**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 | 12/4/2023-12/8/2023 |
| | FEI NUMBER<br>3009483004 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Dr. Ranjana B Pathak, Global Head of Quality

| FIRM NAME | STREET ADDRESS |
|---|---|
| Dr Reddy's Laboratories Limited | Innovation Plaza, Survey Nos 42, 45, 46 & 54 |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| Bachupally, Medchal-Malkajgiri, Telangana, 500090 India | Drug Testing Establishment |

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

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

Specifically, laboratory data generated to demonstrate sameness of (b) (4) Injection (b) (4) (b) (4) to the reference listed drug (RLD) for secondary structure by Circular Dichroism Spectropolarimeter lacks accuracy and reliability.

The sameness study to demonstrate that the test drug, (b) (4) Injection is the same as reference listed drug (RLD) was conducted as per protocol # PDSP-(b) (4) INJ-SAM-834-00, "Study Protocol for Evaluation of Sameness for Secondary Structure by CD Spectropolarimeter for (b) (4) (b) (4) API and Injection". During this study three submission batches of the firm's Test Drug (b) (4) batch # (b) (4) were compared with the three RLD batches (batch # (b) (4) During this study samples were scanned for Circular Dichroism under varying conditions of temperature (b) (4) pH (b) (4) The data was reported in Sameness Study Report # PDSR (b) (4) INJ-SAM-834-00. The firm approved this report on 12/9/2016 and submitted to the Agency to support (b) (4) During the review of the analytical laboratory

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| | Saleem A Akhtar, Investigator<br>X Saleem A Akhtar Investigator Signed By: 2001638440 Date Signed: 12-08-2023 16:37:28 | 12/8/2023 |

raw data following deficiencies were observed:

A. Original electronic data is omitted and not reported: For example:

a. On 11/25/2016, Lab Analyst (b) (6) prepared sample of Dr. Reddy's Test Drug batch (b) (4) and tested for Circular Dichroism at room temperature conditions (b) (4) °C) using CD Spectropolarimeter (equipment ID: AA266). The spectra scan was created at (b) (4) and identified as "DRL42_(b) (4)C_251116". However, review of the meta data indicated the presence of other spectra scan for the same batch (b) (4) created under room temperature conditions i.e., (b) (4) °C. This spectra was created at (b) (4) and was identified as "N_DRL42(b) (4) C_251116". The Lab Analyst stated after the first scan at (b) (4) she observed fluctuation in temperature when the same sample was being heated in the cuvette to be tested at (b) (4) °C. The analyst discarded the sample in the cuvette and retested the sample even though the original scan at (b) (4) was created before the temperature fluctuation was observed. The QC Lab did not report the spectra created at (b) (4) in analysis. The only spectra in the analysis was that was created at (b) (4) The quality unit did not raise any incident to investigate the temperature fluctuation. This incident was not reported to the agency until it was discovered during the inspection.

b. Laboratory data generated on 11/28-29/2016 pertaining to Circular Dichroism study for RLD batch # (b) (4) and Test Drug (DRL batch (b) (4) was not reported and invalidated without scientific justification. This data was generated as per following information:

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| Sr. No. | Spectra Identified as | Date |
|---|---|---|
| 1 | (b) (4) _WIFI_ProductpH_281116 | 11/28/2016 1:51 PM |
| 2 | (b) (4) _WIFI_pH(b) (4) 281116 | 11/28/2016 2:53 PM |
| 3 | (b) (4) _WIFI_pH 281116 | 11/28/2016 3:13 PM |
| 4 | (b) (4) _WIFI_pH o Product pH_281116 | 11/28/2016 4:08 PM |
| 5 | (b) (4) _WIFI_pH(b) (4) to Product pH_281116 | 11/28/2016 4:29 PM |
| 6 | DRL41_ProductpH_291116 | 11/29/2016 1:54 PM |
| 7 | DRL41_ProductpH(b) (4) 291116 | 11/29/2016 2:32 PM |
| 8 | DRL41_pH(b) (4) _291116 | 11/29/2016 3:42 PM |
| 9 | DRL41_pH(b) (4) to ProductpH_291116 | 11/29/2016 4:22 PM |
| 10 | DRL41_pH(b) (4) to ProductpH_291116 | 11/29/2016 4:48 PM |

On 11/30/2016, the lab initiated a Laboratory Investigation Report (# LIR-A-AD-16-980) stating "Ambiguity in pH was observed by the scientist while adjusting the pH as well as instrument was constantly fluctuating while reading the pH". However, the Lab Analyst (b) (6) did not document this fact in her laboratory notebook when she adjusted the pH for all these samples on 11/28/2016 and 11/29/2026. Instead, the analyst recorded this incident on her laboratory notebook more than a week later on 12/7/2017 at 4:51 pm. Review of the investigation report LIR-A-AD-16-980 indicated the firm did not identify which pH meter was used in analysis and invalidated all then scans and sample solution.

