DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10/12/2023 C 10/12/2023 10/12/2023 DER/OPQ/OPMA/Division of Biotechnology Manufacturing 10903 New Hampshire Avenue; White Oak Building 51, Room 2269 Silver Spring, MD 20993 E-mail: OPFBLAInspection483Responses@fda.hhs.gov	10/04/2023-10/12/2023
	FEI NUMBER 3014250111

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Gopalkrishna Lakkireddy, Head – Quality

FIRM NAME	STREET ADDRESS
Dr. Reddy's Laboratories, Ltd, Biologics	Hyderabad, Telangana
CITY, STATE, ZIP CODE, COUNTRY India	TYPE ESTABLISHMENT INSPECTED Drug Substance and Drug Product manufacturing

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

The viral control strategy at Dr. Reddy's Laboratories is inadequate to mitigate the virus cross contamination risk of (b) (4) and does not align with current industry standards and ICH Q5A guidelines. Specifically, no adventitious virus testing is performed on unprocessed bulks in the manufacturing process to produce (b) (4) and other products for non-US market. These processes share common equipment and materials with (b) (4) manufacturing for the US market and thus, could potentially cross contaminate the (b) (4) for the US market. The shared equipment include;

a. All the upstream and downstream equipment for (b) (4) drug substance manufacturing for non-US market in (b) (4) are shared with (b) (4) drug substance manufacturing for US market.
b. The (b) (4) and (b) (4) including (b) (4) have been shared for manufacturing of (b) (4) for non-US markets and for US market.
c. The (b) (4) housing in (b) (4) has been used in (b) (4) to support the manufacturing of (b) (4) and (b) (4) for non-US market with their own respective (b) (4) in 03/2022 and 11/2022 respectively.
d. The manufacturing of (b) (4) drug product for the US market shares the common equipment for the manufacturing of drug products for non-US markets (b) (4) (b) (4) in (b) (4)

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		Madushini Dharmasena, Ph.D., Senior Pharmaceutical Quality Assessor Zhong Zhao, Ph.D., Biologist	10/12/2023

OBSERVATION 2

The [redacted] drug substance manufacturing areas are not under control for mold.

a. There is an unacceptably high number of mold recoveries in the classified rooms used for manufacture of [redacted] drug substance. Specifically, there were 696 mold recoveries in [redacted] since 2021 January (157, 372 and 167 mold recoveries in 2021, 2022 and 2023, respectively). The mold action limits (Grade C [redacted] CFU and Grade D [redacted] CFU) are inadequate to initiate additional cleaning, environmental monitoring investigation or deviation.
b. The mold contaminants recovered via the Environmental monitoring Program have not been trended in a meaningful manner to identify trending patterns. There have been 166 Settle plate mold recoveries and 521 active air sampling mold recoveries compared to only 9 surface monitoring since 2021 January. No investigation was performed to identify the trending mold recovery pattern and corrective and preventive actions (CAPAs) have not been implemented due to recurring mold recoveries.

OBSERVATION 3

The investigations and corrective actions due to visual inspection limit excursion are inadequate to address defective [redacted] drug product trends.

a. The extrinsic fibers are classified as major defect types, although they may pose higher risk and cause serious adverse reaction.
b. Atypical defective product trends such as fibers or particles have not been adequately investigated, although there have been extrinsic fibers in 45 drug product batches out of [redacted] and black particles in 17 batches out of [redacted] during 100% visual inspections. The potential risk such as sterility assurance issues or other CGMP violations have not been adequately investigated or addressed.
c. CAPA CP-010-10 implemented is inadequate as it did not resolve reoccurring fibers and particles in [redacted] drug product vials.

OBSERVATION 4

The post PPQ [redacted] drug substance manufacturing process is not consistent. The termination, cancel, and rejection percentage for [redacted] drug substance in post-PPQ manufacturing is [redacted]% (8 batches from total [redacted] batches). Among them,

a. Three (3) batches were terminated due to contaminations in the production bioreactors [redacted]-CC-FR08 and [redacted]-CC-FR10.
b. Two (2) batches were rejected due to the out of specification for the drug substance releasing testing.
c. Three (3) batches were terminated due to the changes of the manufacturing plan.

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OBSERVATION 5

(b) (4) drug product manufacturing process is not under adequate control. Specifically,

a. On October 6th 2023 during the filling of (b) (4) drug product in the restrictive access barrier system (RABS) of (b) (4) vial fill line, a droplet of product was frequently observed at the (b) (4) (b) (4) before dispensing the product into the vials. Occasionally the droplets formed at the (b) (4) of the (b) (4) dripped on to the tray table below.
b. There is no assurance that the (b) (4) pressure is within the validated pressure range as (b) (4) pressure is not controlled or monitored during (b) (4) The (b) (4) speed is controlled as a process parameter by (b) (4) pump speed setting. The pump speed/flowrate upstream of the (b) (4) will not detect (b) (4) overpressure. The overpressure may deform the (b) (4) causing a failure in (b) (4) and potential for bacteria passing through the (b) (4) and may result in product contamination.

