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	07/15/19 - 07/19/19
	FEI NUMBER 3002806691

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Daniel Boppuri, Senior Director and Site Head

FIRM NAME	STREET ADDRESS
Cipla, Ltd - Virgonagar Site	Old Madras Road, Virgonagar
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Bangalore, Karnataka, 560049, India	API Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1. Investigations into out-of-specification (OOS) QC analytical results, related to finished API product quality failures, are not adequate.

Specifically, your investigations do not always determine root causes for API drug substance failures. Review of several OOS investigations revealed that your personnel conducting the investigations are not always adequately assessing the analytical data to evaluate/eliminate all possible sources of the OOS results. Examples include, but are not limited to:

* 1021_LAB1/INV/10/18/05 - (b) (4) Lots: (b) (4) and (b) (4). Investigation reports OOS for "any other individual impurity around RRT (b) (4)" during 36 month long-term stability testing. The root cause for the OOS was determined as "the higher temperature and humidity conditions are not favorable to retain the original characteristics of the (b) (4) USP material". Review of the overlays of the chromatographic data for 0 - 36 months stability testing for Lots: (b) (4) and (b) (4) shows that the main (b) (4) peak shifts from around (b) (4) minutes to around (b) (4) minutes for both lots during the 0 - 36 month period. However, you do not evaluate why the main (b) (4) peak shifts significantly between stability pulls, or compare it to the USP reference standard. Note that these lots of (b) (4) USP are validation batches, and the key starting material is (b) (4) (b) (4) where you do not control or monitor the critical (b) (4) step of (b) (4) at the specified rate of (b) (4) L/hr during the manufacture of the API intermediate (b) (4).

* 1021_LAB1/INV/10/18/02 - (b) (4) Lot: (b) (4). (Same as above OOS)

* 1021_LAB1/OOS/02/19/09 - (b) (4) USP Lot: (b) (4). Investigation reports OOS for "description" during 60 month long-term (25 C/60 % R.H.) stability testing. The root cause for the OOS was determined as "exposure to atmosphere and heat, undergoes colour change, hence material by nature is not stable at higher

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temperature beyond 12 months at any temperature exceeding 25 C." However, you do not adequately explain the failure at 25 C/60% R.H. compared to the explanation of the same description failures at intermediate (30 C/(b) (4)% R.H.) and accelerated (40 C/75% R.H.). Furthermore, many of the stability lots of (b) (4) USP used for comparative analysis are packaged under (b) (4) and (b) (4) which you do not adequately explain/justify why you can compare the results when the container/closure systems are not the same or that (b) (4) are not part of the commercial packaging process.

* 1021_LAB1/OOS/01/18/04 - (b) (4) Lot: (b) (4) Investigation reports OOS for (b) (4) content during residual solvent analysis. Your retest confirmed the original OOS result, where you performed the original sample test on the original GC instrument/column in duplicate. You retested the lot using a fresh sample on a different GC instrument/column. However, you did not perform any retesting of the fresh sample on the original GC instrument/column to evaluate if the original sample may have been contaminated due to preparation/handling error in the lab.

2. Equipment used to control and monitor critical process parameters identified in the manufacture of APIs and API intermediates is not adequately designed, installed, or qualified.

Specifically,

a) Your designs of the (b) (4) installed on (b) (4) E4(b) (4) -04 and E3-(b) (4)-19 do not exist. You could not provide any detailed design schematics for the (b) (4) which were installed on the (b) (4) after the equipment was originally qualified. No re-qualification of the (b) (4) was performed after the (b) (4) were fabricated and installed into the (b) (4) of which you could not provide any work orders or documentation as to when the (b) (4) were installed into the (b) (4) Furthermore, you have not conducted a validated study to show that the (b) (4) was designed in a manner that consistently adheres to the critical process parameter (b) (4) rate (b) (4) L/hr) for the (b) (4) during the manufacture of (b) (4) API intermediate, which is further manufactured into APIs (b) (4) and (b) (4) (b) (4) Currently you use a (b) (4) system for (b) (4) during step (b) (4) in the BMR for both E4(b) (4) -04 and E3-(b) (4)-19, but have never demonstrated that the (b) (4) the (b) (4) is consistent with the (b) (4) rate by validating it against a (b) (4) Note that this (b) (4)

