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	4/2/2018-4/13/2018*
	FEI NUMBER 3008581988

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Ashish Zitshi, Senior Director and Site Head

FIRM NAME	STREET ADDRESS
Cipla Limited	Plot No. 9 & 10, Pharma Zone Phase II, Section IIII, Indore Special Economic Zone
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Pithampur, District Dhar, Madhya Pradesh, 454 775 India	Sterile and Non-Sterile 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 OBSERVED:

OBSERVATION 1

Testing programs are not adequately designed to assess the stability characteristics of drug products.

Specifically, test schedules established by stability protocols do not characterize the degradation of products over their actual shelf-lives. Stability schedules are based on the date of sample incubation rather than the date of manufacturing. Section 2.6.2.6 of SOP 1035-L-0100, "STABILITY STUDIES (LIMS)" (rev. 4.0, eff. 12JAN2018), states that "shelf life intervals and intervals after expiry are to be calculated from the date of manufacturing and not the date of incubation". However, QC management stated that interim stability time points established by the date of sample incubation per Section 2.1.18: "Stability study should be started in LMIS on the date of incubation".

For example, Out-of-Specification LC/OOS/PA/12/15/08 was initiated for the failure of (b) (4) mg/(b) mL (b) (4) solution Batch (b) (4) for high organic impurities, namely Impurity (b) (4). The 21M long-term stability of Batch (b) (4) failed on (b) (4), as anticipated by the extrapolation of impurity data from previous stability time points. No apparent root cause was identified during laboratory investigation and the OOS results were confirmed.

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	Patric C Klotzbuecher, Investigator	X Patric C Klotzbuecher Investigator Signed By: Patric C. Klotzbuecher -S3 Date Signed: 04-13-2018 04:02:44	4/13/2018

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Batch (b) (4) was dispensed on 14JAN2014, compounded on 17JAN2014, sampled for stability studies on 22JAN2014, tested, and finally released by QC on 05MAR2014. The stability samples of Batch (b) (4) were not charged into long-term stability conditions until (b) (4).

As a result of a related investigation for the 12M long-term stability failure of (b) (4) mg/(b) mL (b) (4) solution Batch (b) (4) for high Impurity (b) (4), LC/OOS/PA/03/15/05 (initiated March 2015), additional monthly time points were to be evaluated for Batch (b) (4) from 17M thru end of shelf-life. The 21M stability sample was not analyzed until (b) (4), coincidental with its (b) (4) M expiry, rather than the batch's actual 21M from date manufacture, September 2015. Since interim stability timepoints are based on the date of sample incubation rather than the batch manufacturing date, the 21M stability failure of Batch (b) (4) was not known until (b) (4) months after the batch's actual 21M on market.

OBSERVATION 2

Written procedures for production and process controls are not designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically, there are no established reject limits, either by individual failure modes or cumulative totals, per (b) (4) or batch, for media fill process simulations. For example, the following table shows the number of rejected units of (b) (4) from various media fill batches processed on (b) (4) ((b) (4)) Line (b) (4) coincidental with the simulation of specific process interventions.

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Media Fill	(b) (4)	Intervention	Approx. # of Units Potentially Affected	# of "Other" (b) (4) / Pinhole Rejects	(b) (4) Reject Rate
Batch (b) (4)	Lot (b) (4)	Adjustment of (b) (4) (b) (4)	(b) (4)		~131.9%
Batch (b) (4)	Lot	Media held for (b) (4) prior to filling			~32.8%
	Lot	Shutoff of filling room AHU for (b) (4)			~46.6%
	Lot	(b) (4) re-(b) (4) of filling line			~87.3%
	Lot	(b) (4) re-(b) (4) of filling line			50%
Batch (b) (4)	Lot	Power failure simulated for NLT (b) (4)			~75.3%
Batch (b) (4)	Lot	Changing of (b) (4) (b) (4)			~101.8%
Batch (b) (4)	Lot	No worst-case/un-planned interventions			~42.0%
	Lot	Filling area (b) (4) opened NLT			~104.5%

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		(b) (4)			
	Lot (b) (4)	Alignment of (b) (4) (b) (4)	(b) (4)		~107.0%
	Lot	Changing of (b) (4)			~344.4%
Batch (b) (4)	Lot	(b) (4) alignment			~26.9%
	Lot	Right side (b) (4) lock non-functional			~48.8%
	Lot	(b) (4) adjustment (b) (4) re- (b) (4)			~116.4%

Media fill units that are deemed to have quality-related failures such as "other", (b) (4), and pinhole rejects are not incubated. Thus, the lack of quality defect reject limits for media fill studies does not provide adequate study acceptance criteria to demonstrate aseptic process robustness.

OBSERVATION 3

Scientifically sound and appropriate laboratory control mechanisms are not established to assure that in-process materials or drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically, post-fertility testing (growth promotion testing) is performed independently for samples from the (b) (4) of media fills and documented on Format 1035-MM-011-INH/F2. The current version of SOP 1035-MM-011-INH, "MICROBIOLOGICAL PROCEDURES FOR

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MEDIA FILL" (rev. 3.0, eff. 30SEP2016), consists of Annexure 1035-MM-011-INH/A2, the specimen (or master) copy of Form 1035-MM-011-INH/F2. This current version of 1035-MM-011-INH/F2 consist of no requirement for verification of growth/no growth observed. Observation of the growth promotion samples is performed and documented by a single analyst only with no direct, secondary verification. Lab Quality Assurance verifies the information documented by Quality Control only after completion of the test. For example,

A. There is no documentation of a 2nd analyst or supervisor verifying the turbidity of (b) (4) post-fertility test samples from (b) (4) Line (b) (4) Media Fill Batch (b) (4) as inspected on 27 and 29OCT2016.

B. There is no documentation of a 2nd microbiologist or supervisor verifying the turbidity of (b) (4) post-fertility test samples from (b) (4) Line (b) (4) Media Fill Batch (b) (4) as inspected on 22 and 25SEP2017.

***DATES OF INSPECTION**

4/02/2018(Mon), 4/03/2018(Tue), 4/04/2018(Wed), 4/05/2018(Thu), 4/06/2018(Fri), 4/09/2018(Mon), 4/10/2018(Tue), 4/11/2018(Wed), 4/12/2018(Thu), 4/13/2018(Fri)

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