DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

| DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
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| 12420 Parklawn Drive, Room 2032 Rockville, MD 20857<br>Industry Information: www.fda.gov/oc/industry | 08/29-31/2019 - 09/03-06/2019 |
| | FEI NUMBER<br>3008316085 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Vikram Shukla - Site Head

| FIRM NAME | STREET ADDRESS |
|---|---|
| Pfizer Healthcare India Private Limited | Plots 116-117-118-119-111-123(Part), Jawaharlal Nehru |
| CITY, STATE AND ZIP CODE | TYPE OF ESTABLISHMENT INSPECTED |
| Pharma City, ParVisakhapatnam, Andhra Pradesh, 531019, India | Sterile Drug Product Manufacturer |

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

***AMENDED FDA 483***

PRODUCTION SYSTEM

OBSERVATION 1

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

A. Section 7.1.20 of Procedure no. SOP-98457, titled, Microbiology Laboratory Test Failure Investigation Procedure; effective on 18 Mar 2019, states, "When no assignable cause associated with lab error is found for sterility test, test shall not be repeated, and the lot shall be rejected."

On 25 Feb 2019, sterility testing of (b) (4) % (b) (4) Injection (b) (4) mL: Lot (b) (4) was performed by closed method (b) (4) system in Biological Quality (BQ) lab area, (b) (4) TQME205. Growth was observed in (b) (4) medium (b) (4) canister at the 7th day read for sterility samples. Quality Alert Report (QAR) Investigation PR #2627773 was initiated and disclosed the growth observed in Lot (b) (4) (Run (b) (4) , that was terminally sterilized. The Lot (b) (4) % (b) (4) Injection (b) (4) mL, was filled on (b) (4) Line (b) (4) This batch was sterilized in (b) (4) cycles (i.e. Runs (b) (4) The sterility test results for the other runs of Lot (b) (4) met the requirements for MCD-066107 specification titled "Sterility Test By (b) (4) effective 24 Apr 2018, which states in Sub-Section 5.2.3 "If no evidence of microbial growth is found, the product examined complies with the test for sterility."

The organism isolated was identified as Gram-positive cocci "Kocuria palustris". According to your investigation, this organism inhabits in the skin and mucous membrane of human and animals. During the period of January 2018 through 19 August 2019, Kocuria palustris was recovered approximately 85 times from different sources (i.e.

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EM (b)(4) Block, EM BQ lab, water samples, rinse samples and swab samples). Subject organism was also recovered during EM monitoring of the BQ lab, the same day (25 Feb 2019) that sterility testing for (b)(4) % (b)(4) (b)(4) Injection (b)(4) mL; Lot (b)(4) was carried out. The organism was recovered at the center of the room (Location ID (b)(4)). The count observed was (b)(4) cfu. The established Alert limit is Not More (b)(4) cfu/m3. Per QAR PR #2627773, Kocuria palustris is present in the environment of the (b)(4) area/BQ lab; therefore, is not uncommon in the facility.

Based on the Investigation QAR PR #2627773, and without any evidence to support your conclusion, you determined that the most probable causes of the sterility positive test results obtained from Run (b)(4) of Lot (b)(4) (b)(4) % (b)(4) Injection (b)(4) mL were: the lack of robust (b)(4) integrity testing and the potential of creating a non-integral vial during manufacturing or transfer of the samples from production to BQ lab.

Furthermore, the data available clearly indicates that:

- All the (b)(4) visual examinations carried out during pre-cleaning/post-cleaning process for (b)(4) 205 were found satisfactory.
- Pre/post leak testing performed in (b)(4) TQME 205 were within acceptance criteria.
- No discrepancy was observed during (b)(4) cycle performed in (b)(4) TQME 205.
- Average pressure value for (b)(4) TQME 205 was within acceptance criteria.
- During the sterility testing, settle plates were exposed to monitor the (b)(4) for microbial contamination, and the environment within the (b)(4) monitored on surfaces, (b)(4) and air, showed No growth.
- After the positive was observed in Lot (b)(4) approximately (b)(4) lots were analyzed in (b)(4) TQME 205 for sterility testing (25 February 2019 to 15 March 2019). No discrepancy was observed. On 15 March 2019, the (b)(4) TQME 205 were replaced.

Your investigation QAR PR #2627773 did not consider other potential factors that could contribute with the positive result such as defects related to the integrity of the sample (i.e. container closure systems). Therefore, no unequivocally root cause was identified for the sterility positive results obtained. (b)(4) Injection (b)(4) % (b)(4) mL, Lot (b)(4) was rejected.

