

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 12420 Parklawn Drive, Room 2032 Rockville, MD 20857	DATE(S) OF INSPECTION 9/16/2019-9/27/2019*
	FEI NUMBER 3004081307

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Ashwin Upasane, Site Head

FIRM NAME Cipla Limited	STREET ADDRESS L129 - 146 S - 103 - 105 S - 107 - 112 L147 - L147 1
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CITY, STATE, ZIP CODE, COUNTRY Vasco Da Gama, Goa, 403722 India	TYPE ESTABLISHMENT INSPECTED Pharmaceutical Manufacturer
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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

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

Specifically,

1. Cleaning procedures do not include provisions for routine cleaning or inspection of the air inlet/outlet duct areas. During a facility walkthrough, layers of (b) (4) colored (b) (4) (b) (4) drug products residue were observed on the inside surfaces of air outlet ducts of multiple non-dedicated (b) (4). These air outlets were directly connected to the (b) (4).
 - a. On September 16, 2019, a layer of (b) (4) colored (b) (4) material was seen near the HEPA filter, directly next to the inlet duct of (b) (4) (ID # T-006 Unit (b) (4)). Subsequently, on September 17, 2019, a layer of (b) (4) colored (b) (4) drug product residue was seen on the inside surface of air exhaust duct of (b) (4) ID # T-006 Unit (b) (4). These inlet and exhaust air ducts are the integral part of the drug manufacturing system that are directly connected to (b) (4) (ID # T-006 Unit (b) (4)).

Your cleaning procedure, SOP No. OI-27, Cleaning, Line Clearance and Operation of (b) (4) / Processor (Version 17.0, Effective date 3/29/2019) and

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preventive maintenance procedure, SOP No. EM-029, Preventive Maintenance of (b)(4) (b)(4) (Version 6.0, Effective date 11/20/2018) do not have provisions to clean the air ducts that are contaminated and are integral part of (b)(4) (ID # T-006 Unit (b)(4)). Additionally, your firm's Director of Technical Services confirmed that these ducts are not cleaned as part of the equipment cleaning.

Your (b)(4) (ID # T-006 Unit (b)(4)) is a non-dedicated equipment that has been used to manufacture and ship a number of drug products to the U.S. Market. A list of products manufactured and shipped to the U.S. Market during 2017-2019 include but are not limited to: (b)(4) US (b)(4) mg tablet (b)(4) tablets), (b)(4) (b)(4) mg tablets USP (b)(4) tablets), (b)(4) tablet USP (b)(4) mg (b)(4) tablets).

- b. On September 17, 2019, a layer of (b)(4) colored (b)(4) drug product residue was seen on the inside surface of air exhaust duct of (b)(4) (ID # T-382 Unit (b)(4)). The exhaust duct is an integral part of the drug manufacturing system that are directly connected to (b)(4) (ID # T-382 Unit (b)(4)).

Your cleaning procedure, SOP No. OI-27, Cleaning, Line Clearance and Operation of (b)(4) (b)(4) Equipment / Processor (Version 17.0, Effective date 3/29/2019) and preventive maintenance procedure, SOP No. EM-029, Preventive Maintenance of (b)(4) (Version 6.0, Effective date 11/20/2018) do not have provision to clean the air ducts that are contaminated and are integral part of (b)(4) (ID # T-382 Unit (b)(4)). Additionally, your firm's Director of Technical Services confirmed that these ducts are not cleaned as part of the equipment cleaning.

You (b)(4) (ID # T-382 Unit (b)(4)) is a non-dedicated equipment and has been used to manufacture and ship a number of drug products to the U.S. Market. A list of products manufactured and shipped to the U.S. Market in during 2017-2019 include but are not limited

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to: (b) (4) tablet (b) (4) mg (b) (4) tablets), (b) (4) tablet (b) (4) mg (b) (4) tablets), and (b) (4) tablet USP (b) (4) mg (b) (4) tablets).

- c. On September 20, 2019, a thick layer of (b) (4) colored (b) (4) drug product residue was seen on the inside surface of air exhaust duct of (b) (4) (ID # TL-001 Unit (b) (4)). The exhaust duct is an integral part of the drug manufacturing system that are directly connected to (b) (4) (ID # TL-001 Unit (b) (4)).

Your cleaning procedure, SOP No. OI-27, Cleaning, Line Clearance and Operation of (b) (4) Processor (Version 17.0, Effective date 3/29/2019) and preventive maintenance procedure, SOP No. EM-029, Preventive Maintenance of (b) (4) (Version 6.0, Effective date 11/20/2018) do not have provision to clean contaminated and are integral part of (b) (4) (ID # TL-001 Unit (b) (4)). Additionally, your firm's Director of Technical Services confirmed that these ducts are not cleaned as part of the equipment cleaning.

Your (b) (4) (ID # TL-001 Unit (b) (4)) is a non-dedicated equipment and has been used to manufacture and ship a number of drug products to the U.S. Market. A list of products manufactured and shipped to the U.S. Market in during 2017-2019 include but are not limited to: (b) (4) tablet USP (b) (4) mg (b) (4) tablets), (b) (4) tablet USP (b) (4) mg (b) (4) tablets), and (b) (4) tablet USP (b) (4) mg (b) (4) tablets).

- d. On September 20, 2019 a layer of (b) (4) colored (b) (4) drug product residue was seen on the inside surface of air exhaust duct of (b) (4) ID # TL-232 Unit (b) (4)). The exhaust duct is an integral part of the drug manufacturing system that are directly connected to (b) (4) (ID # TL-232 Unit (b) (4)).

Your cleaning procedure, SOP No. OI-366, Cleaning, Line Clearance and Operation of

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(b) (4) (Version 6.0, Effective date 6/21/2019) and preventive maintenance procedure, SOP No. EM-029, Preventive Maintenance of (b) (4) (Version 6.0, Effective date 11/20/2018) do not have provision to clean the air ducts that are contaminated and are integral part of (b) (4) (ID # TL-232 Unit (b) (4)). Additionally, your firm's Director of Technical Services confirmed that these ducts are not cleaned as part of the equipment cleaning.

Your (b) (4) (ID # TL-232 Unit (b) (4)) is a non-dedicated equipment and has been used to manufacture and ship a number of drug products. You have used this equipment to manufacture registration batches of (b) (4) tablet (b) (4) mg (b) (4) tablets) for US.

e. On September 20, 2019, a layer of (b) (4) colored (b) (4) drug product residue was seen on the inside surface of air exhaust duct of (b) (4) (ID # CL-131 Unit (b) (4)). The exhaust duct is an integral part of the drug manufacturing system that are directly connected to (b) (4) (ID # CL-131 Unit (b) (4)).

Your cleaning procedure, SOP No. OI-366, Cleaning, Line Clearance and Operation of (b) (4) (Version 6.0, Effective date 6/21/2019) and preventive maintenance procedure, SOP No. EM-029, Preventive Maintenance of (b) (4) (Version 6.0, Effective date 11/20/2018) do not have provision to clean the air ducts that are contaminated and are integral part of (b) (4) (ID # CL-131 Unit (b) (4)). Additionally, your firm's Director of Technical Services confirmed that these ducts are not cleaned as part of the equipment cleaning.

Your (b) (4) (ID # CL-131 Unit (b) (4)) is a non-dedicated equipment and has been used to manufacture and ship a number of drug products to the U.S. Market. A list of products manufactured and shipped to the U.S. Market in between 2017-2019 include but are not

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limited to: (b) (4) capsules USP (b) (4) mg (b) (4) tablets), (b) (4) capsules USP (b) (4) mg (b) (4) tablets).

f. On September 20, 2019, a deposition of a (b) (4) colored (b) (4) drug product residue was seen on the inside surface of a (b) (4) aust (b) (4) area of (b) (4) (ID # PD-2 Unit (b) (4)). Upon rubbing the inside of the plenum area with a lint free cloth, a (b) (4) colored material was seen on the portion of the lint free cloth that was rubbed against the inside surface of the (b) (4). The equipment was kept in "clean status". The exhaust (b) (4) is an integral part of the drug manufacturing system that are directly connected to (b) (4) (ID # PD-2 Unit (b) (4)).

