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	05/11/2023-05/19
	FEI NUMBER 3008250362

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Ms. Sun Yanyan, General Manager

FIRM NAME	STREET ADDRESS
Qilu Pharmaceutical (Hainan) Co., Ltd.	No. 273-A Nanhai Avenue, National High-Tech Zone
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Haikou, Hainan 570314	Manufacturer

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

Observation 1:
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 Workshop (b) (4) do not demonstrate airflow without turbulence. For example,
i. The smoke study at the vial (b) (4) in front of the (b) (4) showed turbulence, up flow of smoke over the (b) (4) area of the (b) (4)
ii. The vial track after (b) (4) near the (b) (4) showed turbulence, up flow of smoke near the (b) (4)

b. Not all activities on the Workshop (b) (4) vial filling line is covered by smoke study and not all smoke studies performed demonstrated airflow without turbulence. For example,
i. The (b) (4) at (b) (4) number 5G17 required a (b) (4) intervention for the smoke study. The operator is shown collecting (b) (4) vials from the vial track with smoke returning from the (b) (4) into the filling line.
ii. The smoke study in the LAF used to (b) (4) sterilize stoppers is insufficient to demonstrate the flow of smoke during (b) (4) operations.
iii. The smoke study does not cover activities at the stoppering station, and does not cover collection of environmental monitoring samples.
iv. No smoke study covers the vial track leading to the (b) (4)

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Observation 2:

Procedures designed to prevent microbiological contamination of drug product purporting to be sterile are not followed. Specifically,

a. Media fills conducted in Workshop (b) (4) are deficient in assuring sterile injectable products that are distributed to the U.S. market are aseptically filled. The filling line is used for filling (b) (4) sterile injectable (b) (4) products that are distributed to the U.S. (b) (4)
(b) (4)

i. There is no assurance that media filled vials are visually inspected for microbial growth after (b) (4) of incubation. Media Fill lot # (b) (4) laboratory test records indicates that (b) (4) individuals confirmed "no growth" of (b) (4) vials in (b) (4) (representing (b) (4) vials per minute per person, excluding time to move trays). The firm explained that SOP # QC-3333-05, Incubation of Media Filled Units, allows examination of vials without removing them from the trays. Vials were not picked up individually for visual examination, instead the trays containing (b) (4) vials each stayed in the trays to determine no growth in the vials.

ii. The visual inspection performed at the end of incubation of the media filled vials are conducted in a manner that does not provide assurance that each media filled vial is inspected for microbial growth according to SOP # QC-333-05, Incubation of Media Filled Units, which requires, observe one by one against a light "carefully". For example, Media fill # (b) (4) visual inspection record dated 19 December 2022, indicates (b) (4) trays of media filled vials, containing (b) (4) vials per tray, were examined in (b) (4) vials per minute, not including time to transfer trays).

iii. Media fills do not include use of the (b) (4) transfer pipe used to transfer commercial products distributed to the U.S., from the compounding tank to the filling line. Media fills are set up to bypass the transfer pipe and instead will use (b) (4) hoses to transport media from the compounding tank to the filling line.

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iv. Media fills conducted in Workshop #(b) (4) are not representative of (b) (4) Injection (a product distributed to the U.S.). (b) (4) Injection is filled into a (b) (4) mL vial with a (b) (4) mm vial opening, whereas all media fills for (b) (4) products are conducted using (b) (4) mL vials with (b) (4) mm opening. The last time a (b) (4) mL vial with a (b) (4) mm vial opening was used for media fill as in December 2017.

v. A total of (b) (4) interventions were performed for Media fill # (b) (4) which required simulation of removing a vial with incorrect stoppering. (b) (4) subsequent vials were marked each time the intervention was performed but the vials were not uniquely identified to show where the intervention occurred.

b. Media fills conducted in Workshop (b) (4) are deficient in assuring sterile injectable products that are distributed to the U.S. market are aseptically filled. The filling line is used for filling (b) (4) sterile injectable products that are distributed to the U.S. (b) (4)

i. Media fill for Workshop (b) (4) are not always performed within the (b) (4) timeframe as required by SOP GR-0055-06, Guidelines for Validation of Production Process. In 2021, media fill was performed in FEB 2021 with next media fill conducted in (b) (4)

ii. There is no assurance that media filled vials are visually inspected for microbial growth after (b) (4) of incubation. Media Fill lot # (b) (4) laboratory test records indicates that (b) (4) individuals confirmed "no growth" of (b) (4) vials in (b) (4) (representing (b) (4) vials per minute per person, excluding time to move trays). The vials were not picked up individually for visual examination, instead the trays containing (b) (4) vials each stayed in the trays to determine no microbial growth in the vials.

iii. The visual inspection performed at the end of incubation of the media filled vials are conducted in a manner that does not provide assurance that each media filled vial is inspected for microbial growth according to SOP # QC-333-05, Incubation of Media Filled Units, which requires, observe one by one against a light "carefully". For example, Media fill # (b) (4) visual inspection record dated 06 May 2023, indicates (b) (4) trays of media filled vials, containing (b) (4) vials per tray, were examined in (b) (4) vials per minute, not including time to transfer trays).

