

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

DISTRICT ADDRESS AND PHONE NUMBER 300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax: (313) 393-8139	DATE(S) OF INSPECTION 9/10/2018-9/19/2018* FEI NUMBER 3014483112
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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED Craig E. Else, Director

FIRM NAME IntegraDose Compounding Services LLC	STREET ADDRESS 719 Kasota Ave Se
CITY, STATE, ZIP CODE, COUNTRY Minneapolis, MN 55414-2842	TYPE ESTABLISHMENT INSPECTED 503B 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:
PRODUCTION SYSTEM**

OBSERVATION 1

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,

Your firm received the following out-of-specification results for release testing and did not identify a laboratory error or root cause, and released product based solely on retesting.

For example:

Ephedrine Sulfate 25mg/5mL in 0.9% Sodium Chloride Syringe for Injection Lot 20180228EPH-1, produced on 2/28/2018, received a "Positive -(b) (4)" result (specification "Negative at (b) (4)") on 3/7/2018, which indicates possible microbiological contamination. This lot was released for distribution on 4/23/18 without adequate investigation into the sterility failure.

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Hydromorphone 1MG/ML 0.2ML syringe for injection Lot 20171025HYD-1, produced on 10/25/2017, received the following potency results:

132.6% (specification (b) (4) %) on 11/6/2017
 135.9% (specification (b) (4) %) on 11/15/2017
 136.7% (specification (b) (4) %) on 11/15/2017
 This lot was released for distribution on 11/27/2017.

Hydromorphone 0.5mg/0.5mL in 0.9% Sodium Chloride Syringe for Injection (Concentration 1mg/mL) Lot 20171219HYD-1, produced on 12/19/2017, received the following potency results:

130.1% (specification (b) (4)) on 12/22/2017
 127.9% (specification (b) (4) %) on 01/02/2018
 127.8% (specification (b) (4) %) on 01/02/2018
 This lot was released for distribution on 1/17/2018.

Hydromorphone Hydrochloride 0.2mg/0.2mL in 0.9% Sodium Chloride Syringe for Injection (Concentration 1mg/mL), Lot 20180123HYD-2, produced on 01/23/2018 received the following potency results:

94.8% (specification (b) (4) %) on 1/26/2018
 93.8% (specification (b) (4) %) on 2/1/2018
 93.6% (specification (b) (4) %) on 2/1/2018

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This lot was released for distribution on 2/22/2018.

Hydromorphone Hydrochloride 0.2mg/0.2mL in 0.9% Sodium Chloride Syringe for Injection (Concentration 1mg/mL), Lot 20180124HYD-2 received a potency result of 94.8% (specification (b) (4) (b) (4) %) on 1/26/2018. This lot was released for distribution on 2/22/2018.

Hydromorphone Hydrochloride 0.2mg/0.2mL in 0.9% Sodium Chloride Syringe for Injection (Concentration 1mg/mL), Lot 20180329HYD-2, produced on 03/29/2018 received the following potency results:

106.5% (specification (b) (4) %) on 4/10/2018

106.4% (specification (b) (4) %) on 4/17/2018

106.4% (specification (b) (4) %) on 4/17/2018

This lot was released for distribution on 4/20/2018.

Hydromorphone Hydrochloride 0.5mg/0.5mL in 0.9% Sodium Chloride Syringe for Injection (Concentration 1mg/mL), Lot 20180531HYD-1, produced on 05/31/2018, received a potency result of 106.7% (specification (b) (4)) on 6/8/2018. This lot was released for distribution on 6/26/2018.

OBSERVATION 2

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

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Specifically,

(A) Your firm does not conduct media fills or process simulations, at least (b) (4), for each operator, that also include: stressful/challenging conditions, all possible interventions (planned or unplanned), or simulations of the maximum number of persons allowed in the clean room.

