DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
19701 Fairchild Irvine, CA 92612-2445 (949)608-2900 Fax:(949)608-4417	3/20/2024-4/5/2024* FEI NUMBER 3013438582

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Harry R. Gill, Chief Quality Officer

FIRM NAME	STREET ADDRESS
Denver Solutions, LLC DBA Leiters Health	13796 Compark Blvd
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Englewood, CO 80112-7145	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

There is a failure to thoroughly review any unexplained discrepancy and 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.

This was a repeat observation from the 2021 FDA inspection

Specifically,

A. Investigation of potency testing out-of-specification (OOS) for finished products was inadequate.

Deviation D23637-DEN was initiated for the OOS report of Vancomycin HCL 1.5 g PF added to 0.9% Sodium Chloride 250 mL IV Bag, batch # (b) (4) failed release potency testing at 205% due to an IV bag being dosed twice, date of event: 10/19/2023. Also, D23382-DEN was initiated for OOS report of Oxytocin for injection, Lot# (b) (4) due to an IV bag with potency of 0% (non-dosed) during the stability study on Day (b) (4) date of event 12/4/2023. Your firm conducted an investigation by weighing whole batches to identify any potential OOS IV bags to be an outlier (approximately (b) (4) more than average weight). Three batches of vancomycin (batch# (b) (4)) produced from (b) (4) were released for distribution based on the weighing data; however, your OOS investigation was inadequate for the following:

- Your investigation of deviation D23637-DEN was insufficient as it concluded that there were no notable dosage irregularities regarding double-dosed and other non-dosed instances within three of your vancomycin batches (batch# (b) (4)), citing their representation of merely

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	Taichun Qin, Investigator X Taichun Qin Investigator Signed By: 2001324646 Date Signed: 04-05-2024 10:39:02	4/5/2024

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(b) (4) of the total batch size of (b) (4). However, sampling approximately few samples from a batch of approximately (b) (4) units lacks the statistical significance required to justify such a conclusion. For example, your firm took one to two random samples for release testing or stability testing and detected one sample double-dosed and the other non-dosed for (b) (4) different product batches.

- No deviation was initiated to address the inconsistencies discovered during the reconciliation of total units in batch records for three batches of vancomycin injection (batch# (b) (4), #(b) (4), #(b) (4)) in order to investigate the causes behind the discrepancies in the actual yield of units with batch # (b) (4) having more units, and batch #(b) (4), #(b) (4) having less units than the expected described as follows:

Reconciliation of total units in batch records for the three batches of vancomycin for injection with total units weighed for the same batch found apparent discrepancies

Batch Number	Expected units	Actual units	Differences
(b) (4)	(b) (4)		

- Your firm does not have adequate weight information of IV bags used in production (e.g. weight variations) to conclude your OOS investigation despite limited data available for samples weighed upon release of materials. Assessment of whether an unit is OOS is based on the weight of final products within assumed acceptance range.

B. Investigation into endotoxin testing OOS for finished products was inadequate described as follows:

- Your firm invalidated OOS # 22008-DEN for Bevacizumab 2.5 mg/0.1 mL (25mg/mL) Repackaged, Ophthalmic Injection, 0.1 mL in a 1 mL Syringe, Lot # (b) (4), dated 2/23/2022,

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regarding endotoxin levels by testing new sample vials and did not conduct testing on the original sample vial to determine whether the root cause stemmed from the tubes used in assay testing or the original sample itself. Despite your investigation finding that the likely root cause was low-level contamination of endotoxin in the test tubes used for the assay.

- Your firm invalidated the OOS results from your contract laboratory without adequate justification. For example, OOS 22015-DEN for Ketamine HCl (10 mg/mL) 5mL in a 5mL Syringe, Date: 6/23/2022 and OOS 23024-DEN for Ketamine HCl (10 mg/mL) 5mL in a 5mL Syringe, Lot # (b) (4), Date: 8/19/2023 showed initial OOS results in the contract laboratory, but passing results for in-house testing and/or from a second contract laboratory. Investigation from the first contract laboratory confirmed the initial OOS results, and the endotoxin test method for ketamine has been validated by that laboratory.

All three batches were released for distribution.

C. Your firm has received 6 unexpected adverse drug reaction (ADR) for endophthalmitis after use of Avastin and 4 ADRs after use of Moxifloxacin for injection since 2021. Investigations into each ADR could not identify definite root causes with no deficiencies being observed in the product and process; however, your firm did not conduct microbiology testing of retain samples during the investigation.

