DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032; Rockville, MD 20857 email: ORAPHARMInternational483responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	05/22-05/30/2023
	FEI NUMBER 3009831352

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. FU Jinglong, General Manager

FIRM NAME	STREET ADDRESS
Qilu Antibiotics Pharmaceutical Co., LTD.	849 Dongjia Street
CITY, STATE AND ZIP CODE Licheng District, Shandong 250105	TYPE OF ESTABLISHMENT INSPECTED Manufacturer

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

OBSERVATION 1:
Procedures designed to prevent microbiological contamination of drug product purporting to be sterile are not followed. Specifically,
a. The process simulations do not represent actual production operations for your sterile API in Unit (b) (4) of Workshop (b) (4) APIs filled in Unit (b) (4) (Sterile (b) (4) and Sterile (b) (4) are used to manufacture sterile injectable products distributed to the U.S. market.
(b) (4) Sterile (b) (4) batches were manufactured in manufacturing campaign from 13 June 2022 to 25 August 2022 (74 days) without cleaning or sterilization of manufacturing equipment. At the end of the campaign and prior to initiation of Media fill # (b) (4) equipment with sterile product contact surfaces were cleaned by (b) (4)
i. The (b) (4) cycle on 26 August 2022 for (b) (4) 33105 was (b) (4) and (b) (4) 3106 was (b) (4) (b) (4) using (b) (4) of (b) (4) for each.
ii. The (b) (4) cycle on 28 August 2022 for (b) (4) 33101, (b) (4) 33102, (b) (4) 33103, and (b) (4) 33104 ranged from (b) (4) to (b) (4) using (b) (4) of (b) (4) for each.
iii. The (b) (4) cycle on 29 August 2022 for (b) (4) tank and API filling line was (b) (4) using (b) (4) of (b) (4)
iv. After (b) (4) an additional (b) (4) was added to equipment and this volume was used to calculate the level of residue and the quantity of (b) (4)

b. For Media fill # (b) (4) (b) (4) were reportedly placed in the drains to capture (b) (4) for the above listed equipment and subsequently emersed into (b) (4) media for media simulation incubation. There were no instructions and no documentation in the batch records for the ad

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	Cynthia Jim Suzanne N. Vallez	Cynthia Jim, CSO Dedicated Foreign Drug Cadre Suzanne N. Vallez, CSO	05/30/2023

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c. For Media fill #(b) (4) two separate preparations of non-sterile (b) (4) were dissolved in (b) (4) and used for contact with (b) (4) 3105 and (b) (4) 3106 (without (b) (4) After contact with equipment, all of the (b) (4) were (b) (4) (b) (4) and emersed into (b) (4) canisters of (b) (4) media for media simulation incubation. There were no instructions and no documentation in the batch records for the (b) (4) to each canister of (b) (4) to inhibit the antibiotic residues in production equipment.

d. For Media fill #(b) (4) two separate preparations of non-sterile (b) (4) were dissolved in (b) (4) and transferred to the (b) (4) The sterile (b) (4) preparations were dissolved using (b) (4) further transferred to the (b) (4) and transferred to the (b) (4) tank as (b) (4) The (b) (4) were filled on the Unit (b) (4) Sterile API filling line into canisters. Two separate preparations of sterilized (b) (4) media, with (b) (4) were (b) (4) filled into canisters, and incubated for media simulation. No (b) (4) was added to the (b) (4) encountering product contact surfaces.

e. For Media fill # (b) (4) incubation records for (b) (4) in (b) (4) media are lacking testing details.
i. The dates of incubation at (b) (4) C and movement to (b) (4) C were not documented in media fill testing records.
ii. The growth promotion records do not have documentation of inoculum verification.

f. The process simulations do not represent actual production operations for aseptic filling of finished product in Unit (b) (4) of Workshop (b) (4) Unit (b) (4) was used to fill (b) (4) batches, (b) (4) Injection.
i. Two preparation of (b) (4) was prepared for Media Fill # (b) (4) filled on 24 March 2023. The first preparation, (b) (4) was (b) (4) and filled starting from 8:26 am. The second preparation, (b) (4) was (b) (4) and filled starting from 2:03 pm. The firm reported preparing two media batches to prevent microbial build up for the expected (b) (4) filling operation, but this is not a practice performed for routine production.

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ii. Not all filled vials are incubated. Media Fill #(b) (4) conducted a fill of (b) (4) vial, but only incubated (b) (4) (b) (4) filled vials were not processed through the (b) (4) because the firm only planned for filling (b) (4) (b) (4) and the remaining vials were rejected.
iii. Not all media prepared are incubated as required by SOP # QUAL1009.B, Guideline of Aseptic Processing Simulation for FDF, "all media in the simulation should be incubated". The (b) (4) media in the (b) (4) tank (b) (4) was discarded for Media Fill #(b) (4)
iv. Two (b) (4) interventions were performed to correct malfunctions at the (b) (4) after (b) (4) for Media Fill # (b) (4) The firm is not able to trace when vials are filled to link filling to specific interventions performed.

