DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
FDA/CDER/OPQ/OPMA/Division of Biotechnology Manufacturing 10903 New Hampshire Avenue, Silver Spring, MD 20993 Email: OPMABLAInspection483Responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	02/27/2023-03/07/2023
	FEI NUMBER 1000291122

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Ms. Christiane Bardroff, Chief Operating Officer

FIRM NAME	STREET ADDRESS
Rentschler Biopharma SE	Erwin-Rentschler-Str. 21, Laupheim
CITY, STATE, ZIP CODE, COUNTRY Baden-Wurttemberg, 88471 DE	TYPE ESTABLISHMENT INSPECTED Drug Substance Intermediate 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

Procedures to prevent microbial contaminations are inadequate. For example,

a. Your firm continuously recovered endospore formers, objectionable microorganisms, and human isolates in GMP suites that are used for upstream and downstream processing of the (b) (4) and (b) (4) drug substance intermediates, and product samples. For example, numerous deviations (DEV-2021-0027, 2021-0046, 2021-0058, 2021-0060, 2021-0133, 2021-0145, 2021-0196, 2021-0268, 2021-0322, 2021-0324, 2021-0436, 2021-0544, 2022-0004, 2022-0030, 2022-0066, 2022-0230, 2022-0264, 2022-0313, and 2023-003) were raised between 2021-2022 for recoveries of *Bacillus spp, Paenibacillus glucanolyticus* spore formers, *Enterococcus spp,* and various human isolates during environmental monitoring, and in product samples as per OOS-OOT-2021-0077, OOS-OOT-2021-0080, OOS-OOT-2021-0161, and OOS-OOT-0131 which resulted in batch (b) (4) of (b) (4) being rejected and designated as "Not for Human Use" due to *Bacillus spp.* contamination in the product or product samples.

b. The (b) (4) Point of Use (POU) identified as (b) (4) used for batching and product manufacturing processes are infrequently monitored for endotoxins. According to RL-SOP-000876 Rev 18 Item 11 of the SOP, the monitoring frequency for endotoxins is "after maintenance" for the POUs. Endotoxin monitoring for (b) (4) should be performed with frequencies that commensurate with manufacturing usage to ensure conformance to USP monograph for (b) (4) microbial control limits.

	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
SEE REVERSE OF THIS PAGE		Wendy G Tan, PhD, Microbiologist Leiyun Boone, PhD, Pharmaceutical Scientist Caryn McNab, CSO	03/07/2023

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OBSERVATION 2

Environmental monitoring culture plates are placed in closed (b) (4) boxes in the (b) (4) incubators at (b) (4) C and (b) (4) C incubation conditions. Your firm has not evaluated the impact of utilizing these (b) (4) boxes in the (b) (4) incubators for optimal cultural conditions to obtain environmental microbial recoveries that may be sensitive to sub-optimal cultural conditions (e.g., strict aerobes, temperature-sensitive, slow growers etc.).

OBSERVATION 3

Responsibilities of the quality unit are not always fully followed. For example,

a. Document RL-SOP-00830 "GMP-Occurrences: Documentation, Event, Deviation" (Rev. 13, Effective Date 29 Jan 2023) requires that batch-related deviations with potential risks on product quality should be classified as major. DEV-2022-0428 was raised due to the (b) (4) running marks on the (b) (4) of (b) (4) system (b) (4) used for (b) (4) and (b) (4) process during (b) (4) purification process. The (b) (4) has direct contact with products during the manufacture of (b) (4) batches (b) (4) and (b) (4) (PPQ batches (b) (4) (b) (4) indicating potential impact on product quality of the associated batches. However, both the initial and final classification of the deviation was minor.

b. The inventory of (b) (4) reference standards in LIMS was updated on October 5, 2022, including removal of (b) (4) vials of (b) (4) primary reference standard, (b) (4) vials of (b) (4) primary reference standard, and (b) (4) vials of (b) (4) secondary reference standard. However, no documentation or event could be located regarding these changes.

OBSERVATION 4

The cell bank transport system for internal transfer of (b) (4) cell banks are not qualified. Specifically, no qualification data are available to support the cell bank handover procedure from the storage location to inoculum suite.

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OBSERVATION 5

Nine bags of rejected biological intermediate (b) (4) batch (b) (4) (bags 3 – 11) were not promptly moved to the reject cage at the time of rejection on or about 1/13/2022 as required by SOP 01027 "Quarantine Store", section 6.3.3. The bags were in blocked status in SAP, but they were still stored in the high-rack warehouse at the time of the inspection on 3/1/23.

DATES OF INSPECTION: *2/27/2023 (Mon), 2/287/2023 (Tue), 3/01/2023 (Wed), 3/02/2023 (Thurs), 3/03/2023(Fri), 3/06/2023(Mon), 3/07/2023(Tue)*

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SEE REVERSE OF THIS PAGE	Wendy Tan Leiyun Boone Caryn McNab	Wendy G Tan, PhD, Microbiologist Leiyun Boone, PhD, Pharmaceutical Scientist Caryn McNab, CSO	03/07/2023