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	5/11/2023-5/19/2023*
	FEI NUMBER 3010705046

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Ibon Gutierro Aduriz, PhD, Corporate R&D 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

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

The following discrepancies were noted during the review of the aseptic filling of (b) (4)

A. (b) (4) gloves can continue to be used after the detection of a pinhole during the filling of (b) (4) Routinely (b) (4) gloves are used with an additional sterile glove placed over the (b) (4) glove. FAB-006 Aseptic Practice for Accessing and Working in Classified Rooms and (b) (4) v7, dated 11AUG22, section 5.5 states (paraphrasing) that after environmental monitoring of the outer sterile glove, instead of removing, clean with a cloth impregnated with (b) (4) to remove the remaining culture medium. Then, without removing the sterile glove, a new one is placed on it that will be monitored and changed as appropriate for the remainder of the batch. Batch (b) (4) continued to be filled after pinholes were discovered on the (b) (4) gloves at locations (b) (4) on 25JUL22 and (b) (4) on 28JUL22. End of filling took place on 31JUL22. Batch (b) (4) was released to the EU market.

B. There is no procedure for when to use the "(b) (4) tool". The Industrial Development Manager stated they sometimes have a problem with the (b) (4) used in the filling of excipient and API. Although not specified in a procedure, she stated the operators need to fill the (b) (4) only ¾ full for better flowability and that they need to use the (b) (4) to help with the process. These activities are not specified in a procedure and this training is not documented.

C. Storage of sterilized equipment is inadequate in that the scoops and (b) (4) tools used to fill the excipient and API bins as well as other utensils are used the length of the production (up to (b) (4) These utensils are stored on a wipe or directly on floor of (b) (4) and are not periodically disinfected.

D. Rejects obtained during aseptic filling of (b) (4) are not tracked. (b) (4) can be rejected at the excipient fill station, the API fill station, or the (b) (4) station. During reconciliation of the batch, only the total number of rejects are recorded.

E. Data obtained during integrity testing of the (b) (4) gloves, performed before and after aseptic processing, is not reviewed,

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printed or retained.

OBSERVATION 2
Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include adequate validation of the aseptic and sterilization process.

A. Media Fills are not representative of routine production. During review of media fill (b) (4) the following discrepancies were noted:
   1. Critical interventions performed during the media fill are not representative of routine production. (b) (4) assembly/disassembly of the stopper machine interventions have been noted during routine production however, only two were performed during media fill (b) (4) Instead, the procedure states in each aseptic filling validation batch, a minimum of (b) (4) interventions of the highest risk identified (corrective actions) and at least 1 of the rest will be challenged in order to establish this number as the maximum number allowed under routine conditions.
   2. Media fill length is not representative of routine production. PNT-UDMI-VAL-009 Validation of the Aseptic Filling Process at ROVI Laboratories' Manufacturing Plants procedure, v5 states filling simulation validation batches should be challenged the maximum time or holding time of process: including the time from the beginning of the filling of the (b) (4) to the dosing and capping of the (b) (4) Media fill (b) (4) dated 15DEC22, was run for (b) (4) Of the (b) (4) batches of (b) (4) produced since 17JUL22, 13 out of (b) (4) batches exceeded this time with the longest batch running (b) (4)
   3. AR-UDMI-18-003/03 Risk Analysis for the Validation Design of Aseptic Filling in th (b) (4) Filling Line of Building (b) (4) 25OCT22 states the maximum number of people who can be simultaneously inside the (b) (4) must always be included in the validation plan. This was not challenged since the execution of media fill (b) (4) dated May 2022. Maximum number of people was not challenged in media fills (b) (4) (Mar 2023), (b) (4) (Dec 2022), Personnel Qualification MF (Nov 2022), and (b) (4) (Aug 2022).

B. Not all non-viable monitoring excursions taking place inside the (b) (4) are investigated. As the filling of (b) (4) is a (b) (4) non-viable monitoring does not take place during filling. PNT-UDMI-FAB-017 Processing for Filling (b) (4) with (b) (4) Product in (b) (4) Packaging Lines, v16, dated 7OCT22, states before considering a status as resting, it is necessary to fulfil a "cleaning period", i.e. a recovery time, after the operation ends, which means that it is necessary to wait (b) (4) before starting the particle count. This 'recovery time' is also applied for excursions. The procedure states when monitoring at rest or in operation, if an alarm is triggered during monitoring wait for the particle count to finish or stop it, wait (b) (4) and start counting again. If it persists, notify Maintenance/Production/QA. This is significant as if the non-viable monitoring is within specification during the second sampling, the initial excursion is not investigated.

   During media fill batch (b) (4) dated 14DEC22, a non-viable alarm was trigger during the 'at rest' monitoring of the (b) (4) prior to set up (b) (4) and during a materials transfer. The monitoring was

retaken, passed and the initial alarms were not investigated.