OBSERVATION 2:
Adequate exhaust systems or other systems to control contaminants are lacking in areas where air contamination might occur during production.
a. Smoke studies performed in Unit (b) (4) of Workshop (b) (4) do not demonstrate airflow without turbulence. The filling line was used to fill (b) (4) batches of (b) (4) product (b) (4) Injection. For example,
i. The dynamic smoke study videos showed the (b) (4) of vials, vials traveling on the vial track line, movement of (b) (4) stoppering action, and travel out of the filling line, but the video view is narrow. The videos show closeup views of the vials and do not demonstrate smoke from (b) (4) to the vial filling line is without turbulence.
ii. The study does not show the impact on smoke flow during (b) (4) manipulations. 15 (b) (4) manipulations were demonstrated during the smoke study, but the flow of smoke is not near the (b) (4) where the operator is performing an intervention.
iii. The smoke study videos showed allowed interventions using (b) (4) but the view is narrow (only a closeup view of vials) and does not demonstrate the flow of smoke is without turbulence from (b) (4) to the vial filling line.

iv. Personnel are required to pass through the Grade A filling line to access the backside of the filling line for every filling operation. The intervention requires (b) (4) lifting the vial track line, walking through to the other side, and (b) (4) to access the backside of the filling line. No smoke study was performed demonstrating the impact of (b) (4) lifting the vial track line, or a person walking through the Grade A filling line.

b. Smoke studies performed in Unit (b) (4) of Workshop (b) (4) do not demonstrate airflow without turbulence. The filling line was used to fill (b) (4) batches of (b) (4) product (b) (4) Injection. For example,
i. The dynamic smoke study videos showed the (b) (4) of vials, vials traveling on the vial track line, movement of (b) (4) stoppering action, and travel out of the filling line, but the video view is narrow. The videos show closeup views of the vials and do not demonstrate smoke from (b) (4) to the vial filling line is without turbulence.
ii. The study does not show the impact on smoke flow during (b) (4) manipulations. 10 (b) (4) manipulations were demonstrated during the smoke study, but the flow of smoke is not near the (b) (4) where the operator is performing an intervention.
iii. The flow of smoke over (b) (4) vials on the path to the (b) (4) were not covered by smoke study. (b) (4) vials travel a distance of (b) (4) before reaching (b) (4) # (b) (4) 37101; (b) (4) vials travel a distance of (b) (4) before reaching (b) (4) # 37102; and (b) (4) vials travel a distance of (b) (4) before reaching (b) (4) # 37103.
iv. The smoke studies for the loading of (b) (4) vials for (b) (4) # (b) (4) 37102 and (b) (4) # (b) (4) 37103 is insufficient to demonstrate the impact of airflow during movement of vials into the

OBSERVATION 3:
Aseptic processing areas are deficient regarding the system for monitoring environmental conditions. Specifically,

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a. Monitoring of nonviable particles on Unit (b) (4) filling line of Workshop (b) (4) is not located within (b) (4) of the vial track where (b) (4) vials move towards the (b) (4) The point where vials turn left towards the (b) (4) is monitored by an online nonviable particle port that is located (b) (4) from the vial track.

b. Personnel working in the aseptic filling lines are not required to monitor gloves and gown for each exit as required by SOP QCJ723L, Microbiological Monitoring of Aseptic Processing Environments, which requires for Grade A and Grade B personnel, "before exiting from the aseptic room, the operator will be sampled". Operators in all the FDF filling suites are allowed to exit as needed but are only required to sample upon final exit.

c. (b) (4) used in the formulation of sterile FDF product in Unit (b) (4) of Workshop (b) (4) is not monitored at point of use. (b) (4) (b) (4) is collected in a (b) (4) tank and the (b) (4) from this tank is used for compounding (b) (4) product (b) (4) Injection. The point of use is not monitored.

OBSERVATION 4:
Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity. Specifically,

a. Sterility testing of sterile injectable products distributed to the U.S. market requires determination of microbial growth in (b) (4) canisters. There is no requirement to document a check for the (b) (4) for each read and also at final evaluation for microbial growth.

b. Environmental monitoring samples, water samples, and product bioburden samples are incubated on (b) (4) plates which are placed in the incubators stored in plastic bags. The firm has not conducted a study which demonstrates no impact on the growth of environmental isolates and other stressed organisms.

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c. Growth promotion testing of media fill samples do not have verification of the inoculum of microbial organisms.

OBSERVATION 5:
The responsibilities and procedure applicable to the quality control unit are not in writing. Specifically,
Your firm does not have established training procedures to oversee the initial and requalification of aseptic filling operators and visual inspection personnel for workshop (b) (4) units (b) (4)
A. Your firm has one SOP titled QUAL116.P "Training for Manufacturing and Quality System Personnel" governing the training program in workshop (b) (4) units (b) (4) This procedure lacks quality oversight in the qualification process for aseptic filling personnel's gowning qualification and media fill participation requirements and qualification of visual inspection personnel. The procedure fails to establish set requirements for each specified training, identify the process for qualification and delegate the responsibilities to each department reviewing and approving personnel qualifications.

B. Your Quality Manager recognized that the qualification record for visual inspection personnel is solely the completion of the (b) (4) defect test form number PLA1160.ATCH-02-F03. The reviewer signature is not always the QA personnel and visual inspection personnel can be approved for requalification by production workshop personnel.
C. The (b) (4) eye exam record received from the doctor does not provide details on the test evaluation preformed. The test does not discuss if personnel was tested for far-sight or near sight vision. Additionally, there are no procedures discussing the review of this record for the qualification of visual inspection. Quality Manager confirmed that the eye exam information is not reviewed to qualify personnel.

D. Review of the media fill batch record (b) (4) dated 06/01/2022 and batch record 01/12/23 showed an aseptic operator not receiving sampling training for either media fill conducted within (b) (4) The simulation protocol and report for unit (b) (4) workshop (b) (4) dated 01/18/2023 indicates that the operator is required to complete the sampling training but does not show as completed over the last two media fills. The operator is still participating in aseptic filling activities as an operator since 01/18/2023. There is no procedure establishing operators as different roles and tasks and needing different media fill requirements.

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