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	7/8/2025-7/17/2025*
	FEI NUMBER 3007549629

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Amit Sareen, Site Head and Sr. Vice President - Manufacturing

FIRM NAME	STREET ADDRESS
Lupin Limited	Unit-2, Plot No. M-2 & M-2-A, SEZ, Phase II, MISC. Zone, Apparel Park, Dist. Dhar
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Pithampur, Madhya Pradesh, 454775 India	Human 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

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

Specifically,

1. During set-up and aseptic filling of [redacted] (b) (4) solution batch [redacted] (b) (4) (US market) on July 9, 2025, the following deviations were observed:

a. During interventions (Intervention #26 at [redacted] (b) (4) & [redacted] (b) (4) to remove jammed and fallen vials from the [redacted] (b) (4) conveyor, the operator reached the [redacted] (b) (4) over open vials. Exposed vials were not removed. Similar observations were made during media fills [redacted] (b) (4)

b. During interventions (Intervention #18 at [redacted] (b) (4) & [redacted] (b) (4) to remove jammed bottle from the [redacted] (b) (4) the operator reached over open sterile bottles. Exposed bottles were not removed.

c. An operator performed a [redacted] (b) (4) intervention for environmental monitoring. During activity, a [redacted] (b) (4) typically stored in the Grade B area, was introduced into the Grade A environment, and seen contacting the interior surface of the [redacted] (b) (4) without undergoing sanitization to all areas.

d. There is no environmental monitoring for the Grade A area where [redacted] (b) (4) operators routinely stand to conduct weight checks and start/stop the filling line.

e. The only environmental monitoring in the Grade A area where the aseptic connection occurs is a settle plate. Non-viable particle monitoring is done [redacted] (b) (4) and [redacted] (b) (4) air sampling is done [redacted] (b) (4) at locations throughout the filling room and regardless of production status.

f. During production, operators travel between the Grade A and Grade B areas however operator gowning is held to Grade B limits.

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g. The bowel use for (b) (4) remains on the line where it is sanitized, but not sterilized. There is no environmental monitoring of the sides of the bowel directly in contact with the open, sterilized bottles used in production.

2. During review of media fills recordings:

a. During media fill (b) (4) Aseptic Process Simulation (b) (4) mL (b) (4) Bottle), operator was observed reaching over exposed bottles while conducting an intervention to set the (b) (4) station (b) (4) Operator was observed with their arm extended over open, exposed vials. Operator gowning is held to Grade B standards.

b. During media fill (b) (4) Aseptic Process Simulation (b) (4) mL (b) (4) Bottle), the following personnel monitoring event was observed at (b) (4) in the Grade A area: An operator placed a clipboard directly onto a used sanitizing wipe located in the (b) (4) (b) (4) of the environmental monitoring (b) (4) This wipe had previously been used to sanitize the (b) (4) in the Grade B area before the (b) (4) was transferred into the Grade A area. After completing finger dab sampling, the operator retrieved the contaminated clipboard and continued operations within the Grade A area.

c. During media fill (b) (4) Aseptic Process Simulation (b) (4) manufacturing with (b) (4) operator was observed reaching over open exposed bottles while conducting an intervention to remove a jammed bottle from the location where the (b) (4) conveyor transfers bottles to the (b) (4) conveyor.

d. During media fill (b) (4) Aseptic Process Simulation (b) (4) mL (b) (4) Bottle), operator was observed with their (b) (4) hand resting on the (b) (4) while conducting an intervention for the removal of a jammed bottle from the (b) (4) The (b) (4) is used to transfer open bottles from the (b) (4) conveyor to the filling and sealing area.

e. During media fill (b) (4) video footage of routine personnel monitoring revealed that an operator did not perform fingertip monitoring in accordance with the firm's written procedure. The procedure requires that each finger and thumb be rolled across the (b) (4) surface, including sampling of the fingertip. However, the footage shows the operator touching their fingers to the contact plate using a vertical dabbing motion, without rolling or sampling the tips of the fingers and thumbs.

