DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
404 BNA Dr., Bldg. 200, Ste. 500 Nashville, TN 37217-2597 (615) 366-7801 Fax:(615) 366-7802 Industry Information: www.fda.gov/oc/industry	06/22/2015 - 07/10/2015 FEI NUMBER 3007045542

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Mr. John F. Toth, Director of Quality

FIRM NAME	STREET ADDRESS
PharMEDium Services, LLC.	6100 Global Dr
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Memphis, TN 38141-8385	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

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,

1. A review of your firm's assay analysis for 10mcg/ml, 20mcg/ml, and 25mcg/ml Fentanyl Citrate in 0.9% Sodium Chloride packaged in 30mL BD Syringes from July 2014 found sub potent products with unknown impurities present. Your firm initiated an investigation in August 2014. The investigation did not properly identify the unknown impurities and your firm's conclusion was the extraneous peaks in the chromatograms were being caused by 30mL BD syringes that come packaged in multi-packs as opposed to 30mL BD syringes that are individually wrapped. Your firm switched to individually wrapped syringes on 08/18/14; however, on 08/19/14, Fentanyl Citrate 10mcg/mL, lot 14231147M, packaged in a individually wrapped 30mL BD syringe was tested and found to be sub potent with extraneous peaks observed. This product was distributed.

2. Since 08/20/14, Your firm has produced (b) (4) batches of 10mcg/ml, 20mcg/ml, and 25mcg/ml Fentanyl Citrate in 0.9% Sodium Chloride packaged in 30mL BD syringes. None of these lots were tested to determine if the extraneous peaks were present or if the product was sub potent. These lots were distributed.

3. On 01/12/15, your firm was made aware of unknown impurities also present in 5mcg/mL and 10mcg/mL Fentanyl Citrate packaged in 3mL BD syringes after lots 15002077M and 15002250M were sampled and tested as part of your monitoring program. From 01/12/15 to 05/28/15 your firm produced (b) (4) batches of the 5mcg/mL and 10mcg/mL Fentanyl Citrate packaged in 3mL BD syringes, but only 1 of these batches was pulled for testing. Your firm did not initiate an investigation into the 3mL BD syringes until 06/17/15 when your firm received a complaint for 10mcg/mL Fentanyl Citrate being in-effective.

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OBSERVATION 2

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release.

Specifically,

Your firm does not perform finished product potency/sterility testing on each lot of finished injectable drug product produced prior to being distributed. Testing is performed on a fraction of the batches produced, samples are (b) (4) (b) (4) and batches are released for distribution prior to the completion of testing. During a review of your firm's records for batches that were tested from 01/01/14-06/01/2015 the following was found:

- Fentanyl 2mcg/mL- 18 sub potent out of (b) (4) batches tested
- Fentanyl 5mcg/mL- 103 sub potent and 1 super potent out of (b) (4) batches tested
- Fentanyl 10mcg/mL- 11 sub potent out of (b) (4) batches tested
- Fentanyl 20mcg/mL- 6 sub potent out of (b) (4) batches tested
- Fentanyl 25mcg/mL- 3 sub potent out of (b) (4) batches tested
- Hydromorphone 100mcg/mL- 1 sub potent out of (b) (4) batches tested
- Hydromorphone 2mcg/mL- 4 sub potent out of (b) (4) batches tested
- Hydromorphone 2mg/mL- 2 sub potent and 2 super potent out of (b) (4) batches tested
- Phenylephrine 10mcg/mL- 4 sub potent out of (b) (4) batches tested
- Phenylephrine 80mcg/mL- 1 sub potent out of (b) (4) batches tested
- Methadone 1mg/mL- 3 sub potent and 3 super potent out of (b) (4) batches tested

THIS IS A REPEAT OBSERVATION

OBSERVATION 3

Buildings used in the manufacture, processing, packing or holding of drug products are not maintained in a clean and sanitary condition.

Specifically,

During a review of your firm's environmental monitoring for the ISO 5 hoods (surface and air) and technician's fingertips, we found results of 1-3 CFUs frequently occured. Organisms persistantly identified for (b) (4) hoods and fingertips include, but are not limited to: *Staphylococcus epidermidis, Staphylococcus hominis, Bacillus subtilis, Bacillus circulans, Bacillus cereus, and Paenibacillus urinalis.*

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OBSERVATION 4

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

Specifically,

Your firm failed to follow procedure CPS-305, "PERSONNEL GOWNING AND ASEPTIC TECHNIQUE AND CONTROLS" in regards to:

1. On 06/22/15, we observed an employee who was aseptically filling Fentanyl Citrate reach over the product to retrieve material they had placed behind the rack of product on two separate occasions. This action placed the technician's arm in front of the laminar air flow allowing for turbulence to occur above the product.

