot (b) (4). Operators must also leave the Grade A area to access the other side of the room where the empty bottles are (b) (4) with (b) (4) prior to filling.

- While loading the bottles, caps, and (b) (4) into their respective (b) (4) during production the

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outside non-sterile (b) (4) bags contacted the inside of the (b) (4).

- Operators stopped the line and opened the (b) (4) of the RABS a minimum of (b) (4) times over the course of ~(b) (4) of filling to address issues such as bottle jams. These interventions are not documented in the batch records for Filling Line (b) (4). On several occasions after removing jams the operator leaned their torso and head inside the RABS to clean the equipment with a clean room cloth.

- Operators did not always demonstrate slow and deliberate movements within the Grade A area during filling activities, including during loading of supplies into (b) (4), spraying of hands with (b) (4), and removing jammed bottles from the belt.

- Operators sprayed (b) (4) multiple times in the vicinity of the open active and passive settling plates used for environmental monitoring, as well as the filling line where open bottles were located.

On 1/31/18 during filling preparation and set-up of (b) (4) Solution Lot (b) (4) on Line (b) (4) the following was observed:

- While setting up the filling equipment, including the filling (b) (4) and tubing, an operator exited the Grade A area through a (b) (4) into the Grade B corridor twice using his hands to open the (b) (4). He continued with set-up activities, which involved leaning into the RABS, without spraying his hands with (b) (4) after touching the (b) (4). The operator responsible for setting up the filling equipment does not perform personal monitoring after set-up activities.

US products filled on Line (b) (4) include (b) (4)

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**OBSERVATION 2**

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.

Specifically,

a) QA staff who perform inspection of bottles following incubation during media fill validations are not given adequate training. The "Training on Media Fill Test Regulation UT16-QA-1108-R" conducted on 2016.11.08 states in section 6.4 "Judging of the Test" that during inspection the media fill bottles should be compared with a control bottle to see if there is any contamination. Section 6.4.2 states if contamination is suspected to send the bottle to QC for evaluation. The training did not include how to perform the inspection (e.g. rotating the bottle) or what a contaminated bottle looks like. On 2018.01.03 a Media Fill Validation Training for QA was held which instructed media fill inspectors to use a light intensity of (b) (4) - (b) (4) LUX and to hold the bottles (b) (4) away from their eyes. It also stated to look for microbial growth (turbidity). However, the training did not require the QA participants to identify actual contaminated units and the trainer who gave the training is not a microbiologist.

b) There is no documentation of the inspection of media fill units, including results, prior to November 2017. A media fill validation was performed for the (b) (4) Solution Filling Line (b) (4) on 2017.06.16 (routine) and 2016.11.18 (routine), for the (b) (4) Solution Filling Line (b) (4) on 2017.06.16 (routine) and 2016.12.13 (routine), and for the (b) (4) Ointment Filling Line (b) (4) on 2017/04/26 (change to process), 2017/02/08 (change to equipment), 2017/02/02 (change to equipment), and 2016/09/29 (routine). All Media Fill Validation summary reports for the above listed validations document passing results.

Laboratory System

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## OBSERVATION 3

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically,

c) (b) (4) solutions ((b) (4)) and (b) (4) ointments are not tested for impurities during finished product release testing or stability testing.

d) There is no finished product or stability specification established for osmolality for (b) (4) solutions ((b) (4)), with the exception of (b) (4) and (b) (4) ((b) (4)). Instead, either (b) (4) ml or (b) (4) ml of the bulk solution is sampled per lot and tested for osmolality for informational purposes. This data is not documented as part of the test record which is reviewed prior to release of the lot.

e) An assessment has not been made of the (b) (4) ointments which follow USP Monograph, "(b) (4) Ointment" or "(b) (4) Ointment" to determine whether they are inherently (b) (4) over their shelf-life period and therefore, do not require the (b) (4) of a (b) (4).

f) An assessment of leachables and/or extractables has not been performed for (b) (4) solutions ((b) (4)) and (b) (4) ointments to demonstrate that the packaging systems do not interact physically or chemically with the products in any manner to alter the strength, quality, or purity of the drug products over their shelf-life period.

g) There is no viscosity test performed on lots of (b) (4) Ointment, which contain the active ingredient (b) (4), to ensure the product has the appropriate drug diffusion rate and

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residence time in the (b) (4).

