DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
550 Main Street, Ste 4-930 Cincinnati, OH 45202 (513)322-0700 Fax:(513)679-2772	9/17/2024-9/27/2024* FEI NUMBER 3011967886

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Raymond R. Carlson, Owner	
FIRM NAME RC Outsourcing, LLC	STREET ADDRESS 102 E Water St
CITY, STATE, ZIP CODE, COUNTRY Lowellville, OH 44436-1117	TYPE ESTABLISHMENT INSPECTED Outsourcing Facility

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.

Specifically,

Environmental monitoring (EM) is conducted for every batch including active air, work surfaces and gloved hands. However, your EM program is inadequate for the following:

A. No EM is required for gowns during aseptic processing. Given that one operator is responsible for producing a batch in each ISO 5 LAFW, during the production of Avastin 1.75 mg/0.07 mL, Lot# (b) (4), it was observed that the operator moved finished syringes out of the ISO 5 LAFW and introduced supplies, such as syringes and caps, into the ISO 5 LAFW regularly. The operators' sleeves were exposed to the ISO7 environment. Additionally, gowning was conducted in the ISO 8 anteroom. However, no EM is required to be performed on the sleeves inside the ISO 5 LAFW during aseptic processing, as per SOP-57, Testing of Sterile Environment, Version 1.0, Effective Date: 8/16/2024.

B. The EM monitoring of non-viable particles and active air sampling are inadequate. The non-viable air count and active air monitoring are monitored for (b) (4) near the (b) (4) for every batch as per SOP-57, Testing of Sterile Environment, Version 1.0, Effective Date: 8/16/2024. For example, during the production of Avastin 1.75 mg/0.07 mL, Lot# (b) (4), the non-viable air particle

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monitoring and active air sampling were performed for (b) (4). However, it took approximately (b) (4) to produce a batch of Avastin 1.75 mg/0.07 mL. There is no assurance that the non-viable air particle count and active air monitoring consistently remain within the ISO 5 standards throughout the entire batch processing.

Since September 2023, your firm has produced approximately (b) (4) batches of sterile products. Sterility failures were reported for 11 batches. Among those, five microorganisms were identified Staphylococcus hominis, Pseudomonas asplenii, Micrococus luteus in Avastin, Staphylococcus epidermis, Staphylococcus). During the same period since September 2022, your firm identified two microorganisms from EM for the following:

- Bacillus pumilus in EM surface sample in the ISO 5 LAFW for Avastin 2.5mg/0.1mL, Lot# (b) (4), Manufacturing Date: 2/20/2023
- Corynebacterium mucifaciens in the ISO 8 anteroom, Date: 3/16/2023

However, none of the microorganisms detected in the finished batches were found during your EM. There is no assurance your EM program can effectively detect potential microorganisms in the ISO 5 environment during aseptic processing.

C. Uncapped syringe tips made direct contact with the working surface, posing a potential risk of product contamination. The smoke study conducted 2/24/2024 in LAFW (b) (4) showed tips of uncapped syringes directly touched the working surfaces prior to be filled with the solution simulating routine batch processing; however, there is no assurance that the working surface was free of microbial contamination. For example, environmental monitoring during the production of Avastin 2.5mg/0.1mL, Lot# (b) (4), BUD: 5/26/2023 detected 1 CFU (bacillus pumilus) from a surface sample in the Direct Compounding Area from ISO 5 Laminar Airflow Hood (LAFW) (b) (4) on

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February 27, 2023. Your investigation identified the likely root cause as unintentional introduction of bacteria into the ISO 5 LAFW by materials. Your firm conduced a risk analysis indicating all tests met specifications, however, your investigation did not assess the risk posed by the direct contact between syringe tips and the working surface, as seen in the smoke study video. The batch was released.

D. On 9/17/2024, during the production of Avastin 1.75 mg/0.07 mL, Lot# (b) (4), it was observed an operator produced the batch inside the ISO 5 LAFW (b) (4) did not fully place her hood inside the gown. Additionally, the QC director did not place her hood inside the gown, nor did she wear a goggle in the ISO 7 filling room.

OBSERVATION 2

Laboratory records do not include the initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness and compliance with established standards.

Specifically,

All EM raw data are recorded in an Excel sheet without a secondary review process in place.

Your firm conducts EM for an active air sample, a surface sample, and fingertip samples from both the left and right gloved hands during the production of each batch. All (b) (4) plates are read by the quality director and the results are recorded in an Excel sheet. However, the raw EM data can be altered in the Excel sheet, and no secondary review process exists for the raw data.

OBSERVATION 3

There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

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Your firm did not investigate failures of initial visual inspections. Since 2023, your firm has reported the initial 100% visual inspection failures for seven batches due to defects (e.g. black particles or white particles) exceeding the acceptable limit. Even though reinspection yielded passing results, your firm failed to investigate the out-of-specification (OOS) results. For example, the visual inspection of Avastin 2.0 mg/0.08 mL, Lot#(b) (4), Manufacturing Date: 11/21/2023 identified 48 white particles (Major) , exceeding the limit of Major(b) (4) as defined in SOP P 4.7.1.2 , Preparation - Testing – Visual Inspection for Visible Particulate – All Compounded Preparations, Issue Date: 1/28/2020. The batch was released after a reinspection showed passing results, ; however, no investigation has been conducted for this OOS result.