Fresh samples of Test Drug DRL batch (b) (4) were prepared and tested on the same date (11/30/2016) when the LIR-A-AD-16-980was initiated. This discrepancy was not discussed in the Sameness Study Report PDSR(b) (4)INJ-SAM-834-00 that was submitted to the Agency.

c. The Lab Analyst (b) (6) stated she used pH meter equipment ID: AA363 to adjust the pH of RLD and Test Drug batches used to Circular Dichroism test. Review of the equipment use logbook (ARD0525/15; a 100-page bound book) indicated the last entry on this book was made page 98 on 11/26/2016. Blank page 100 of this notebook was voided with an additional note stating, "Page 99 is missing". The site started a new equipment use logbook (ARD0374/16) for this pH meter AA363 and recorded the pH reading of the RLD batch (b) (4) on 11/28/2016 (the 3 preparations that were invalidated). The site Quality Head provided the scanned copy of the use logbook ARD0525/15 and stated the original notebook has been destroyed as per the firm's policy. The site failed to provide a reasonable justification why page 99 of this book got missing and why the site voided page 100 of this notebook.

B. Original electronic data is not attributable: Lab Analyst (b) (6) scanned about 11 samples of Dr. Reddy's Laboratories (DRL) batches of the Test Drug (TD) and Reference Listed Drug (RLD) batches under varying temperature conditions using CD Spectropolarimeter (equipment ID: AA266) and generated the CD spectra using software Spectra Manager/v2.15. The spectra pertaining to these 11 samples (as shown below) were named in a way that it could not be established as which spectra belongs to which specific batch of DRL batch or RLD batch.

| Sr. No. | Spectra Identified as | Date |
|---|---|---|
| 1 | DRL_(b) (4)C_251116 | 11/25/2016 |
| 2 | RLD_(b) (4)C_251116 | 11/25/2016 |
| 3 | RLD _(b) (4)C_241116 | 11/24/2016 |
| 4 | RLD _(b) (4)C_241116 | 11/24/2016 |
| 5 | RLD _(b) (4)C _241116 | 11/24/2016 |
| 6 | RLD_(b) (4)C_251116 | 11/24/2016 |
| 7 | RLD_(b) (4)C_251116 | 11/25/2016 |
| 8 | DRL_(b) (4)C_251116 | 11/25/2016 |
| 9 | N-Cooling_RLD-(b) (4)C_241116 | 11/24/2016 |
| 10 | Cooling_RLD-(b) (4)C_251116 | 11/25/2016 |
| 11 | Cooling_DRL-(b) (4)C_251116 | 11/25/2016 |

C. Laboratory data is not recorded contemporaneously: On 11/25/2016, the Lab Analyst (b) (6) prepared a sample of DRL Exhibit batch (b) (4) for Circular Dichroism analysis un varying temperature conditions (b) (4) This experiment started at (b) (4) and ended at (b) (4) However, the sample preparation for this analysis was recorded in the analyst notebook next day on 11/26/2016.

This is the only sameness study the site has performed in support of (b) (4) to demonstrate that the secondary structure of the Test Drug (b) (4) Injection (b) (4) mg/mL and

(b) (4) mg/mL) is comparable to the Innovator's Reference Listed Drug (RLD).

**OBSERVATION 2**

Determinations of conformance to appropriate written specifications for acceptance are deficient for drug products.

Specifically, you do not have detailed control procedures in place to review technical data generated utilizing complex analytical techniques and equipment to ensure the reported data is accurate and complete.

For an example, on 7/28/2023, the firm's Quality Unit approved a study report "Quantification of (b) (4) and (b) (4) Content in (b) (4) by NMR Spectroscopy" to support (b) (4) shelf life of (b) (4) API. During this study three exhibit batches of (b) (4) API (batch # (b) (4) were tested using Nuclear Magnetic Resonance Spectrometer (NMR, equipment ID: AA574) to quantify (b) (4) content in (b) (4) The site does not have control procedure in place for NMR data review to ensure data accuracy and completeness.

The site routinely performed GMP testing of drug products supporting multiple regulatory submission utilizing following major equipment.

| Sr. No. | Equipment Name | Test Name | Equipment ID | Supported (b) (4) numbers |
|---|---|---|---|---|

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| | | | |
|---|---|---|---|
| 1 | SEC-MALLS | Molecular weight distribution | AA265 |
| 2 | NMR | (b) (4) content & (b) (4) content & Uncapped C-terminal/ Capped C-terminal ratio | AA574 |
| 3 | (b) (4) Analyzer | (b) (4) composition | FS044 |
| 4 | CD Spectropolarimeter | Secondary Structure analysis | AA266 |
| 5 | Protein Sequencer | (b) (4) Terminal sequencing analysis (mole ratios of individual (b) (4) at (b) (4) Terminal of (b) (4) chains) | AA446 |
| 6 | NMR | Higher order structure & Structural Elucidation | AA574 |
| 7 | Cryo Transmission Electron Microscopy (Cryo-TEM) | Lamellarity Nano particle size | FA866 |
| 8 | ICPOES (Inductively Coupled Plasma | (b) (4) impurities (b) (4) | AA275 |

