DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	3/18/2024-3/27/2024* FEI NUMBER 3007621329

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Prashant Sharma, Chief Technical Officer

FIRM NAME	STREET ADDRESS
Zydus Lifesciences Limited	Plot 1a, 8a Pharmez Special Economic Zone; Sarkhej-Bavla N H No
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Matoda, Gujarat, 382213 India	Human Sterile Drug 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 WE OBSERVED:

OBSERVATION 1

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically,

A. From May 2023 until December 2023, your firm manufactured and distributed human drug products intended to be sterile when your environmental monitoring program for viable microorganisms was not in a state of control. During this time period, you documented 337 action level environmental monitoring excursions for bacterial and fungal recoveries in Grade-A and B aseptic processing areas for aseptic filling line (b) (4) to include critical aseptic filling areas, equipment, and personnel. Your firm's actions in response to the environmental monitoring excursions are inadequate as noted below:

- Your firm documented moisture and microbial contaminated (b) (4) environmental monitoring plates received from your supplier in July 2023 in excursion investigation IMDD-EM/23/010 (media lot (b) (4) Despite the documented contamination of the media plates themselves, your firm attributed multiple action level environmental monitoring excursions for the line (b) (4) aseptic manufacturing area and the plate contamination to a contaminated incubator and continued using (b) (4) plates from the same supplier until December 2023. In December 2023, your firm again documented (b) (4) media lots not meeting your acceptance criteria (b) (4) media lots (b) (4) The potentially

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contaminated plates from (b) (4) media lots (b) (4) were utilized in aseptic processing areas (line (b) (4) during drug product manufacture to include for (b) (4) Injection (b) (4) mg/ml lot (b) (4) (media lot (b) (4) which was shipped for the US market on (b) (4)

- Your firm's retrospective evaluation of media used in your environmental monitoring program conducted for laboratory investigation LIN-0318-2023-0206 (Attachment-XVIII, conducted December 2023) for a failed negative control during aseptic processing line (b) (4) environmental monitoring, is inadequate as a media lot with previous unacceptable and failing results was evaluated and documented as compliant. For example, (b) (4) lot (b) (4) was documented as compliant in the retrospective evaluation conducted in December 2023, however, moisture and microbial contamination (bacterial and fungal) of the media lot was documented 5 months earlier in excursion investigation IMDD-EM/23/010.

B. Your firm's airflow visualization studies (smoke studies) are inadequate for aseptic filling line (b) (4) as they use insufficient smoke to demonstrate unidirectional airflow and they demonstrate inadequate aseptic technique as exampled below:

- Insufficient smoke was noted in the 2021 smoke studies videos to include:
  - Shoot 10: During unloading of sterile items from the (b) (4) LAF to the RABS, insufficient smoke is visible (b) (4) the RABS to demonstrate unidirectional non-turbulent airflow (for example during transfer of (b) (4) from 16:27:32-16:27:43, camera (b) (4)
  - Shoot 35: During (b) (4) assembly, no smoke is observed over the operator's hands as critical operations are performed (for example from 10:46:53 to 10:47:11, camera (b) (4)

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- Shoot 36: During aseptic connection of fill tubing from the (b) (4) vessel to the (b) (4) (b) (4) inadequate smoke is observed near the critical area where the fill tubing is aseptically connected to the (b) (4) (for example from 11:48:53 to 11:49:49, camera (b) (4)

- Inadequate Aseptic Technique - In shoot 35-camera (b) (4) the operator's sleeve appears to rest against the fill tubing and (b) (4) assembly (b) (4) the RABS at 10:47:11 to 10:47:50 and extensively contacts the tubing and (b) (4) assembly again at 10:49:43 to 10:50:00. Procedure 0318-SOP-MFG-00028 "Operation of Vial Filling and Stoppering Machine" states in item 6.7.33, "During (b) (4) assembling, ensure that garment should not touch the any machine part of filling and stoppering machine." The operator's practices in the smoke study are inconsistent with the instructions in the procedure. Installation of the (b) (4) as shown in the video is inadequately designed as it requires the operator to reach over the fill line causing the operator's gowning to contact the line in multiple areas.

OBSERVATION 2

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

Specifically,

A. On 3/21/2024, we inspected the aseptic filling line (b) (4) room and observed operators loading the (b) (4) for load pattern 45 in preparation for the manufacture of (b) (4) (b) (4) injection lot (b) (4) Per the load pattern, the (b) (4) are to be placed on the (b) (4) in the (b) (4) position for sterilization. When we inspected the (b) (4) (after the operators (b) (4) into the (b) (4) the (b) (4) were noted in the (b) (4)

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position. The noted (b) (4) are used to provide (b) (4) during aseptic operations in the RABS.

B. Your firm's sterility test procedure is inadequate as it only instructs QC microbiologists to observe for microbial contamination via turbidity. Procedure 0318-SOP-QC-00085 does not include instructions for evaluation of samples for atypical microbiological growth that can present as other than turbidity (suspensions, particles, filaments).

OBSERVATION 3

Buildings used in the manufacturing, processing, packing and holding of a drug product are not maintained in a good state of repair.

Specifically,

A. On 3/20/2024, we inspected the HVAC mechanical space and (b) (4) the aseptic filling line (b) (4) ceiling. The roof of the building that covers this area was noted to have multiple holes and visible light to the exterior of the building.

B. On 3/20/2024, we inspected the QC microbiology storage room (b) (4) (controlled non-classified, CNC) and noted what appeared to be mold on and around the air vent in the ceiling of the room. Your firm stores various QC microbiology supplies in room (b) (4) to include testing canisters for drug product sterility and environmental monitoring plates utilized for aseptic filling line (b) (4)

C. Various areas within your facility were observed to have what appeared to be water stained ceilings indicative of prior water leakage events to include:
   - (b) (4) - CNC hallway leading into line (b) (4) production area.

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- (b) (4) - Laboratory change room.
- (b) (4) - Corridor between retain storage room and material storage room.
- - Drug product retain storage room.

OBSERVATION 4

Equipment and utensils are not cleaned and maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically,

On 3/26/2024, we inspected (b) (4) vessel (b) (4) /MFG (b) (4) V/648 in the line (b) (4) aseptic manufacturing equipment storage area. Vessel (b) (4) /MFG (b) (4) V/648 was documented as being in clean status. We inspected the (b) (4) from the interior side of the tank and noted what appeared to be discolored (b) (4) tape hanging from the (b) (4) fitting. The fitting also appeared to be discolored brown with a portion that appeared to be rusting. Vessel (b) (4) /MFG (b) (4) V/648 is utilized to (b) (4) drug product (b) (4) (b) (4) and is the vessel your firm utilizes to perform aseptic filling from in room (b) (4) Vessel (b) (4) /MFG (b) (4) V/648 was utilized to manufacture (b) (4) injection, (b) (4) mg/mL lot (b) (4) (b) (4) which was shipped for the US market on (b) (4)

***DATES OF INSPECTION**

3/18/2024(Mon), 3/19/2024(Tue), 3/20/2024(Wed), 3/21/2024(Thu), 3/22/2024(Fri), 3/26/2024(Tue), 3/27/2024(Wed)

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X Sean R Marcsisin
Investigator
Signed By: Sean R. Marcsisin -S
Date Signed: 03-27-2024 05:19:25

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