C. Validation of the (b) (4) cycle for the sterilization of equipment used in the filling of (b) (4) is inadequate in that the BI locations are not positioned in the worst case positions.
   - The (b) (4) and nozzle used for the addition of excipient and API during the filling of (b) (4) was inadvertently not challenged with a BI due to a calculation error performed during the risk assessment.
   - The BIs are located inside the packaging and not placed in the worst-case locations, i.e. (b) (4) of equipment.

D. Validation of the (b) (4) cycle used to sterilize the (b) (4) is inadequate in that the BI locations during (b) (4) are not located in worst case positions. The firm uses bi test strips which are positioned on the (b) (4) leaving the bi pointing into the air and not the (b) (4) or (b) (4)

E. Smoke studies are inadequate in that they do not demonstrate unidirectional air flow in the following instances:
   1. The "smoke" is not always positioned above the intervention taking place.
   2. Not all activities which take place in the (b) (4) during the filling of (b) (4) is simulated in the smoke studies including:
      - Opening of equipment bags prior to set. This activity takes place after the sterilization of the (b) (4)
      - Filling of the excipient canisters
      - Opening of the stopper bags

OBSERVATION 3
Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

The following discrepancies were noted during the review of the procedures and documents associated with the visual inspection and qualification of the visual inspectors of aseptically filled (b) (4) Specifically,

A. No procedure exists for how to perform the inspection of embedded particles in the stoppers of (b) (4) Currently the critical "particle - stopper" defects of random batches of (b) (4) are reinspected to determine if the critical defect is actually a non-critical embedded particle for trending purposes as all are rejected. The assessment, performed by production, is made by moving the stopper to see if the particle moves. How far or how many times the visual inspector has to move the stopper is not specified. No documentation exists for how the operators were trained on this activity and the raw data from this evaluation is not retained. No documentation could be provided showing whether moving the stopper can differentiate between an embedded particle and a stuck particle which may come loose later.

   The trend of embedded particles found justified the increase of the visual inspection defects from (b) (4)% total defects to (b) (4)% total defects as well as justifying low yield investigations.

No procedure exists for when to identify particulates found during visual inspection of (b) (4) As of this inspection, the particles found during the visual inspection of commercialized batches of (b) (4) (not for U.S.) have never been identified.

B. Initial qualification of visual inspectors require (b) (4) challenges with a test kit containing (b) (4) defects in (b) (4) total (b) (4) Each challenge requires the visual inspector to review the kit (b) (4) as (b) (4) is a (b) (4) which is hard to inspect and requires a (b) (4) % inspection during routine production. The test kit were not changed between challenges. This was observed during the initial testing of (b) (4)

C. Visual inspectors can fail the initial requalification test without triggering an investigation. UDMI-PF-013 Training Protocol for the Qualification of Visual Inspectors states the requalification of the personnel must be carried out (b) (4) that includes a (b) (4) visual inspection, in the event that it is not passed it may be repeated once again; if it is not passed, the possible causes will be evaluated by the production and quality department, and they will determine if the test will be repeated.

(b) (6) ailed the initial requalification on 10FEB23. He repeated the qualification using the same qualification kit on 15FEB23. An evaluation of the activities performed by (b) (6) prior to his initial requalification was not performed.

D. It is unclear whether the qualification of visual inspectors is reflective of routine production as the inspection times of routine batches of (b) (4) are not documented.

E. The visual inspection test kit is not representative of all potential defects found in (b) (4) Visual inspectors are not evaluated on their ability to detect the following:

- (b) (4) critical defects including fibers in the stopper, fibers in the product, broken (b) (4) and broken stopper
- (b) (4) major A defects including incorrectly position stopper (b) (4) without stopper and absence of nozzle-cap
- (b) (4) major B defect including broken/damaged without affecting integrity

OBSERVATION 4

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

A. Quality oversight is inadequate in that quality does not oversee aseptic filling activities which take place on (b) (4) while oversite on (b) (4) is minimal. For following table compares the time production was aseptic filling to the time Quality was overseeing aseptic activities from Jan - Apr 2023:

Month	Filling Time	Quality Oversite
January	(b) (4)	(b) (4)

February	(b) (4)	(b) (4)
March		
April		

Management confirmed Quality has never observed setup or a corrective intervention during the filling of (b) (4)

B. Adequate justification could not be provided for changing the total defects obtained during visual inspection of (b) (4) from (b) (4)% to (b) (4)%

C. The specification for the visual destructive testing of (b) (4) is inadequate in that the level of particles is not specified and instead based on the number of particles noted in the excipient. The appearance specification for (b) (4) injection (b) (4) mg (USA) (b) (4) states (b) (4) visible particles.

