DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Division of Biotechnology Manufacturing 10903 New Hampshire Avenue; White Oak Building 51, Room 2269, Silver Spring, MD 20993 Email: OPFBLAInspection483Responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	02/07/2022 - 02/15/2022
	FEI NUMBER 1000291122

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dr. Christian Schetter, Chief Scientific Officer

FIRM NAME	STREET ADDRESS
Rentschler Biopharma SE	Erwin-Rentschler-Strasse 21
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Laupheim, Baden-Wuerttemburg-Germany 88471	Drug Substance Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

Observation 1

On February 11, 2022, we (WS and JM) observed the simulated fill process ((b) (4) simulation) of the (b) (4) drug substance into (b) liter (b) (4) bottles, with the drug substance dispensed by (b) (4) fill (b) (4) via (b) (4) pump. There is no RPM specification for the pump nor is there documentation of the RPM setting, with mitigation of (b) (4) during drug substance dispense to be avoided. The process is not controlled to an established specification.

Furthermore, the cap with liner applied to the treaded drug substance bottle post filling operation is by hand without a known torque. The manufactures recommended bottle cap torque of (b) Nm is not applied to assure an integral seal, with the process not controlled to an established specification.

Observation 2

Cleaned and pending use (b) (4) and (b) (4) have rings of discoloration below the top of the (b) (4) assembly. You indicated that the root cause of the (b) (4) discoloration is unknown, with no formal risk assessment or corrective action to address the discoloration.

Observation 3

Laboratory procedures or testing to assure compliance with established specifications and standards is not available. Specifically,

a. Standard operation procedure Doc No.: RL-TP-00048, Prufung auf Bakterien-Endotoxin: Kinetic-Turbidmetrischer Test/Testing on Bacterial Endotoxins: Kinetic Turbidimetric Test, Rev 14 describes the overall facility approach for drug substance in-process control and release testing, with no time limit for endotoxin testing

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to occur based on validation.

b. The (b) (4) drug substance is (b) (4) um filtered into a (b) (4) bag system where release and stability samples are acquired. The release and stability samples are not representative of the final (b) (4) drug substance container closure system.

Observation 4

The (b) (4) drug substance excipient, (b) (4) is not adequately controlled. Specifically, There is no risk assessment or analytic assessment of potential (b) (4) formation in either the main drug substance (b) (4) % solution or the diluted (b) (4) % formulation (b) (4) (b) (4) % (b) (4) can be manufactured and stored in process bags for (b) (4) with the color test for the (b) (4) % (b) (4) showing a slight color change at (b) (4)

Observation 5

Equipment and facility systems in support of manufacture have not been adequately validated. Specifically,

a. (b) (4) incubators used in inoculum (b) (4) have an operating specification of (b) (4) °C, with seven incubators having no chamber distribution profile assessment, with all (b) (4) units having no penetration profile to assure conformance to specification.

b. (b) (4) liter (b) (4) hold tanks (b) (4) are cleaned (b) (4) and (b) (4) with (b) (4) um filtered into the vessels and held for up to (b) (4) (approximate). There is no validation in support of the (b) (4) hold time from a microbiological control perspective nor is there a procedure that describes the hold time limit or documentation practice for batch manufacture. You indicated within SAP, the materials management system that a (b) (4) expiry has been set for (b) (4) maintained by the hold tanks.

c. On 07 February 2022, (b) (4) were observed within (b) (4) in areas (b) (4) and (b) (4) with the condition for storage (b) (4) - (b) (4) °C. You indicated that (b) (4) can be stored up to (b) (4) within the areas, with the areas not

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validated for (b) (4) - (b) (4) °C temperature control.

d. Post (b) (4) of the (b) (4) A2173, the system can be held sanitized up to (b) (4) pending manufacture, with no hold time validation to assure the sanitized state can be maintained.

e. For (b) (4) there is no routine physical and biological requalification of the worst-case load to assure the validated state is maintained.

f. Under Dok. Nr.: RL-Report-06128, Reinigungsvalidierung fur Kleinteile Produktion USP in der Spulmaschine A0488, parts washer performance qualification, the validation for study 1 and 2 did not meet the acceptance criteria of < (b) (4) CFU/100 mL for rinsate samples for all equipment tested, with study 3 having a mechanical failure, and study 4 passing using another soiling material. According to your master validation plan at the time, Dokumententitel: Cleaning of Process Equipment in the Departmens (b) (4) v2, Section 17 Execution indicates: According to cleaning validation concepts, a minimum of 3 successful cleaning validation runs have to be performed to reach the validated state. The validation did not meet the pre-approved acceptance criteria.

g. Filled (b) (4) drug substance bottles are frozen at (b) (4) °C in (b) (4) followed by the frozen drug substance transported in a passive shipper to the main warehouse for long term storage at (b) (4) °C. There is no validation of the shipping system to maintain temperature.

