DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA OPQO HQ, Room #2032 12420 Parklawn Drive, Room 2032 Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	7/12/2021 - 7/20/2021
	FEI NUMBER 3008481334

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Hongwei Zhu, Hisun Hangzhou Site Quality VGM

FIRM NAME	STREET ADDRESS
Hisun Pharmaceutical Hangzhou Co., Ltd	No. 1 Fuyang District, Haizheng Road, Xukou Town
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Hangzhou, Zhejiang, 311404 China	API & Sterile Finished Dose Human / Animal Drug Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

Observation 1

Written methods of cleaning, sterilizing, and processing are not fully validated and followed to limit, control, and remove pyrogens and pyrogenic properties of intermediates, APIs, and drug products.
Fermentation cultures used for API product (b) (4) have bacteria levels of (b) (4) and endotoxin levels of (b) (4) EU/mg (b) (4) EU/mg). Not all production processes have been validated and strictly controlled to limit the carryover from batch-to-batch and prevent additional or new microbial contamination.

Specifically,
a. All components including (b) (4) water and recycled solvents used in the production and purification of APIs from fermentation are not fully validated for risks from pyrogenic substance carryover and the specific types of pyrogens and endotoxins introduced into the batch. Cleaning and sterilization of production equipment and (b) (4) methods has not been fully validated to control endotoxins and pyrogens in fermentation APIs including (b) (4)

b. (b) (4) batches (b) (4) (b) (4) and test development batches (b) (4) do not conform to pyrogen test specifications.

c. (b) (4) API batch (b) (4) contains levels of bacteria (b) (4) CFU/g and yeast (b) (4) CFU/g.

d. (b) (4) API batch (b) (4) contains levels of endotoxin < (b) (4) EU/mg, bacterial < (b) (4) CFU/g, and yeast < (b) (4) CFU/g.

e. Sterile finished product (b) (4) Injection USP made with (b) (4) API batch (b) (4) and administered to patients resulted in endotoxin-like reactions adverse drug events.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Roger F. Zabinski	Roger F. Zabinski, Investigator, Dedicated Foreign Drug Cadre	07/20/2021

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Observation 2

Critical process parameters are not fully monitored or controlled during aseptic production.

Specifically,

a. (b) (4) stoppers used from suppliers (b) (4) and (b) (4) have not been fully assessed for evidence of degradation and particles during sterilization method.

b. Aseptic production was observed in Line (b) (4) for production of (b) (4) NJ, (b) (4) This line is also used for (b) (4) NJ USP (b) (4) Operators were observed to be performing almost constant interventions in the (b) (4) RABS at the (b) (4) filling machine in order to separate stoppers that are stuck or partially interlocking together prior to them being used in the stopper machine.

c. Detailed analysis has not been completed on whether particles are generated by the stoppers, the effect of extensive interventions while unsticking the stoppers, and whether (b) (4) product results in particles released from the stoppers.

Observation 3

Buildings used in the manufacture, processing, packing or holding of drug products are not maintained in a clean and sanitary condition.

Specifically,

a. During visual inspection of the aseptic filling line (b) (4) production area and (b) (4) on 7/14/2021, some foreign matter and dust contamination was observed including two pieces of white rubber material, apparently sealant, approximately 0.5-1 cm in length that were on the (b) (4) frame in the Class-C area near (b) (4) used for interventions into Class-A area inside the (b) (4) It was suggested from your firm that the pieces of sealant may

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have fallen from a nearby (b) (4) panel at the top of the (b) (4) near the ceiling that had white sealant around the four edges. This suggests that the panel may not be sealed, that there may be exposure between the inner machine area of the (b) (4) and the Class-C area, and that additional pieces of sealant may continue to fall off. Sterile products such as (b) (4) Injection USP, (b) (4) Injection USP, and (b) (4) (b) (4) Injection USP are produced in Line (b) (4)

b. Some dust was observed on product shelves in Long Term Stability room in building (b) (4) and apparent mold and chemical residue was observed in the return air vent area. A condensation drain tube from the fans allows water to drain across the return vent area, contributing to insanitary conditions. Chemical residue that produced an apparent green fluorescent–like color with use of a UV inspection flashlight was observed.

c. API building (b) (4) clean-room area equipment including (b) (4) (b) (4) weigh balances, and (b) (4) showed significant amounts of chemical residue around three (b) (4) around the inside of the (b) (4) machine, around the top and sides of the balances, and on the (b) (4) and (b) (4) The residues produced apparent green fluorescent–like color with use of a UV inspection flashlight and confirmed with use of lint-free wipes.

d. Some dust was observed on HPLCs and GC instruments in the API-QC and FDF-QC laboratories around the sample vial compartment, near the HPLC injector needle, and around some HPLC column holding compartments. Use of a lint-free wipe confirmed the dust.

e. Cleaning methods to prevent contamination in aseptic production line (b) (4) analytical instruments, stability rooms, and API production tanks and equipment lack instruction to ensure that equipment are effectively cleaned, including difficult to reach areas, visual inspection and wiping/swabbing techniques, and scientific evidence for limits of detection from visual inspection methods.

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."