DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave,Bldg 51,Rm 4225 Silver Springs, MD 20993 (301)796-3334 Fax:(301)847-8738	8/22/2016-8/30/2016* FEI NUMBER 3004081307

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Tapas Datta , Site Head	
FIRM NAME Cipla Limited	STREET ADDRESS S103 - 105 S107 - 112 L - 147 L138 L150, Verna Industrial Estate
CITY, STATE, ZIP CODE, COUNTRY Salcette, Goa, 403722India	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 I OBSERVED:

Quality System

OBSERVATION 1

Investigations of an unexplained discrepancy and a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product.

Specifically,

a. Regarding (b) (4) (b) (4) Solution, approximately 7 complaints have been received for lot (b) (4), exp. (b) (4), between April 2015 and June 2016, describing empty containers or similar issues. Approximately 9 complaints have been received for this issue across other lots. Investigation has found that the container-closure system was being damaged during the assembly of the (b) (4) and sterile integrity of the containers was compromised, allowing product to evaporate or leak out of the container. Although (b) (4) line (b) (4) is believed to be an appropriate corrective action to eliminate the defect, prevalence and severity of the defect has not been thoroughly investigated, and inspection for the container-closure defect has not yet been assessed throughout an entire filling run. The product has not been filled since January, 2016, but there are approximately 11 lots on the market within expiry, in addition to lot (b) (4) for which the integrity of the sterile barrier may be questionable.

b. (b) (4) (b) (4) Solution, lot (b) (4), is failing to meet the specification limit for content of (b) (4) (b) (4) the 25˚ (b) (4) %RH stability condition at 18 months. Values were reported at (b) (4)%, (b) (4)%, (b) (4)%, and (b) (4)%, and the limit is (b) (4)% to (b) (4)%. The root cause of the failure is not clear, and the investigation has not expanded to other lots. There are approximately 12 lots on the market within expiry.

c. (b) (4) Tablets, lot (b) (4) was found to be out of specification for assay at the 3-month 25 ˚C/60%RH stability station (stability limit (b) (4)% - (b) (4)%). This batch was placed on stability due to it having a lower-than-usual assay value at release, of (b) (4)%, but other batches were released with similarly low values and not placed on stability. For example, (b) (4)% (lot (b) (4)) and (b) (4)% (lot (b) (4)). Although the 3-month OOS was initiated

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recently on 08/01/2016, other lots with low assay values at release were not also investigated.

Facilities and Equipment System

OBSERVATION 2

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

Specifically, items that are not easily cleanable or sanitizable were observed in aseptic processing and support areas during a walkthrough of Unit (b)(4) on 08/24/2016. For example:

a. On Line (b)(4) an HMI panel operating the filling line, which is located in the Grade B area where operators are working, had an ordinary computer mouse attached to it. This could be used in the event the sanitizable touch screen is not functioning. The buttons on the mouse may be difficult to clean and sanitize effectively for use in the cleanroom environment.

b. On Line (b)(4) the batch record was observed being held together with a metal binder clip, being used just outside the filling area. This clip may be difficult to clean and sanitize to ensure that it does not potentially contribute to contamination by operators working in the cleanroom environment.

c. On Line (b)(4) a floor balance used for collecting process data had a display panel mounted to the wall, which had a bundle of wires hanging from it. These wires may be difficult to clean and sanitize effectively for use in the cleanroom environment.

d. On Line (b)(4) in the bulk manufacturing area, prior to (b) (4) of product, the room contained both a sanitizable cleanroom phone panel on the wall, as well as a traditional telephone with coiled cord, which may be difficult to clean and sanitize. Raw materials in (b) (4) form may be handled in this room for bulk manufacture.

Products produced in Unit (b)(4) which may be processed on Line (b)(4) include (b) (4) (b) (4)

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OBSERVATION 3

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

Specifically, at the (b) (4) of each of (b) (4) (b) (4) machines, the process includes a (b) (4) system, but it is only validated to (b) (4) holes that may occur at the (b) (4) of each vial, and not throughout the container itself. This is performed following (b) (4), by which a (b) (4) (b) (4) There is no routine vial integrity testing performed after this. There is no assurance that if a leak were (b) (4) in any other part of the (b) (4) container that it would be (b) (4). Products filled on these lines include (b) (4) Suspension and (b) (4) and (b) (4) Solution.

Postmarket Reporting

OBSERVATION 4

An (b) (4) Field Alert Report was not submitted within three working days of receipt of information concerning significant chemical, physical, or other change or deterioration in a distributed drug product.

Specifically, an (b) (4) Field Alert Report (FAR) was filed only after 7 complaints for empty container in sterile product (b) (4) Solution, lot (b) (4) were received, between April 2015 and June 2016. This product is contract manufactured for (b) (4) who holds the product application. The FAR was not filed until 08/01/2016, approximately 16 months after the first complaint, which is indicative of a breach in the sterile barrier of the product, was received.

Additionally, complaints of this nature were also received for lots (b) (4) (b) (4), (b) (4), (b) (4) and (b) (4), but this has not been described in reporting to the Agency.

*DATES OF INSPECTION

8/22/2016(Mon),8/23/2016(Tue),8/24/2016(Wed),8/25/2016(Thu),8/26/2016(Fri),8/29/2016(Mon),8/30/2016(Tue)

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