**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 12420 Parklawn Drive, Room 2032<br>Rockville, MD 20857<br>ORAPHARMInternational483responses@fda.hhs.gov | 01/20/2020-01/28/2020 |
| | FEI NUMBER<br>3002949085 |

| NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED | |
|---|---|
| Mr. Arun Gupta, Vice President & Location Head | |
| FIRM NAME<br>Dr. Reddy's Laboratories Limited CTO Unit VI | STREET ADDRESS<br>APIIC Industrial Estate, Pydibhimavarama (Village) |
| CITY, STATE, ZIP CODE, COUNTRY<br>Srikakulam District, Andhra Pradesh, India | TYPE ESTABLISHMENT INSPECTED<br>API 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 WE OBSERVED:

### OBSERVATION 1

Process Validation is not performed adequately for manufactured products at the facility.

Specifically, your process validation for (b) (4) is inadequate because your firm has (b) (4) Out of Specification (OOS) results from December 26, 2017 – December 9, 2019 for manufacturing of commercial batches. The batches have OOS's for Residual Solvents (RS) by Gas Chromatography (GC) test for (b) (4) content against the specification limit of NMT (b) (4) ppm. The (b) (4) batches documented in the (b) (4) OOSs were rejected and (b) (4) of these batches were (b) (4) and are approved for shipment. (b) (4) batches are awaiting to be (b) (4)

Your firm reported a full-scale investigation summary report OOS # 310018090 on November 30, 2019 to investigate the failure batches of (b) (4) content in (b) (4) (b) (4). The OOS evaluated an out of specification result for (b) (4) by Gas Chromatography for batch # (b) (4). That investigation concluded that a correction with an issue with the (b) (4) was rectified and no similar incidents were reported. Additionally, "no impact on the further batches execution." However, batches

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(b) (4) were tested and failed against your specification of NMT (b) (4) of (b) (4) content. Batch results were as follows:

| Notification Number | Date Observed | Batch Number | (b) (4) Content (ppm) |
|---|---|---|---|
| (b) (4) | December 3, 2019 | (b) (4) | (b) (4) |
| | December 23, 2019 | | (b) (4) |

Where a list provided during the inspection states that batch numbers (b) (4) (b) (4) will be (b) (4) Additionally, during the inspection we found that your firm documented incidents for failed results during process validation. The details are as follows:

| Notification Number | Initiated Date | Category | Batch Number | (b) (4) Content (ppm) |
|---|---|---|---|---|
| (b) (4) | October 3, 2018 | Incident | (b) (4) | (b) (4) |
| | August 13, 2019 | OOS | | |
| | August 20, 2019 | Incident | lot (b) (4) | |
| | August 20, 2019 | Incident | (b) (4) | (b) (4) and (b) (4) |

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Your firm continues to have recurrent failures for (b) (4) residual solvent intended for process validation batches and commercial batches without have a scientifically justified root cause analysis.

**OBSERVATION 2**

Investigations are inadequate in that they do not evaluate all potential root causes.

Specifically,

A. Investigations for the following Out of Specifications (OOS) and Incidents were not performed adequately. For example,

1. For OOS # 310018104 and Incident # 200338632 the initial investigation for (b) (4) batch (b) (4) with report date December 01, 2019 and December 09, 2019 resulted in an in-process (b) (4) (b) (4) The resample passed with (b) (4) % and the root cause is determined to be by inadvertent human error documented in Incident # 200338632. The batch was then moved for further production, however, during release testing an OOS # 310018104 was observed. The batch failed for Solubility testing on December 09, 2019 and failed for residual solvent ((b) (4) content (b) (4) ppm with release specification of (b) (4) ppm) on December 23, 2019. During the final release investigation, the most probable cause was identified that the original test results for the in-process (b) (4) was accurate which was initially identified to be (b) (4) % initially identified to be the sample. The resampled results were discarded with documented justification.
2. OOS # 310017867 with report date October 17, 2019 for (b) (4) batch # (b) (4) an OOS result was reported for (b) (4) content by LCMS tested at contract laboratory identified as (b) (4) The OOS was for (b) (4) impurity which was reported as (b) (4) ppm against the specification limit of (b) (4) ppm. Your firm only performed a laboratory investigation. The documented most probable root cause was determined to be cross contamination of the

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weighing balance or the micropipette during laboratory analysis without an investigation in the manufacturing area.

3. OOS# 310016984 with report date April 05, 2019 for (b) (4) batch number (b) (4) with an OOS result was reported for Assay analysis. (b) (4) %, (b) (4) (b) (4) %. According to specification # S-08-IJ-USP/08 states that the specifications are NLT: (b) (4) % and NMT: (b) (4) %. The investigation revealed to be instrumentation failure. A re-analysis was conducted on April 05, 2019 in which results were found not meeting specifications (b) (4) (b) (4) %, (b) (4) (b) (4) %. Inadequate scientific justification was provided for the failing reanalysis result stating the hypothesis that there is a chance of (b) (4) from the already used injected vials. (b) (4) product is approved for the United States market.