D. Since 2022, your firm has documented 19 OOS potency deviations linked to inaccurate tare weights. For example, on 4/20/2023, OOS # for Succinylcholine Chloride 20 mg/mL PF (from API), 10mL in 10mL BD Syringe, Batch #(b) (4), was reported with low potency, likely due to inaccurate tare weight. However, it was not until 4 months later, on 8/22/2023, that CAPA #23009 was initiated to address this issue. The CAPA remained open without valid justification during this inspection period. Consequently, your firm continued to report potency deviations associated with inaccurate tare weight (OOS# 24008, OOS# 24009 in 2024).

E. The alarms for non-viable particles in the ISO 5 aseptic processing area were not thoroughly

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investigated before batch release. For example, deviation (#D22272, dated 5/7/2022), during the filling of Ropivacaine for injection, Lot# (b) (4) , on 5/7/2022, stated "unknown FMS alarms persisted for approximately 5 minutes". The root cause of this occurrence remained undetermined; nevertheless, the batch was released based on environmental monitoring data, including units filled during the alarm period.

F. Your current visual inspection qualification does not cover some types of rejects identified and characterized from visual inspection in both syringes and vials described in the defect library found from the executed batches and identified later. A comparison of particle types in your defect library to the visual inspection (b) (4) in vials and syringes is described as follows:

Particle Type in Vial	Defect Library Entry	Current (b) (4) for Vial
Glass	DLR24019-VI-DEN	Yes
Steel	DLR22007-VI-DEN	No
Cellulose	DLR22037-VI-DEN	No
Polyester	DLR22039-VI-DEN	No
Dark Fiber	To be added	No
Light Fiber	To be added	No
Rubber	To be added	No
Silicone	To be added	No
Crack	To be added	No
Scratch	To be added	No

Particle Type in Syringe	Defect Library Entry	Current (b) (4) for Syringe
Dark Fiber	DLR23008-VI-DEN	Yes
Light Fiber	DLR22019-VI-DEN	Yes

Steel	DLR22014-VI-DEN	Yes
Silicone	DLR24021-VI-DEN	Yes
Cellulose	DLR24002-VI-DEN	No
Polyethylene	DLR24004-VI-DEN	No
Polypropylene	DLR23007-VI-DEN	No
Polyester	DLR23003-VI-DEN	No

However, your firm has not investigated these discrepancies and its impact on visual inspection qualifications.

OBSERVATION 2

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

This was a repeat observation from the 2021 FDA inspection

Specifically,

A. The smoke study performed in July 2023 in the ISO 5 LAFW - (b) (4) (Equipment ID: D-LFH-003) for syringe filling was inadequate for the following:

- The smoke did not cover sterile operations and worksurfaces simulating syringe production including removing syringe box covers and capping the syringes by an operator. The (b) (4) was placed too close to the entry of the ISO 5 LAFW during the dynamic smoke study, so non-unidirectional airflow went out of the hood below the protection glass without reaching operator's gloved hands and supplies.

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- There was a (b) (4) Syringe Filler placed in the center of the ISO 5 LAFW for syringe filling while operators perform aseptic processing including opening syringe boxes and capping syringes near this equipment on the left side and right side; however, your smoke study did not go near or behind the equipment to show impact on aseptic processing.

- The smoke study failed to show the impact on unidirectional airflow by the 6 inch horizontal gaps below the back and side walls of the ISO 5 LAFW, D-LFH-00. The smoke study shows airflow going out of the hood in the front; however, there was no smoke study showing airflow could exit gaps of other three sides to prevent airflow from the ISO 7 cleanroom entering the ISO 5 LAFW, equipment ID: D-LFH-003.

B. Deficiencies in your aseptic techniques were observed for the following:

- During the aseptic processing of Avastin for injection, lot # (b) (4) on 3/20/2024, it was observed the primary operator blocking first air during capping of sterile tip caps and open tray of (insert item). The operator used both gloved hands to cap two filled syringes simultaneously, reaching over the opened tray with exposed sterile tip caps. Also, production camera footage for Cyclopentolate HCl 1%-Tropicamide 1%-Phenylephrine HCl 2.5% (from API), Ophth Sol, 1 mL in 11 mL Dropper Bottle, lot# (b) (4) dated 3/18/2024 shows the primary operator's gloved hands reached over the opened tray during batch processing.

- During aseptic processing of Bevacizumab 2.75 mg/0.11 mL (25 mg/mL) Repackaged, Ophthalmic Injection, 0.11 mL in 0.25 mL Syringe, lot # (b) (4) on 3/20/2024, it was observed an primary operator moved his gloved hands fast inside the ISO 5 laminar flow hood while taking syringes out of a bag, placing filled syringes into a tray for capping, moving to a plastic box and sanitizing his gloved hands.

