DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612)334-4100 Fax:(612)334-4134	2/12/2024-3/1/2024* FEI NUMBER 3014483112

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Craig E. Else, Director and Chief Operating Officer

FIRM NAME	STREET ADDRESS
IntegraDose Compounding Services LLC	719 Kasota Ave Se
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Minneapolis, MN 55414-2842	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 WE OBSERVED:

Observation for the Quality System

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.

Specifically,

a) Your firm invalidated a positive sterility test result without a root cause identified for Cefazolin 2 Gram/20 ML Syringe for Injection, Batch# (b) (4), manufacturing date (MFG): 07/20/2022. Your contract testing laboratory stated they could not invalidate their result based on your response and their findings. Your investigation resulted in a batch rejection, but you failed to identify the root cause for the positive sterility test result and your firm did not implement any corrective actions within your facility in response to the test results.

b) During your firm's visual inspection of Cefazolin 3 Gram/30 mL in Sterile Water Syringe for Injection (Batch#(b) (4) MFG: 09/26/2022]), you initially identified 45 leaking syringes. During your re-inspection, you found 20 additional leaking syringes. There were 65 total leaking syringes for Batch# (b) (4) classified as critical defect units out of an actual yield of (b) (4) syringes for the batch. No investigation was initiated to determine the root cause of the 65 leaking container closure systems. Your firm disposed of the leaking container closure systems, and the remaining units from this batch were released by your Quality Unit on 10/05/2022. A change order was issued on 09/15/2022 to address fluid leaking in 30 mL cefazolin syringes. The change order states that

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Robert J Ham, Investigator Kevin P Regan, Investigator - GDUFA (Lead) Melissa M Steiger, Investigator	X Kevin P Regan Investigator - GDUFA (Lead) Signed By: 2003098957 Date Signed: 03-01-2024 12:19:35	3/1/2024

"By changing to a 50 mL syringe with final volume 30 mL it will potentially avoid the leaking which is suspected to occur from (b) (4)." After identifying 65 leaking finished products in Batch# (b) (4) your firm continued to manufacture / release eight 30 mL syringe batches before changing to the 50 mL syringes per your change order:

Production Date	Batch#	Released Date
(b) (4)	(b) (4)	(b) (4)

Leaking was still discovered in an incident (non-investigative event) for (b) (4) [MFG: (b) (4):

Incident #	Batch#	Description
INC-0797	(b) (4) MFG: (b) (4)	"1 sterility sample leaking. Relpaced [sic] with 1 unit from conforming inventory."

Additionally, at the time of this leaking event on 09/26/2022, you had two batches ((b) (4) [MFG: 09/12/2022], (b) (4) [MFG: 08/22/2022]) of this product that were released and still within your established BUD.

c) Your firm lacks investigations into personnel monitoring growth during production. A spore-forming

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bacterium was identified on an ISO-5 technician's forearm during the production of Batch# (b) (4) MFG: 06/23/2023. Since 01/2022, there have been two other incidents (non-investigative events) of forearm PM personnel growth (Batch# (b) (4) [MFG: 02/06/2023], Batch# (b) (4) [MFG: 04/03/2023]), one incident of forehead personnel growth (Batch# (b) (4) [MFG 09/25/2023]), and one incident of both forearm and forehead growth (Batch# (b) (4) [MFG: 08/09/2022]). We observed personnel breaches of the forearms and foreheads in the ISO-5 during our video review of production. All of these batches were released.

d) Your firm fails to investigate leaks in the container closure system of Fentanyl Citrate 2500 mcg/50 mL, CADD for Injection during production. There were five separate batches (Batch# (b) (4) [MFG: 10/20/2023], Batch# (b) (4) [MFG: 07/11/2023], Batch# (b) (4) [MFG: 12/29/2022], Batch# (b) (4) [MFG: 11/22/2022], Batch# (b) (4) [MFG: 07/01/2022]) where a CADD was found to be leaking during production. Your firm only logged an incident (non-investigative event) to account for the leak. Your firm does not include these non-conforming units in your visual inspection calculations, rather the CADD is just discarded. All of these batches were released.