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is (b) (4) and can easily form undesired side (b) (4) products if the (b) (4) rate deviates from (b) (4) L/hr. Note that during the inspection we observed several OOS events for APIs (b) (4) and (b) (4) where (b) (4) is used as the key starting material for both APIs.

b) The equipment used in the manufacture ((b) (4) steps) of your APIs and API intermediates is manually monitored for temperature during that particular stage of manufacturing, by having the production operator read the temperature on the display and record in the batch record. However, review of the batch records shows that (b) (4) /processing time temperatures are only monitored and recorded in the batch records at the start and stop times of (b) (4) or during periodic intervals (b) (4) etc) during (b) (4) You do not have any alarm system monitoring the temperature probes which would identify if any temperature excursions occur in critical manufacturing steps.

c) Your sensor panel for (b) (4) E3-(b) (4)-19 is not working as intended-for-use. During the facility tour on 07/15/19, we observed that the sensor for the (b) (4) line was not illuminated during the (b) (4) step (b) (4) during the manufacture of (b) (4) Lot: (b) (4) The sensor indicates whether the (b) (4) line to the (b) (4) is open or closed. A (b) (4) is a required critical process parameter for the (b) (4) during Step (b) (4) Note that none of your staff could identify if the (b) (4) line was open or closed, since the light did not appear to be in working order.

3. Preventative controls over your electronic inventory and warehousing management systems are not effectively established to prevent product mix-ups and ensure traceability for the life cycle of the material.

Specifically, you did not appropriately qualify/validate your SAP inventory management system in accordance with ICH and Part 11 requirements for validation of electronic systems. You did not effectively develop the vaildation protocol with the required challenges of your warehouse management system to demonstrate that the system would perform in a first-in/first-expiry/first-out (FI/FE/FO) manner, or that a reconciliation of materials challenge was performed by reconciling the quantities from your goods issue slip with the consumption bill of materials with any leftover returned raw materials, since you do not always return all raw materials specific to a batch production order to the warehouse.

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During the inspection, your SAP validation team conceded that they did not perform the required negative challenges to the system in the raw material product warehouses to ensure the system would reject a material if it was incorrectly selected for a bill of materials/pick list in a FI/FE/FO fashion, or that any raw materials reconciliation was performed, where difference between quantities listed on the SAP-generated goods issuance sheets and the consumption bill of materials were challenged against excess returned raw materials not consumed in the production processes.

Additionally, your SAP inventory management system is deficient in the following aspects:

* You do not attach the SAP-generated goods issue slips (Proposed work order for API), which your warehouse personnel use to pick the specific raw materials in your batch production order, to the batch production records. As such, your QA department has no way to verify during final batch record review if the raw materials listed on the goods issue slip match the materials which were picked from the warehouse and weighed/dispensed for batch production.

* You do not perform raw materials reconciliation, where any excess materials not used in production are returned to the warehouse by the production staff and reconciled by the warehouse personnel. Additionally, you identify certain materials issued from the raw materials warehouse as "non-dispensed", despite that they are not utilities or solvents from the (b) (4) However, you could not provide an adequate explanation/justification as to why these materials are not returned to the warehouse after use in the production process. Subsequently, the warehouse personnel are not performing a final reconciliation, where excess raw materials are accounted for against the consumption bill of materials and checked back into the warehouse.

* You do not return all issued raw materials to the storage warehouse after production is completed. During the inspection, we observed raw materials staged in the dispensed material staging area which were not part of the production lots identified in the staging area. Only 2 lots were identified; however, we discovered additional raw materials from three other production lots which were identified as either "not yet consumed" or "not yet dispensed".