3. The qualification process for aseptic personnel does not specify required activities to be performed during a media fill to demonstrate competency. Multiple operators are responsible for setup activities during media fills and routine production, but the specific activities performed by each operator are not documented. As a result, an operator may be qualified to conduct the aseptic connection without ever having performed this task during a media fill.

4. Media fill interventions performed during media fill (b) (4) do not accurately represent the actual manufacturing process. Deficiencies include but were not limited to:

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a. During intervention #42 for bottle sealing (b) (4) and track maintenance in media fill (b) (4) the operator (b) (4) RABs (b) (4) stepped back, and waited (b) (4) before (b) (4) During the actual intervention, the operator extends his arms into the RABs unit to perform the maintenance work. However, the intervention description documented in the media fill batch record specifies that the intervention should take place over not less than (NLT) (b) (4) and that surface sanitization should be conducted.

b. Intervention frequency during media fill does not represent worst-case production scenarios. The number of times each intervention was performed during the media fill simulation does not reflect the maximum number of times the same intervention is actually conducted during routine production operations.

c. Intervention #26, (b) (4) replacement, performed solely for the purpose of collecting finger dab samples did not include contact with all equipment and surfaces that an operator would typically touch during the actual performance of the intervention. During (b) (4) replacement intervention for finger dab collection, the operator (b) (4) RABs (b) (4) and touched the (b) (4) and (b) (4) whereas actual (b) (4) replacement requires (b) (4) RABs (b) (4) (b) (4) Additionally, the (b) (4) replacement intervention performed for finger dab collection was completed in less than (b) (4) However, the procedure specifies that the time required to perform this same intervention shall be not less than (NLT) (b) (4)

OBSERVATION 2

Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.

Specifically,

The smoke studies conducted to evaluate airflow patterns within the controlled environment exhibit deficiencies that compromise their ability to demonstrate proper unidirectional airflow. Observed deficiencies include turbulent airflow patterns with smoke swirling towards the ceiling rather than following the expected laminar flow path, insufficient smoke generation to visualize and assess airflow direction, and unclear directionality of smoke as it exits the smoke wand, making it impossible to determine the intended airflow pattern. For example, in Air Flow Visualization Study SP/4/026-04, Dynamic Condition 2025:

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1. Clip #22 - Replacement of (b) (4) When the operator (b) (4) RABs (b) (4) smoke rises upward and swirls back towards the (b) (4) rather than flowing away from the critical area. The settle plate located (b) (4) the (b) (4) is (b) (4). On February 10, 2024, during release of environment and personnel monitoring plates, Employee (b) (6) identified Out Of Action Limit (OOAC) results in settle plates (b) (4) as well as in Personnel Monitoring locations (CH and FH) of Operator (b) (6)

2. Clip #1 - Assembling of Filling Machine Parts (b) (4) Station): When the operator moves and installs parts for the (b) (4) Station, turbulent smoke is observed moving upward and swirling towards the ceiling rather than following proper laminar flow patterns.

3. Clip #3 - Assembling of Filling Machine Parts (b) (4) Station) and Placement of Sterile (b) (4) at (b) (4) Station: The operator (b) (4) RABs unit, but the smoke is positioned behind the operator, making it impossible to determine the directionality of airflow as the (b) (4)

In each of the examples above, the direction of smoke as it leaves the smoke wand cannot be clearly observed, whether vertically upward, downward, or horizontal, making it impossible to determine the intended airflow pattern and verify proper unidirectional flow. This aseptic room and assembly line is used to manufacture (b) (4) products for the US market, including (b) (4)

OBSERVATION 3
Written procedures are not established and followed that describe the examinations to be conducted on appropriate samples of in-process materials of each batch.

Specifically,

1. Your firm failed to conduct visual inspections of batches of (b) (4) suspensions shipped to the US market including but not limited to:

Product Name	Batch No.	Qty Shipped	Date of Ship
(b) (4)			

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[redacted] (b) (4)

You [redacted] (b) (4) visual inspections conducted on [redacted] (b) (4) suspensions are for container defects.