US (b) (4) solutions ((b) (4)) include (b) (4)

US (b) (4) ointments include (b) (4) Ointment, (b) (4) Ointment, and (b) (4) Ointment. Several of these products are packaged under multiple brand names.

**OBSERVATION 4**

Established test procedures are not documented at the time of performance.

Specifically, on 1/30/18 an analyst and a team leader in the QC laboratory were observed signing and back-dating a test record for 12/27/2017. On 1/31/18, during reading of environmental monitoring plates an analyst was observed recording a "0 cfu" result prior to observing the sample. In addition, the analyst was observed recording data for the previous day, which had been mistakenly omitted. An individual from QA was observing the plate reading.

Quality System

**OBSERVATION 5**

Employees engaged in the processing of a drug product lack the training required to perform their assigned functions.

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Specifically, the qualification of visual inspectors for sterile (b) (4) solutions ((b) (4)) does not reflect the actual conditions under which operators perform their inspections.

As described in SOP MC-106, Foreign Material Inspection Control, dated 2017-12-13, during qualification for (b) (4), inspectors are given (b) (4) bottles to inspect. (b) (4) of the (b) (4) bottles have a defect, including incorrect fill volume, speck on cap or bottle, scratch on bottle, foreign matter, missing cap, or improper seal. The inspection of the bottles takes place on a table under no time constraints; however, the inspection typically takes ~(b) (4). Inspectors must score a (b) (4) % (identify (b) (4) of the (b) (4) defects correctly) to be considered qualified.

In comparison, visual inspection of commercial lots occurs online during production operations. The belt speed of Filling Line (b) (4) ranges from (b) (4) - (b) (4) bottles/minute and the belt speed of Filling Line (b) (4) ranges from (b) (4) – (b) (4) bottles/minute. The bottles do not rotate as they move past the inspectors on the belt. Inspectors work (b) (4), inspecting for (b) (4) and taking a break for (b) (4).

Approximately (b) (4) bottles/(b) (4) were inspected in (b) (4) Lot (b) (4), approved March 14, 2017, and (b) (4) Lot (b) (4), approved August 1, 2017.

US products filled on Line (b) (4) include (b) (4)

US products filled on Line (b) (4) include (b) (4)

Facilities and Equipment System

**OBSERVATION 6**

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Backup data is not assured as secure from alteration, erasure or loss through keeping hard copy or alternate systems.

Specifically, (b) (4) team leaders in the QC department have administrator privileges which allow them to delete projects, delete data, delete results, and save and delete instrument and processing methods, among other things. In addition, the time and date function is not locked on the computers which run EMPOWER and EZChrome software used to generate and integrate HPLC data during testing of US (b) (4) products. The data is stored on the local computer hard drives and backed up to a USB on a (b) (4) basis.

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**OBSERVATION 7**

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically, no viable environmental monitoring, including active and passive settling plates, occurs in the Restricted Access Barrier (RABS) on (b) (4) Solution Line (b) (4) during filling operations. Surface sampling near the filling (b) (4) is performed after completion of filling activities with a contact plate. In addition, the operator who performs set-up activities, including setting up the filling (b) (4) and tubing, is not included in personal monitoring.

US products filled on Line (b) (4) include (b) (4)

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***DATES OF INSPECTION**

1/29/2018(Mon), 1/30/2018(Tue), 1/31/2018(Wed), 2/01/2018(Thu), 2/02/2018(Fri), 2/05/2018(Mon), 2/06/2018(Tue)

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