DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA OPQO HQ, 12420 Parklawn Drive, Room #2032 Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	06/24/2019 - 06/28/2019
	FEI NUMBER 3003999190

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Baohua Chen, President

FIRM NAME	STREET ADDRESS
Zhejiang Huahai Pharmaceutical Co. Ltd.	Xunqiao
CITY, STATE AND ZIP CODE Linhai, Zhejiang 317024, China	TYPE OF ESTABLISHMENT INSPECTED API & Drug Product 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) (WE) OBSERVED:

OBSERVATION 1
There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically, Deviation Investigations RDF-17038 and RDF-18010 were initiated to investigate white particulates observed during the manufacturing of (b) (4) Injection, Batches (b) (4) respectively. The investigations concluded the probable root cause and likely source of the white particulates were caused by inadequate cleaning of the CIP Skid tanks and pipes (i.e., RDF-17038) and (b) (4) mL (b) (4) (i.e., RDF-18010). However, the investigations into the root cause of the white particulates were incomplete in that they failed to evaluate the identity of the white particulates as part of the investigation into the potential source(s) of their origin.

OBSERVATION 2
Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established.

Specifically,
A) Your firm has not established adequate procedures to ensure investigations into visual inspection failures are conducted. For example, SOP L6-071-3, entitled The AQL Standard Operating Procedure for Visual Inspection of Injection, does not require a deviation investigation to be initiated into an AQL visual inspection failure until the AQL visual inspections fails twice.

In addition, descriptions of the defect types described in SOP L6-071-3 are not adequate to ensure consistency in classification amongst operators performing visual inspection activities. For example, the procedure describes a critical defect as a vial with a fiber exceeding (b) (4) mm in length and a major defect as a vial with a fiber smaller than (b) (4) mm in length. No scientific justification was provided as to how a visual inspection operator could effectively

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	Jonathan Chapman	Jonathan W. Chapman, Investigator	06/28/2019

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perform this determination.

B) Your firm's procedures for performing the routine monitoring of HEPA filters, which supply air to the Class A and Class B areas, are inadequate in that they do not require an assessment of the uniformity of air velocity across the HEPA filters nor do they require an assess of the air velocity relative to those adjacent HEPA filters. For example, SOP N-438-4, section 6.3.5, requires only (b) (4) be collected during the routine (b) (4) air velocity challenge.

OBSERVATION 3
Changes to written procedures are not drafted, reviewed and approved by the appropriate organizational unit.

Specifically,
Your firm failed to follow the requirements specified in SMP-018.09, entitled Change Control System, to ensure all affected documents (procedures, batch records, etc.,) impacted by a change were evaluated and revised prior to implementing the change. For example:

A) Change Request Q/ZHH JL6-146-2 was initiated to implement changes to the commercial production batch record for (b) (4) Injection (b) (4) mg/(b) (4) mL. One proposed change was a modification of the filling volume, filling weight and target value of the finish drug product. The commercial batch record was updated and the change was approved by QA. However, the evaluation of other affected documents do to this change was inadequate. For example, a review of SOP L6-059, which documents the key parameters of the program recipe used to operate the filling and stoppering machines, identified this document was not updated. The fill volumes and fill weights identified in SOP L6-059 did not match those listed in the proposed commercial batch record.

B) Change Request 06 was initiated to update SOP L6-059, to revise the process recipe for the filling and stoppering machine, to change the (b) (4) mL (b) (4) to a (b) (4) mL (b) (4) . The recipe was updated and the change was approved by QA. However, the evaluation of other affected documents do to this change was inadequate. For example, a review of the proposed commercial batch record for (b) (4) Injection (b) (4) mg/(b) (4) mL, revealed the name of the recipe identified was not updated and listed the name for the now retired recipe.

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OBSERVATION 4
The master production and control records are deficient in that they do not include complete manufacturing, control and instructions.

Specifically, the exhibit batch manufacturing records for (b) (4) Injection (b) (4) mg (b) (4) mL and (b) (4) mg (b) (4) mL and the current proposed commercial production batch record do not include adequate instructions and documentation of process parameters to ensure process conditions critical to the sterile filtration process are maintained throughout the production run. For example, a review of the sterile filtration procedures listed in the proposed commercial batch record for (b) (4) Injection (b) (4) mg (b) (4) mL and (b) (4) mg (b) (4) mL, revealed the differential pressure of the filter is required to be document at the beginning of filtration with an acceptance limit of ≤ (b) (4) bar. However, no subsequent pressure reading is recorded during and/or at the end of filtration operations to ensure the filtration pressure remained below the limit challenged during your bacterial retention validation of your sterile filter.

OBSERVATION 5
Written specifications for laboratory controls do not include a description of the sampling testing procedures used.

Specifically, testing procedure M-F62601.01, entitled (b) (4) Injection, Testing Method: HPLC Identification and Assay, does not include examples of typical chromatograms (i.e., sample solution chromatograms) for analyst to use as reference when establishing suitable integration parameters and/or assessing for atypical peaks. For example, while reviewing assay stability data for (b) (4) Injection, Lots (b) (4) the integration for both samples were inhibited from (b) (4) This inhibition was noted to be performed to inhibit the integration of known peaks (e.g., excipients) in the samples. However, a review of the testing method, M-F62601.01, identified it only included a typical chromatogram of the working standard solution, which did not contain these peaks. It was explained, analyst can reference the method validation report to verify common peaks when establishing integration parameters, however, the typical chromatograms which document these peaks are not included in the routine standard testing procedures used by analyst.

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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."