2. In reviewing the destructive testing for [redacted] (b) (4) Solutions, the following deficiencies were observed:
   a. Defect characterization is inadequate. Defects identified during destructive visual inspection are not measured and do not represent the full visual spectrum of potential particulate matter and defects that could be present in [redacted] (b) (4) products.

   b. Training documentation and challenge materials are absent. There is no challenge kit or documented training program to ensure visual inspectors are qualified to detect the range of defects that may occur in [redacted] (b) (4) products.

   c. Inspection parameters lack standardization. No time limit has been established for qualification testing, and there is no guidance specifying how long a visual inspector needs to examine each container in front of [redacted] (b) (4) during the inspection process.

   d. Test units and volumes for operator qualification do not match routine production parameters. The test units and volumes used for qualifying visual inspectors differ from those used for destructive testing during routine production. Operator qualification utilizes a sterile jar containing [redacted] (b) (4) mL of liquid (large volume parenteral sizes), while routine production destructive testing uses test tubes containing no greater than [redacted] (b) (4) mL of liquid product.

3. Your firm uses a single, general SOP for reviewing electronic data including audit trails across multiple computerized systems used in GMP operations, such as [redacted] (b) (4) sterilization, [redacted] (b) (4) integrity tester, [redacted] (b) (4) viable particle counter, [redacted] (b) (4) integrity testing system, manufacturing vessel, cleaning and sanitization [redacted] (b) (4) and [redacted] (b) (4) machines.
   a. This SOP does not include or reference system-specific instructions, such as:

      i. Identifying critical audit trail events relevant to each system (e.g., parameter changes, alarm acknowledgments,

aborted runs, manual interventions).

ii. Locating and interpreting audit trail entries specific to each software/system architecture.

iii. Documenting and justifying the audit trail review performed per system. During interviews, inconsistent audit trail review practices were observed, with staff relying on experience rather than documented procedures. The SOP does not differentiate between systems, functionalities, or risk levels, nor does it specify review triggers or expectations per equipment.

4. Quality Assurance (QA) employees lack independent login access to manufacturing equipment software and were found to rely on Information Technology (IT) employee assistance to access these systems during quarterly audit trail reviews. This practice compromises the independence of QA oversight.

5. During batch release, QA employees did not review audit trails directly on the manufacturing equipment but instead reviewed only printed copies provided by the operations department.

OBSERVATION 4

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.

Specifically,
Your firm failed to implement adequate Corrective and Preventive Action (CAPA) procedures for out-of-specification (OOS) microbiological results detected in Grade A environmental monitoring including

1. Microbiological OOS (OOAC/M/25/IN2/EM/001) detected in (b) (4) air sample within Grade A environment of the (b) (4) LAF-402 during the assembly of filling machine for the production of (b) (4) Suspension, batch (b) (4) on January 22, 2025.

2. Microbiological OOS (OOAC/M/25/IN2/EM/004) detected in (b) (4) air sample within Grade A environment of (b) (4) Filling Line (b) (4) during (b) (4) of sterile bottles (b) (4) for the production of (b) (4) Suspension, batch (b) (4) on January 25, 2025.

3. Microbiological OOS (OOAC/M/25/IN2/EM/004) detected in (b) (4) air sample within Grade A environment of (b) (4) Filling

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Line (b) (4) during initial machine setting for production of (b) (4) Suspension, batch (b) (4) on January 24, 2025.

As part of the investigation, your firm identified the root causes as 1) inadequate disinfection 2) movement of air sampling equipment from Grade B to Grade A environment. However, your firm failed to place the affected batches on stability testing program to evaluate the potential impact of the microbiological excursion on product quality and sterility over the product's shelf life. In addition, your firm failed to implement increased monitoring of the Grade A environment following the microbiological deviation to ensure the controlled environment remains in acceptable conditions.

***DATES OF INSPECTION**

7/08/2025(Tue), 7/09/2025(Wed), 7/10/2025(Thu), 7/11/2025(Fri), 7/12/2025(Sat), 7/14/2025(Mon), 7/16/2025(Wed), 7/17/2025(Thu)

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