DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	3/28/2024 - 4/4/2024
	FEI NUMBER 3002806710

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Vijayasarathi Ramaswami, Head - Global Quality

FIRM NAME	STREET ADDRESS
Cipla Limited	Patalganga Industrial Area, Plot No A-2, A-33, A-37/2/2, A-42
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Raigad, Maharashtra, 410220, India	Human and animal API and human drug product 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 (I) (WE) OBSERVED:

OBSERVATION 1

Failure to clean and maintain equipment and utensils to prevent contamination or carry-over of a material that would alter the quality of the API beyond the official or other established specifications.

Specifically,

Your firm does not properly clean and maintain [redacted] (b) (4) -405 which is utilized in the manufacture of [redacted] (b) (4) USP active pharmaceutical ingredient intended for the US market as noted below:

• On 4/2/2024, we inspected [redacted] (b) (4) -405 in room [redacted] (b) (4) (ISO-8). Upon opening the [redacted] (b) (4) we noted what appeared to be two flying insects in the [redacted] (b) (4) bowl of the [redacted] (b) (4) near the [redacted] (b) (4)

• On 4/3/2024, we inspected the [redacted] (b) (4) duct of [redacted] (b) (4) -405. The [redacted] (b) (4) duct [redacted] (b) (4) to the [redacted] (b) (4) during API manufacture. The [redacted] (b) (4) duct is located outside of building [redacted] (b) (4) and exposed to external conditions. Upon inspection of the duct, multiple areas of external damage (dents) were observed and a large gap in the duct seal was noted approximately 4 feet from the [redacted] (b) (4) valve). We were able to insert a folded 8 x 11 inch piece of paper into the duct seal gap and confirmed that the duct seal was non-integral and breached. Your firm was unaware of the breach, the cause, and the duration for which the breach has been present.

Add Continuation Page

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Lori Newman Sean Marcisin	Lori M. Newman, Investigator Sean R. Marcisin, Investigator	04/04/2024

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	3/28/2024 - 4/4/2024
	FEI NUMBER
Industry Information: www.fda.gov/oc/industry	3002806710

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Vijayasarathi Ramaswami, Head - Global Quality

FIRM NAME	STREET ADDRESS
Cipla Limited	Patalganga Industrial Area, Plot No A-2, A-33, A-37/2/2, A-42
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Raigad, Maharashtra, 410220, India	Human and animal API and human drug product manufacturer

Additionally, what appeared to be white (b) (4) caulking was noted to have been applied around the affected duct joint in an attempt to seal around the duct gasket. Your firm has no documentation as to when the (b) (4) caulking was applied to the (b) (4) duct or the reason(s) why (since 2023). The last preventative maintenance of the (b) (4) 405 (b) (4) duct was conducted on 2/21/2024 when your firm documented that the gasket/seals were inspected. Additionally, your firm lacks evidence that one of the engineering technicians who performed the preventative maintenance was trained on the associated procedure. Since 2/21/2024, your firm has manufactured (b) (4) ots of (b) (4) USP API intended for use in the manufacture of drug products for the US market.

• On 4/3/2024, we inspected the interior of the (b) (4) -405 (b) (4) duct directly adjacent to the (b) (4) (b) (4) valve. We noted various debris in the duct to include what appeared to fragments of duct sealant (caulking) material and unknown residue.

OBSERVATION 2

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

Specifically,

A. We inspected the (b) (4) manufacturing area which is utilized in the manufacture of US drug products to include (b) (4) tablets USP. The following deficiencies were noted:

• On 3/28/2024, we noted unknown (b) (4) residue on the (b) (4) shaft and (b) (4) bolt of the (b) (4) (b) (4) The (b) (4) was in the process of being cleaned of the previous batch (b) (4) mg tablets, lot (b) (4) The (b) (4) material is white in color.

Add Continuation Page

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Lori Newman Sean Marcsisin	Lori M. Newman, Investigator Sean R. Marcsisin, Investigator	04/04/2024

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	3/28/2024 - 4/4/2024
	FEI NUMBER
Industry Information: www.fda.gov/oc/industry	3002806710

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Vijayasarathi Ramaswami, Head - Global Quality

FIRM NAME	STREET ADDRESS
Cipla Limited	Pataiganga Industrial Area, Plot No A-2, A-33, A-37/2/2, A-42
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Raigad, Maharashtra, 410220, India	Human and animal API and human drug product manufacturer

• On 4/1/2024, we noted an unknown (b) (4) spot on the (b) (4) bolt and (b) (4) bearing housing, and unknown white residue on the shaft bolt of the (b) (4) assembly. The shaft bolt of the (b) (4) assembly is exposed to the drug product discharge flow path during (b) (4) operation. The above equipment was documented as being in clean status.

B. SOP MT-308 "Operation and Cleaning of (b) (4) Cleaner, Duct Cleaning (b) (4) and Pipe Inspection (b) (4) System" is inadequate because it lacks a mechanism to trigger an investigation in the case of a failed cleaning. MT-308 states in section 2.5.4 that after review of the (b) (4) of a cleaned duct, if any residue is observed, the cleaning procedure should be repeated until results are satisfactory. On 04/01/2024, we observed on the log "Details of Numbering and Cleanliness Verification of (b) (4) Duct After Cleaning by Using (b) (4) System or After Dismantling (b) (4) -500)" in (b) (4) Manufacturing Area that on 10/16/2023, powder was observed in (b) (4) ducts 23015 (b) (4) 05 and 23015 (b) (4) 06 of (b) (4) 500 (b) (4) -500) after cleaning and (b) (4) inspection. The ducts were recleaned and found satisfactory with no investigation as to why cleaning had initially been insufficient. (b) (4) -500 is used in the production of drug products for the US market such as (b) (4) tablets USP.