Your cleaning procedure, SOP No. OI-48, Cleaning, Line Clearance, and Operation of (b) (4) (b) (4) Version 9.0, Effective date 6/8/2017) and preventive maintenance No. EM-029, Preventive Maintenance of (b) (4) (b) (4) (Version 6.0, Effective date 11/20/2018) do not have provisions to clean the exhaust air duct that are contaminated and are integral part of (b) (4) (ID # PD-2 Unit (b) (4)). Additionally, your firm's Director of Technical Services confirmed that these ducts are not cleaned as part of the equipment cleaning.

Your (b) (4) (ID # PD-2 Unit (b) (4)) is a non-dedicated equipment. You have used this equipment to manufacture and ship a number of drug products to the U.S. Market. A list of products manufactured and shipped to the U.S. Market during 2017-2019 include but are not limited to: (b) (4) capsule (b) (4) mg (b) (4) capsule), (b) (4) capsule (b) (4) mg (b) (4) capsule), and (b) (4) capsule (b) (4) mg (b) (4) capsule).

g. On September 21, 2019, a layer of a (b) (4) colored (b) (4) drug product residue was seen on the inside surface of air exhaust duct o (b) (4) 139 Unit (b) (4). The

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exhaust (b)(4) is an integral part of the drug manufacturing system that are directly connected to (b)(4) (ID # HE-139 Unit (b)(4)).

Your cleaning procedure, SOP No. OI-69, Cleaning, Line Clearance and Operation of (b)(4) (b)(4) (Version 7.0, Effective date 3/29/2019) and preventive procedure, SOP No. EM-029, Preventive Maintenance of (b)(4) (Version 6.0, Effective date 11/20/2018) do not have provisions to clean the exhaust air ducts that are contaminated and are integral part of (b)(4) ID # HE-139 Unit (b)(4). Your firm's Director of the Technical Operation stated that the inside of the exhaust was never opened and evaluated for cleanliness.

Your (b)(4) (ID # HE-139 Unit (b)(4)) is a non-dedicated equipment and has been used in the manufacture of tablets. A list of drug products manufactured and shipped to Rest of the World (ROW) during 2017-2019 include but are not limited to: (b)(4) (b)(4) mg tablet (b)(4) (b)(4) tablets), (b)(4) mg tablet (b)(4) (b)(4) tablets), and (b)(4) mg tablet (b)(4) (b)(4) tablets (b)(4) tablets).

h. On September 23, 2019, a layer of a (b)(4) colored (b)(4) drug product residue was seen on the inside surface of air exhaust duct of (b)(4) (ID # ON-148 Unit (b)(4)). The exhaust plenum is an integral part of the drug manufacturing system that are directly connected to (b)(4) (ID # ON-148 Unit (b)(4)). Your firm's Director of Engineering stated that the equipment was commissioned in 2013 and the exhaust duct was never opened to evaluate the cleanliness.

Your cleaning procedure, SOP No. OI-27, Cleaning, Line Clearance and Operation of (b)(4) (b)(4) / Processor (Version 17.0, Effective date 3/29/2019) and preventive maintenance procedure, SOP No. EM-029, Preventive Maintenance of (b)(4) (Version 6.0, Effective date 11/20/2018) do not have provision to clean the air ducts that are

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contaminated and are integral part of (b) (4) (ID # ON-148 Unit (b) (4)). Your firm's Director of Technical Services confirmed that these ducts are not cleaned as part of the equipment cleaning.

Your (b) (4) (ID # ON-148 Unit (b) (4)) is a non-dedicated equipment. You have used this equip (b) (4) manufacture and ship a number of drug products to Rest of the World (ROW). A list of products manufactured and shipped to ROW during 2017-2019 include but are not limited to: (b) (4) mg tablets (b) (4) tablets), (b) (4) mg tablet (b) (4) tablets), and (b) (4) t (b) (4) tablets).

2. Layers of colored (b) (4) drug product residues were observed on the inside surfaces of air outlet ducts of multiple (b) (4) machines. These exhausts ducts were directly connected to the (b) (4). Your cleaning procedures do not include provisions for routine cleaning or inspection of the air inlet/outlet duct areas.

a. On September 17, 2019, layers of (b) (4) colored (b) (4) drug product residues were seen on the inside surface of air exhaust duct of (b) (4) (ID # T-025 Unit (b) (4)). The exhaust duct is an integral part of the drug manufacturing system that is directly connected to (b) (4) (ID # T-025 Unit (b) (4)).

Your SOP No. OI-450 Cleaning, Line Clearance and Operation of (b) (4) (b) (4) (Version 11.0, Effective date 6/14/2019) and preventive maintenance procedure SOP No. EM-030 Preventive Maintenance of (b) (4) Machine and (b) (4) (Version 7.0, Effective date 11/3/2018) do not have provisions to clean the air ducts that are contaminated and are integral part of (b) (4) (ID # T-025 Unit (b) (4)). Your firm's Director of Technical Services confirmed that these ducts are not cleaned as part of the equipment cleaning.

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Your (b)(4) (ID # T-025 Unit (b)(4)) is a non-dedicated equipment. You have used this equipment to manufacture and ship a number of drug products to the U.S. Market. A list of products manufactured and shipped to the U.S. Market during 2017-2019 include but are not limited to: (b)(4) tablets USP (b)(4) mg (b)(4) tablets), and (b)(4) (b)(4) mg tablets (b)(4) capsule).

- b. On September 17, 2019, layers of (b)(4) colored (b)(4) drug product residues were seen on the inside surface of air exhaust duct of (b)(4) ID # T-180 Unit (b)(4). The exhaust duct is an integral part of the drug manufacturing system that are directly connected to (b)(4) (ID # T-180 Unit (b)(4)).

Your cleaning procedure Your SOP No. OI-30 Cleaning, Line Clearance and Operation of (b)(4) (Version 12.0, Effective date 6/2/2017) and preventive maintenance procedure SOP No. EM-030 Preventive Maintenance of (b)(4) and (b)(4) (Version 7.0, Effective date 11/3/2018) do not have provision to clean the air ducts that are contaminated and are integral part of (b)(4) ID # T-180 Unit (b)(4). Your firm's Director of Technical Services confirmed that these ducts are not cleaned as part of the equipment cleaning.

Your (b)(4) (ID # T-180 Unit (b)(4)) is a non-dedicated equipment. You have used this equipment to manufacture and ship a number of drug products to the U.S. Market. A list of products manufactured and shipped to the U.S. Market during 2017-2019 include but are not limited to: (b)(4) ablets (b)(4) mg (b)(4) tablets), and (b)(4) (b)(4) mg tablets (b)(4) tablets).

- c. On September 17, 2019, layers of (b)(4) colored (b)(4) drug product residues were seen on the inside surface of air exhaust duct of (b)(4) Machine (ID # T-492 Unit (b)(4)). The exhaust duct is an integral part of the drug manufacturing system that are directly

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connected to (b)(4) Machine (ID # T-492 Unit (b)(4)).

