DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration/ORA/OPQO/HQ 12420 Parklawn, Room 2032, Rockville, MD 20857 ORAPHARMInternationalresponses@fda.hhs.gov	03/09/2023-03/17/2023
	FEI NUMBER 3002806978

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Roland P. Holmqvist, CEO	
FIRM NAME Rechon Life Science AB	STREET ADDRESS Soldattorpsvagen 5
CITY, STATE, ZIP CODE, COUNTRY Limhamn, Skane Lan, 216 13, Sweden	TYPE ESTABLISHMENT INSPECTED Human Drug 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

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically,

You have not established scientifically justified contamination recovery rate limits in aseptic environments.

A. According to your SOPs, microbial contamination recovery limits for the (b) (4) of operators are set at Alert: (b) (4) CFU and Action: (b) (4) CFU, while limits for (b) (4) entering the Grade A area are Alert and Action < (b) (4) CFU. However, when operators conduct interventions in which they (b) (4) the RAB (b) (4) (b) (4) enter the Grade A area. This poses an increa risk of microbial contamination to the Grade A environment. We reviewed environmental results from one week of each month in 2021 and 2022. During the weeks we reviewed, operators had microbial growth of (b) (4) CFU for (b) (4) samples a total of 125 times. Since this recovery of growth is below the alert value and no deviation is initiated, it is unclear if operators with microbial growth on the (b) (4) performed interventions with the RAB (b) (4) or made aseptic connections before start of fill in the Grade A area.

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	Monica E. Murie, Investigator	Monica Murie -S Digitally signed by Monica Murie -S Date: 2023.03.17 08:27:32 -05'00'	03/17/2023

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B. The microbial contamination recovery limits for the (b) (4) of operators in the Grade B area are set at levels that are equivalent to or greater than those in a Grade B area. Microbial contamination recovery limits include:
   a. (b) (4) Alert: (b) (4) CFU and Action: (b) (4) CFU
   b. (b) (4) Alert: (b) (4) CFU and Action (b) (4) CFU

   We reviewed environmental results from one week of each month in 2021 and 2022. During the weeks we reviewed, operators had 280 occurrences of microbial growth up to (b) (4) CFU for (b) (4) samples. During the weeks we reviewed, operators had 86 occurrences of microbial growth of (b) (4) CFU for (b) (4) samples. Since this recovery of growth is below the alert value and no deviation is initiated, it is unclear if operators with microbial growth on the (b) (4) entered the Grade A area to perform the aseptic connections (b) (4) fill. The aseptic connection is performed (b) (4) step.

   There is no scientific justification for setting contamination recovery rates in accordance with Grade B standards when operators routinely conduct interventions and perform aseptic connections in Grade A environments.

C. The Grade A area of the (b) (4) line (room (b) (4), which is (b) (4) is not being monitored for particles, including viable and non-viable particles, as well as active air. Specifically, there was no continuous monitoring system in place to detect and alert personnel of any deviations from the established limits for particle counts and air quality. The only monitoring method used was periodic manual sampling, which is not representative of the actual conditions in the Grade A area during the filling process.

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OBSERVATION 2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written, or followed.

Specifically,

A. Disinfection performed between production runs is conducted using [redacted] Your firm has not qualified [redacted] for disinfection of molds, bacteria including Burkholderia cepacia complex, and spore-forming bacteria such as Bacillus species. Multiple positive growth results for molds and Bacillus species, including but not limited to Bacillus subtilis, have been recorded in aseptic manufacturing cleanrooms and on personnel gowning after aseptic production from January 26, 2021, to November 2, 2022. Disinfection with [redacted] which me [redacted] criteria for Aspergillus brasiliensis and Bacillus subtilis, is only conducted [redacted] and not in direct response to observation of these objectionable microorganisms in the environment during production.

B. Operators who are qualified during media fills are not consistently performing all the interventions that are typically encountered during annual production. For example, during the filling of batch [redacted] on or around September 22, 2022, operator [redacted] conducted intervention [redacted] adjusted when [redacted] on two ate occasions. Operator [redacted] was last certified to perform this intervention during a media fill on August 10, 2018. During the filling of batch [redacted] on or around [redacted] operator [redacted] conducted intervention [redacted] on two separate occasions. Operator [redacted] was last cer [redacted] g a media fill on [redacted] During the filling of batch [redacted] on or around [redacted] operator [redacted] conducted intervention [redacted] Since November 4, 2016, there is no record showing that [redacted] has been certified to perform this intervention.

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Furthermore, aseptic connections are not tracked or trended in order to qualify operators during media fills. This lack of tracking and trending presents a potential risk to the aseptic process and the quality of the final product.

The failure to track aseptic connections makes it difficult to determine whether operators are consistently performing aseptic techniques during media fills. Without trending data, it is impossible to determine whether operators are improving or worsening their aseptic techniques over time, which could have a significant impact on the quality of the final product.

C. Smoke studies do not accurately reflect the conditions that would be encountered during actual manufacturing processes. Operators involved in the studies were not wearing the gowning that they would typically wear during production, and the interventions that were performed during the studies did not necessarily replicate the same procedures that would be used during actual production. For example, during the smoke study for intervention (b) (4) (b) (4) the filter was not covered prior to wheeling the tanks from the Grade A area to the Grade B area and out of room (b) (4)

It is important to note that this discrepancy between the smoke studies and real-world manufacturing processes could have significant implications for the validity of the data collected during these studies. Without accurate and representative data, it may be difficult to make informed decisions about the safety and efficacy of the manufacturing processes being studied.