For example:

- (1) Only (b) (4) media fill lot (out of (b) (4) attempted since February 2016), has been successfully completed and representative of syringe production conditions. The other syringe Media Fill failed, and the (b) (4) Media Fill lots for IV bag production have either failed sterility testing or are not representative of production practices.
- (2) Individual Media Fills performed by personnel are limited to (b) (4) syringe units and not representative of production quantities. For example, Lot 20180115CEF-2, produced on 1/15/2018, filled (b) (4) IV bags of drug product. This lot was released for distribution on 2/7/18.

(B) During production of Phenylephrine Hydrochloride, Lot 20180911PHE-2, produced on 9/11/2018, I observed a pharmaceutical technician leaning into the ISO-5 hood with her elbows and forearms placed on the table inside the ISO-5 processing space.

LABORATORY SYSTEM

OBSERVATION 3

Test devices are deficient in that instruments not meeting established specifications are used.

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Specifically,

The "room-temperature" incubator, equipment ID (b) (4), is not qualified for your intended use. This incubator was initially qualified on 1/27/2016 for incubating personal and surface samples collected as part of your environmental monitoring program. On November 17, 2017, your firm initiated an investigation of "ice buildup" in the incubator and concluded that the unit is functioning as expected but would require regular thawing/defrosting. Since November of 2017, no initial or ongoing operational or performance qualification was performed to ensure that, despite the presence of ice, this incubator could store environmental monitoring samples at optimum temperatures, per USP, to promote growth.

QUALITY SYSTEM

OBSERVATION 4

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

Specifically,

Procedure PQ5085 Deviation Management does not require a time line for the resolution of deviations. Additionally, this procedure states that "[b]ased on the event and severity of impact, the deviation report is closed or elevated to a CAPA for additional investigation along with corrective and/or preventive actions. Approximately 37 Deviations from 2017 and 25 Deviations from 2018 remain open despite that your firm's QA manager has not elevated these deviations to a CAPA.

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FACILITIES AND EQUIPMENT SYSTEM

OBSERVATION 5

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

Specifically,

Smoke studies performed of the ISO-5 hoods were not representative of conditions observed during production. Smoke studies consisted of (b) (4) operators slowly waving their hands, one of whom was not holding any equipment, for (b) (4). Equipment such as large hanging IV bags, packaging, stoppers, vials, caps, and pumps were observed inside the ISO-5 processing area during production of Lots 20180911PHE-2 on 9/11/2018 and 20180918FEN-1 on 9/18/18.

OBSERVATION 6

There is a lack of written procedures describing in sufficient detail the methods, equipment and materials to be used for sanitation.

Specifically,

During production of Phenylephrine Hydrochloride, Lot 20180911PHE, on 9/11/2018, I observed the following:

- While wiping materials for entry into the ISO-7 space, a technician dropped a bottle of (b) (4) on the floor and used the same gloves to pick it up and continue wiping materials, without re-sanitizing her gloves or

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the bottle.

- While cleaning the ISO-5 hoods in preparation for compounding, I observed a technician hang cleaning bottles on the sides of garbage can and repeatedly touch the garbage can in between wiping down the inside of the ISO-5 without sanitizing her hands.

Your firm's SOPs PQ-5050 Product Lifecycle; EV-5005.1 Cleanroom Entry, Garbing, Hand Hygiene; or EQ-5065.1 PECs - Hoods, Use and Cleaning do not describe how to handle cleaning products or items dropped on the floor during the material process steps, nor do these procedures describe where to store cleaning bottles inside the ISO-7 area while preparing the hoods for production.

***DATES OF INSPECTION**

9/10/2018(Mon), 9/11/2018(Tue), 9/12/2018(Wed), 9/13/2018(Thu), 9/14/2018(Fri), 9/17/2018(Mon), 9/18/2018(Tue), 9/19/2018(Wed)

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Annotations to Observations

Observation 1: Not annotated

Observation 2: Not annotated

Observation 3: Not annotated

Observation 4: Not annotated

Observation 5: Not annotated

Observation 6: Not annotated

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