Your SOP No. OI-450 Cleaning, Line Clearance and Operation of (b)(4) (b)(4) (Version 11.0, Effective date 6/14/2019) and preventive maintenance procedure SOP No. EM-030 Preventive Maintenance of (b)(4) Machine and (b)(4) (Version 7.0, Effective date 11/3/2018) do not have provision to clean the air ducts that are contaminated and are integral part of (b)(4) Machine (ID # T-492 Unit (b)(4)). Your firm's Director of Technical Services confirmed that these ducts are not cleaned as part of the equipment cleaning.

Your (b)(4) (ID # T-492 Unit (b)(4)) is a non-dedicated equipment. You have used this equipment to manufacture and ship a number of drug products to the U.S. Market. A list of products manufactured and shipped to the U.S. Market during 2017-2019 include but are not limited to: (b)(4) tablets (b)(4) mg (b)(4) tablets), (b)(4) mg tablet USP (b)(4) tablets), and (b)(4) tablet USP (b)(4) mg tablets).

- d. On September 20, 2019, layers of (b)(4) colored (b)(4) drug product residues were seen on the inside surface of air exhaust duct of (b)(4) (ID # TL-098 Unit (b)(4)). The exhaust duct is an integral part of the drug manufacturing system that is directly connected to (b)(4) (ID # TL-098 Unit (b)(4)).

Your cleaning procedure SOP No. OI-50 Cleaning, Line Clearance and Operation of (b)(4) (Version 12.0, Effective date 10/6/2019) and preventive maintenance procedure SOP No. EM-030 Preventive Maintenance of (b)(4) Machine and (b)(4) (Version 7.0, Effective date 11/3/2018) do not have provision to clean the air ducts that are contaminated and are integral part of (b)(4) (ID # TL-098 Unit (b)(4)). Your firm's Director of Technical Services confirm (b)(4) s are not cleaned as part

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of the equipment cleaning.

Your (b)(4) (ID # TL-098 Unit (b)(4)) is a non-dedicated equipment. You have used this equipment to manufacture and ship a number of drug products to the U.S. Market. A list of products manufactured and shipped to the U.S. Market during 2017-2019 include but are not limited to: (b)(4) tablets (b)(4) mg (b)(4) tablets), (b)(4) tablets (b)(4) mg (b)(4) tablets), and (b)(4) tablets (b)(4) mg (b)(4) tablets).

- e. On September 20, 2019, layers of (b)(4) drug product residues were seen on the inside surface of air exhaust duct of (b)(4) ID # TL-231 Unit (b)(4). The exhaust duct is an integral part of the drug manufacturing system that are directly connected to (b)(4) ID # TL-231 Unit (b)(4).

Your cleaning procedure SOP No. OI-50 Cleaning, Line Clearance and Operation of (b)(4) (Version 12.0, Effective date 10/6/2019) and preventive maintenance procedure SOP No. EM-030 Preventive Maintenance of (b)(4) and (b)(4) (b)(4) (Version 7.0, Effective date 11/3/2018) do not have provision ducts that are contaminated and are integral part of (b)(4) (ID # TL-231 Unit (b)(4)). Your firm's Director of Technical Services confirm (b)(4) ducts are not cleaned as part of the equipment cleaning.

You (b)(4) (ID # TL-231 Unit (b)(4)) is a non-dedicated equipment. You have used this equipment to manufacture and ship a number of drug products to the U.S. Market. A list of products manufactured and shipped to the U.S. Market during 2017-2019 include but are not limited to: (b)(4) tablets USP (b)(4) mg (b)(4) tablets), (b)(4) tablets USP (b)(4) mg (b)(4) tablets), and (b)(4) tablets USP (b)(4) mg (b)(4) tablets).

- f. On September 23, 2019, layers of (b)(4) colored (b)(4) drug product residues

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FEI NUMBER

3004081307

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Mr. Ashwin Upasane, Site Head

FIRM NAME

Cipla Limited

STREET ADDRESS

L129 - 146 S - 103 - 105 S - 107 - 112
L147 - L147 1

CITY, STATE, ZIP CODE, COUNTRY

Vasco Da Gama, Goa, 403722 India

TYPE ESTABLISHMENT INSPECTED

Pharmaceutical Manufacturer

were seen on the inside surface of air exhaust duct of (b) (4) ID # ON-046 Unit (b) (4). The exhaust duct is an integral part of the drug manufacturing system that are directly connected to (b) (4) (ID # ON-046 Unit (b) (4)).

Your cleaning procedure SOP No. OI-40 Cleaning, Line Clearance and Operation of (b) (4) (Version 10.0, Effective date 3/9/2019) and preventive maintenance procedure SOP No. EM-030 Preventive Maintenance of (b) (4) (Version 7.0, Effective date 11/3/2018) do not have provision to clean the air ducts that are contaminated and are integral part of (b) (4) (ID # ON-046 Unit (b) (4)). Your firm's Director of Technical Services confirmed that these ducts are not cleaned as part of the equipment cleaning.

Your (b) (4) (ID # ON-046 Unit (b) (4)) is a non-dedicated equipment. During 2017-2019 you have used this equipment to manufacture and ship (b) (4) tablets (b) (4) mg (b) (4) tablets) to the U.S. Market.

3. The (b) (4) stopper (b) (4) used in Unit (b) (4) Fill Line (b) (4) during the aseptic filling process appears to have some form of visible scoring on the (b) (4) surface with rough and uneven edges, and they are not smooth cleanable surfaces.
4. (b) (4) are used in the Grade A (ISO 5) areas e.g., aseptic filling zones, (b) (4) stoppering and (b) (4) stations and in the (b) (4). The Associate Director of Quality Assurance and Senior Manager Production confirmed that the (b) (4) are not cleaned and sanitized on a periodic base. Rather, the (b) (4) are cleaned at the same time as the (b) (4) HEPA filter integrity testing is performed.
5. The (b) (4) are not cleaned and sanitized on a periodic base. The (b) (4) remained covered during the (b) (4) process and they are not cleaned

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EMPLOYEE(S) SIGNATURE

June P Page, Investigator
Thomas J Arista, National Expert
Rajiv R Srivastava, Investigator

DATE ISSUED

9/27/2019

June P Page
Investigator
Signed By 2000408709
Date Signed 09-27-2019 13:10:47

X

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 12420 Parklawn Drive, Room 2032 Rockville, MD 20857	DATE(S) OF INSPECTION 9/16/2019-9/27/2019*
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prior or post the aseptic filling operations.

OBSERVATION 2

Equipment for adequate control over air pressure, micro-organisms and dust is not provided when appropriate for the manufacture, processing, packing or holding of a drug product.

Specifically,

1. Unit (b) (4) (b) (4) Injection (b) (4) mg (b) (4) ml (b) (4) # (b) (4) establishes in section 3.2.P.3.3 Description of Manufacturing Process and Process Controls, "... filling is done under laminar air flow (class 1000 is surrounded by area which is class 100 at rest and class 1,000 at dynamic, in-process checks of filled vials and then (b) (4) is also done under LAF in sealing area which is classified as class 1,000 at dynamic." The (b) (4) lists the following room classifications i.e., Class 100 [Grade A area] [ISO 4.8], Class 1000 [Grade B Area] [ISO 5], Class 10,000 [Grade C Area] [ISO 7] and Class 100.000 [Grade D Area] [ISO 8]. However, the surround area of the Grade A (ISO 5) aseptic filling performed in the open Restricted Access Barrier (RABs) is not Class 1,000. Rather, the current classification is Grade C (ISO 7) during dynamic and routine aseptic filling operations. There is no non-viable particle (NVP) data to support the Class 1,000 area classification submitted in the (b) (4). In addition;

There is the same concern regarding the classification for the surrounding area around the Grade A (ISO 5) aseptic filling areas for the following (b) (4) manufactured in Unit (b) (4) i.e.,

- a. (b) (4) Injectable Suspension, USP (b) (4) mg/ml (b) (4) # (b) (4) establishes in section 3.2.P.3.3 Description of Manufacturing Process and Process Controls, the "Vial filling, stoppering and (b) (4) s carried out in laminar air flow, surrounded by Grade B environment." The area surrounding the Grade A (ISO 5) aseptic filling performed in the open Restricted Access Barrier (RABs) is not Class 1,000. Rather, the current classification is Grade C (ISO 7) during dynamic and routine aseptic filling operations.

