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	8/16/2022-8/26/2022*
	FEI NUMBER 3004081307

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Pankaj Vijay Shitole, Senior Director Site Head

FIRM NAME	STREET ADDRESS
Cipla Limited	L139 to L146, S-103 to S-105, S-107 to S-112, L147 to L-147/1/2/3, L-147/A, L-138, L-150, S-116, Verna Industrial Area
CITY, STATE, ZIP CODE, COUNTRY Verna, Salcette, Goa, 403722 India	TYPE ESTABLISHMENT INSPECTED 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.

1. The environmental monitoring of the aseptic filling areas in (b) (4) does not ensure microbial contaminants in critical areas will be recognized and investigated for sterile (b) (4) products distributed to the US market.

   From August 2018-January 2019 there were (b) (4) aseptically filled sterile (b) (4) batches rejected due to environmental monitoring excursions from the filling (b) (4) of the (b) (4) aseptic filling machines. Lines (b) (4) are used for manufacturing (b) (4) Suspension for the US market and (b) (4) was used for manufacturing (b) (4) Solution for the US market. The following batches were rejected during this time period:

   - Batch (b) (4) (b) (4) (b) (4) filling machine, (b) (4) CFU/swab recovered from filling (b) (4) on August 3, 2018.
   - Batch (b) (4) (b) (4) Solution, (b) (4) filling machine, (b) (4) CFU/swab recovered from fil (b) (4) (b) (4) mber 23, 2018.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Justin A Boyd, Investigator Teresa I Navas, Investigator - Dedicated Drug Cadre Jonah S Ufferfilge, Investigator X Justin A Boyd Investigator Signed By: 2000358686 Date Signed: 08-26-2022 12:02:35	8/26/2022

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	8/16/2022-8/26/2022* FEI NUMBER 3004081307

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Pankaj Vijay Shitole, Senior Director Site Head

FIRM NAME	STREET ADDRESS
Cipla Limited	L139 to L146, S-103 to S-105, S-107 to S-112, L147 to L-147/1/2/3, L-147/A, L-138, L-150, S-116, Verna Industrial Area
CITY, STATE, ZIP CODE, COUNTRY Verna, Salcette, Goa, 403722 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

- Batch [redacted] Suspension (US Market), [redacted] filling machine, [redacted] CFU/swab recovered from filling [redacted] and [redacted] CFU/swab recovered from filling [redacted] on November 1, 2018.
- Batch [redacted] Solution, [redacted] filling machine, [redacted] CFU/swab from filling [redacted] on December 2, 2018.
- Batch [redacted] Suspension, [redacted] filling machine, [redacted] CFU/swab recove [redacted] illing [redacted] and [redacted] CFU/swab recovered from the filling zone surface on December 3, 2018.
- Batch [redacted] Suspension (US Market), [redacted] filling machine, [redacted] CFU/swab recov [redacted] on December 4, 2018.
- Batch [redacted] Suspension (US Market), [redacted] filling machine, [redacted] CFU/swab recovered from filling [redacted] on December 4, 2018.
- Batch [redacted] Suspension (US Market), [redacted] filling machine, [redacted] CFU/swab recovered from filling [redacted] and [redacted] CFU/swab from filling [redacted] on December 6, 2018.
- Batch [redacted] Suspension (US Market), [redacted] filling machine, [redacted] CFU/swab recovered from filling [redacted] and [redacted] CFU/swab on filling [redacted] on December 6, 2018.
- Batch [redacted] Suspension (US Market), [redacted] filling machine,

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Justin A Boyd, Investigator Teresa I Navas, Investigator - Dedicated Drug Cadre Jonah S Ufferfilge, Investigator	X Justin A Boyd Investigator Signed By: 2000358686 Date Signed: 08-26-2022 12:02:35	8/26/2022

(b) (4) CFU/swab recovered from filling (b) (4) on December 8, 2018.