1. D-UDMI-MA-118/03 Determination of Visible Particulate Matter in (b) (4) method states the acceptance criteria is the comparison between the average values of (b) (4) (excipient) and (b) (4) will be made: the value of total particles greater than (b) (4) µm will be compared with the limit calculated from the data of the (b) (4) analyzed (average number of particles +(b) (4) In the (b) (4) commercial batches analyzed (for the EU market), the acceptance criteria has ranged from < (b) (4) o < (b) (4) particles.
2. D-UDMI-MA-118/03 Determination of Visible Particulate Matter in (b) (4) method states if the average number of particles of (b) (4) is within the acceptance criteria, the test will be considered compliant. This is significant as (b) (4) are tested. This specification results in individual excursions not being investigated or reported. This was noted during the analysis of (b) (4) (b) (4) the test will be considered as compliant.

D. The following discrepancies were noted during the review of the procedures and reports associated with investigations:

1. Investigations are not triggered after confirmed failures of (b) (4) glove Integrity testing/visual inspection. This was observed during the failure of an (b) (4) glove during the end of filling integrity check for (b) (4) and for visual inspection failures during filling of (b) (4)
2. Investigation UDMI-INV-23-050 regarded low yields for (b) (4) mg batches (b) (4) manufactured on 18JAN23 and 10FEB23. Although the total defects (from the (b) (4)% visual inspection + AQL) failed specification of < (b) (4)% (yield ≥ (b) (4)%), the Industrial Development Manager stated these lots were not reinspected due to passing AQL inspections. The investigation concluded the higher particle levels were attributed to an inadequate cleaning after replacement of a stopper joint replacement inside the (b) (4) on 10JAN23. The AQL level used to inspect the batch was based on a stable process. Once the discrepancy was identified in the manufacturing process, the adequacy of the current visual inspection should have been evaluated.

E. There is no procedure for how to perform trend reports or rejects.
   1. Trend reports feed into the following risk assessments:
      - UDMI-II-21-137/02 Report on Trends of Defects Detected in (b) (4) on Visual Inspection, dated 3MAY23: Not all (b) (4) batches are trended. There is no procedure specifying which batches will or will not be monitored. No particles obtained from the (b) (4) % visual inspection, or the AQL evaluation have been identified.
      - AR-UDMI-18-003/03 Risk Analysis for the Validation Design of Aseptic Filling in the (b) (4) Filling Line of Building (b) (4) dated 25OCT22: This risk assessment is used to determine which interventions need to be performed during aseptic process simulations. This risk assessment, along with the trend reports, is updated (b) (4) while media fills are performed (b) (4) This results in the second media fill performed (b) (4) potentially not reflecting current interventions.
   2. The is no procedure of logbook describing the rejection of materials.

F. All environmental monitoring executed inside the (b) (4) is performed by production personnel. This includes surface monitoring (contact plates/swabs) taken at the end of the batch. These activities are not periodically verified by Quality.

G. The Quality Unit does not sample and evaluate (b) (4) batches for AQL testing taken at the end of the (b) (4) % visual inspection. Instead, this activity is performed by production.

   In addition, the test kit used in the qualification of visual inspectors is not prepared and approved by the Quality Assurance staff. This activity as well as Visual Inspector Qualification is performed by production.

H. Documents which contain raw data are not tracked or reconciled. Production and laboratory personnel can print off forms from the public server as needed including environmental monitoring, visual inspection, and container/closure integrity testing.

OBSERVATION 5
Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, sampling plans and test procedures designed to assure that components and drug products conform to appropriate standards of identity, strength, quality and purity.

A. Sterile gloves used to cover the (b) (4) gloves during the aseptic filling of (b) (4) are not inspected upon receipt for package integrity or for conformation of sterility.

B. D-UDMI-MA-018/04 Microbial Count Test, (b) (4) and (b) (4) method used to determine bioburden in (b) (4) has not been proven suitable for use.

C. PNT-UDMI-MC-018 Microbial Control of the Manufacturing Plant in Building (b) (4) specifies how to incubate the EM plates. This

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method as well as ITO-UDMI-MC-001 Microbiological monitoring of the Surfaces with Swabs have not been proven suitable for use.

D. There is no procedure for how to review microbial plates generated from water and environmental monitoring including where to read, whether or not to remove the plate cover, or used a light or magnification during reading.

E. D-UDMI-MA-118/03 Determination of Visible Particulate Matter in (b) (4) method has not been validated.

OBSERVATION 6
The written stability program for drug products does not include reliable, meaningful and specific test methods.

It is unclear whether all unknown impurities can be detected by D-UDMI-MA-013/07 Determination of Impurities in (b) (4) (b) (4) method used during the stability testing of (b) (4) as peak purity was not performed during the stress studies.

***DATES OF INSPECTION**
5/11/2023(Thu), 5/12/2023(Fri), 5/15/2023(Mon), 5/16/2023(Tue), 5/17/2023(Wed), 5/18/2023(Thu), 5/19/2023(Fri)

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