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There is no non-viable particle (NVP) data to support the Class 1,000 area classification submitted in the (b) (4)

b. (b) (4) Injection USP, (b) (4) mg (b) (4) ml (b) (4) mg/ml and (b) (4) Injection USP, (b) (4) mg/ml and (b) (4) mg/(b) (4) ml (b) (4) mg/ml (b) (4) (b) (4) in section 3.2.P.3 Description of Manufacturing Process and Process Controls, the "...vial filling, stoppering and sealing is carried out in laminar air flow, surrounded by Grade B environment." The area surrounding the Grade A (ISO 5) aseptic filling performed in the open Restricted Access Barrier (RABs) is not Class 1,000. Rather, the current classification is Grade C (ISO 7) during dynamic and routine aseptic filling operations. There is no non-viable particle (NVP) data to support the Class 1,000 area classification submitted in the (b) (4)

The Associate Director of Quality Assurance confirmed there have been no supplements to the (b) (4) submitted to the Agency regarding the change of manufacturing room classifications i.e., from "Class 1000 [Grade B Area] [ISO 5]" to the company's current Grade C (ISO 7) surrounding area.

Unit (b) (4)

- The "Mapping Study for Selection of NVPC Monitoring Routine Location" document #SP/U9-61 dated 09 May 2018, objective "is to evaluate the exiting online non-viable particulate matter monitoring locations to ensure; *Appropriate probe orientation to obtain a meaningful sample which indicate true level of extrinsic particle contamination where product is exposed.*" The scope of the study protocol is as follows i.e., "This study shall be conducted for all online NVPC monitoring location in product and sterile container closure exposure path (Grade – A) at sterile product manufacturing lines at Cipla, Verna Goa units." The Associate Director Quality Assurance confirmed that they have not performed the study for the aseptic fill line number (b) (4) in Unit (b) (4)

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OBSERVATION 3

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

Specifically,

Unit ^{(b) (4)}

1. ^{(b) (4)} aseptic filling processing of finished drug products i.e., from aseptic filling to the ^{(b) (4)} processing steps, are performed within a Grade A (ISO-5) environment. The following is in regards to non-viable particle (NVP) monitoring;
 - a. the Grade A ^{(b) (4)} room ^{(b) (4)}, is not monitored for the presence NVP;
 - b. there is no record to document that the ^{(b) (4)} room # ^{(b) (4)} is maintained to the Grade A (ISO 5) classification;
 - c. there is an NVP ^{(b) (4)} positioned on the ^{(b) (4)} system (Grade A - ^{(b) (4)}). However, the ^{(b) (4)} is not positioned immediately beneath the HEPA filters;
 - d. the ^{(b) (4)} are conveyed from the Grade A stoppering station to the ^{(b) (4)} (room # ^{(b) (4)}). there is no NVP measurements taken between the following NVP locations in room # ^{(b) (4)} i.e., stoppering station ^{(b) (4)}
 - e. a ^{(b) (4)} s used to transfer sterile parts and equipment from the ^{(b) (4)} o the ^{(b) (4)} Restriction Access Barrier ^{(b) (4)} RABs). There is no NVP measurements taken during dynamic (in operation) condi
 - f. there are ^{(b) (4)} dynamic ^{(b) (4)} that are designated as Grade A environments. However, the interior of the dynamic ^{(b) (4)} is not monitored for the presence of NVP during routine operations;

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g. regarding the (b) (4) mechanism of the dynamic (b) (4) there is no standard oper and establish the manner of testing and ensuring that the (b) (4) mechanism functions appropriately.

Unit (b) (4)

2. Aseptic filling processing of finished drug products i.e., from aseptic filling to the (b) (4) processing steps, are performed within a Grade A (ISO 5) environment. Regarding monitoring for the NVP, there is an (b) (4) located near the fill line's (b) (4) stoppering station. From the stoppering station to the (b) (4) station it is approximately (b) (4). However;

- a. there is no (b) (4) located between the stoppering station and the (b) (4) tation; and
- b. there is no data to support that the area between the (b) (4) at the stoppering station to the (b) (4) is maintained to Grade A (ISO 5).

3. The "Air Flow Pattern" document #1035-E-0071, dated 26 Jul 2016 establishes "...a procedure for checking of airflow pattern." It is "Applicable to all air handling units (AHU), Laminar air flow (LAF) units, (b) (4) and between adjacent area." There standard procedure establishes, for example, "... (b) (4) (b) (4)

In addition, the "Air Flow Pattern Checking" document #EP-009, dated 20 Sep 2018, establishes "...a procedure for checking of airflow pattern" It is "Applicable to all HVAC of classified areas, (b) (4)

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(b) (4) The standard procedure establishes to (b) (4)
 (b) (4) the following? for example. (b) (4)

 (b) (4)

Representatives from the Production, Quality Assurance, Engineering and Microbiology Departments reviewed and approved the report and air flow pattern videos.

The following table lists several instances where the unidirectional airflow patterns could not be determined and/or observed. Note: the summary provided in the table is not intended to be an all-inclusive and/or exhaustive list of concerns, for example;

Approximate time stamp	Unit (b) (4) - Brief description of manual activities
(b) (4)	(b) (4) unable to observe airflow at back
(b) (4)	(b) (4) obstruct view; unable to observe unidirectional airflow
(b) (4)	(b) (4) obstruct view; unable to observe unidirectional airflow
	Personnel blocking view; unable to observe unidirectional airflow
	Personnel blocking view; unable to observe unidirectional airflow
	Personnel blocking view; unable to observe unidirectional airflow
(b) (4)	(b) (4) RABs, unable to observe unidirectional airflow
Fill (b) (4)	(b) (4) area blocking view; unable to observe unidirectional airflow
	Unable to observe unidirectional airflow when (b) (4) bag
(b) (4)	(b) (4) there is no smoke to observe unidirectional

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(b) (4)	airflow
	There is no smoke to observe unidirectional airflow
	No smoke over personnel movement; cannot observe unidirectional airflow
	No smoke over personnel movement; cannot observe unidirectional airflow
	No smoke over personnel movement; cannot observe unidirectional airflow
	Unable to observe unidirectional airflow pattern due to placement of smoke
	(b) (4)
	No smoke over (b) (4)
	(b) (4)
	Assembly
	Cannot see unidirectional airflow patterns
	(b) (4)
	(b) (4)
	block ability to observe unidirectional airflows
	block ability to observe unidirectional airflows
	(b) (4)
	(b) (4)
	blocking view; unable to observe unidirectional airflow patterns
	blocking view; unable to observe unidirectional airflow patterns
	No smoke; cannot determine unidirectional airflow patterns
	No smoke (b) (4) cannot determine unidirectional airflow patterns
	Cannot observe unidirectional airflow patterns
	Personnel arm blocking view; unable to observe unidirectional airflow
	(b) (4)
	Smoke not (b) (4) unable to determine unidirectional airflow patterns
Cannot see smoke (b) (4) unable to determine unidirectional airflow	
Camera too close; cannot see unidirectional airflow patterns	
(b) (4)	
Cannot see unidirectional airflow patterns	
Top down view; cannot see unidirectional airflow patterns	
(b) (4)	
There is no smoke (b) (4)	
(b) (4) unable to observe unidirectional airflow patterns	
(b) (4)	
(b) (4) No smoke (b) (4) unable to observe unidirectional airflow patterns	