2. On 06/25/15, we observed two employees resting their forearms on plastic totes used to hold components in the Clean Room. One of these employees was also seen at a different time resting their forearms on the handle of a cart used to transport components in and out of the Clean Room which has an ISO 7 classification.

3. On 06/25/15, we observed an employee leaning in to the hood and reaching over vials during aseptic processing of Lidocaine.

4. On 06/22/15 and 06/15/15, we observed employees not adequately sanitizing their gloves prior to entry into the laminar flow hood. The sterile (b) (4) was not distributed over the entire hand to include their wrists.

5. On 06/25/15, we observed an employee storing her sterile (b) (4) spray bottle in a tote, on top of IV bags containing drug product for use in production. This poses a risk for microbial contamination as well as bag integrity.

THIS IS A REPEAT OBSERVATION

OBSERVATION 5

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include validation of the sterilization process.

Specifically,

Media fills performed by your firm for employee qualification/monitoring do not represent the firm processes of (b) (4) . Your firm's procedure is insufficient because the media fill process is

not representative of typical or the most complex manipulations of your aseptic processing.

THIS IS A REPEAT OBSERVATION

OBSERVATION 6

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

Specifically,

1. The upper and lower potency limits established by your firm for injectable drug products are outside of the USP acceptable range of 90%-110%. For example:

- Fentanyl Citrate 5 mcg/ml is (b) (4)
- Fentanyl Citrate 10 mcg/ml is (b) (4)
- Fentanyl Citrate 20 mcg/mL is (b) (4)
- Fentanyl Citrate 25 mcg/mL is (b) (4)
- Hydromorphone 0.2mg/mL is (b) (4)

Your firm does not have the data to support these ranges. Your firm's SOP CPS-1051, "Investigating Atypical Results for the End Preparation Assurance (EPA) Program," indicates that acceptace limits for products analyzed by the EPA lab are based on the (b) (4).

THIS IS A REPEAT OBSERVATION

OBSERVATION 7

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

Specifically,

Your firm does not perform daily personnel monitoring for each technician performing aseptic processes. Each technican's gloves are tested (b) (4) and gowning is tested (b) (4)

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OBSERVATION 8

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

Specifically,

Your firm does not conduct any endotoxin testing on finished drug products purporting to be sterile. Your firm produces injectable drug products, including epidurals, and the components used are labeld for IV use only.

THIS IS A REPEAT OBSERVATION

OBSERVATION 9

The written stability program for drug products does not include meaningful and specific test methods.

Specifically,

We reviewed stability test results for Succinylcholine Chloride, Rocuronium, and Fentanyl Citrate. The following was noted:

1. The stability test methods used to assign expiration dates to finished injectable drug products are not stability indicating. Procedures do not include testing for sterility, impurities, or degradants. Expiration dates of 90 days are assigned to Rocuronium and Succinylcholine Chloride products. Expiration dates assigned to Fentanyl Citrate products range from 30 days to 90 days. The Rocuronium and Fentanyl Citrate your firm receives for use in production are preservative-free.

2. The container/closure systems your firm uses to package finished drug product were not evaluated as part of the stability program.

3. Your stability program did not include a sufficient number of lots. Only one lot per product was tested.

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OBSERVATION 10

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

Specifically,

1. Your firm utilizes (b) (4) and (b) (4) instruments in the laboratory for identity and potency testing. The computer software used to run these instruments does not have proper security. Any employee has the ability to enter into the program, access data, change or delete data, and modify methods without any traceability. The Laboratory Manager, who is the most responsible individual for your firm's lab, was unable to demonstrate that she could determine who last modified testing methods

2. Your firm uses an (b) (4) to back up laboratory testing data. You do not keep a hard copy of this data and it is not stored in an alternate system. Furthermore, this data can be accessed and modified by any lab employee.

OBSERVATION 11

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

1. The date that the drug was compounded.
2. Statement of quantity
3. The inactive ingredients, identified by established name and the quantity or proportion of each ingredient.

The following information is not found on the container labels for products you produce, as described in 503B(a)(10)(B).