- Batch (b) (4) (b) (4) Solution, (b) (4) filling machine, (b) (4) CFU/swab recovered from fi (b) (4) (b) (4) (b) (4) CFU/swab from (b) (4) (b) (4) on December 8, 2018.
- Batch (b) (4) (b) (4) Suspension (US Market), (b) (4) filling machine, (b) (4) CFU/swab recovered from filling (b) (4) (b) (4) and (b) (4) CFU/swab recovered from filling (b) (4) on January 2, 2019.

The investigations identified the likely root cause to be sampling errors in each instance, but rejected the batch out of caution. No actions were taken to further investigate this trend or implement corrective and preventive actions related to repeated sampling errors.

In January 2019 change control 1003-D-19-00006 was opened and proposed eliminating monitoring of the fill (b) (4) and other Grade A surfaces. The change control did not discuss historical data that demonstrated numerous out of limit results for these points resulting in the rejection of batches.

Since the change control approval on January 14, 2019, all surface monitoring of the Grade A filling (b) (4) and filling zone for (b) (4) has been discontinued. There is no data to demonstrate whether there were continued surface excursions in the Grade A surfaces that could have impacted the (b) (4) US market batches manufactured from January 2020-July 2022.

For (b) (4) monitoring of the fill (b) (4) was discontinued. Monitoring for the Grade A fill zone and fill (b) (4) was continued, but only on a (b) (4) basis and not associated with each of the (b) (4)

US market batches manufactured from January 2020-July 2022. Additionally, the limits were assigned the Grade C limits of (b)(4) CFU for an alert and (b)(4) CFU for action, rather than the Grade A limits of <(b)(4) CFU. This is inconsistent with (b)(4) for (b)(4) Suspension, which identifies the limit for surfaces in Grade A areas is <(b)(4) CFU. Surface sampling in the filling zone has recovered microbial growth within the Grade A area that was not further investigated because it was below the Grade C limits. For example:

- (b)(4) CFU was recovered from a filling zone sample of (b)(4) on February 11, 2022, after the manufacturing of batch (b)(4) of (b)(4) Suspension released to the US market (expiration (b)(4)).
- (b)(4) CFUs were recovered from a filling zone sample of (b)(4) on February 26, 2020, after the manufacturing of batch (b)(4) of (b)(4) Suspension released to the US market (expired (b)(4).

For (b)(4) Grade A monitoring of the filling (b)(4) and filling zone were discontinued. (b)(4) mon g of the filling (b)(4) was continued, but assigned the Grade C limits. Surface monitoring recovered growth from a sample at this location was below the Grade C limits, so not investigated:

- (b)(4) CFU was recovered from a filling (b)(4) sample of (b)(4) on June 28, 2021, after the manufacturing of batch (b)(4) of (b)(4) for (b)(4)

2. Sampling locations for non-viable particle counts and viable monitoring in the (b)(4) filling rooms have not established any sampling points within the (b)(4) machines to ensure they

maintain a Grade C environment surrounding the filling zone during routine operations. Some operations in the Grade C areas include (b) (4) (b) (4) to the filling zone.

Failure to have data to support air classification of areas surrounding aseptic filling operations is a repeat observation from the August 2019 FDA 483.

3. Sampling plans do not describe specific locations for collecting surface samples to ensure reproducible results and that the highest risk locations are sampled.

OBSERVATION 2

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

1. Smoke studies to evaluate airflow have not been performed for filling line (b) (4) that are used in the aseptic filling of (b) (4) Suspension.

2. Report VR/C-13 concluded smoke studies conducted in the suspension manufacturing area for filling line (b) (4) were acceptable. The report did not identify and further evaluate the following areas:

   a. Areas that appeared to show turbulence in the (b) (4) where the (b) (4) is kept during aseptic connections directional he (b) (4) For example, (b) (4)

   b. Areas that appeared to show (b) (4) the weighing balance. For example,

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	8/16/2022-8/26/2022*
	FEI NUMBER 3004081307

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Pankaj Vijay Shitole, Senior Director Site Head	
FIRM NAME Cipla Limited	STREET ADDRESS L139 to L146, S-103 to S-105, S-107 to S-112, L147 to L-147/1/2/3, L-147/A, L-138, L-150, S-116, Verna Industrial Area
CITY, STATE, ZIP CODE, COUNTRY Verna, Salcette, Goa, 403722 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

(b) (4)

Inadequate smoke studies of aseptic areas is a repeat observation from the February 2020 Warning Letter.

