DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 ORAPHARMInternationalresponses@fda.hhs.gov	05/30/2024-06/07/2024
	FEI NUMBER 3002949085

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Sunderganesh Sankaran, Site Head

FIRM NAME	STREET ADDRESS
Dr. Reddy's Laboratories Limited CTO - Unit VI	APIIC Industrial Estate
CITY, STATE, ZIP CODE, COUNTRY Pydibhimavaram (Village), Ranasthalam Mandal, Srikakulam District, Andhra Pradesh, 532409 India	TYPE ESTABLISHMENT INSPECTED 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

Analytical methods were not validated or verified under the actual conditions of use. These methods are used for testing of final Active Pharmaceutical Ingredients (API) before releasing the APIs for the manufacturing of drug products.

Specifically,

A. The following test methods, including in-house and compendial test methods, were not validated or verified appropriately for the commercial APIs. These APIs have active US Drug Master Files (DMF) and batches were distributed to customers and are currently in the market.

API	US DMF #	Test Description	Specification #
(b) (4)		Specific Optical Rotation	S-08-ADG-01/08
		Identification by IR	SP-CTO06-003570
		Identification by IR	SP-CTO06-002687
		Specific Optical Rotation	SP-CTO06-003013
		Specific Optical Rotation	SP-CTO06-002538
		Specific Optical Rotation at (b) (4) °C	SP-CTO06-002617

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EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
Joseph Piechocki Tamil Arasu	Joseph A. Piechocki, Investigator Tamil Arasu, Investigator	06/07/2024

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(b) (4) (b) (4)

Identification by IR	S-08-IG/06
Identification By Mass Spectrometry	SP-CTO06-002685
Identification by IR	
Specific Optical Rotation	
Water Content by KF	SP-CTO06-002756
Identification by IR	SP-CTO06-003026
Water Content by KF	
Identification by IR	SP-CTO06-003561
Identification by IR	SP-CTO06-002658
Identification by IR	SP-CTO06-002663
XRD	
Identification test for (b) (4)	SP-CTO06-002807
Identification by IR	SP-CTO06-002676
Identification by IR	SP-CTO06-003929
Identification by (b) (4)	
Identification by (b) (4)	SP-CTO06-002968
Identification by (b) (4)	SP-CTO06-003459
Water Content by KF	
Identification by IR	SP-CTO06-002588
Water Content by KF	
Identification by IR	SP-CTO06-002677
Water Content by KF	

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	JP TA	Joseph A. Piechocki, Investigator Tamil Arasu, Investigator	06/07/2024

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(b) (4)		
	Optical Rotation (b) (4) by Polarimeter	
	XRD	SP-CTO06-002894
	Water Content by Coulometer	SP-CTO06-004059
	Identification by IR	SP-CTO06-003243
	Identification by IR	SP-CTO06-003495
	Specific Optical Rotation	SP-CTO06-003679
	Identification for (b) (4)	SP-CTO06-002622

You received a customer complaint # 200428799 for the API (b) (4) ((b) (4)), which identified that the API you supplied (Batch# (b) (4)) showed OOS for Water Content test, with a result of (b) (4) % against specification limit NMT (b) (4) % which had been released with non-validated test method.

B. The analytical method used to quantitate residual (b) (4) in (b) (4) API was not adequately validated prior to the release of API batches. From 2020 to 2023, an unknown peak characterized as (b) (4) was identified during the GC residual solvent analysis release testing in approximately (b) (4) batches of (b) (4) API. Once the characterization of the unknown peak as (b) (4) was completed, an internal control limit of not more than (b) (4) ppm was determined and established for this impurity. Of the (b) (4) batches of (b) (4) manufactured, approximately (b) (4) batches were released and shipped, including batches (b) (4) and (b) (4) , which were intended for use in US marketed products, based on results obtained for the (b) (4) content following a GC developed method. However, analytical method validation was not performed for this GC method. Subsequently, an ion chromatography method was developed and validated on 01May2022 for quantitation of (b) (4) . However, the (b) (4) batches shipped were not retested using this validated procedure to ensure the

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(b) (4) content was within the internal specification, including batches (b) (4) and (b) (4).

Furthermore, batches (b) (4) and (b) (4) were released on 26Jun2021; however, communication about the detection of (b) (4) and the subsequent control limit was not communicated to the customer until November 2022.

OBSERVATION 2

There is a failure to ensure that manufacturing processes are maintained in a validated state.

Specifically,

From May 2022 to January 2024, 17 out-of-specification results have been obtained for (b) (4) API from in-process checks or during final release testing due to elevated levels of (b) (4) not meeting the pre-defined specification limit. These investigations led to the reprocessing of all 17 batches of (b) (4), including approximately (b) batches intended for use in US marketed products. Various root causes have been hypothesized and addressed through corrective actions, including but not limited to, correction of the (b) (4), additional controls of humidity during the stages of (b) (4) and controlling the length of time in which the material can be held before further processing during various stages.

Since the implementation of (b) (4) corrections and (b) (4) clarifications, two additional investigations were also initiated due t(b) (4) content out of specification results following the reprocessing batch record for (b) (4).

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1) Incident 200429644 was initiated on 20Apr2024 due to an out of specification result obtained for (b) (4) of (b) (4) ppm (specification not more than (b) (4) ppm) during in-process sampling of Batch (b) (4). The root cause of the investigation was identified as smaller API particles being generated during the (b) (4) phase of the manufacturing process.