B. On 08 Apr 2019 your BQ lab, plate reading team observed Over Action Level (OAC) excursions in active air sampling location (ID (b)(4) located near the (b)(4) in your

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sterility testing (b) (4) TQME 205. This EM monitoring was performed at end of sterility analysis on 02 Apr 2019. The product tested during the monitoring were: (b) (4) Injection (b) (4) mg/mL (b) (4) mL; Lot (b) (4) and (b) (4) Injection USP (b) (4) mL, Lot (b) (4) respectively. The EM result obtained was (b) (4) cfu/m3. The established acceptance criteria is (b) (4) m3.

After the microbial excursion of 02 Apr 2019, several EM excursions were also observed in sterility testing (b) (4) TQME 205 during the period 02 Apr 2019 to 11 Jun 2019. Approximately, 15 investigations were initiated due to EM excursions observed in your sterility testing (b) (4) TQME 205 during the referenced period. QAR Investigation PR #2666606 was initiated to identify the potential source(s) of contamination for the series of EM excursions observed in (b) (4) TQME 205. Per QAR Investigation PR #2666606, the excursions were observed in 2 settle plates monitoring sessions, 14 air sampling sessions and 9 (b) (4) monitoring sessions. The microorganisms recovered are: Bacillus cereus, Pseudomonas stutzeri, Micrococcus luteus, Staphylococcus cohnii ssp, Staphylococcus hominis and Staphylococcus haemolyticus, respectively.

Based on the Investigation QAR PR #2666606, the root causes for this trend in EM excursions of the (b) (4) TQME 205 are:

(b) (4) integrity testing methodology
•Improper fixing of (b) (4) connectors creating air pockets
•Fast (b) (4) movement during production phase creating negative pressure inside the (b) (4)
(b) (4) not in open state during bio decontamination phase
•Open drain line during analysis allowing ingress of outside air into (b) (4)
•Air sample by (b) (4) technique using MD8 air scan sampler.

Nonetheless,

•All the (b) (4) visual examinations carried out during pre-cleaning/post-cleaning process for (b) (4) 205 were found satisfactory.
•Pre/post leak testing performed in (b) (4) TQME 205 were within acceptance criteria.
•No discrepancy was observed during (b) (4) cycle performed in (b) (4) TQME 205.

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•Average pressure value for (b) (4) TQME 205 was within acceptance criteria.

NOTE: Between July 2018 to September 2019, your firm has observed one (1) sterility failure, one (1) recall and one (1) DI event, which have resulted in several FARS submitted to the agency. These adverse events in combination with the deficiencies found during current FDA inspection are indicative that your Quality Unit has not taken the necessary steps to fully ensure the adequacy of the sterile operations, the accuracy of the analytical test results and that each event reported during manufacturing or testing are appropriately investigated.

QUALITY SYSTEM

OBSERVATION 2

The responsibilities and procedures applicable to the quality control unit are not fully followed.

A. Your Quality Unit failed to conduct a thorough evaluation of the Direct/Indirect (b) (4) alarms to establish preventive actions for minimizing and decreasing the likelihood of re-occurrence. Specifically,

1. On 05 Feb 2019 the manufacturing operator identified "Operating (b) (4) Excess" (Direct/Indirect) alarms during the sterilization of (b) (4) % (b) (4) mL, Lot (b) (4) Run (b) (4) in (b) (4) TSSE003.

Specifically, (b) (4) sensor showing fluctuations and sterilization cycle went to emergency phase. However, phase step utilized, and cycle continued from sterilization phase after resuming the cycle "Sterilization (b) (4) lack" and "Sterilization time suspended" alarms" observed. Investigation QAR PR #2590733 was initiated and disclosed the parametric release table was not in compliant. (b) (4) of functioning (b) (4) sensors (b) (4) (b) (4) were within limits. Nonetheless, the investigation revealed that only (b) (4) of malfunctioning (b) (4) sensor (b) (4) was found out-of-limit. Per procedure VTPD037, one (1) sensor alone can represent (b) (4) (b) (4) value) of sterilization cycle. As a corrective action, (b) (4) sensor was replaced with new (b) (4) sensor and calibrated. The incident was classified as unexpected malfunctioning of (b) (4) sensor. Hence, no further preventive actions. There is no impact to product quality for (b) (4) % (b) (4) mL, Lot AP (b) (4) Run (b) (4) Nonetheless, Lot (b) (4) was later rejected due to a positive sterility test.