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(b) (4)	(b) (4) no smoke; cannot observe unidirectional airflow due to angle of the camera
	Line Dynamics (b) (4)
(b) (4)	unable to determine unidirectional airflow due to equipment blocking the view
	Camera too far from activity cannot see details of airflow
	Smoke not over hands; unable to determine unidirectional airflow
	Camera too close cannot see unidirectional airflow
	Cannot see unidirectional airflow during movement of (b) (4)
	Adjustment of (b) (4) no smoke over personnel arm; unable to observe unidirectional airflow
	(b) (4)
The air flow pattern studies did not include an evaluation to determine and visualize the air flow between (b) (4) equipment, the dynamic movement for the (b) (4)	
(b) (4)	

Approximate time stamp	Unit (b) (4) - Brief description of manual activities
(b) (4)	(b) (4) (b) (4)
	No smoke over personnel (b) (4) during set up
	No smoke over personnel (b) (4)
	No smoke over personnel's (b) (4)
	Air flow video documenting smoke moving in an (b) (4) direction; near smok (b) (4)
	No smoke over personnel's (b) (4)
	No smoke (b) (4)
	Air flow video documenting smoke moving in an (b) (4) direction
	No smoke over personnel's (b) (4) manual activity performed (b) (4)
	No smoke over personnel hands (b) (4)
(b) (4)	(b) (4)

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(b) (4)	No smoke over personnel hands during the manual activity
	Aseptic Connection Part (b) (4) (b) (4)
	No smoke over personnel activity regarding the (b) (4)
	No smoke over personnel activity occurring (b) (4)
	No smoke over personnel activity occurring (b) (4)
	No smoke over personnel activity occurring (b) (4)
	Personnel blocking view; unable to determine unidirectional air flow
	Piston valve assembly; no view of air flow when open access panel (b) (4)
	(b) (4)
	Production operator (b) (4) unable to observe manual acti onal air flow
	No smoke over (b) (4)
	No view to verify air movement when (b) (4)
	(b) (4) no view to verify air movement
	(b) (4) cannot see unidirectional air flow; view is blocked
	Cannot see unidirectional air flow; view is blocked
Manual Interventions - (b) (4)	
(b) (4)	
No smoke over manual operation	
(b) (4) stopper - cannot see unidirectional air flow due to angle of camera	
Mimic the breakdown activities of fill machine - personnel blocking view of air flow	
Power Failure - no air flow pattern performed to mimic intervention	

4. A (b) (4) is used to transfer, for example, sterilized equipment, equipment parts, and utensils used during the aseptic filling operations, from the (b) (4) area (Grade A) to the LAF (Grade A) unit that is positioned adjacent to the (b) (4) fill line. The interior of the

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(b) (4) has HEPA filtered air, the interior is classified as Grade A and it has (b) (4) air flow. There is no air flow pattern evaluation of the (b) (4) interior with a typical load configuration. In addition,

a. No evaluation has been performed to determine when the (b) (4) are (b) (4) if the (b) (4) air flow is impacted by the (b) (4) air movement provided by the LAF unit and/or the converse.

OBSERVATION 4

Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable size and construction to facilitate cleaning, maintenance, and proper operations.

Specifically,

1. The "Visual Assessment of Aseptic Manufacturing Process" document #QA-32 dated 23 Mar 2017 establishes "...a procedure for observations and recording of aseptic areas status/activity during aseptic processing." The standard procedures include but are not limited to, for example, "Behavior of production personnel during aseptic operations and interventions. Movement in aseptic area (i.e., fast/moderate/slow). Intervention performed in the aseptic area. Aseptic techniques observed during handling of sterilized equipment/accessories. Problem encountered (if any)." The Associate Director of Quality Assurance explained, to reduce the number of personnel during the aseptic filling operations, the In-Process Quality Assurance (IPQA) personnel can observe the aseptic filling via the (b) (4). The (b) (4) in Unit (b) (4) are approximately (b) (4) and in Unit (b) (4) the (b) (4) are approximately (b) (4). Due to the size of the (b) (4) and due to the viewing angle, there is a limitation with regards to adequately observing the aseptic filling operations. In addition;
 - a. A Closed-Circuit Television (CCTV) system was installed and qualified (I/OQ) on February

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2014 and a performance qualification (PQ) was executed on March 2104. The CCTV provides a real time and a direct and an unobstructed view. For example, for Unit (b) (4) the CCTV provides the ability to observe the (b) (4) rea (room # (b) (4)), (b) (4) area (room # (b) (4)), filling area (room # (b) (4)), (b) (4) area (room # (b) (4)), active dispensing and excipient dispensing areas; for Unit (b) (4) the CCTV provides the ability to observe the external corridor near change room (b) (4) and filling, (b) (4) and (b) (4) manufacturing areas. The "Continual Process Verification" document #CQA 386/1035-G-0172 dated 26 Apr 2019, establishes the "...procedure for a continuous process verification that shall assure the process in the state of control (validated state) during commercial manufacturing." Regarding the aseptic filling process, personnel activities and manual manufacturing operations, the company does not use the CGMP CCTV technology to observe the aseptic filling process. Rather, as noted in the preceding observation, the aseptic processing is observed via the use of the (b) (4)

OBSERVATION 5

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

Specifically,

- Unit (b) (4) The Investigation Report OOAC number 1010_LAB1/OOAC/06/19/10 and 1010_LAB1/OOAC/06/19/11 dated 31/08/2019 is in regards to an aseptic process simulation (aka media fill) carried out on (b) (4). There was an excursion observed at sampling poin (b) (4) and excu (b) (4) n observed in post batch bioload (total count cfu/swab (b) (4) for an external surface of (b) (4) internal surface of (b) (4) respectively), (b) (4) and (b) (4). The microbial contaminants recovered are noted as

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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Ashwin Upasane, Site Head

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Sample locations	Site	Grade	Isolates
(b) (4)	(b) (4)	(b) (4)	<i>Micrococcus luteus</i>
			<i>Brevibacterium casei</i>
			<i>Bacillus subtilis</i>
			<i>Bacillus amyloiquefaciens</i>
			<i>Brevibacterium casei</i>
			<i>Bacillus amyloiquefaciens</i>
			<i>Bacillus amyloiquefaciens</i>
			<i>Bacillus amyloiquefaciens</i>
			<i>Bacillus amyloiquefaciens</i>
			<i>Bacillus amyloiquefaciens</i>

The investigation conclusion describes “The most probable cause for the ingress of the contamination inside the (b) (4) was identified as contamination during (b) (4) connection or (b) (4) connection for (b) (4). The probability of contamination of (b) (4) could be due to the complex structure of the (b) (4) and product in to the (b) (4) as the (b) (4) vessel had limitation to sanitize when moved from Grade (b) (4) to Grade (b) (4).”

The current standard procedure “Sanitization of Critical Area (For Grade (b) (4) Areas)” document #MT-180, dated 20 Sep 2018, establishes “...a procedure for sanitization of manufacturing and filling areas along with associated areas.” The standard procedure provides guidance that includes, for example, “The flow of cleaning activity should be as per the below order: (b) (4)” and cleaning instructions regarding a manual

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

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(b) (4) cleaning scheme and manual (b) (4) cleaning scheme. However, the standard procedure is silent with respect to provide directions, guidance and/or instructions with regards to sanitizing the complex (b) (4) piping connection and piping configurations of the (b) (4) skid. Note: Please refer to the objectionable conditions regarding the personnel gow es, (b) (4) and sanitization efficacy observations.