2) Out-of-specification 310026212 was initiated on 09Apr2024 due to an out-of-specification result obtained for (b) (4) of (b) (4) ppm (specification not more than (b) (4) ppm) during release testing of Batch (b) (4). The root cause was determined to be improper sampling during in-process sampling and testing since there is a chance of non-material uniformity by inadequate mixing prior to sampling.

Although corrective actions have been identified and have been or are being implemented into the (b) (4) API Master Batch Record, there has been no holistic review or assessment performed to ensure that the process is under adequate control and the process has been maintained in a validated state. In addition, the recent investigations conducted indicate a lack of process controls during (b) (4) operations as well as potential non-homogeneity of the material during (b) (4) operations.

OBSERVATION 3

There is a failure to thoroughly review any unexplained discrepancy and 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,

A. The attributed root causes for the Out of Specification (OOS) investigations are not adequately supported with scientific evidence. For example,

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1) OOS# 310024156 – An investigation was initiated on April 21, 2023, when an annual stability batch of (b) (4) (Batch# (b) (4)) (DMF# (b) (4)) gave an OOS result for (b) (4) in Related Substances by HPLC (Method-1) at 12M long term stability conditions (25±2°C,60±5%RH). The result was (b) (4)% against a specification of NMT (b) (4)%. The investigation concluded that sample pouch might have exposure to light/air during sampling of individual stability interval station and resulting in increase of the (b) (4) However, this root cause was not adequately justified with scientific evidence.

2) OOS# 310023442 – (b) (4) API (batch# (b) (4)) gave (b) (4) content by potentiometry a result of (b) (4)% (Specification limit: (b) (4)). Attributed root cause: Air bubbles in the dispensing tube. However, this root cause was not adequately justified with scientific evidence.

3) OOS# 310023657/310023658/310023685/310023686/310023704/310023705 – (b) (4) API, six batches ((b) (4), (b) (4), (b) (4), (b) (4), (b) (4), (b) (4)), residual solvents by GC in (b) (4) content (range of ~(b) (4) ppm to (b) (4) ppm against specification limit of NMT (b) (4) ppm). Attributed root cause: cleaning of sampling area with (b) (4). However, this root cause was not adequately justified with scientific evidence.

4) OOS# 310026212, (b) (4) API (batch# (b) (4) (b) (4) residual solvents by GC ((b) (4) ppm against a specification limit of NMT (b) (4) ppm). Attributed root cause: in-process sampling may be an issue. However, this root cause was not adequately justified with scientific evidence.

B. Investigations do not always implement adequate corrective and preventive actions to address the identified root causes and prevent recurrence. For example,

1) During the GC residual solvents release testing performed for (b) (4) API from January 2020 to June 2023, an unknown peak identified as (b) (4) was observed in approximately (b) (4) batches. The batches were subsequently investigated, and the root cause of the unknown peak was attributed to the key starting material, (b) (4) as (b) (4) is a key raw material in its synthesis. The corrective action identified for controlling the presence of (b) (4) in the final API was to maintain a

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higher volume of retained (b) (4) during the (b) (4) operation as the impurity can be (b) (4) during the manufacturing process. The corrective action to maintain the volume between (b) (4) to (b) (4) was implemented in June 2020, however, this volume value was changed back to the original control in October 2020. Since October 2020, 60 instances of the unknown peak present were obtained with the same root cause, however no additional corrective actions were implemented to adequately control the manufacturing process as identified originally in June 2020 until September 2023.

2) Incident 200414087 was initiated on 22Apr2023 due to residual (b) (4) solvent content in (b) (4) result exceeding the cleaning specification of not more than (b) (4) ppm during cleaning validation of (b) (4) . The root cause of the investigation was contamination in the (b) (4) container used for (b) (4) rinsing which (b) (4) is also used. It was concluded that no impact to any other batches, and corrective actions, including incorporating (b) (4) cleaning procedures between solvent changes, were identified. Additionally, Incident 200426113 was initiated on 23Jan2024 with a similar root cause for inadequate cleaning of (b) (4) containers and similar corrective actions identified. However, there was no assessment performed of other cleaning records where there is lack of instruction in cleaning and use of the (b) (4) containers nor were preventive actions identified to correct any other cleaning records.

OBSERVATION 4

There is a failure to ensure that materials are not released before the satisfactory completion of evaluation by the quality unit.

Specifically,

Batches of (b) (4) API intended for use in US marketed products were released by the quality unit without completion of all applicable release tests prior to distribution. (b) (4) API is tested following specifications SP-CTO06-002815 and CS-(b) (4) -012/04 and requires additional testing for particle size distribution.

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Change controls CC1000087928 and CC1000098929 were initiated on 14Jul2022 for batch (b) (4) and on 03Dec2022 for batches (b) (4), (b) (4), (b) (4), (b) (4), (b) (4), and (b) (4), respectively, to release the batches without completion of the particle size distribution testing, as required per the specification. The Certificates of Analysis were issued with a note indicating that particle size testing was not performed with reference to the respective change controls. Change controls CC1000087928 and CC1000098929 were closed and approved by the quality unit on 19Jul2022 and 28Dec2022, respectively.

***DATES OF INSPECTION**
05/30/2024(Thu), 05/31/2024(Fri), 06/03/2024(Mon), 06/04/2024(Tue), 06/05/2024(Wed), 06/06/2024(Thu), 06/07/2024 (Fri)

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