* You do not perform line clearances for the non-dedicated production staging areas, where all traces of raw

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	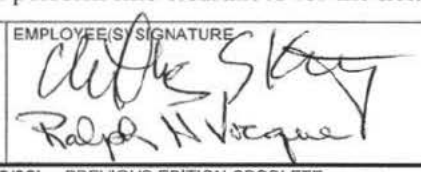	Christopher S. Keating, Investigator Ralph H. Vocque, Analyst	07/19/2019

materials specific to a production lot are removed from the area and returned to the warehouse.

* You often stage non-dispensed materials (normally held in warehouse) in the dispensed material staging areas for long periods of time (> (b) (4)), despite that you have no validated study or scientific evidence to support that the long-term storage in these production areas affect the quality, potency, purity, and strength of the raw materials during long-term storage outside of the warehouse.

* Your SAP-generated "Proposed work order for API" issuance sheets have a design/validation flaw where the "proposed work order date" is populated with the date when the sheets are printed/reprinted from SAP, and do not reflect the actual work order date.

4. Process validations of API intermediates are not designed and executed in a manner consistent with the original change control proposals, using all equipment specified in the change control.

Specifically, you did not adequately perform the process validation for the manufacture of (b) (4) in API-(b) (4) block as described in Change Control: 1024-P-18-00012. You did not perform an appropriate comparative analysis of all proposed manufacturing equipment, you did not perform all process validation manufacturing using only the equipment in API-(b) (4) Block, and you did not place all API lots manufactured (using the (b) (4) API intermediate process validation lots) on stability monitoring.

5. Stability studies performed to determine the expiry dates for finished APIs are not conducted in the same container closure system as the packaging procedure specified in the batch records.

Specifically, your stability protocol for (b) (4) USP API (Protocol: SP/BL/DS/(b) (4) 0001) states that the (b) (4) USP stability samples are to be packaged in (b) (4) and (b) (4) bags which contain (b) (4) (b) (4) and (b) (4) and placed in (b) (4) drums. This is not in accordance with the batch packaging records for (b) (4) USP, where the API material is packaged without (b) (4) and not (b) (4) (b) (4) . You are not conducting long-term and accelerated stability studies for (b) (4) USP in the same container closure systems as which you package the material for shipment. Your projected shelf life is (b) (4)

based on the studies conducted with (b) (4) and (b) (4) despite that it is not commercially packaged in the same manner. Note that your firm has several confirmed OOS failures for long-term stability at 30 +/- 2 C and (b) (4) +/- 5% R.H., which have been attributed to "exposure to atmosphere and heat, undergoes colour change, hence material by nature is not stable at higher temperature beyond 12 months at any temperature exceeding 25 C."

6. Written procedures for packaging operations are not established.

Specifically, your batch manufacturing record for (b) (4) states that packaging of the intermediate must be performed in a dry environment and packaged (b) (4) You do not have a detailed written procedure for packaging (b) (4), or identify the (b) (4) line used for packaging in the batch manufacturing record. Furthermore, your firm management informed us during the inspection that the packaging rooms are not controlled or monitored for temperature and humidity. As such, you have no way to identify or confirm if personnel are performing packaging of the intermediate under the specified conditions. Note that (b) (4) intermediate is temperature, moisture, and oxygen sensitive and can easily form degradation/ decomposition products upon exposure to these conditions.

7. Records not made readily available during an FDA inspection.

Specifically, you were not able to provide the requested photographs of raw materials located in the API (b) (4) dispensed material staging areas and the control panel display for (b) (4) E3-(b) (4)-19 in API-(b) (4) Block manufacturing area. Because of explosion-prone conditions in production areas and warehouses, we allowed your personnel to collect photographs, which your staff explained were to be taken with explosion-proof cameras. You did not capture all requested photographs in real time and did not verify all photos before rearranging items which we wanted captured. Additionally, all of the photographs collected by your staff were acquired using a normal camera with a flash option, despite your instruction to us that we were not allowed to have cellular phones or our own cameras in those areas where photos were collected.