

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

DISTRICT ADDRESS AND PHONE NUMBER

10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054
(973)331-4900 Fax: (973)331-4969

DATE(S) OF INSPECTION

4/18/2016-5/26/2016*

FEI NUMBER

2242985

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Walter T. Kelso, Plant Manager

FIRM NAME

PharMEDium Services, LLC

STREET ADDRESS

36 Stults Road

CITY, STATE, ZIP CODE, COUNTRY

Dayton, NJ 08810

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 WE OBSERVED:

OBSERVATION 1

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

Specifically, there is no assurance that the ISO-5 (b) (4) laminar flow hoods and ISO-7 Clean Room, which are used to fill sterile drug products, continually provide an adequate environment.

- a. A (b) (4) check of the "mini helic gauge" that measures differential pressure across the HEPA filters providing "first air" in the (b) (4) ISO-5 hoods is documented by the technician's initials, signifying "hoods are operating within an indicated range of (b) (4) of W.C on the magnehelic pressure gauge." No pressure value is recorded. The supplier of the hoods describes the uncalibrated gauge is for reference use only, as an indicator for filter loading, suggesting a gauge reading between (b) (4) and that "When the reading on the gauge (b) (4) (b) (4) by (b) (4) % of what it read at certification...the certifier (b) (4) (b) (4) (b) (4) There is no other mechanism that captures differential pressure data for the hood filters, and a range of (b) (4) WC allows more than (b) (4) % fluctuation.
- b. There are approximately (b) (4) (b) (4) HEPA units supplying filtered air throughout the approximate (b) (4) square-foot ISO-7 Clean Room, but these are not periodically monitored to ensure they are all continuously functioning. There is no assurance that all units are currently operational, as routine performance is measured by maintenance of positive pressure (b) (4) (b) (4)
- c. A positive pressure cascade is not continuously maintained from the ISO-7 Clean Room to the

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Barbara J Wilimczyk-Macri, Investigator
Nicholas A Violand, Investigator
Mina Ahmadi, FDA Center Employee or
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surrounding areas (b) (4) the first two of which connect to unclassified areas). Pressure data is captured (b) (4) and the (b) (4) system has (b) (4) readings below the (b) (4) limit, of which approximately 130 show negative pressure readings, between 10/01/2015 and 05/03/2016. The system will only alarm if this differential drops below (b) (4) which does not appear to be scientifically justified. There are no recorded alarms for this despite data showing loss of pressure for periods as long as 12 consecutive minutes (pressure readings ranging from -0.001" to (b) (4)). Investigations have not been performed for any pressure differential excursions.

- d. Smoke studies have been performed in both the ISO-7 Clean Room and in (b) (4) of the ISO-5 hoods under dynamic conditions to demonstrate airflow patterns and unidirectional airflow continuity, respectively. However, dynamic conditions do not represent routine operations, in that (b) (4) performed filling, and disruption of laminar flow was only challenged by (b) (4). On (b) (4), we observed routine movement of personnel and carts behind technicians actively working in the hoods, with as many as (b) (4) personnel working (b) (4). In addition, smoke studies did not demonstrate that air consistently flows from the ISO-7 Clean Room to surrounding areas when doors are opened and personnel are walking near the doors.

OBSERVATION 2.

Each batch of drug product purporting to be sterile and pyrogen-free is not laboratory tested to determine conformance to such requirements.

Specifically, testing of finished product is deficient in that:

- a. Sterility testing is not performed for each batch of finished drug product produced. Approximately (b) (4) of (b) (4) batches produced since October 2015 have been submitted for testing. Sterility testing has not been performed for products such as Epinephrine, Furosemide,

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Norepinephrine, Ondansetron, Phenylephrine, Potassium Acetate, and Vecuronium, which may be filled in IV bags or syringes in various strengths.

- b. Sterility samples from batches produced in October 2015, December 2015, and January 2016 were not submitted for testing as per SOP CPS-775, On-Going Sterility/Endotoxin Monitoring Program.
- c. Approximately (b) (4) of (b) (4) batches submitted for sterility testing since November of 2015 do not have completed results. Since October 2015, the sterility test results for approximately (b) (4) of (b) (4) batches submitted were received after the product had expired and been released.
- d. Potency testing is not performed (b) (4) the latter of which (b) (4) batches are tested (b) (4)

OBSERVATION 3

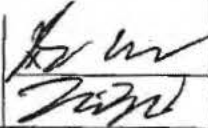
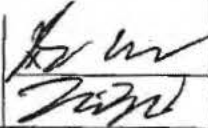
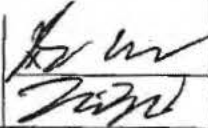
Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the equipment to produce aseptic conditions.