OBSERVATION 6

The (b) (4) sterilization validation of direct and indirect sterile product-contact items is not sufficient to demonstrate sterility assurance:

c. Bioindicators (BI) incubation conditions used during sterile drug product contact and indirect contact equipment (b) (4) validation studies are inadequate to demonstrate that the (b) (4) cycle provides a sterility assurance level of at least (b) (4) and, thus, there is no assurance that the direct and indirect sterile drug product contact equipment is sterilized during (b) (4) sterilization. The BIs (b) (4) BI) used for the (b) (4) (b) (4) (b) (4) are incubated for (b) (4) during the (b) (4) validation studies. An incubation of (b) (4) is not sufficient to determine whether BI spores exposed to the sterilization cycle exhibit growth.

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d. BI placement during [redacted] sterilization validation of [redacted] is not sufficient to demonstrate sterility assurance. One tube of BI was placed [redacted] between [redacted] and the [redacted] for sterilization validation of [redacted] There is no assurance that the [redacted] is [redacted] through [redacted] surfaces of the [redacted] to sterilize the [redacted] during [redacted] sterilization.

OBSERVATION 7

The [redacted] drug substance manufacturing process is not adequately controlled to ensure that the in-process intermediates did not become contaminated to assure product quality.

a. The microbial testing is inadequate to ensure that the [redacted] and the [redacted] used for the [redacted] drug substance manufacturing process is under microbial control as the [redacted] and [redacted] storage [redacted] (worst case sampling) are not routinely tested for bioburden and endotoxin.
b. [redacted] drug substance manufacturing process do not include microbial controls at critical steps of the manufacturing process to assure that the process is under microbial control.
c. The bioburden test volume of [redacted] mL for in-process [redacted] and [redacted] retentate is too low. The sample size is not representative of the process [redacted] and thus, bioburden assay sensitivity may not be sufficient to detect all the contaminating microorganisms.
d. The bioburden in-process test limit of [redacted] CFU/mL for in-process [redacted] and [redacted] retentate is too high to provide assurance that the in-process [redacted] are under microbial control.

OBSERVATION 8

Your firm failed to provide adequate assurance that your cleaning validation procedures are effective to prevent contamination of [redacted] product-contact process equipment in [redacted] Specifically,

a. Your cleaning validation (CV) study for the [redacted] drug product [redacted] does not include swab samples therefore, there is no assurance that the parts washer cleaning cycle is effective in removing all the worst case hard to clean equipment locations and non-soluble material.
b. Cleaning validation of shared equipment is not adequate to ensure prevention of cross-contamination between products. Specifically, product contact items such as [redacted] in [redacted] area are not sampled and tested for residues after cleaning to demonstrate that the cleaning process adequately and consistently removes product residues and environmental contaminants.

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OBSERVATION 9

The documentation and assessment of potential risks and abnormalities during GMP manufacturing are deficient. Specifically,

a. The current (b) (4) that is used for the (b) (4) step in the (b) (4) process has been used for up to (b) (4) cycles from 2020 and exhibits pronounced coloration changes. The color was changed from the normal white to current dark grey. However, the (b) (4) color has not been observed during the small-scale study for up to (b) (4) runs. The abnormal color change for (b) (4) during the GMP manufacture has not been documented, therefore, it is not known about the start of color change as well as the process and speed of color change. No risk assessment or investigation for this (b) (4) color change, such as the identity for the materials resulted in the abnormal color, its impact on the (b) (4) (b) (4) capacity and virus removal efficiency (b) (4) is one important step in viral clearance study), and potential leachable and/or additional impurities introduced into the (b) (4) (b) (4) drug product were performed.

b. The batch production and control records are deficient in that they do not include documentation of maximum allowable hold time during each significant step in manufacturing and processing.

c. The (b) (4) of (b) (4) used for the filling of (b) (4) drug product in (b) (4) is not documented or tracked. These (b) (4) identical (b) (4) of (b) (4) are also used for filling of other drug products and media (aseptic process simulation) in (b) (4) The wear and tear of the (b) (4) may be different and thus filling properties may be different.

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	Zhong Zhao -S Digitally signed by Zhong Zhao -S Date: 2023.10.12 04:09:36 -04'00' Madushini N. Dharmasena -S Digitally signed by Madushini N. Dharmasena -S Date: 2023.10.12 04:17:35 -04'00'	Madushini Dharmasena, Ph.D., Senior Pharmaceutical Quality Assessor Zhong Zhao, Ph.D., Biologist	10/12/2023