OBSERVATION 3

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the to produce aseptic conditions.

1. During cleaning of the (b) (4) filling machine August 18, 2022, after batch (b) (4) of (b) (4) for (b) (4)

   a. The operator was observed to place his hand on the filling assembly and an inner surface of the (b) (4) inside of the Grade A filling zone. Additionally, the operator was observed to r s that had already been wiped within the Grade A areas. The operator did not wipe any of these areas before finishing the cleaning of this area. There is no additional cleaning prior to filling of the next batch.

   b. The operator did not wipe all reachable areas outside of the (b) (4) For example, the (b) (4) inside of the machine.

2. During cleaning of the (b) (4) filling machine on August 18, 2022, after batch (b) (4) of (b) (4) Suspension, the operator did not wipe all surfaces including rior surfaces of the (b) (4) of the machine. The operator leaned over areas that had already been wiped without returning to wipe those areas.

3. Cleaning procedure CT-413 "Cleaning of (b) (4) lacks detail of the sequence of cleaning activities, does not provide instruction on cleaning complex utility connections, and does not identify those areas that the operator is permitted to omit wiping and instead rely on (b) (4)

   Insufficient details in cleaning procedures for the aseptic areas is a repeat observation from the August 2019 FDA 483.

4. (b) (4) with the scheduled disinfectant is intended to disinfect places the operators cannot he (b) (4) process has not been qualified to show it is effective or establish parameters for its use.

   Failure to qualify a (b) (4) process for disinfection of aseptic manufacturing areas is a repeat observation from the 2019 FDA 483.

OBSERVATION 4

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

1. The Human Machine Interface (HMI) for the (b) (4) filling machines use a shared password, do not have audit trails, and do not allow for the printing or transfer of electronic data. Controls have not been established to ensure there are no changes to parameters in the approved recipe. Critical machine parameters established during qualification are not otherwise documented in the batch records or checked during production. For example, during investigation OOS-1003-2022-00022 for deliverable volume variations in (b) (4) Suspension batch (b) (4) the machine parameters that could impact fill volume could not be

evaluated.

2. Electronic laboratory notebooks are used to document analysis in the chemistry and microbiology laboratories. Analysts can make changes to data entries without triggering an event in the audit trail until they manually click the save button. For example, routine review and approval of QC data by a second person would not be able to determine if the data was original or had been changed prior to the analyst manually saving the entries.

OBSERVATION 5

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

1. Procedures for reviewing electronic data and audit trails for production equipment (1035-G-0213) and in the QC laboratory (1035-L-0058) are general to apply to software used for different equipment. They do not identify and describe the items specific to the software to ensure the reviewer will effectively recognize and evaluate the relevant entries in the electronic data and audit trail. For example:

    a. The reviewer of the audit log for the enVigil non-viable particle count software uses a general procedure and was unable to explain what different entries in the audit trail meant and their impact including: “flow error”, “process autolog parmas terminated”, “bad response”, or “no response”. Additionally, the approved list of users did not match the enabled user list in the software.

    b. The reviewer for the Lab Solutions UV software explained that although not described in the procedures, he reviews errors, warnings, or abnormal audit trail entries. However, the was unable to explain which errors, warnings, or audit trail entries would be relevant

during the review.

2. Procedure 1035-L-0064 "Good Chromatographic Practices" requires a (b) (4) review of chromatography data by the software functional head. The reviewer only do he number of sequences chosen for review and does not specify which sequences were reviewed. The procedure gives no guidance as to how many sequences to review or from what analysis type (finished product, stability, raw material, validation, etc.). For example:

   a. During review for unreported data/manipulation/data integrity in August-October of 2021 there were 9 sequences chosen to review, November 2021-January 2022 there were 12 sequences chosen for review, and February-April of 2022 there were 15 sequences chosen for review.

   b. During review of appropriate integration in August-October of 2021 there were 20 sequences chosen to review, November 2021-January 2022 there were 11 sequences chosen for review, and February-April of 2022 there were 10 sequences chosen for review.