e) Since 01/2022, your firm has had over 30 documented incidents (non-investigative event) of leaking (b) (4) bags during production of cefazolin syringes. The following descriptions were included in a sample of these:

Incident #	Batch#	Description
INC-0453, INC 0454	(b) (4) MFG: 06/22/2022	"Bag (b) (4) and bag (b) (4) began leaking at the seam prior to shaking. Bag (b) (4) leak discovered during filling, no final weight recorded." and "Bag (b) (4) leaking at the seam."
INC-0698	(b) (4) MFG: 08/29/2022	"Bag (b) (4) leaking from seam."

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INC-2250	(b) (4) MFG: 11/17/2023	"Bag leaked while Shaking/mixing"

f) During our visual inspection of finished product on 2/16/2024, we found white particulate matter on the outside of syringes near the needle port of Cefazolin 3 Gram/30 mL, Syringe for Injection (Batch# (b) (4) [MFG: 01/26/2024]) and Cefazolin 2 Gram/20 mL, Syringe for Injection (Lot# 2(b) (4) [MFG: 01/10/2024]). You have failed to establish a root cause and identification for this observed white particulate matter.

g) Your firm fails to investigate all incidents that impact the final product. Specifically in Event Investigation EV-1699, described as "Hydromorphone HCl and Fentanyl Citrate CADD release testing samples were received by lab with liquid in the pack bags: (b) (4) and (b) (4) ": there was no investigation into the potential overfilling of the CADDs and the potentially overfilled CADDs were released with the batch; there was no formal retraining for the shipper who packaged room temperature lots in ice, and there is no procedure on how to address potential damage and leaks caused by shipping.

Observation for the Production System

OBSERVATION 2
Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written and followed.

Specifically,

Repeat observation from FDA inspections ending on 09/19/2018 and 08/02/2021

a) Dynamic smoke studies performed in the ISO-5 hoods are not representative of conditions observed during production. We observed the production of Fentanyl Citrate 400 mcg/200 mL + Ropivacaine HCl

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200 mg/200 mL in 0.9% Sodium Chloride, CADD for Injection on 02/13/2024 (Batch# (b) (4) (b) (4) and reviewed video of production on 01/23/2024 (Batch# (b) (4) [MFG: 01/23/2024]). Your firm has only conducted dynamic smoke studies on smaller cassettes (50 mL) compared to the larger cassettes (200 mL) observed. We observed that the production process had far more obstructions to airflow in the ISO-5 hood with stacked container closures systems than you challenged in the dynamic smoke studies of the small cassettes. Batch# (b) (4) was released by your Quality Unit on 02/05/2024.

b) Your firm does not have a dedicated garbing area for cleanroom operations. Your garbing area acts as a centralized ISO-8 corridor with access to (b) (4) ISO-7 production suites (b) (4) and the cefazolin visual inspection room (b) (4). We reviewed video of your firm's garbing from 02/14/2024 that shows ungloved staff approximately two feet from garbed technicians.

c) On 02/13/2024, we observed that (b) (4) Pair gloves were being used in direct contact with sterile filling operations within the ISO-5 hoods in (b) (4) and (b) (4) Your vendor qualification/incoming material controls did not include appropriate assessment of the gloves for use in aseptic operations. The Certificate of Compliance / Sterility for the gloves doesn't include expiration dates.

d) We reviewed production videos of Fentanyl Citrate + Ropivacaine HCl 200 CADD for Injection (Batch# (b) (4) [MFG: 01/23/2024]), as well as Fentanyl Citrate 2500 mcg/50 mL CADD for Injection (Batch# (b) (4) [MFG: 01/12/2024]). We observed the following during aseptic operations:

i) Compounding technicians will open the door to (b) (4) (ISO-8 area) during production to receive materials from non-production garbed individuals. Your firm does not always utilize your dedicated material (b) (4).