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

a. Personnel working in Workshop (b) (4) aseptic filling operations were observed taking finger samples prior to exit of the filling suite. Personnel simulated personnel monitoring and were observed touching the (b) (4) plate with fingertips that reach beyond the (b) (4) plate. The (b) (4) plate was not of sufficient size to capture placement of four fingers (other than thumb) at the same time.

b. Not all tools used during aseptic filling operations, including tweezers which are used to pick up vials and stoppers, are monitored.

c. Nonviable particle monitoring is performed (b) (4) per filling operation: (b) (4) liters in the Grade B surrounding the Grade A filling line. One filling operation could be (b) (4) long. There is no instructions on when the sample should be obtained and could be obtained in static condition.

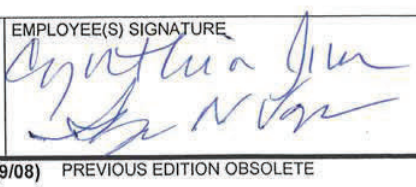
d. Active air monitoring in Workshop (b) (4) is (b) (4) performed (b) (4) before equipment setup and not during filling operations.

e. The location where personnel stand and document in the batch record (outside the (b) (4) loading/unloading) is not monitored.

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

Specifically, (b) (4) batches of (b) (4) API lot number (b) (4)

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were accepted from the manufacture with an impurity (b) (4) value of (b) (4) ppm, which is historically higher than the normal accepted API range of (b) (4) ppm to (b) (4) ppm. These (b) (4) API lots were used in the manufacturing of the (b) (4) finished product batches for (b) (4) lots (b) (4) (b) (4) The finished product testing for impurity (b) (4) also showed the batches at historically high values of (b) (4) ppm respectively. The normal finished product range is between (b) (4) ppm to (b) (4) ppm for all other U.S and domestic batches.

An investigation was conducted for (b) (4) finished batches with out of trend impurity (b) (4) results. Of the finished batches, lot (b) (4) was rejected for its impurity level at (b) (4) ppm. Batch number (b) (4) was rejected in anticipation that based on the 24-month completed stability data the maximum degradation value is (b) (4) ppm and lot (b) (4) might meet the impurity (b) (4) threshold of no more than (b) (4) ppm. The remaining (b) (4) lots (b) (4) (b) (4) were approved for released on April 25th, 2023, by the QP.

For the (b) (4) marketed product with 0-month value ranging from (b) (4) ppm to (b) (4) ppm. The completed long-term, accelerated and stress test stability conditions do not have the rational to support the (b) (4) shelf-life for impurity (b) (4) with high values of (b) (4) ppm to (b) (4) ppm at month 0. All the completed lots on long-term and accelerate study have a starting impurity (b) (4) value of (b) (4) ppm for 0-months and the stress study has a starting impurity (b) (4) value of (b) (4) ppm at 0 months. The (b) (4) batches currently on stability also have low starting impurity (b) (4) values of (b) (4) at 0-months. Your firm does not have the scientific rational for concluding these lots (b) (4) (b) (4) will not exceed specification by the end of shelf life.

Observation 5:
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,

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a. Sterility testing of sterile injectable products distributed to the U.S. market requires determination of microbial growth in (b) (4) canisters. Microbiologist were observed on 16 May 2023 failing to ensure that the (b) (4) was present prior to performing the inspection of the (b) (4) canisters. There is no requirement to document a check for the (b) (4) and there is no assurance that the canisters observed without the (b) (4) on 16 May 2023 could support growth of anaerobic organisms.

b. The second review of the sterility test results is not performed before the second reviewer can examine the (b) (4) canisters for growth prior to disruption of the media by swirling the sample.

Observation 6:
Complaint procedures are deficient in that they do not include provisions that allow for the review to determine if the complaints represent serious and/or unexpected adverse drug experiences which are required to be reported to FDA. Specifically,

a. 21 of 28 reports of adverse events received have been closed classified as "Invalid report [lack of identifiable information of the patient]) because the firm has not been able to gather complete information to complete reporting requirement. Pharmacovigilance Agreements are made with U.S. distributors for the distributors to provide this firm with adverse event information. The agreement does not specify type of "patient" information the distributors agree to provide this firm.

b. Adverse event investigation was initiated for report of "Death" received 06 February 2023 regarding (b) (4) lot # (b) (4) but no information was obtained from the reporter. The reporter is a U.S. distributor who declined to provide information due to "HIPPA Law in the USA". The request made to the distributor was for "patient's information" including patient's initials.

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c. The Pharmacovigilance Agreement with distributors does not clarify the responsibility of the distributor to provide all requirement information needed for this firm to comply with FDA reporting requirements.

Observation 7:
The calibration of instruments is not done at suitable intervals. Specifically,
a. The temperature probes in (b) (4) incubators (b) (4) used for incubation of media filled vials, environmental monitoring samples, product bioburden samples, sterility test samples, etc., cannot be accessed for calibration. Instead, a temperature map of the incubators is performed (b) (4)

b. The function of the alarms in the (b) (4) incubators (b) (4) is tested (b) (4)

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