(b) (4)

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| | | | | |
|---|---|---|---|---|
| | Optical Emission Spectrometry) | | | |
| 9 | ICPMS (Inductively Coupled Plasma Mass Spectrometry) | Low molecular weight (b) (4) | AA584 | (b) (4) |
| | | | AA585 | |
| 10 | HRMS (High Resolution Mass Spectrometry) | Structural Elucidation and Sameness | FA1242 | |
| 11 | Q Exactive™ HybridQuadrupole Orbitrap Mass Spectrometer | Structural Elucidation and Sameness | FA1027 | |
| | | | FA1290 | |
| 12 | Small angle X-Ray Scattering (SAXS) | (b) (4) | AA393 | |
| 13 | SYNAPT G2-Si (HRMS) | Structural Elucidation and Sameness | AA447 | |
| 14 | Atomic Force Microscopy (AFM) | Nanoparticle size and Diameter | AA563 | |
| 15 | Zetasizer Nano ZSP | Nanoparticle size | AA383 | |
| 16 | XRD | Particle (b) (4) | AA387 | |

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|---|---|---|---|---|
| 17 | LC MS ABSCIEX 4500 | Mass Identification | AA527 | (b) (4) |
| 18 | METROHM POLOROGRAPH | Reduced (b) (4) content | FA833 | |
| 19 | Ion Chromatograph | Ionic impurities | AA291 | |
| 20 | Ion Chromatograph | Ionic impurities | FA1302 | |
| 21 | SHIMADZU GCMS | Organic impurities | FA1277 | |
| 22 | AGILENT GCMS | Organic impurities | FA1247 | |
| 23 | Shimadzu GC-MS | Organic impurities | AA665 | |
| 24 | AGILENT GCMS | Organic impurities | AA788 | |
| 25 | LCMS 5500 | Organic impurities | FA1289 | |
| 26 | LCMS 6500 | Organic impurities | FA1353 | |

The site's Quality Head stated the firm does not have technique specific control procedures in place to

review data generated from these equipment.

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**OBSERVATION 3**

Employees are not given training in the particular operations they perform as part of their function and current good manufacturing practices.

Specifically, the firm's Quality Unit failed to ensure all the employees involved in day to day GMP activities have completed the required training. During the review of the training program, it was observed that an employee in lead role was overdue for an SOP training, "Countermeasures: Do it the right way on Kaizen Optimizer" for more than two years.

Following is a list (not all inclusive) of the trainings that were observed overdue:

| Training Description | Document No. | Employee ID | Employee Role | Due Date |
|---|---|---|---|---|
| Countermeasures: Do it the right way on Kaizen Optimizer | 3PE00164 | (b) (6) | Team Lead | Dec 4, 2021 |
| User Management for GxP Computerized Systems (3.0) | SOP-IPDO-CAD-0170 3.0 | | Team Lead | Nov 28, 2022 |
| CHANGE CONTROL PROCEDURE (3.0) | SOP-IPDO-CDQ-0028 3.0 | | Team Lead | Feb 17, 2023 |
| HANDLING OF INCIDENTS AND DEVIATIONS (5.0) | SOP-IPDO-CDQ-0001 5.0 | | Team Lead | May 4, 2023 |
| DOCUMENTING THE | SOP-IPDO-CAD- | | Team Lead | May 8, 2023 |

| | | | | |
|---|---|---|---|---|
| EXPERIMENTAL DATA IN E-LAB NOTEBOOK(ELN) (4.0) | 0068 4.0 | | | |
| cGMP in Drug Manufacturing - 2023 | 3QA00148 | (b) (6) | Analytical xpert | May 28, 2023 |
| cGMP in Drug Manufacturing - 2023 | 3QA00148 | | eam Lead | May 28, 2023 |
| Good Analytical Practices (8.0) | SOP-GLOB-QC-0085-8.0 | | eam Lead | May 30, 2023 |
| Reprocessing of analytical data for non-chromatographic systems for batch release And method validation in GMP laboratories (2.0) | SOP-IPDO-CAD-0181 2.0 | | eam Lead | Jun 3, 2023 |
| Analytical Method Transfer (9.0) | SOP-GLOB-QC-0010-9.0 | | eam Lead | Jul 6, 2023 |
| Rounding Rules (5.0) | SOP-GLOB-QA-0010-5.0 | | Analytical xpert | Sep 23, 2023 |

The employee training (including the GMP training) program is implemented as per SOP-IPDO-CDQ-0004, “Employee Training”. This SOP does not specify minimum number of days within which the employees have to complete the required training.

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