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	1/22/2018-1/25/2018 FEI NUMBER 3004081307

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Tappas Datta, Senior Vice President

FIRM NAME	STREET ADDRESS
Cipla Limited	Plot No. L-139, S-103 & M-62, Verna Industrial Estate
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Salcette, Goa, 403722 India	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:
PRODUCTION SYSTEM

OBSERVATION 1

There is a failure to thoroughly review 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, exhibit batch (b) (4) Capsules (b) (4) mg number (b) (4) samples failed your in-process test for content of (b) (4) ((b) (4)) with results (b) (4) % (specification (b) (4) % - (b) (4) %). Your OOS investigation LC/OOS/OC/09/16/09 did not include a thorough review of the failure and a scientifically sound investigation in that (This is a repeat observation):

a) your aforementioned OOS Investigation (Amendment 02) -

i) reported in your conclusion "this is the first time in-process testing was performed for (b) (4) content of the (b) (4) ". However, this statement is incorrect. Your Head of Quality Unit (b) (4) stated you tested the first exhibit batch (b) (4) for (b) (4) content and waited for the test results before proceeding to the encapsulation stage of your manufacturing process. Your Head of Quality Unit (b) (4) also stated you tested batches (b) (4) and (b) (4) at the same time using the aforementioned test method. You also tested exhibit batches (b) (4) and (b) (4) for (b) (4) content using the aforementioned test method.

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ii) stated the higher % RSD is due to variation in the results. You do not have data to show the % RSD variation is not due to non-uniform (b) (4) content in the (b) (4). You did not test spiked samples for (b) (4) content on different days to demonstrate intermediate precision. You did not test spiked (b) (4) samples to demonstrate the accuracy and intermediate precision of your (b) (4) content test method.

iii) stated initial OOS results are due to either handling or exposure of samples based on a literature review regarding (b) (4). Your (b) (4) sample is a (b) (4) not a (b) (4). You do not have data to show improper handling of samples or sample exposure are the root cause(s) of content of (b) (4) OOS results.

iv) stated (b) (4) content is found uniform in the filled capsules. You do not have data to show your (b) (4) Content by HPLC test method STP-17-005238 effective March 28, 2017 is capable of identifying inconsistent (b) (4) content in the (b) (4) or finished product capsules.

b) did not include development of a CAPA (Corrective Action and Preventive Action) plan to prevent future (b) (4) content failures in (b) (4) samples and to ensure a uniform (b) (4) content in (b) (4).

c) stated "the cause of the OOS was attributed to a method that is not amenable to in-process (b) (4) assessment". Your Head of Quality Unit (b) (4) stated the first batch of (b) (4) Capsules (b) (4) mg manufactured in Unit (b) (4), batch number (b) (4), results for (b) (4) content were within specification. Your Head of Quality Unit (b) (4) stated you intend to continue using the aforementioned test method to test (b) (4) samples. You do not have data to show your (b) (4) content test method can identify non-uniform (b) (4) content in your (b) (4) samples or finished product samples.

OBSERVATION 2

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The batch production and control records are deficient in that they do not include documentation of the accomplishment of each significant step in manufacturing, processing, packing and holding.

Specifically, the batch record for (b) (4) Capsules (b) (4) mg including but not limited to the batch record for (b) (4) Capsules (b) (4) mg batch number (b) (4) does not:

a) identify the sampling plan or acceptance criteria for Rejection Analysis for finished product capsules.

b) reference an SOP (Standard Operating Procedure) describing how to conduct reject analysis or include the acceptance criteria for each type of rejects. Exhibit batch (b) (4) Capsules (b) (4) mg number (b) (4) included 203 minor defects for dull capsules and 525 minor defects for smudge printing for a total of 728 minor rejects. A total quantity of (b) (4) capsules were sent for packaging.

c) include documentation for the number of defects identified from each container so that if a high number of defects are found in a specific drum/container QA can be informed as specified in your written procedure for Acceptable Quality Limit (AQL) MT-61 version 12.0 effective March 22, 2017 section 2.1.15.

d) include calculation of the % AQL defects.

e) include documentation of review of the batch record and raw electronic data by QA prior to batch approval and release.

LABORATORY CONTROL SYSTEM

OBSERVATION 3

Laboratory records are deficient in that they do not include a complete record of all data obtained during testing.

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Specifically, laboratory records do not always include a complete record of all data obtained during testing in that:

a) your Standard Test Procedure (b) (4) Content STP-17-005238 does not specify the stability of the standard and sample solutions. You do not document the date and time standards and sample solutions are prepared in your Test Data Sheets to ensure standard and sample solutions are stable at the time of testing.

c) you do not always document known lab errors on your Test Data Sheets. Laboratory Investigation Report (LIR) LC/OOT/OC/12/16/05 initiated December 23, 2016 for (b) (4) Capsules (b) (4) mg batch (b) (4) OOT (Out-of-Trend) dissolution test identified the root cause as the cannula in vessel 6 was out of alignment. Misalignment of the cannula in vessel 6 was not documented on the Test Data Sheet.