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2. On 30 Jan 2019 the manufacturing operator identified that the sterilization phase (Phase (b) (4) was exceeded by (b) (4) as observed dwell time value is (b) (4) against set value of (b) (4) during the sterilization of (b) (4) Injection (b) (4) mL; Lot (b) (4) Run (b) (4) in (b) (4) TSSE002. Investigation QAR PR #2585749 was initiated and disclosed the parametric release table was not in compliant. Specifically, (b) (4) sensor errors were found out-of-limits. (b) (4) of functioning (b) (4) sensors (b) (4) (b) (4) were within limits. Nonetheless, the investigation revealed that only (b) (4) of malfunctioning (b) (4) sensor (b) (4) was found out-of-limit. Per procedure VTPD037, one (1) sensor alone can represent (b) (4) (b) (4) value) of sterilization cycle. As a corrective action, (b) (4) sensor was replaced with new (b) (4) sensor and calibrated. The incident was classified as unexpected malfunctioning of (b) (4) sensor. Hence, no further preventive actions. There is no impact to product quality for (b) (4) Injection (b) (4) mL; Lot (b) (4) Run (b) (4)

3. On 16 Nov 2018, the manufacturing operator observed the "Steriliz (b) (4) Excess" alarm at sterilization phase during execution of (b) (4) % (b) (4) Injection (b) (4) mL; Lot (b) (4) Run (b) (4) in (b) (4) TSSE006. Investigation QAR PR #2493768 was initiated and disclosed the parametric release table was not in compliant. As part of the investigation, the (b) (4) sensor (b) (4) sensor) was verified and found (b) (4) sensor error not within the limit. As a corrective action the (b) (4) sensor was replaced with new (b) (4) sensor and calibrated. The incident was classified as unexpected malfunctioning of (b) (4) sensor. Hence no further preventive actions. (b) (4) % (b) (4) Injection (b) (4) mL; Lot (b) (4) Run (b) (4) was rejected.

4. On 29 Oct 2018, the manufacturing operator observed the "(b) (4) Excess" and "Operating (b) (4) Excess" alarms during Run (b) (4) in (b) (4) TSSE002 of the (b) (4) % (b) (4) mL ampoule; Lot (b) (4) Investigation QAR PR #2470625 was initiated and disclosed the parametric release table was not in compliant. As part of the investigation, the (b) (4) sensor (b) (4) sensor) was found to be malfunctioned. The (b) (4) sensor (b) (4) is a (b) (4) instrument. The (b) (4) of the sensor was verified at (b) (4) and found to be (b) (4) As the (b) (4) sensor is a (b) (4) type, if the (b) (4) is (b) (4) then it will show (b) (4) Thus, the (b) (4) on the Human Machine Interface (HMI) was shown (b) (4) As a corrective action the (b) (4) sensor was replaced with new (b) (4) sensor and calibrated. The incident was classified as unexpected malfunctioning of

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(b) (4) sensor. Hence no further preventive actions. (b) (4) % (b) (4) mL ampoule; Lot (b) (4) Run (b) (4) was rejected.

5. On 8 Oct 2018, the manufacturing operator observed the "(b) (4) Monit. Calc Suspended" and "Operating (b) (4) excess" alarms during Run (b) (4) in (b) (4) TSSE006 of the (b) (4) mL plastic vials; Lot (b) (4) Investigation QAR PR #244727 was initiated and disclosed the parametric release table was not in compliant. As part of the investigation, the (b) (4) sensor (b) (4) was found to be malfunctioned. As a corrective action the (b) (4) sensor (b) (4) was replaced with new (b) (4) sensor and calibrated. The incident was classified as unexpected malfunctioning of (b) (4) sensor. Hence no further preventive actions. (b) (4) mL plastic vials; Lot (b) (4) Run (b) (4) was rejected.

B. Your Quality Unit failed to ensure that all biological quality laboratory operations are adequately implemented. For example, between September 2017 – July 2018 a total of fifty-nine (59) instances were reported due to recovery of microbial growth in negative control plates collected during viable EM sessions in the (b) (4) manufacturing area. The number of positives results obtained in your negative controls demonstrates the Quality Unit does not ensure that each event reported during testing are appropriately investigated and resolved with an effected CAPA. Moreover, the objectionable conditions documented during the inspection suggest that personnel may not have the necessary understanding or training with respect to the controls/procedures and CGMP activities they perform in the BQ lab.
Procedure no. SOP-98433, titled, "Receipt, storage and handling of De-Hydrated Media and Ready to Use Media", effective on 11-Jun-2018, states the following:

•Section 7.1.4 "The material does not meet visual inspection requirements when there is evidence that material had been compromised. In this case, inform the same to Quality Control-Microbiology laboratory management personnel or his designee and take corrective action by informing to vendor who has supplied the material."
•Section 7.1.7 "Visually inspect the materials for the pack integrity and the details on the packing. Ensure the materials are stored as per the manufacturers storage recommendations."
•Section 7.4.3 "Discard the Ready to Use Media that shows signs of cracks, dehydration, moisture, discoloration and any contamination."
In addition,

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Procedure no. SOP-98510, titled, "Environmental Monitoring Program in (b) (4) Block (b) (4) Block)", effective on 12 Mar 2018, states "Inspect visually each media plate at a minimum for cracks, over fill, low fill, air bubbles and contamination before starting the environmental monitoring activity".
On 01 Jun 2018, QAR Investigation PR #2298791 was initiated due to the incidents related to microbial growth in negative control plates during EM in the (b) (4) manufacturing area. The investigation disclosed, the media upon receipt to the site is quarantined and is released for usage upon successful completion of testing (e.g. growth promotion test and pH) and found within the acceptance criteria. Media plates are also inspected at the time of use for contamination/cracks/dryness/particles/damages etc. If any discrepancies are observed the plates are not be used.

Per QAR Investigation PR #2298791, the media plate lots used for EM between September 2017 to July 2018 were: (b) (4) respectively. There were 13 cases for negative control failures reported using media Lot (b) (4) (b) (4) and there were 7 cases for negative control failures reported using media Lot (b) (4) In addition, the investigation revealed that during the period of 20 May 2018 to 14 Jul 2018, there were occurrences where incubation time was extended more than (b) (4) During that period, the negative controls reported growth in 19 times for EM. Gram nature of organism identified confirmed that Gram negative, Gram positive organisms and fungal colonies were isolated.

QAR Investigation PR #2298791 did not establish a definitive root cause for the failures of negative control plates. However, the investigation identified moisture in the inner pack of the media plates as a vector to carry the contamination from extraneous environment during handling. The root cause for the moisture on the media plates could be due to variation in shipping and storage temperatures. Nonetheless, media plate Lots (b) (4) were found within acceptance criteria for appearance, color, pH and growth promotion test. No discrepancy was observed either during incoming evaluation or before use examination.

In addition,

On 24 Oct 2018, QAR Investigation PR #2465140 was initiated, due to testing plates were not released within the incubation time. Per subject investigation, "the microbial recovery obtained from the plates that are impacted by

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the extended incubation are most likely elevated and are not a true representation of the conditions maintained during the manufacturing of the impacted batches. Hence the data is not reliable".

The control procedure no. SOP-98510, Section 7.10.4 states "Incubate all the monitored plates and negative control plates in inverted position at (b) (4) °C for (b) (4) and followed by (b) (4) °C for (b) (4) .
QAR Investigation PR #2465140 disclosed that approximately 113 batches were potentially impacted due to the extended incubation period. The results obtained from the plates impacted showed results below defined alert level, exceeded the alert/action levels and recovery of the negative control plates. In addition, Gram positive spore forming rods, Gram negative rods and fungal isolates were identified in EM of (b) (4) of (b) (4) Block (b) (4) Per QAR Investigation PR #2465140, since the incubation period was extended for these plates, the obtained results may not represent the true and are considered as not reliable. In addition, subject investigation revealed that several EM and the corresponding negative control plates that have been incubated beyond the timeline have shown a fungal growth. The most probable root cause for the recovery of objectionable organism and fungi is extended incubation.

FACILITIES AND EQUIPMENT SYSTEM

OBSERVATION 3

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

Your firm failed to validate the disinfectants solutions used on surfaces in non-dedicated manufacturing areas (e.g. filling and stoppering machines), other facility-controlled areas and BQ laboratory are effective in inactivation or removal of Gram-positive cocci Kocuria palustris organism.

Specifically, the study performed to validate the efficacy of the disinfectant solutions titled "Disinfectant Validation Programme in-Vizag Facility"; Protocol No. VM 14053; approved on 06 Sep 2014, failed to evaluate and demonstrate the efficacy of the disinfectants (i.e. (b) (4) (b) (4) against Gram-positive cocci Kocuria palustris. For the period from January 2018 to May 2019, this organism has been recovered in at least 85 times from different sources (i.e. EM (b) (4) Block, EM BQ lab, water

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samples, rinse samples and swab samples). Moreover, it cannot be assured that the microorganisms selected for evaluation in Protocol VM 14053 represent the current flora of the site, due to the increase in the manufacturing operations/number of operators/flow of materials.

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