

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 6th & Kipling St. (P.O. Box 25087) Denver, CO 80225-0087 (303) 236-3000 Fax: (303) 236-3100	DATE(S) OF INSPECTION 9/23/2021-10/7/2021*
	FEI NUMBER 3013438582

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Christopher F Zuccarelli, Chief Operating Officer

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

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.

For example:

a) Visual inspection results of filled syringes were found to contain extraneous unidentified visible materials (particles and fibers) during 100% visual inspection processes, but no timely investigations were opened to identify the foreign materials, determine root cause as to how visible substances are found in a drug that is (b) (4) and containerized/filled in a HEPA filtered (ISO 5) environment, and prevent recurrence. For example, the following lots were found with some syringes containing foreign substances:

i) Lidocaine Lot (b) (4) found 30 syringes with particles and 1 syringe with a fiber manufactured in March 2021.

ii) Phenylephrine Lot (b) (4) found 107 syringes containing particles and 17 syringes with fibers manufactured in February 2021.

iii) Fentanyl Citrate Lot (b) (4) found 20 syringes with particles and 25 syringes with fibers manufactured in January 2021.

iv) Bevacizumab Lot (b) (4) found 8 syringes with particles manufactured in April 2021.

b) A complaint (PC21106) received in June 2021 found, in a returned syringe, a fiber for Lot (b) (4) of Bevacizumab. Found in another returned syringe was a particle from Bevacizumab Lot (b) (4). Batch records record that Lot (b) (4) found particles during visual inspection and Lot (b) (4) found particles and fibers in

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visual inspection. The investigation did not result in any corrective/preventative actions. Other complaints were received with similar inquiries but resulted in no corrective/preventative actions:

- i) A complaint received in May 2021 (PC21090) reports the customer stated that they saw something floating in the syringe for Lot (b) (4) of Bevacizumab. The batch record shows visual inspection found two syringes with visible particulates.
- ii) A complaint received March 2020 (PC20039) reports a floating visible particle in a syringe of Bevacizumab Lot (b) (4). Batch record shows 19 syringes had visible particles during visual inspection.
- c) Deviation 21191 concerns environmental monitoring results from the sleeve of the Primary Operator involved in aseptic filling of Rocuronium into syringes on the (b) (4). Results were 1 CFU with the action limit being ^{(b) (4)}CFU, as the primary Operator works within the ISO 5 area of the filling operation conducting various interventions. The conclusion was that "Batch (b) (4) is not impacted by this event." As a result, this batch was released.
- d) Deviations, per SOP 002, Deviations-Planned And Unplanned, are not fully investigated unless like deviations occur more than (b) (4) period. For example, Deviation 21191 reads in part, on page 4, "A CAPA is not required as this is not a recurring deviation..." See item c) above.

OBSERVATION 2

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

- a) The Smoke Study performed for the (b) (4) (an open RABS) is not adequate to show all production areas have unidirectional airflow, as the Study shows detection of instances where there is turbulence.
- i) The Smoke Study for the (b) (4) shows that air (smoke) rises towards the ceiling in areas adjacent to the door that opens to the syringe bowl, and instead of air cascading towards the floor where uptakes are located, there

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is turbulence instead of unidirectional airflow. Turbulence is indicated in this area (Starting at 2:18 in the (b) (4) Smoke Study) where ISO 5 air meets ISO 7 air when this door is open, such as conducting set-up.

b) Disinfecting procedures (SOP 0090, Cleaning and Disinfection of ISO 7 and ISO 8 Areas and SOP 0088, Material Transfer) do not include an established contact time for (b) (4) in order to ensure disinfection. Procedures read that the application of (b) (4) should be "until dry" but this process gives varying time results, depending upon how much (b) (4) is applied. (b) (4) is used on surfaces and on gloved hands as a disinfectant.

c) Transfer of items from ISO 7 to ISO 5 are transferred directly in laminar flow hood (LFH) aseptic operations, and not fully in an aseptic manner. For example, bagged syringes and caps are wiped in ISO 7, placed on a table in ISO 7, then later transferred directly by a support Operator without an aseptic disinfecting step at the point of transfer from ISO 7 to ISO 5. Subsequently an Operator working in the ISO 5 LFH opens the bagged items that are placed into the hood. This was observed on 9/23/2021 during the filling of Midazolam.

d) On the (b) (4) the Operator must fully squat in order to set up the (b) (4), which is located on a shelf near the floor, which may result in bellowing of viable and non-viable particulate from gowning.

e) Chairs are located in LFH and (b) (4) ISO 7 areas. Operators fully sitting and then standing may result in bellowing of viable and non-viable particulate from gowning. An Operator was observed sitting at LFH 7 on 9/23/2021 while filling Midazolam Lot (b) (4).

f) Goggles used by Operators to protect against exposed skin in the ISO 7 areas during aseptic operations have built-in unprotected openings (holes) in the top, creating a lack of protection against a source of particles generated by, and microorganisms shed from, the body, having a potential affect on the sterile drug product during aseptic filling activities.