Specifically, (b) (4) is defined in procedure CPS-301, Facility Cleaning, as an effective sporicide used to clean the ISO-5 and ISO-7 environments (b) (4). There is no scientific justification to support the effectiveness of (b) (4) as a sporicide for the minimum contact time of (b) (4), as defined in the procedure.

OBSERVATION 4

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

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Specifically, a. Performance of 100% visual inspection of finished sterile drug products for particulate matter is not performed against a dark and light background for visualization of various types of particles throughout the filled container. There is no defined process that establishes details such as minimum time of inspection per unit for IV bags and syringes, and whether to swirl or invert the unit. b. There is currently no qualification process for personnel performing the visual inspection process to assess visual acuity and ability to detect defects and particles. Additionally, a representative library of potential defects is not used in training activities.							
OBSERVATION 5 Each lot of components and drug product containers is not withheld from use until the lot has been sampled, tested, examined, and released by the quality control unit. Specifically, incoming physical components that are received as sterile and (b) (4) within the (b) (4) inventory control system. There is no sampling or routine review and approval of the supplier's Certificate of Analysis to ensure critical attributes such as sterility or integrity. For example, the following items are routinely received in this manner: a. (b) (4) IV bags (b) (4) and finished product storage b. (b) (4) syringes c. (b) (4) tube sets							
OBSERVATION 6 Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not written and followed.							
SEE REVERSE OF THIS PAGE		<table border="0" style="width: 100%;"> <tr> <td style="width: 60%; vertical-align: top;"> EMPLOYEE(S) SIGNATURE Barbara J Wilimczyk-Macri, Investigator Nicholas A Violand, Investigator Mina Ahmadi, FDA Center Employee or Employee of Other Federal Agencies </td> <td style="width: 40%; vertical-align: top; text-align: center;">  </td> </tr> <tr> <td colspan="2" style="text-align: right; vertical-align: top;"> DATE ISSUED 5/26/2016 </td> </tr> </table>		EMPLOYEE(S) SIGNATURE Barbara J Wilimczyk-Macri, Investigator Nicholas A Violand, Investigator Mina Ahmadi, FDA Center Employee or Employee of Other Federal Agencies		DATE ISSUED 5/26/2016	
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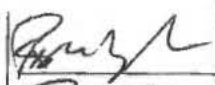
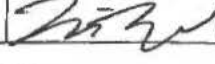
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Specifically,

- a. On 4/20/2016, an employee was observed picking up a filled syringe of Buffered Lidocaine 1% in Sodium Bicarbonate 8.4% 5 mL Total volume, Lot #161110022D, which had fallen on the floor of the ISO-7 Clean Room. The employee was observed sanitizing the outside of the syringe with a cleaning wipe and then placing the syringe in the gray tote of accepted product, containing an unknown quantity of already-filled units. Although management stated the batch would be destroyed due to handling uncertainty, the batch was inadvertently released on 4/20/2016, after approximately 3 syringes were rejected for falling on the floor.
- b. Paper batch records are used in the ISO-7 Clean Room to document processes by the employees, are (b) (4) next to components or materials that have already been (b) (4). There is no assurance that these do not shed particles or microorganisms, as the records are not sanitized or prepared in any way before they are brought into the ISO-7 Clean Room from the unclassified prep/staging areas.
- c. (b) (4), which are not easily cleanable/sanitizable surfaces, are used in the ISO-7 Clean Room, and (b) (4) next to components being transferred into the ISO-5 environment. On 4/18/2016, we observed (b) (4) being used inside Hood (b) (4) to (b) (4) that had already been (b) (4).
- d. (b) (4) near the ISO-5 hoods in the ISO-7 Clean Room. On 4/19/2016, we observed technicians transfer IV bags into the ISO-5 hood by placing the bottom of the (b) (4) on their chest, and with a forward motion into the hood, dropping the IV bags. There is no assurance this technique does not disrupt the airflow within the hood since this action was not challenged during dynamic smoke studies, or that this technique does not transfer bioburden into the hood.