B. During the inspection, we observed that your firm did not initiate investigations for (b) (4) batch # (b) (4) for unknown peaks in residual solvents. According to section 6.1.2 of your firm's SOP SOP-GLOB-QC-0018, titled 'Handling of Extraneous Peaks' criteria for investigations for residual solvents states (b) (4) (b) (4) consistently". Batch # (b) (4) was determined to have (b) (4) and no investigation was conducted. The investigation states that these unknown peaks appear to be isomers of (b) (4) and no investigation was conducted.

C. Risk Assessments titled 'Assessment of (b) (4) and (b) (4) in (b) (4) APIs Manufactured at CTO—VI Dr. Reddy's Laboratories Limited' with approved date of March 25, 2019 conducted to assess the potential presence of (b) (4) (b) (4) and other (b) (4) impurity in (b) (4) API's. Only a theoretical evaluation of the Key Starting Material (KSM) was evaluated and no KSM was tested by your firm. Additionally, your firm doesn't test for (b) (4) (b) (4) for United State bound products. Your firm has shipped multiple batches of (b) (4) API's to United States and it appears that your costumers were not notified.

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**OBSERVATION 3**

Your firm's cleaning processes for equipment have not been adequately established and validated.

Specifically, your firm's Quality Unit failed to do the following:

A. According to section 5.13.1 of your firm's Standard Operating Procedure SOP-GLOB-QA-0048, Cleaning Validation Program for Drug Substance states, "Validation of cleaning process involves successful completion of minimum (b) (4) cleaning runs either (b) (4) ". However, your cleaning validation report, CVP/(b) (4) /15/001, titled 'Report on Equipment cleaning validation during product change over from (b) (4) (b) (4) of (b) (4) any other Product in (b) (4) dated February 17, 2017 was performed with only (b) (4) cleaning run. According to the cleaning validation report section VIII states, "As there is no current production plan and no visibility of future plan for (b) (4) of (b) (4) product in (b) (4) facility, the cleaning validation study for (b) (4) of (b) (4) s closed with the execution of (b) (4) A new cleaning validation study shall be initiated with the current approach of cleaning validation, if warranted." The Head of Quality Assurance also stated that the firm did not manufacture any (b) (4) during the cleaning validation done in February 17, 2017. He further stated the (b) (4) batch of (b) (4) hat the firm manufactured was on September 10, 2018. The firm manufactured (b) (4) batches of (b) (4) in 2018, (b) (4) (b) (4) in 2019 and (b) (4) batches in 2020 without conducting a cleaning validation with (b) (4) runs as required by SOP-GLOB-QA-0048.

B. During our review of the surface area of each equipment documented in the cleaning validation, we asked for the raw data for the surface calculations for each equipment. According to the Team Member Process Engineer and Head Quality Assurance, there is no raw data for the surface area calculation for each manufacturing equipment. Because there is no raw data, there is no evidence that swab samples were actually analyzed. He further stated that they do not have raw data calculations for all the cleaning validations of all equipment.

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C. According to the Team Member Quality Assurance the Quality Unit's choice of sampling point locations for swab samples of product contact surfaces during cleaning validation were based on "experience" and not scientific justification.

D. During our review it was observed that the firm has (b) (4) unknown peaks related to (b) (4) (b) (4) observed in the analysis of (b) (4) API

(b) (4)

In addition, the firm has recorded (b) (4) unknown peaks in other manufactured APIs such as (b) (4) which are pending applications in United States.

**OBSERVATION 4**

Trend Analysis of manufactured API's are not conducted.

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Specifically, no trend analysis was conducted on peaks related to (b) (4) in the firm's manufactured APIs. Your firm has approximately nineteen (19) incidences that were found during our review of the residual solvent from 2018 – 2019.

**OBSERVATION 5**
Your Quality Unit lacked oversight of your quality documents.

Specifically,

A- On January 24, 2020, while we were reviewing the issued / retrieval and reconciliation of documents, we observed that that your firm's booklets for document titled 'Phase 1 Laboratory Investigation' in 2019 three (3) booklets were destroyed, in 2018 two (2) booklets were destroyed and in 2017 two (2) booklets were destroyed. In one instance the firm was missing sequence number page 186 of the investigation. These booklets are used to document your firm's OOS investigations.

B- On January 27, 2020, while we were reviewing analytical method transfer from (b) (4) to your firm, we discovered that the initial method transfer of (b) (4) API for residual solvent was performed on July 1, 2009. That method transfer is incomplete because it lacked analytical test conclusions, test results, etc.

C- On January 27, 2017, we reviewed Specification and Method of Analysis for (b) (4) USP with specification number (b) (4) and found that the system suitability criteria is less than (b) (4) % RSD for (b) (4) USP peak standard injection. However, during review of the Method Validation, Addendum Report Number TDC/ARD/MVR/(b) (4) 002 stated that the method is validated for less than (b) (4) % system suitability requirement without any documented justification.

D- On January 25, 2020, we observed that sample (b) (4) batch # (b) (4) 3-month intermediate stability sample was not available. According to firm's records the sample was not tested.

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January 20, 2020; January 21, 2020; January 22, 2020; January 23, 2020; January 24, 2020; January 25, 2020; January 27, 2020; January 28, 2020

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