ii) The entrance door to (b) (4) (ISO-8 area) in (b) (4) (ISO-7 area) was left fully open for 20 seconds during production to move out environmental monitoring equipment at 11:10 AM on 01/23/2024.

iii) From 9:52:29 AM to 9:53:52 AM in (b) (4) during the production of Batch# (b) (4) a

compounding technician completely leaves the ISO-7 area to the ISO-8 during active production for well over a minute and then reenters. No personnel sampling was conducted after leaving and reentering the ISO 7 cleanroom during active production.

iv) At approximately 1:53 PM during production of Batch# (b) (4) in room (b) (4) the compounding technicians begin fully cleaning one production hood ((b) (4)) while production is still going on at the other hood (b) (4) which results in clutter and increased people near ongoing filling.

v) Production supplies travel directly from ISO-7 to ISO-5 without sanitization. Your firm stated that the last line of sanitization is in the ISO-8 area (b) (4)

vi) We observed the production tablet within the ISO-5 hood (Hood (b) (4) on 1/12/2024 at 9:07:11 AM.

Observation for the Production System

OBSERVATION 3

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

Specifically,

Repeat observation from FDA inspection ending 08/02/2021

a) Your firm only monitors non-viable particles in your ISO-5 hoods for production on (b) (4) basis.

b) Your firm only monitors active viable air within your ISO-5 hoods for production on (b) (4) basis.

c) We observed the following during our review of your firm's dynamic smoke studies:

i) Adequate smoke is not being used to assess airflow during all dynamic operations. Additionally,

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angles of certain smoke study videos prevent proper assessment of airflow.
ii) Components in the hood are touching the back HEPA filter grate.
iii) Movements by the operator during the smoke study are fast and turbulent.

Observation for the Production System

OBSERVATION 4

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

Specifically,

Repeat observation from FDA inspection ending 08/02/2021

a) We reviewed video of (b) (4) cleaning within room (b) (4) performed on 01/19/2024, as well as in (b) (4) performed on 01/12/2024. Your (b) (4) cleanings of the walls and ceilings are conducted by an external contractor. The following was observed:

i) The cleaner only submerses the mop once outside of the ISO-7 room to fully clean the entirety of the walls. This was observed in both (b) (4) and (b) (4).
ii) The cleaner did not move the large utility cart to clean the wall behind it in both production suites in both (b) (4) and (b) (4).
iii) While sticky rolling the floor in (b) (4), the cleaner only sticky rolled half of the floor.

b) During a walk-through of the ISO 8 areas on 2/14/2024, it was observed you had approximately 8 sprinkler head covers with chipped/rubbed off paint; there were rust marks trailing on the floor in (b) (4) two chairs in the ISO 8 area had rust on them; HEPA return vent covers in (b) (4) had chipped paint; and chipped paint on a support column next to the visual inspection table in (b) (4).

Observation for the Quality System

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OBSERVATION 5

Your firm failed to establish adequate written procedures for production and process controls designed to assure that the drug products have the identity, strength, purity, and quality that they are purported or represented to possess.

Specifically,

Your firm has not performed process validation for your drug products. You have made the following products since Summer 2022:

Product	Batches Made
Cefazolin 2G in 30 mL Syringe for Injection	(b) (4)
Cefazolin 3G in 30 mL Syringe for Injection	
Cefazolin 3G in 30 mL Syringe for Injection (50 mL syr)	
Ephedrine Sulfate 25 mg/5 mL in 0.9% Sodium Chloride Syringe for Injection:	
Fentanyl Citrate 2500mcg/50mL CADD for Injection	
Hydromorphone HCl 20mg/100mL CADD for Injection	
Oxytocin 30 Units in 0.9% Sodium Chloride Bag for Injection	
Vasopressin 2 Units per 2ml syringe for inj	
Fentanyl Citrate 400 mcg/200 mL + Ropivacaine HCl 200 mg/200 mL CADD mg/200 mL in 0.9% Sodium Chloride	
Fentanyl Citrate 400 mcg/200 mL + Ropivacaine HCl 200 mg/200 mL Bag mg/200 mL in 0.9% Sodium Chloride	
Bupivacaine HCl 0.25% + Epinephrine 1:200,000 30 mL Vial	
Bupivacaine HCl 0.5% + Epinephrine 1:200,000 30 mL Vial	