2. The "Entry and Exit Procedure for Production Areas of Injectable Department" document #MT-631, dated 20 Jun 2019 establishes "...a procedure for entry and exit to different production areas such as (b) (4) area of injectable department." The Senior Director Operations and Senior Manager explained that production staff that enters the filling area for injectable are required to don disposable socks, that is after removing their personal socks and prior to sitting and crossing over the cross over bench. It was also explained that personnel are required to disinfect with a (b) (4) disinfectant solution. Regarding the recovery of Bacillus microorganisms during e investigation, the standard procedure does not include directions, instructions and/or contains language regarding the removal of the personnel's personal socks. And, the standard procedure does not provide directions, instructions and/or contains language regarding the use of (b) (4) disinfectant solution. In addition;

- a. During the initial entry into Unit (b) (4) all personnel are required to don factory attire. Briefly, they remove their street cloths and don a specific color coded (b) (4) and required to wear dedicated factory shoes. The (b) (4) dedicated shoes are cleaned on a periodic base. They remove their personal attire and street shoes in a dedicated area prior to physically cross over a (b) (4) bench. As personnel stand in front of the cross over bench, they are standing with their personal socks in the same floor area where their street shoes have previously walked upon. Personnel cross over the cross over bench and then don the factory attire and dedicated factory shoes. As noted above, personnel that enter into the filling area for injectable

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must don disposable socks, which requires the removal of the personal socks. Regarding the above investigation, the root cause of the Bacillus contamination did not include and evaluation to determine if the personal socks is a source of the microbial contamination;

- i. There has been no evaluation to determine if the personnel entry area where personnel remove their personal street shoes is a possible source of the Bacillus contamination;
- ii. As previously noted, the (b) (4) and the factory dedicated shoes are cleaned on a periodic base. However, regarding the disposable socks that are required to be worn when entering and working in the fill area for injectable department, there is no information with regards to their cleanliness and there has been no evaluation to determine if the disposable socks are a source of the Bacillus contamination;
- iii. The "Determination of Antibacterial and Antifungal Efficacy of Disinfectant" batch number (b) (4) AR number (b) (4) dated 04/01/2008, acceptance criteria are as follows. "The disinfectant solution must demonstrate at least (b) (4) log reduction (for bacterial spores) and (b) (4) log reduction (for fungi and vegetative bacteria) in the viable count of the test organisms used within (b) (4) sections for hand disinfectants and within (b) (4) for other disinfectants." The evaluation conclusion describes (b) (4) shows greater than (b) (4) log reduction for fungi and vegetative bacteria but does not show any reduction with bacillus spores within (b) (4) of contact time."

3. The "Microbiological Monitoring of Environment, Surfaces and Personnel in Production Area" document #1035-L-0086 dated 09 Apr 2019 establishes "The limits given in this SOP are

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guidance limits. Hi Control 2 and Hi Control 1 (Alert and action limits) should be calculated as per SOP 1035-L-0089 / SOP 1035-L-0029 from historical data.

The “Establishment of Alert and Action Levels” document #1034-L-0089 dated 23 Aug 2019 provides guidance for establishing the Alert and Action levels for (b) (4) Environmental monitoring, Surface and Personnel monitoring. The (b) (4) defines Action Level (Hi Control 1) as “Levels which when exceed shall trigger an investigation and corrective and prevention action based on the investigation.” Alert Level is defined as “Levels which when exceed may result in an investigation, to determine if the process is still within control.” Despite the establishment of the aforementioned standard operating procedures, the microbial alert and action levels have not been established.

- The “Tests on Disinfectants” document #MM-24, dated 11 May 2015 establishes “To provide a method and frequency for determining the antibacterial and antifungal efficacy of disinfectants.” The standard procedure lists typical surfaces (i.e., “representative surfaces should be used in form of (b) (4) coupons”) to be decontaminated by disinfectants the pharmaceutical areas, for example;



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- a. Regarding the Mincare cold sterilant Surface Challenge Test dated 17/03/2018 and 12/02/2018 the tests challenge coupons included (b)(4) (b)(4) (grade unknown) and (b)(4). The March 2018 analysis did not include remaining materials of construction noted in the standard procedure;
 - b. The (b)(4) Surface Challenge Test 20/07/2010 tests challenge coupons consisted of (b)(4) (b)(4) (grade unknown). The July 2010 analysis did not include the remaining materials of construction noted in the standard procedure;
 - c. The preceding observations document that the surface challenge testing performed for the representative surfaces and materials established in the standard procedure is inconsistent with, and a departure from, the requisite tests procedure. And, it precludes the company from substantiating and "...determining the antibacterial and antifungal efficacy of disinfectants."
5. The "Investigations of Aberration Microbiological Test Result" document number 1035-G-0174, is intended "To provide a procedure to describe the investigation / evaluation / retesting / resampling and reporting of microbiological tests results which are out of specifications to assist in recommending acceptance or rejection of material / product under investigation and leading to appropriate actions related to but not limited to procedures, personnel processes, facilities, equipment, Starting material, Finished Products, Primary Packaging Material, Media Filled Units and Medical and Medical Devices." The standard procedure establishes "The labeled plates, tubes, Canisters should be stored at 2-8 degree Celsius and not discarded or cleaned until the outcome of any investigation is known (Example, identification of the isolates is completed). Photographs of all the plates under investigation should be retained." The Associate Director Microbiologist and Manager Microbiology confirmed they do not take photographs of the microbiological contaminants on the (b)(4) plates that are under investigation. In addition;

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- a. Not obtaining the required photographs of the microbiological contaminants that are under investigation is inconsistent with, and a departure from, the established standard operating procedure.

Unit (b) (4)

- 6. There are (b) (4) photographs in the Microbiology Observation Room that provide instructions and illustrations regarding "Use colony counter for count colonies", "This type of growth should be counted as two colonies", "Merged colonies distinctly different should be counted separately. In this picture the colonies which should be counted as (b) (4)", "For counting merged fungal colonies (b) (4)" and "Label plates in legible handwriting. Use appropriate permanent pen marker". The Associate Director of Quality Assurance explained the photographs are for "awareness" purposes and confirmed that the (b) (4) photographs illustrating microbiological colonies and microbiological instructions are not part of the standard operating procedures. In addition;
 - a. There are multiple "awareness" (b) (4) photographs with instructions that illustrate the personnel gowning requirements when entering and exiting the Unit (b) (4) manufacturing facilities, which include entry into the Injectable Department. The Associate Director of Quality Assurance confirmed that the color photographs and instructions are not part of the standard operating procedures.

OBSERVATION 6

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include adequate validation of the aseptic and sterilization process.

Specifically,

- 1. Unit (b) (4) - Regarding microbiological trending from 02/2018 to 07/2018 there have been numerous instances when there was >(b) (4) CFU recovered from the personnel garment cubicle,

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which is classified as Grade A. The Senior Manager confirmed the microbial contaminants are not identified in that the CFUs did not exceed the microbial limit of (b)(4) CFUs. In addition;

a. From 08/2018 to 12/2018 there were several instances when (b)(4) or >(b)(4) CFU was recovered from the Grade A environment of the (b)(4) there are (b)(4) used in the facility. The Senior Manager confirmed the microbial contaminants are not identified in that the CFUs did not exceed the microbial action limit i.e., (b)(4) CFU/plate (settle plate) and (b)(4) CFU/m³ (air sample).