OBSERVATION 7

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

Specifically, environmental monitoring is not performed at sufficient frequencies that represent routine manufacturing conditions within the ISO-7 Clean Room or ISO-5 (b) (4) laminar flow hoods, nor at times that represent the most challenging conditions. For example:

- a. Surface monitoring for viable microorganisms is frequently performed (b) (4) though manufacturing routinely occurs (b) (4) (b) (4).
- b. Personnel monitoring is not performed after every batch of drug product produced, or prior to glove changes.
- c. The documentation for the (b) (4) surface monitoring of the door, wall, cart, and tote within the ISO-7 Clean Room does not include the specific locations sampled.
- d. The (b) (4) monitoring of floor surface samples of the ISO-7 Clean Room does not include the documentation of specific locations. Locations are described as being in (b) (4) within the (b) (4)-square-foot clean room.
- e. Non-viable air (particulate) monitoring of the ISO-5 hoods is performed (b) (4). This is described as being performed under dynamic conditions, but the time of collection is not captured to demonstrate this.
- f. Non-viable air monitoring of the ISO-7 Clean Room is not performed routinely, it is performed (b) (4). The time of collection is not being captured.

OBSERVATION 8

Clothing of personnel engaged in the manufacturing and processing of drug products is not appropriate for the duties they perform.

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Specifically, on 4/18/2016, we observed a technician walking around the gowning room holding their unwrapped sterile gown. Before donning, the gown touched the garbage can and the wall.

OBSERVATION 9

The labels of your outsourcing facility's drug products do not include information required by section 503B(a)(10)(A). Specifically, the following information is not found on some of your drug product labels required per 503B(a)(10)(A):

A. The statement "This is a compounded drug."

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

- Oxytocin 30 units added to 500 mL 5% Dextrose/Lactated Ringer's USP
- Calcium Gluconate 4 g (16 mg per mL) 250 mL Total Volume in Sodium Chloride 0.9%
- Buffered Lidocaine 1% in Sodium Bicarbonate 8.4% 5 mL Total Volume
- 4% Sodium Citrate 40 mg per mL (120 mg per 3 mL) 3 mL Total Volume
- Sodium Phosphate added to 0.9% Sodium Chloride 10 mMol 100 mL Bag

B. The dosage form.

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

- Oxytocin 30 units added to 500 mL 5% Dextrose/Lactated Ringer's USP
- Calcium Gluconate 4 g (16 mg per mL) 250 mL Total Volume in Sodium Chloride 0.9%
- Buffered Lidocaine 1% in Sodium Bicarbonate 8.4% 5 mL Total Volume
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C. The strengths of lidocaine and sodium bicarbonate on the label for Buffered Lidocaine product appear to be inaccurate (i.e., there is less than 1% of lidocaine and 8.4% of sodium bicarbonate in the final product).

D. The date that the drug was compounded.

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

- Oxytocin 30 units added to 500 mL 5% Dextrose/Lactated Ringer's USP
- Calcium Gluconate 4 g (16 mg per mL) 250 mL Total Volume in Sodium Chloride 0.9%
- Buffered Lidocaine 1% in Sodium Bicarbonate 8.4% 5 mL Total Volume
- 4% Sodium Citrate 40 mg per mL (120 mg per 3 mL) 3 mL Total Volume
- Sodium Phosphate added to 0.9% Sodium Chloride 10 mMol 100 mL Bag

E. The inactive ingredients, identified by established name and the quantity or proportion of each ingredient [this information can be included on the container if there is insufficient space on the product label].

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

- Oxytocin 30 units added to 500 mL 5% Dextrose/Lactated Ringer's USP
- Calcium Gluconate 4 g (16 mg per mL) 250 mL Total Volume in Sodium Chloride 0.9%
- Buffered Lidocaine 1% in Sodium Bicarbonate 8.4% 5 mL Total Volume
- 4% Sodium Citrate 40 mg per mL (120 mg per 3 mL) 3 mL Total Volume
- Sodium Phosphate added to 0.9% Sodium Chloride 10 mMol 100 mL Bag
- Potassium Chloride in 0.9% Sodium Chloride 40 mEq in 250 mL
- Potassium Chloride in 0.9% Sodium Chloride 40 mEq in 500 mL
- Labetalol HCl 5 mg per mL (25 mg per 5 mL) 5 mL Total Volume

***DATES OF INSPECTION**

4/18/2016(Mon), 4/19/2016(Tue), 4/20/2016(Wed), 4/21/2016(Thu), 4/26/2016(Tue), 4/27/2016(Wed), 4/28/2016(Thu), 4/29/2016(Fri), 5/12/2016(Thu), 5/26/2016(Thu)

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