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We reviewed the current status of your ongoing recall (D-0258-2024) for Vasopressin 2 Units / 2 mL in 0.9% Sodium Chloride which includes nine sub-potent batches within your 180-day BUD that failed from 67 to 109 days after production. All of these sub-potent batches were the initial batches of a process change from using a (b) (4) pump (100 syringe units) to a repeater pump (400 syringe units). Your firm's change request form only states that "Change in process is minor but requires review of updated process training for production staff" for this process change. The root cause of your recall investigation is still ongoing.

Observation for the Production System

OBSERVATION 6

The control systems necessary to prevent contamination or mix-ups are deficient.

Specifically,

a) Your firm lacks a risk assessment / mitigation strategy for spills of non-penicillin beta-lactam liquid (cefazolin) within your ISO-5 compounding hood in suite (b) (4). Your firm's spill clean-up procedure is non-specific to the type of spill and contains no mention of a deactivating agent.

b) During our visual inspection of finished product on 2/16/2024, we found unidentified white particulate matter on the outside of syringes near the needle port of Cefazolin 3 Gram/30 mL, Syringe for Injection (Batch# 20240126CEF(b) (4) [MFG: (b) (4)]) and Cefazolin 2 Gram/20 mL, Syringe for Injection (Lot# 20240110CEF(b) (4) [MFG: (b) (4)). These two batches were released.

c) We reviewed video of visual inspection of cefazolin syringes conducted on 02/12/2024. Your firm isn't properly using (b) (4) per your training and visual inspection protocol. The visual inspectors are trained differently than what is conducted during production visual inspection. We observed during video review that the inspectors are either not using (b) (4) since they are (b) (4), or (b) (4) is nearly fully obstructed by syringes on it.

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Observation for the Quality System

OBSERVATION 7

The quality control unit lacks responsibility to approve all procedures or specifications impacting on the identity, strength, quality and purity of drug products.

Specifically,

a) Training SOPs reviewed on 02/14/2024 are lacking refresher training frequencies. Refresher training is being conducted on competencies such as "Garbing" but is not specifically written in an SOP. Additionally, training records reviewed on 02/14/2024 were missing signatures by trainers and Quality Unit in both employee binders that were reviewed.

b) After reviewing Certificates of Validation for Rapid Sterility on all products currently being compounded onsite on 02/20/2024, it was observed your firm failed to adequately assess the use of rapid sterility for your products including but not limited to reviewing the validation, reviewing the method for acceptability of use, and reviewing the equivalency testing to USP <71> for the release of all final products using rapid sterility.

OBSERVATION 8

Your outsourcing facility did not submit a report to FDA identifying the drugs compounded during the previous six month period.

Specifically,

The following products were compounded but were not reported in your December 2023 product report:

a) Bupivacaine HCl 0.25% + Epinephrine 1:200,000, 30 mL Vial for Injection
b) Bupivacaine HCl 0.5% + Epinephrine 1:200,000, 30 mL Vial for Injection

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*DATES OF INSPECTION

2/12/2024(Mon), 2/13/2024(Tue), 2/14/2024(Wed), 2/15/2024(Thu), 2/16/2024(Fri), 2/20/2024(Tue), 2/21/2024(Wed), 2/29/2024(Thu), 3/01/2024(Fri)

X Melissa M Steiger
Investigator
Signed By: Melissa M. Steiger -S
Date Signed: 03-01-2024 12:19:58

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Robert J Ham, Investigator
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Melissa M Steiger, Investigator

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Signed By: 2003098957
Date Signed: 03-01-2024 12:19:35

DATE ISSUED
3/1/2024

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."