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OBSERVATION 3

Written procedures are not established and followed that describe the in-process controls and examinations to be conducted on appropriate samples of in-process materials of each batch.

Specifically,

You have not performed a scientifically justified risk assessment defining the critical parameters of the visual inspection processes used in the (b) (4) vial/cartridge line, the (b) (4) line and the (b) (4) 100% visual inspection. The following observations were

A. The (b) (4) visual inspection process established for the vial/cartridge line has an inspection time of approximately (b) (4) per unit, which is shorter than the recommended time of (b) (4) per unit in (b) (4) This raises concerns about the adequacy of the inspection time to detect all potential defects. The line speed for both (b) (4) visual inspection lines is set at (b) (4) units per (b) (4) which is approximately (b) (4) per unit. This is (b) (4) established in (b) (4) for visual inspection of (b) (4) This raises concerns about the adequacy of the n time to detect all potential defects.

B. Only (b) (4) kit is used to certify operators for the visual inspection process in both the (b) (4) (b) (4) line and the (b) (4) inspection. All vials in the certification kit are numbered. (b) (4) (b) (4) at a minimum. However, there is no defined time between qualifying runs, allowing operators to potentially see the same kit (b) (4) times on the same shift. This raises concerns about the potential for operators to memorize the kit, which could compromise the accuracy of the visual inspection process.

Overall, without a scientifically justified risk assessment defining the critical parameters of the visual

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inspection processes, it is difficult to ensure that the visual inspection process is reliable and consistent, which may lead to a higher risk of defective products reaching the market.

OBSERVATION 4

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically,

A. During the period of September 10, 2021, through January 13, 2022, operator (b) (6) was identified as having three separate trend events for abnormal flora recovered from gowning sample locations.

2021-365 was initiated on September 29, 2021, after abnormal flora was recovered on eleven gowning samples from dominant (b) (4) ocations. Corrective actions were taken, including requalifying (b) (6) on gowning in September and October with restrictions that required wearing specific undergarments beneath the sterile clean room outer garment. However, no effectiveness check was documented.

2022-030 was initiated on February 3, 2022, after a trend was identified on (b) (4) consecutive samples recovered from the (b) (4) location on January 11, January 12, and January 13, 2022. Each sample was positive for the growth of abnormal flora, specifically gram-negative rods. During a review of environmental sample results, it was discovered that another trend of (b) (4) consecutive samples from the (b) (4) location on November 23, November 29, and December 16, 2021, had been missed. Each sample was positive for the growth of abnormal flora, specifically gram-negative rods. It is unclear when they were discovered, but the deviation referencing them

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was not initiated until February 3, 2022, or week 5 of 2022, seven to nine weeks after the samples were collected. No corrective actions for the operator were implemented, and no effectiveness check was performed.

After these trending events and accompanying deviations, a fourth trend was identified.

2022-394 was initiated on September 29, 2022, after abnormal flora was recovered from (b) (4) gowning samples, including (b) (4) samples from October 3, 2022, and a (b) (4) sample from October 4, 2022.

B. Leak test failures with no preventive actions, or effectiveness checks.

2022-212 opened 5/24/2022; Date of Occurrence 5/23/2022; Closed 7/21/2022: During the integrity test in room (b) (4) the RABS (b) (4) failed due to a (b) (4) The cause of the (b) (4) was not determined, and no preventiv ken to prevent future occurr s. Although one preventive action was identified, it was not implemented. No effectiveness checks were performed to ensure that the preventive actions taken were effective.

2022-257 opened 6/29/2022; Date of Occurrence 6/21/2022; Closed 8/25/2022: During the filling process, filling operator (b) (6) discovered a hole in the RABS (b) (4) at (b) (4) (b) (4) on the aseptic filling line in (b) (4) The (b) (4) was discovered closer end of the and no root cause was identified. Two preventive actions were implemented, including adding a visual inspection after the integrity test and trending by location and replacement frequency. However, no effectiveness check has been conducted on either of these preventive actions to date.

2022-377 opened 10/04/2022; Date of Occurrence 10/03/2022; Closed 11/13/2022:

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During the leak test in room (b) (4) the RABS (b) (4) failed, and no preventive actions were implemented to prevent future occurrences. No effectiveness check was performed to ensure that the preventive actions taken were effective.

These investigations indicate a recurring issue with leak test failures and the lack of preventive actions taken to address the issue. A total of 14 deviations related to (b) (4) RABS (b) (4) were registered, with eight of them occurring in 2022 alone. This indicates a lack of effec corrective and preventive actions to address the issue.

C. Deviation AV2021-317, initiated on August 25, 2021, originated due to the presence of (b) (4) particles in the (b) (4) preparation vessel during the production of (b) (4) batch no. (b) (4) This deviation also applies to the previously (b) (4) (b) (4) but no samples were taken as the bulk had been discarded before operators noticed particles in batch no. (b) (4) A Rechon Summary of Deviations AV2021-317 and AV2021-333 states that API lot numbers (b) (4) used in production of batches (b) (4) were found to be contaminated with (b) (4) particles from (b) (4) (b) (4) used during manufacturing of the API. This investigation was not expanded to include any previous lots of (b) (4) API used in production. This investigation did not assess the potential impact of the (b) (4) particles on the production process itself, which could result in additional deviations or de . No corrective or preventive actions were identified or implemented to reduce the potential for compromising the quality and safety of subsequent batches.

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