OBSERVATION 6

Procedures for the cleaning and maintenance of equipment are deficient regarding maintenance and cleaning schedules, including, where appropriate, sanitizing schedules.

SOP MT-654, "Hold Time for Clean and Unclean Area and Equipments" version (b) (4) section (b) (4) and (b) (4) define (b) (4) for cleaning of (b) (4) processing equipment such as (b) (4) (b) (4) as batches and for (b) (4) processing equipment such as (b) (4) , , as (b) (4) b es. However, your cleaning va your 2022 schedule for units (b) (4) do not show that any of the cleaning validation studies

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	8/16/2022-8/26/2022*
	FEI NUMBER 3004081307

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Pankaj Vijay Shitole, Senior Director Site Head

FIRM NAME	STREET ADDRESS
Cipla Limited	L139 to L146, S-103 to S-105, S-107 to S-112, L147 to L-147/1/2/3, L-147/A, L-138, L-150, S-116, Verna Industrial Area
CITY, STATE, ZIP CODE, COUNTRY Verna, Salcette, Goa, 403722 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

executed for products support the established (b) (4) The following is a non-exhaustive list of examples:

- Schedule for the year 2022 of (b) (4) (b) (4) located in manufacturing (b) (4) shows that the initial cleaning ase product based on solubility, potency was conducted on three batches. During routine manufacturing (b) (4) consecutive batches are manufactured.
- Schedule for the year 2022 of (b) (4) located in manufacturing (b) (4) shows that initial cleaning validation was completed for the second worst case product after a single batch, three different times, in 2019, 2020, and 2021. During routine manufacturing (b) (4) consecutive batches are manufactured.
- Schedule for the year 2022 of (b) (4) located in manufacturing (b) (4) shows that initial cleaning validation for w sed on solubility was executed using one batch in 2018, subsequent verification studies were also completed using one batch. During routine manufacturing (b) (4) consecutive batches are manufactured.

***DATES OF INSPECTION**
8/16/2022(Tue), 8/17/2022(Wed), 8/18/2022(Thu), 8/19/2022(Fri), 8/22/2022(Mon), 8/23/2022(Tue), 8/24/2022(Wed), 8/25/2022(Thu), 8/26/2022(Fri)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Justin A Boyd, Investigator Teresa I Navas, Investigator - Dedicated Drug Cadre Jonah S Ufferfilge, Investigator	X Justin A Boyd Investigator Signed By: 2000358686 Date Signed: 08-26-2022 12:02:35	8/26/2022

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	8/16/2022-8/26/2022*
	FEI NUMBER 3004081307

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Pankaj Vijay Shitole, Senior Director Site Head

FIRM NAME	STREET ADDRESS
Cipla Limited	L139 to L146, S-103 to S-105, S-107 to S-112, L147 to L-147/1/2/3, L-147/A, L-138, L-150, S-116, Verna Industrial Area
CITY, STATE, ZIP CODE, COUNTRY Verna, Salcette, Goa, 403722 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

X Teresa I Navas
Investigator - Dedicated Drug Cadre
Signed By: Teresa I. Navas -S
Date Signed: 08-26-2022 12:03:13

X Jonah S Ufferfilge
Investigator
Signed By: Jonah Ufferfilge -S
Date Signed: 08-26-2022 12:03:46

SEE REVERSE OF THIS PAGE

EMPLOYEE(S) SIGNATURE

Justin A Boyd, Investigator
Teresa I Navas, Investigator - Dedicated Drug Cadre
Jonah S Ufferfilge, Investigator

X Justin A Boyd
Investigator
Signed By: 2000358686
Date Signed: 08-26-2022 12:02:35

DATE ISSUED
8/26/2022