OBSERVATION 4

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications designed to assure that conform to appropriate standards of identity, strength, quality and purity.

Specifically,

Your firm failed to provide scientific rationale to support established limits for subvisible particles in Avastin 2.5 mg/0.1 mL and Avastin 1.75mg/0.07mL. For example, your firm currently manufactures Lidocaine HCL 2% Injection and repackages Avastin 1.75mg/0.07 mL, both of which have been used for intravitreal injection, with examples of particulate matter testing described as follows:

• Avastin 1.75mg/0.07 mL (for intravitreal injection), Lot# (b) (4), Manufacturing Date: 7/9/2024, BUD: 10/7/2024. Specification for Particulate Matter:

(b) (4) particles/container
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• Lidocaine HCL 2% Injection, 0.4 m, Lot# (b) (4), Manufacturing Date: 7/24/2024, BUD: 10/24/2024. Specification for Particulate Matter:

(b) (4) particles/mL
(b) (4) particles/mL
(b) (4) particles/mL

However, particulate matter (b) (4) (Specification: (b) (4) particles/mL) is conducted only for Lidocaine HCL 2% Injection, but not for Avastin 1.75 mg/0.07 mL. Additionally, the specifications for particles (b) (4) differ between these products, with no scientific justification provided for this inconsistency.

OBSERVATION 5

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

Specifically,

A. No disinfectant efficacy testing has been conducted for the disinfectants used on supplies and work surfaces. Your firm uses (b) (4)) to disinfect all surfaces when transferring supplies from lower-grade to higher-grade areas. For example, on 9/17/2024, during the production of Avastin 1.75 mg/0.07 mL, Lot# (b) (4), it was observed operators uses (b) (4) to disinfect supplies to be introduced into the ISO 5 LAFWs. Also, (b) (4), and/or (b) (4) are used for routine cleaning in the ISO 5 LAFWs and cleanroom. However, no efficacy studies have been conducted for any of these disinfectants.

B. Cleaning of the ISO 5 LAFW was inadequate. Wires used to connect UV lights near the ceiling inside the ISO 5 LAFW were observed not being cleaned after batch processing. For example, on 9/18/2024, operators failed to clean these wires during the production of Avastin 1.75 mg/0.07 mL, Lot# (b) (4)

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(b) (4). Additionally, uncapped outlets on the ceiling of both LAFWs were present, making thorough cleaning difficult.

OBSERVATION 6

Complaint procedures are deficient in that they do not include provisions that allow for the review and determination of an investigation by the quality control unit.

Specifically,

Your firm failed to investigate customer complaints regarding syringes that were underfilled, empty, contained bubbles, or not tightly capped. For example, in 2024, your firm received ten complaints about underfilled syringes, four complaints about empty syringes, and four complaints about syringes with large bubbles. Your firm stated that all syringes had passed visual inspection and suggested the root cause might be improper use by customers. However, no documented investigations were conducted for any of these complaints, and no follow-up communications with customers were reported to verify improper syringe use, other than sending replacements.

OBSERVATION 7

Reserve drug product samples are not appropriately identified and representative of each lot or batch of drug product.

Specifically,

Your firm does not maintain retention samples for any finished product batches, nor has your firm established a procedure for the retention of such samples. For example, Your firm received five complaints of endophthalmitis associated with the use of Avastin in 2024 for the following:

- Avastin 2.5mg/0.1mL, Lot# (b) (4), Reporting Date: 2/2/2024

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- Avastin 2.5mg/0.1mL, Lot# (b) (4), Reporting Date: 2/2/2024
  (same lot for a different patient)

- Avastin 2.5mg/0.1mL, Lot # (b) (4), Reporting Date: 4/2/2024
- Avastin 2.5mg/0.1mL, Lot# (b) (4), Reporting Date: 7/29/2024
- Avastin 2.5mg/0.1mL, Lot# (b) (4), Reporting Date: 7/29/2024
  (same lot for a different patient)

The investigation did not reveal any deficiencies in the operations conducted at your facility, and no definitive root causes have been identified. However, your firm did not retain samples of the finished batch, resulting in no samples being available for further examination and/or testing during the complaint investigation.

OBSERVATION 8

Written production and process control procedures are not followed in the execution of production and process control functions.

Specifically,

The visual inspection of a finished batch fails to follow your procedures.

During the visual inspection of Avastin 1.75mg/0.07mL, Lot# (b) (4), BUD: 12/13/2024, it was observed the (b) (4) visual inspection operators did not (b) (4) the syringes for visual inspection, as required by SOP-43, 100% Visual Inspection, Version: 3.0, Effective Date: 7/10/2024. Section 5.4.5 of this SOP states "The syringes shall be carefully (b) (4) are visualized. (b) (4) the syringe can displace the particles and put them (b) (4), making them visible."

***DATES OF INSPECTION**

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9/17/2024(Tue), 9/18/2024(Wed), 9/19/2024(Thu), 9/20/2024(Fri), 9/23/2024(Mon), 9/24/2024(Tue), 9/25/2024(Wed), 9/26/2024(Thu), 9/27/2024(Fri)

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."