2. The "Validation of (b)(4)" protocol document #JU09/(b)(4) VP/01 and validation report document #JU09/(b)(4) dated 19/02/2011, establishes the objective is "To validate the (b)(4) procedure and its effectiveness." The tests to be performed consists of the following;

Tests	(b)(4)	Hold Time	(b)(4)
Test (b)(4)	(b)(4)		time
Test (b)(4)	(b)(4)		
Test (b)(4)	(b)(4)		

The acceptance criteria include (b)(4)
(b)(4)

Associate Director of Quality Assurance explained the intent of the (b)(4) process is to reduce the "bioload" within the (b)(4) designated area. Regarding the (b)(4) validation;

a. There are no developmental studies to document and support the (b)(4) time and (b)(4) hold time performed in the (b)(4) validation;

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- b. There is no microbiological data regarding the initial “bioload” and/or data to document the reduction of the “bioload” subsequent the ^{(b) (4)} process; There is no data regarding some form of microbial challenge to demonstrate effectiveness.
- c. There is no standard procedure to establish the quantity of ^{(b) (4)} that is needed and used for a given volume in cubic feet. For example, for AHU ^{(b) (4)} vial filling area, ^{(b) (4)} area, sterile filtration area and extended corridor the quantity of ^{(b) (4)} used is ^{(b) (4)} ml for an area of ^{(b) (4)} cubic feet.
3. The “Identification and Maintenance of Inhouse Isolates” document number 1035-L-0087, dated 27 Sep 2018, scope is “Applicable to Isolates from Water, Environmental Monitoring, Finished Products, Raw materials, Packaging, In process, Readymade media plates, Inhouse prepared plates and other utilities such steam, compressed air and nitrogen.” The standard procedure establishes in the identification policy, “Identification to be completed in ^{(b) (4)} once the analytical section Microbiologist hands over the plate to the person performing the identification.” The Associate Director Microbiologist and Manager Microbiology confirmed that there is no data regarding the scientific rationale for the establishment of the ^{(b) (4)} identification policy. In addition;
- a. The technician who performed the morphology and identification steps confirmed that there is no record to document that a verification has been performed to affirm that the microbial contaminants’ morphological characteristics have not changed from their initial characterization and/or negatively impacted other unknown microbes on the ^{(b) (4)} plate.

OBSERVATION 7

Written procedures are not established for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically,

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You have not validated the cleaning process for a number of manufacturing equipment that have been used to manufacture and ship a number of drug products to US such as;

1. The cleaning validation for your (b) (4) (ID # TL-232 Unit (b) (4)) is not current. You completed the cleaning validation in 2013. As of September 27, 2019, you have neither carried out cleaning verification nor cleaning validation. Your (b) (4) (ID # TL-232 Unit (b) (4)) is a non-dedicated equipment and has been used to manufacture registration batches of (b) (4) (b) (4) tablet (b) (4) mg (b) (4) tablets) for US.
2. You have not validated the cleaning process for your (b) (4) (ID # CL-131 Unit (b) (4)). Your (b) (4) (ID # CL-131 Unit (b) (4)) is a non-dedicated equipment and has been used to manufacture and ship a number of drug products to US. A list of products manufactured and shipped to US in between 2017-2019 include but not limited to; (b) (4) capsules USP (b) (4) mg (b) (4) tablets), (b) (4) capsules USP (b) (4) mg (b) (4) tablets).
3. The cleaning validation for your equipment (b) (4) (ID # PD-2 Unit (b) (4)) is not adequate. You completed the cleaning validation in 2013 for (b) (4) mg (Batch Nos. (b) (4)). You completed cleaning verification of this equipment on 2/7/2019 with a different drug product, (b) (4) mg (Batch No. (b) (4)). Your (b) (4) (ID # PD-2 Unit (b) (4)) is a non-dedicated equipment. You have used this equipment to manufacture and ship a number of drug products to US. A list of products (b) (4) mg (b) (4) capsule), (b) (4) capsule (b) (4) mg (b) (4) capsule), and (b) (4) capsule (b) (4) mg (b) (4) capsule).
4. The cleaning validation for your equipment (b) (4) (ID # T025 Unit (b) (4)) is not adequate. You completed the cleaning validation in 2012 for (b) (4) mg, (b) (4) mg, (b) (4) mg, and (b) (4) mg tablets (Batch Nos. (b) (4)). You

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completed cleaning verification of this equipment on 10/3/2017 with a different drug product, (b) (4) tablet (b) (4) mg (Batch No. (b) (4)). Your (b) (4) (ID # T-025 Unit (b) (4)) is a non-dedicated equipment. You have used this equipment to manufacture and ship a number of drug products to US. A list of products manufactured and shipped to US during 2017-2019 include but not limited to; (b) (4) tablets USP (b) (4) mg (b) (4) tablets), and (b) (4) mg tablets (b) (4) capsule).

OBSERVATION 8

The specifications for in-process materials are deficient in that they do not include a description of the sampling plan for in-process materials.

Specifically,

Your manufacturing record for (b) (4) Tablet (b) (4) mg, Batch Record No. (b) (4) did not include sampling procedure for in-process materials testing for specifications including;

- (b) (4) as per SOP No. OI-04 (b) (4) (Version 13.0, Effective date 7/21/2017) and SOP No. OI-49 (b) (4) (b) (4) (Version 11.0, Effective date 11/4/2017). This procedure does not have instruction for obtaining the representative samples.
- (b) (4) as per SOP No. OI-05 Operation of (b) (4) Apparatus Model ETD-1020 (Version 8.0, Date of Issue 5/29/2015). This procedure does not have instruction for obtaining the representative samples.
- (b) (4) as per SOP No. OI-06 Operation and Cleaning of (b) (4) (b) (4) (Version 8.0, Effective date 2/15/2019). This procedure does not have instruction for

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obtaining the representative samples.

In addition, your manufacturing record did not include in-process testing for (b) (4). You stated that the requirement for in-process testing for (b) (4) was waived by the Agency on June 14, 2011 based on abundant historical data. However, you revalidated your process in 2019. Your initial process validation is summarized in Summary of Product Assessment: (b) (4) Tablet (b) (4) mg. This report confirmed that the process was validated on November 30, 2006 on a (b) (4) kg (b) (4) units scale in (b) (4) (ID # T-144). Your current process was validated on January 30, 2019 that is summarized in Document No. VAL/31002626/0004/REP/SUM Version No. 02. This document confirmed that the current process was validated on (b) (4) kg (b) (4) in (b) (4) (ID # T-382).

Since February 2019, you have manufactured and shipped (b) (4) tablets of (b) (4) (b) (4) tablet (b) (4) mg) to the U.S. Market. These tablets were manufactured using the current process that was validated in January 30, 2019 and lacked (b) (4) test along with sampling plans for in-process materials.

OBSERVATION 9

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically,

Your equipment qualification did not include the qualification of (b) (4) gasket that is designed to provide a barrier between the (b) (4) from the outside atmosphere during the (b) (4) process. I reviewed the following qualification report for (b) (4) ID # ON-148 Unit (b) (4)

- Installation Qualification Protocol No. IQ/GOA10/14 (b) (4) P/01 (Version No. 1, Dated 1/20/2014).

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- Operation Qualification Protocol No. OQ/GOA10/14/(b)(4) 01 (Version No. 1, Dated 1/30/2014).
- Performance Qualification Protocol No. PQ/GOA10/14/(b)(4) 01 (Version No. 1, Dated 4/10/2014).

I observed that the above report did not include qualification to establish and challenge the desired function of the (b)(4) gasket during the (b)(4) process.

During the inspection of you (b)(4) (b)(4) drug product residue were found in the exhaust ducts of (b)(4) in your multiple units including but not limited to:

(b)(4)
(b)(4). The exhaust ducts are integral part of the (b)(4) system and (b)(4) drug product residue present in the exhaust ducts provide opportunity for potential cross contamination of the drug substance during the (b)(4) operations.

OBSERVATION 10

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use and cleaning and maintenance.