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g) On 9/28/2021 an Operator was observed in the ISO 7 of the (b) (4) during set-up with goggles not fully fitted, leaving a gap about a 1/4 inch in the lower portion of the goggles that could allow the shedding of particles into the controlled area.

h) On 9/28/2021 Operators were observed in the (b) (4) area disinfecting surfaces, such as bagged syringes and caps, prior to transfer of the contents into the RABS for filling. An Operator used the same surface of a single wipe over and over during disinfection of several bagged syringes. Also, an Operator used the same surface of a single section of another wipe over and over during disinfection of several bagged caps.

OBSERVATION 3

Aseptic processing areas are deficient regarding air supply that is (b) (4) through high-efficiency (b) (4) (b) (4) under positive pressure.

Specifically, ISO 5 hoods used for aseptic filling of compounded drug product are located in ISO 7 room (b) (4). A review of alarms for differential pressure readings in room (b) (4) for the first six months of 2021 indicated 2,738 alarms reported. Of these alarm conditions, 58 days of commercial compounding show conditions of negative pressure into room (b) (4). A total of (b) (4) commercial batches were filled on these 58 days. No investigations are performed when an alarm condition is recorded. No root cause for the condition is determined. No corrective action is taken to prevent reoccurrence.

OBSERVATION 4

Deviations from written production and process control procedures are not recorded.

Specifically,

a.) OOS 20007-DEN for potency of cyclopentolate/tropicamide/phenylephrine (CTP) batch (b) (4) was confirmed by the firm's contract laboratory. A root cause of a weighing error during production was determined. The firm did not complete a deviation investigation to determine corrective action.

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b.) OOS 21004-DEN for potency of CTP batch (b) (4) was confirmed by the firm's contract laboratory. A root cause of a weighing error during production was determined. The firm did not complete a deviation investigation to determine corrective action.

OBSERVATION 5

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

a) During aseptic operations within the RABS of the (b) (4) line, in ISO 5, where sterilized syringes and caps are brought together, filled and sealed, there is an absence of continuous monitoring of viable air in the immediate proximity of exposed syringes and caps in a quantity and location intended to optimize detection of potential viable environmental contamination during aseptic operations. There is only one location where continuous viable air is monitored within (b) (4) of RABS space, which is a location where the filling operation is.

b) There is no viable air monitoring of aseptic setup operations in the ISO 5 (b) (4).

OBSERVATION 6

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

When there is no scientific basis found for invalidating initial out-of-specification (OOS) test results and no assignable cause for the OOS is determined, procedures allow re-testing, which permits reporting additional analyses that meet specifications as the final result [SOP 0003, Out Of Specification Investigations, and per 2.1 of the procedure, "This procedure is applicable to OOS test results for any material or process controlled under specifications. This applies to release of raw materials, in-process, final product release, stability (including proposed shelf-life and accelerated studies), environmental and equipment OOS test results."]. Procedures in

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section 9.3.17 read in part, "If the preliminary investigation of the OOS result clearly demonstrates the result is attributable to indeterminate error, repeat the test (b) (4)
(b) (4) " And continues in section 9.3.18. "If repeat results (b) (4)
(b) (4) are within normal specification range (review historical result trend), record all repeat results on the investigation form. (b) (4) should perform a replacement retest on a new unit from the batch and report that result as part of the batch or process record. Indicate the material as passing the specification."

OBSERVATION 7

Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to the holding of rejected components, drug product containers, closures and labeling before disposition.

Specifically, on 09/23/2021 a portable cage marked "Rejected Materials" was observed to be unlocked and unattended. Several plastic bins were seen inside the cage with at least one containing compounded product.

***DATES OF INSPECTION**

9/23/2021(Thu), 9/24/2021(Fri), 9/27/2021(Mon), 9/28/2021(Tue), 10/01/2021(Fri), 10/07/2021(Thu)

Michael A Charles
Investigator - Dedicated Drug Cadre
Signed By: Michael A. Charles-S
Date Signed: 10-07-2021 10:21:48
X _____

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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."