OBSERVATION 3

Failure to adequately investigate out-of-specification results

Specifically,

Since May 2020, your firm has documented 8 OOS investigations related to particle size distribution (PSD) for the (b) (4) USP active pharmaceutical ingredient (API) manufactured at Unit (b) (4) to include OOS-1030-2024-00013. OOS-1030-2024-00013 remains open as of the current inspection for (b) (4) USP lot (b) (4) and root cause(s) of the PSD OOS results remain to be determined. As of 4/3/2024, your firm has failed to holistically evaluate the (b) (4) USP API manufacturing process and PSD OOS results to ensure all factors that contribute to (b) (4) USP particle size variation and (b) (4) are identified and remediated.

Add Continuation Page

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Lori Newman Sean Marcsisin	Lori M. Newman, Investigator Sean R. Marcsisin, Investigator	04/04/2024

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	3/28/2024 - 4/4/2024
	FEI NUMBER 3002806710

Industry Information: www.fda.gov/oc/industry

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	
TO: Vijayasarathi Ramaswami, Head - Global Quality	
FIRM NAME Cipla Limited	STREET ADDRESS Patalganga Industrial Area, Plot No A-2, A-33, A-37/2/2, A-42
CITY, STATE AND ZIP CODE Raigad, Maharashtra, 410220, India	TYPE OF ESTABLISHMENT INSPECTED Human and animal API and human drug product manufacturer

OBSERVATION 4

Equipment qualification procedures are not followed

Specifically,

Your firm did not follow procedure 1035-G-0042 - Qualification of Equipment for the [redacted] (b) (4) Your firm acquired and began using the [redacted] (b) (4) in 2023 for [redacted] (b) (4) USP active pharmaceutical ingredient manufacture to help [redacted] (b) (4) during [redacted] (b) (4) operations to address particle size OOS events. Per procedure 1035-G-0042, your firm is to perform a risk assessment for new equipment to identify equipment criticality and guide qualification activities. As of 4/3/2024, your firm has not conducted a risk assessment nor qualification activities for the [redacted] (b) (4)

OBSERVATION 5

Failure to ensure all production deviations are reported and evaluated, and that critical deviations are investigated and the conclusions are recorded.

Specifically,

Your firm does not evaluate atypical events during [redacted] (b) (4) active pharmaceutical ingredient packing. The [redacted] (b) (4) API is to be packed into [redacted] (b) (4) [redacted] (b) (4) per procedure PROD-39 - Packing with special protection. [redacted] (b) (4) of the finished API and [redacted] (b) (4) QC sampling of the batch [redacted] (b) (4) events). Your firm has documented API batches for which there were more than [redacted] (b) (4) events that your firm cannot account for. For example, [redacted] (b) (4) [redacted] (b) (4) API lot [redacted] (b) (4) have [redacted] (b) (4) events occurring [redacted] (b) (4) [redacted] (b) (4)

Add Continuation Page

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Lori Newman Sean Marcsisin	Lori M. Newman, Investigator Sean R. Marcsisin, Investigator	04/04/2024

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	3/28/2024 - 4/4/2024
	FEI NUMBER 3002806710

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Vijayasarathi Ramaswami, Head - Global Quality

FIRM NAME	STREET ADDRESS
Cipla Limited	Patalganga Industrial Area, Plot No A-2, A-33, A-37/2/2, A-42
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Raigad, Maharashtra, 410220, India	Human and animal API and human drug product manufacturer

OBSERVATION 6

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

Specifically,

The procedures 1035-G-0196 "Categorization and Handling of Alarms" and MT291 "Operation of [(b) (4)] System" are not adequately followed in case an alarm occurs for high [(b) (4)] value in the [(b) (4)] This [(b) (4)] is used for cleaning drug product manufacturing equipment and as a component of various drug product formulations for the US market, including [(b) (4)] tablets USP.

1035-G-0196 "Categorization and Handling of Alarms" defines a critical alarm as an alarm that may have a direct impact on product quality. Annexure to MT291 (MT291/A5 "List of Alarms, Possible Causes, and Rectification") classifies [(b) (4)] as a noncritical alarm.

Annexure MT291/A5 states on p. 9 that if an alarm sounds for the system stopping due to very high [(b) (4)] in the [(b) (4)] the rectification steps are to inform all user departments, acknowledge the alarm, check and ensure functioning of the [(b) (4)] meter, and check the [(b) (4)] in the [(b) (4)] in the [(b) (4)] It says if the [(b) (4)] of the [(b) (4)] is high, a [(b) (4)] sample should be sent to QC for checking of the [(b) (4)]

On 3/16/2024 at 16:50, there was an audiovisual alarm for [(b) (4)] exceeding the limit (value: [(b) (4)]; spec NMT [(b) (4)] in the [(b) (4)] system. While the alarm was acknowledged and the system automatically began dumping [(b) (4)] that exceeds [(b) (4)] specifications, you did not provide evidence that a [(b) (4)] sample was sent to QC for verification of the [(b) (4)] value as required for rectification in Annexure MT291/A5.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Lori Newman Sean Marcsisin	Lori M. Newman, Investigator Sean R. Marcsisin, Investigator	04/04/2024

Add Continuation Page