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	6/16/2022-6/27/2022*
	FEI NUMBER 3010705046

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Ibon Gutierro Aduriz PhD, Corporate Director

FIRM NAME	STREET ADDRESS
Laboratorios Farmaceuticos Rovi S. A.	Calle De Julian Camarillo 35
CITY, STATE, ZIP CODE, COUNTRY Madrid, Madrid, 28037 Spain	TYPE ESTABLISHMENT INSPECTED Sterile 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 I OBSERVED:

OBSERVATION 1

Written records of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications do not always include the conclusions and follow-up.

Specifically,

A. Investigations relevant to the [(b) (4)] mg and [(b) (4)] mg [(b) (4)] or [(b) (4)] njection commercial manufacturing process have not been appropriately evaluated with respect to multiple performance issues with the [(b) (4)] Human Machine Interface (HMI), used for [(b) (4)] which could affect the performance and capability of the commercial equipment planned for use in the proposed commercial batch record.

Specifically, starting around 06/10/2022, your firm began experiencing operational issues with your [(b) (4)] HMI, in which the [(b) (4)] would be "blocked", leading to stoppage of filling operations in your [(b) (4)] Deviations UDMI-NOT-22-120 and UDMI-INV-22-041 were initiated and remained open as of the close of the current inspection for blocked HMI due to network connection issues. During the inspection on 06/21/2022, an attempt was made to observe the manufacturing filling operations for [(b) (4)] mg lot [(b) (4)] inside the production suite, however, due to HMI being "blocked" multiple times, to observe filling operations. Attempts by your firm and vendor were made throughout the inspection to solve the issue, however, were not successful. Furthermore, it was observed that your firm has

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initiated up to nine (9) deviations/investigations starting from December 2017 for "blocked" HMI, with a short-term solution utilized by turning on and off the HMI, to continue using the filling equipment.

As a result of this performance issue with your equipment, I was not able to observe (b) (4) (b) (4) filling operations during the current inspection, which requires manual operations performed by (b) (4) operators at (b) (4) different stations of the (b) (4) There is no assurance that your firm is prepared for the proposed commercial manufacturing process at commercial scale for (b) (4) including that there are appropriate controls in place to detect and mitigate such significant problems.

B. Investigations initiated, performed and reviewed by your Quality Unit in response to out-of-specification (OOS) microbiology test results for packaging components used during manufacture of (b) (4) do not always include the conclusions and follow-up. Specifically, Corrective/Preventive Action (CAPA's) as a result of investigation root cause determination were not performed. For Example:

-OOS No. OOS-MC-20-010, dated 07/30/2020: During endotoxin testing for packaging material stopper lot (b) (4) test result was found to be OOS with result of (b) (4) EU/unit versus a specification of (b) (4) EU/unit. Your firm's investigation determined that the root cause for the OOS was potentially due to cross contamination of samples due to spillage when preparing the positive control. The investigation was closed without the issuance of any corrective actions to control or prevent a similar situation from reoccurring.

-OOS No. OOS-MC-20-020, dated 05/24/2022: During endotoxin testing for packaging material (b) (4) (b) (4) ml (b) (4) lot (b) (4) test result was found to be OOS with results of (b) (4) EU/unit and (b) (4) EU/unit versus a specification of (b) (4) EU/unit. Similar to the OOS

investigation conclusion above, your firm's investigation determined that the root cause for the OOS was potentially due to cross contamination of samples due to spillage when preparing the positive control. The investigation was closed without the issuance of any corrective actions to control or prevent a similar situation from reoccurring.

OBSERVATION 2

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

Validation master plan for the aseptic filling process of (b) (4) in (b) (4) UDMI-PMV-21-013/00 describes different types of interventions to be performed during aseptic filling operations. These interventions are detailed in your recent validation report UDMI-IVP-22-010 for aseptic filling of (b) (4) on your (b) (4) line performed around (b) (4) which covers the process simulatio (b) (4) filling operations. This validation of the aseptic filling process appears to be inadequate: Specifically, only three (3) out of more than (b) (4) production operators who participated in the approximate (b) (4) process simulation performed "corrective interventions" your firm identified in the validation master plan. In addition, after review of operator qualification procedures, the operators who performed the interventions did not appear to be adequately qualified to perform these interventions during the process simulation.

OBSERVATION 3

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

Equipment qualification activities for (b) (4) (b) (4) line does not appear to be adequate for its intended performance and use. Specifically, your firm has initiated up to nine (9)

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deviations/investigations starting from December 2017 for "blocked" filling HMI, with a short-term solution utilized by turning on and off the HMI, in order to continue using the filling equipment. My review of equipment qualifications performed as a result of changes to the line revealed deficiencies in your firm's approach to qualifying the (b) (4) given the prevalence of these performance issues with your HMI.

OBSERVATION 4

The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

Specifically,

(b) (4) niection (b) (4) (b) (4) mg and (b) (4) mg is comprised of (b) (4) (b) (4) manufactured at your firm. (b) (4) (b) (4) (b) (4) Per your batch review procedures, your firm is responsible for (b) (4) (b) (4) however, procedures for production batch and analytical raw test data review by your Quality Unit for production operations and testing performed by your contract manufacturer are lacking, in that your firm does not request these records for review, prior to (b) (4) batch release and distribution of the (b) (4) drug product package with (b) (4) In lieu of review of the (b) (4) (b) (4) production and analytical batch records to assure that no errors have occurred and fully investigate errors that have occurred, your firm accepts a certificate of conformance with respect to manufacturing and certificate of analysis with respect to testing operations from the contract manufacture for batch release. As a result, your quality control unit lacks responsibility to assure that the drug product will meet appropriate standards of safety, identity, strength, quality, and purity.

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*DATES OF INSPECTION

6/16/2022(Thu), 6/17/2022(Fri), 6/20/2022(Mon), 6/21/2022(Tue), 6/22/2022(Wed), 6/23/2022(Thu), 6/24/2022(Fri), 6/27/2022(Mon)

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