OBSERVATION 4

Established test procedures are not followed.

Specifically, your standard test procedures do not always include sufficient detail to ensure consistent implementation in that:

a) (b) (4) Content STP-17-005238 effective March 28, 2017 states to "(b) (4) each capsule and carefully transfer the contents of each capsule into a clean and clear dry beaker". On January 24, 2017 I observed a QC Analyst use scissors to cut off an end from each capsule and squeeze the contents of each capsule into a beaker. The aforementioned procedure does not state to use scissors to cut off an end from each capsule.

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b) Traces of (b) (4) COCB004 version 1 effective June 28, 2016 does not specify the concentration of the (b) (4) to use to prepare the sample solution for swab testing and it does not specify how to prepare the swab prior to taking a swab sample.

c) Laboratory Investigation Report (LIR) (b) (4) Capsules (b) (4) mg LC/OOS/OC/09/16/14 Summary of the OOS Investigation [Amendment-1] dated September 27, 2016 initiated for OOS assay testing states on page 1 "critical steps were not explicitly specified in the method". The Standard Test Procedure Assay (b) (4) Capsules (b) (4) mg effective September 3, 2016 did not include sufficient details to ensure capsules shells are dispersed in the sample flask prior to testing.

OBSERVATION 5

Reserve samples from representative sample lots or batches of drug products selected by acceptable statistical procedures are not examined visually at least once a year for evidence of deterioration.

Specifically, your written procedure for visual examination of reserve samples, Visual Inspection 1035-L-0036 version 3 effective March 8, 2017 does not:

a) include visual examination at least annually of reserve samples from exhibit batches.

b) specify storage of reserve samples in the same package configuration as the intended commercial package configuration. Your intended commercial package size is (b) (4) count capsules in an (b) (4) bottle with a (b) (4) cap. Your reserve samples contain (b) (4) capsules in the same size (b) (4) bottle as your intended commercial package with a (b) (4) cap. The head space in an (b) (4) bottle containing (b) (4) capsules is not the same as the head space in an (b) (4) bottle containing (b) (4) capsules. Head space can impact product deterioration.

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c) specify to visually examine reserve samples for evidence of deterioration with the aid of a light and magnifying lens.

d) specify how to evaluate the appearance of the (b) (4) inside the finished product (b) (4) capsules. (b) (4) Capsules (b) (4) mg contain a (b) (4) of the drug product formula.

OBSERVATION 6

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications prior to release.

Specifically, you do not always issue one authentic CoA (Certificate of Analysis) for each batch of (b) (4) Capsules (b) (4) mg in that:

a) for each batch you generate a CoA for microbial test results for the finished product, a CoA for different stages in the manufacturing process, and a CoA containing both chemical and microbial test results for the finished product. You use the same format for all CoAs. There is no clearly identifiable distinction to identify the one authentic CoA for the finished product.

b) the number of authentic CoAs printed for a batch prior to release is not identified on the CoA.

c) Standard Operating Procedure Generation of Certificate of Analysis (LIMS) 1035-L-0093 effective June 30, 2017 section 2.1.10 states "The CoA generated for every lot (after its authorization by QA in LIMS) remains available in LIMS repository, which can be recalled as such and printed as and when required through the option provided through 'Macros' menu in toolbar". Your Head of Site Quality stated you generate a CoA from LIMS for each quantity shipped.

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QUALITY SYSTEM

OBSERVATION 7

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

Specifically, your quality unit does not always ensure

a) risk assessments are appropriate and properly categorized in that your Risk Management by Failure, Mode, Effects and Criticality Analysis version 2 effective June 29, 2016 could result in a failure predicted to cause a life threatening illness or irreversible injury which happens unexpectedly and for which you do not have detection control categorized as minor criticality based on calculation.

b) written procedures are not always followed in that Standard Operating Procedure Batch Release System of Formulations 1035-G-0019 effective December 26, 2017 section 3.15 specifies the Batch Documentation Checklist executed during batch release shall be attached with the completed batch record. The batch records for exhibit batches of (b) (4) Capsules (b) (4) mg including but not limited to the batch record for batch (b) (4) did not have an attached executed Batch Documentation Checklist.

FACILITIES AND EQUIPMENT SYSTEM

OBSERVATION 8

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

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Specifically, you do not always adequately qualify/re-qualify equipment used in the manufacture of drug products such as (b) (4) Capsules (b) (4) mg in that:

a) you did not have an approved protocol for equipment re-qualification of your (b) (4) Encapsulation Machine moved from Unit (b) (4) to Unit (b) (4) with acceptance criteria for each critical variable prior to initiation of performance re-qualification operations.

b) you do not have data showing your (b) (4) Encapsulation Machine is capable of successful operation over the full range of your acceptance criteria for critical variables.

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