C. Your firm states that personal monitoring of operators with positive CFUs on sleeves is considered as low risk without affecting batch release per deviations investigations (e.g., DR # E022666-DEN). Since

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2022, your firm has reported 11 batches with CFU counts exceeding limit of (b) (4) from sleeves of primary operators including 3 batches of Avastin that have been (b) (4), 7 batches released and distributed and 1 pending investigation; however, it is observed operators sleeves could go inside the ISO 5 LAFW during routine aseptic processing. For example, Ropivacaine HCl 0.2% (2 mg/mL) (Injection) 545 mL fill in ON-Q, CB004, 400 mL, Batch # (b) (4) was released although the primary operator had growth on the second left sleeve sample.

OBSERVATION 3

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

Specifically,

Implementation of CAPA by your quality unit was inadequate for the following:

A. CAPA (# CAPA23037-DEN) was initiated on 12/14/2023 due to potential risk of bags being dosed twice. You action plan was (b) (4) (b) (4) to prevent a bag from being double-dosed; however, your estimated CAPA closure date has not been defined, and no action has been taken to date except that production of IV bags are temporarily ceased. Also, CAPA has not been opened for potential risk of bags not being dosed per Deviation # D237832-DEN. Your inspection could not identify the definite root cause for an IV bag being double-dosed or non-dosed as equipment malfunction or operators error given that the camera footage for production was only kept for (b) (4) prior to be removed, and videos for those batches were unavailable for review during the investigation; however, your CAPA does not have an action plan to address this issue.

B. Deviation # DR-D22367 dated 6/16/2022 reported a media fill failure with the root cause

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identified as placing the clean IV bag into a non-sterile (b) (4) that introduced organisms to the surface of the IV bag. Your firm took corrective and preventive actions including providing training of impacted personnel and updating SOP 0088 to add an additional step of sanitizing the IV bag surfaces with (b) (4) in addition to sporicidal disinfectants; however, this CAPA does not address prevention of contamination from the source of the contaminant – (b) (4) in the ISO 7 cleanroom used for weighing IV bags.

OBSERVATION 4

The written stability testing program is not followed.

Specifically,

Your firm used the extended BUD of 150 days without performing stability study on (b) (4) Avastin. Your firm has performed stability study to determine an extended BUD from 90 days to 150 days for Bevacizumab for injection; however, it has not been performed for Avastin for injection after (b) (4) (b) (4) of Avastin for injection was performed in the event of environmental monitoring excursion, equipment malfunction, etc; however, the stability study was inadequate as it was only conducted for 90 days but not for 150 days to support the newly assigned shelf life for the product after (b) (4) .

OBSERVATION 5

Written procedures are not followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically,

A. Camera footage dated 3/18/2024 shows an operator did not clean the LAFW interior surfaces under (b) (4) Syringe Filler on 3/18/2024 after completion of batch Avastin (b) (4) inside the ISO 5 LAFW. Your SOP - 0028 Use of The ISO 5 Laminar Flow Hoods, Revision Number 5 does not define

activities required to be performed for cleaning of hard-to-reach areas of the syringe filler.
B. On 3/28/2024, during production of Moxifloxacin 1 mg/mL PF in BSS, Intracameral Injection, 1 mL in 3 mL Syringe (Stability Batch), Lot # (b) (4), unknown brownish stains were observed at the joint of a non-viable particle counter stand.

OBSERVATION 6

The container of your outsourcing facility's drug products does not include information required by section 503B(a)(10)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Specifically,

Your containers do not include the following information:

a. The dosage form

Examples of your container labels that do not contain this information:

- Dexmedetomidine HCL NDC 71449-131-11 (F3151)
- Bevacizumab 2 mg/0.08 mL NDC 71449-091-98 (F1032

OBSERVATION 7

The labels of your outsourcing facility's drug products do not include information required by section 503B(a)(10)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Specifically,

The following information is not found on your drug product labels

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a.The dosage form

Examples of your drug product labels that do not contain this information:

- Dexmedetomidine HCL NDC71449-131-11 (F3151)
- Fentanyl Citrate PF NDC 71449-013-05 (F3054) label
- Morphine Sulfate PF 150 mg per 30 mL NDC 71149-022-32 (F3065)

***DATES OF INSPECTION**

3/20/2024(Wed), 3/21/2024(Thu), 3/22/2024(Fri), 3/25/2024(Mon), 3/26/2024(Tue), 3/27/2024(Wed), 3/28/2024(Thu), 3/29/2024(Fri), 4/01/2024(Mon), 4/02/2024(Tue), 4/03/2024(Wed), 4/04/2024(Thu), 4/05/2024(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."