Observation 6

Rejected materials are not always controlled under a quarantine/hold classification in SAP system to prevent their unauthorized use. Specifically,

Process Deviation Report DEV-19-0364 was initiated on 02 July 2019 for batch (b) (4) This batch was filtered (b) (4) filtration) (b) (4) imes total due to failure events associated with the post-use filter integrity test and low pressure observed at the inlet of the filter. Deviation Report DEV-19-0364 concluded that there was no impact to product quality. The batch (b) (4) was released.

A comparability protocol # STAB-102777 was initiated to assess whether the batch (b) (4) was statistically

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similar to batches of (b) (4) previously manufactured with only (b) (4) filtration. During this assessment, the batch was never locked (e.g., hold or quarantine) in SAP system. Protocol # STAB-102777 confirmed that Batch (b) (4) is not comparable to historical batches, with batch (b) (4) rejected on 2 February 2022.

Observation 7

Your firm failed to establish an adequate system for monitoring environmental conditions of critical process equipment. Specifically,

On 07 February 2022, twelve (12) out of approximately (b) (4) °C ultracold freezers located in Building 10, GMP warehouse and available for use in (b) (4) drug substance storage were observed in a state of local alarm. There is no procedural requirement to acknowledge a local alarm condition or to assess the impact of the alarm on the qualified state of the equipment. The qualified state of the freezers is not maintained.

Observation 8

Facilities and equipment in support of manufacture are not adequately maintained. Specifically,

a. On 10 February 2022, observed within Building (b) (4) was the (b) (4) water system, with the floor area observed in a deteriorated state.

b. Procedure RL-SOP-00368 titled (Guidelines for the use of material (b) (4) ; Revision 8, describes that mobile equipment (e.g., vessels, (b) (4) containers, containers, etc.) brought into hygienic Zone (b) (4) and hygienic Zone (b) (4) via material (b) (4) must not be visibly damaged. However, on 08 February 2022, during the inspectional walk through of the production area, I (JM) observed a rusty container chassis located in front of the GP Suite (b) (4) Suite. There is no procedure that defines/describes the process for maintenance of damaged/deteriorated container chassis.

c. On 07 February 2022, observed within Building 10 shipping and receiving was a loading dock (b) (4) door leading to the outside with an inadequate door seal, with a gap of about 1/4 inch between the floor and the door.

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d. The area between GMP warehouse walls and raw materials/intermediates storage racks are not kept clean. On 07 February 2022, the area was observed dirty with accumulation of dust and papers, including a (b) (4) container used to store raw materials and a brown cardboard box with filters (Material No. 4006691; Lot (b) (4) Furthermore, the drain and the (b) (4) grid located in front of the warehouse (b) (4) and (b) (4) pallet washing area was observed dirty that included material residues.

Observation 9

Procedural controls in support of manufacture are not followed. Specifically,

a. (b) (4) retain samples are handled by the LIMS system in the Quality Control (QC) Laboratory, with the system assigning a storage location to each retain sample lot. If the sample is acquired from the retain sample room, a new storage location is assigned in LIMS.

On 10 February 2022, I (JM) made an evaluation of the retain samples flow/transfer in the LIMS system. Retain samples corresponding to (b) (4) USP batches # (b) (4) and (b) (4) were selected, with the samples not found in the storage location described in LIMS.

b. According to SOP Doc. No.: RL-SOP-00830, GMP-Occurrences: Documentation, Event, Deviation, Rev 11, you indicate under Section 7.2, Timelines in the context of processing a deviation, a minor deviation report shall be processed within a processing period of (b) (4) days from the date of discovery to the date of the completion of the deviation. In the event that the deviation cannot be completed with the allotted processing period, an interim report (extension request triggered from the deviation report) shall be prepared upon detection of the delay. In a review of eleven (11) deviations where an extension would be required, only three (3) had an extension prepared.

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