Specifically,

1. Your (b)(4) (ID # T-006 Unit (b)(4) is open to outside atmosphere. On September 24, 2019, I observed a (b)(4) diameter (b)(4) in your (b)(4) (ID # T-006) that was open such that air was freely coming inside the (b)(4). Upon opening the (b)(4) I observed a (b)(4) was attached on the (b)(4) valve. I saw the (b)(4) was not sealed and there was a gap between the (b)(4) and the valve. I also saw the (b)(4) was covered with a bird mesh. There was a layer of dust and foreign materials inside the (b)(4). There

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 12420 Parklawn Drive, Room 2032 Rockville, MD 20857	DATE(S) OF INSPECTION 9/16/2019-9/27/2019*
	FEI NUMBER 3004081307

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Ashwin Upasane, Site Head

FIRM NAME Cipla Limited	STREET ADDRESS L129 - 146 S - 103 - 105 S - 107 - 112 L147 - L147 1
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CITY, STATE, ZIP CODE, COUNTRY Vasco Da Gama, Goa, 403722 India	TYPE ESTABLISHMENT INSPECTED Pharmaceutical Manufacturer
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was also (b) (4) colored substance around outside the (b) (4) and near the (b) (4) valve.

Your (b) (4) ID # T-006 Unit (b) (4) is a non-dedicated equipment that has been used to manufacture and ship a number of drug products to the U.S. Market. A list of products manufactured and shipped to the U.S. Market during 2017-2019 include but are not limited to: (b) (4) US (b) (4) mg tablet (b) (4) tablets), (b) (4) (b) (4) mg tablets USP (b) (4) tablets), and (b) (4) tablet USP (b) (4) mg (b) (4)

2. Your (b) (4) (ID # TL-192 Unit (b) (4) is open to outside atmosphere. On September 24, 2019, I observed a (b) (4) diameter (b) (4) in your (b) (4) (ID # TL-192) that was open such that I could feel the air flow inside of the (b) (4) (from outside) through the (b) (4) valve. Upon opening the (b) (4) I observed a (b) (4) was attached on the (b) (4) (b) (4) valve. I (b) (4) t sealed such that the (b) (4) was freely vibrating and letting the air inside the (b) (4) I also saw the (b) (4) was covered with a bird mesh. There was a layer of dust and foreign materials inside the (b) (4)

Your (b) (4) (ID # TL-192 Unit (b) (4) is a non-dedicated equipment that have used to manu (b) (4) nd ship a number of ug products to the U.S. Market. A list of products manufactured and shipped to the U.S. Market during 2017-2019 include but are not limited to: (b) (4) tablet (b) (4) mg (b) (4) tablets), (b) (4) tablet (b) (4) mg (b) (4) tablets), and (b) (4) tablet USP (b) (4) mg (b) (4) tablets).

Your firm's Director of the Technical Operation stated that all the (b) (4) have the similar (b) (4) (covered with a (b) (4) that opens to the atmosphere. The firm has no record/verification that ensure (b) (4) are covered/sealed to prevent entry of foreign materials from outside atmosphere.

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
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OBSERVATION 11

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,

- DEV-1011-2018-00246 documents HEPA Filter Integrity Test (FIT) failures on 13 September 2018, for Unit (b)(4) Sterile Injectable Filling Line (b)(4) “Filter media leakage observed in (b)(4) (b)(4) (b)(4)”, - (b)(4); “Side leakages observed in (b)(4)”; “Deterioration in gaskets observed in (b)(4) (b)(4)”. The last passing HEPA FIT for this area was performed on (b)(4)

On 25 September 2019, your Unit (b)(4) QA Deputy Manager, who conducted the review of this deviation, stated during the QA Impact Assessment Review, the Non-Viable Particle Counts (NVPC) were assessed in the Sterile Filtration Area (Room (b)(4)). However, your firm’s Deviation documents the Sterile Filtration Area passed the HEPA FIT and HEPA FIT failures were observed in the following Grade A Areas: Vial Filling and Plugging Area (Room (b)(4)), (b)(4) Area (Room (b)(4)).

Sterile injectable drug products and (b)(4) drug products are filtered in the sterile filtration area (Room (b)(4)), which passed HEP 3 September 2018; then proceed to the vial filling area (Room (b)(4)), which failed HEPA FIT on 13 September 2018; then proceed to the (b)(4) area (Room (b)(4)), which failed HEPA FIT on 17 September 2018.

Your QA impact assessment review is deficient with regards to conducting a review of the NVPC in the areas which failed HEPA FIT. In addition, **OBSERVATION 3** addresses NVPC concerns in the (b)(4) Area (Room (b)(4)).

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FOOD AND DRUG ADMINISTRATION**

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Your firm aseptically filled (b) (4) batches of sterile injectables and (b) (4) drug products from approximately (b) (4) of these batches were distributed to the US Market).

- DEV-1011-2018-00322 documents HEPA FIT failures for Unit (b) (4) Sterile Injectable Filling Line (b) (4) Laminar Air Flow (LAF) for Equipment IDs: IE/153, IE/154, IE/155, and IE/156, located in the Sterile Filtration Area (Room (b) (4)) on 8 December 2018. The last passing HEPA FIT for this area was performed on 1 July 2018.

However, during your QA review for impact assessment, particle counts were assessed in the (b) (4) Area (Room (b) (4)) during batch production, not the Sterile Filtration Area. The (b) (4) Area utilizes AHU #15 and the Sterile Filtration Area utilizes AHU #15A.

Your QA impact assessment review is deficient with regards to conducting a review of the Particle Counts in the area where the HEPA FIT failed. In addition, **OBSERVATION 3** addresses smoke study concerns related to air flow pattern evaluations.

Your firm aseptically filled (b) (4) batches of sterile injectables and (b) (4) drug products from approximately (b) (4) of these batches were distributed to the US Market).

- DEV-1011-2018-00261, documents damage of the (b) (4) on 05 October 2018, for Unit (b) (4) Sterile Injectable Filling Line (b) (4) in the Sterile Filtration Area (Room (b) (4)). The last passing HEPA FIT for this (b) (4) was performed on 2 August 2018.

Your QA categorized this deviation as “Minor” since the “damaged (b) (4) is not under direct product pathway” and “the batches of (b) (4)” will undergo a (b) (4)

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Your QA impact assessment review is deficient with regards to conducting a review of the Particle Counts in the area where the HEPA FIT failed. In addition, **OBSERVATION 3** addresses smoke study concerns related to air flow pattern evaluations.

Your firm aseptically filled (b) (4) batches of sterile injectables and (b) (4) drug products from approximately (b) (4) of these batches were distributed to the US Market).

OBSERVATION 12

Written procedures are not reviewed and approved by the quality control unit.

Specifically,

An (b) (4) Test for (b) (4) batch number (b) (4) dated 09 Apr 2016 was performed "To provide method and frequency for determining the antibacterial and antifungal efficacy of disinfectants." The individuals that reviewed and authorized the analysis no longer work at the company. The Associate Director of Quality Assurance confirmed no one within the current Quality Assurance department has reviewed and approved the study protocol and report.

***DATES OF INSPECTION**

9/16/2019(Mon), 9/17/2019(Tue), 9/18/2019(Wed), 9/19/2019(Thu), 9/20/2019(Fri), 9/21/2019(Sat), 9/23/2019(Mon), 9/24/2019(Tue), 9/25/2019(Wed), 9/26/2019(Thu), 9/27/2019(Fri)

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X Thomas J Arista
National Expert
Signed By: Thomas J. Arista -S
Date Signed: 09-27-2019 13:11:19

X Rajiv R. Srivastava
Investigator
Signed By: Rajiv R. Srivastava -S
Date Signed: 09-27-2019 13:11:56

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