1. Information to facilitate adverse event reporting: www.fda.gov/medwatch and 1800FDA1088 <http://www.fda.gov/medwatch and 1800FDA1088>.

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

- Fentanyl Citrate 250 mcg in 50 mL of Sodium Chloride Injection 0.9%
- Bupivacaine HCl 0.2% in Sodium Chloride 0.9%
- Fentanyl Citrate 5,000 mcg in 250 mL of Sodium Chloride Injection 0.9%
- Fentanyl Citrate 750 and Bupivacaine 0.1% in 150 mL of Sodium Chloride Injection 0.9%
- Hydromorphone HCl 20 mg in 100 mL Sodium Chloride 0.9% Cassette Reservoir

For purposes of 503B(a)(10)(B) container labeling, the clear plastic bag (b) (4) enclosing some of your products should be considered the "container" for purposes of this requirement and bear the information required by 503B(a)(10)(B).

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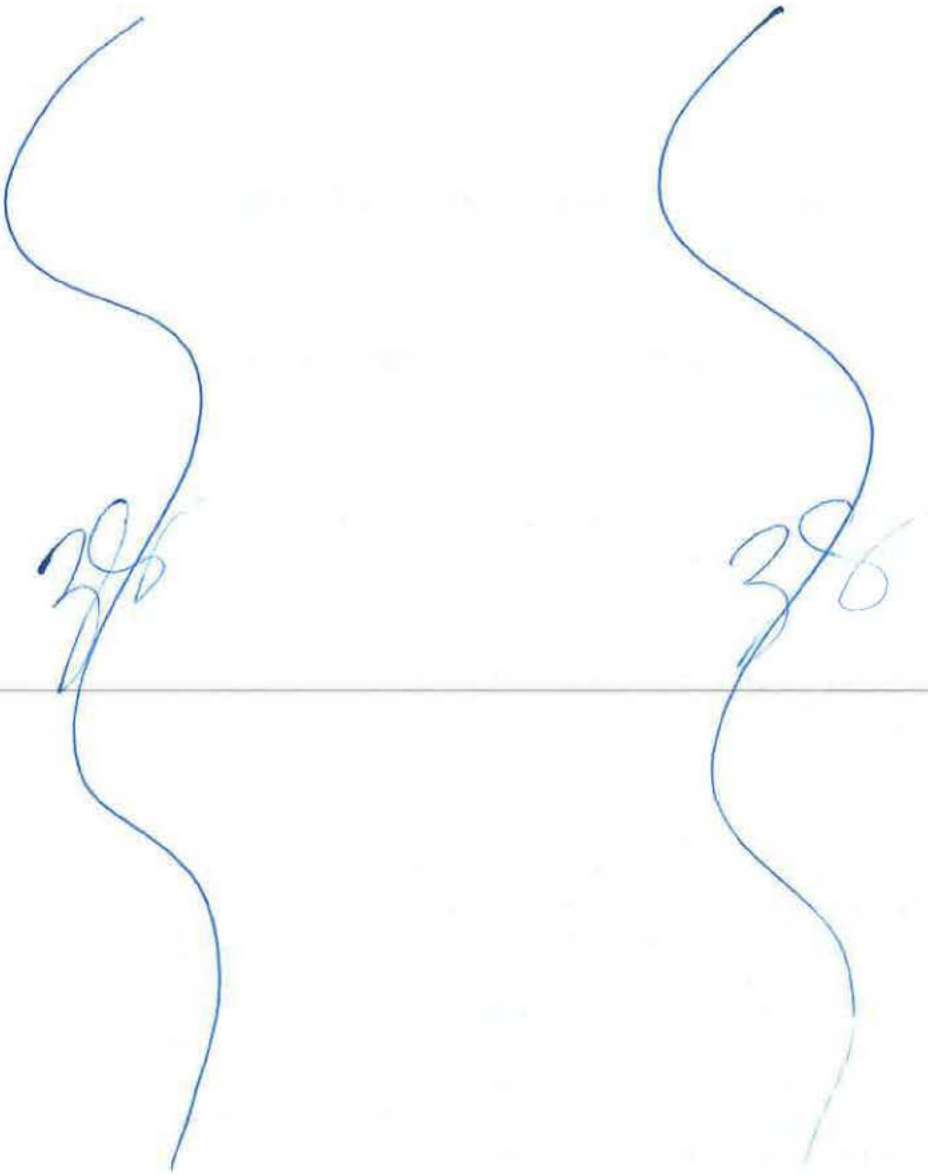

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The observations of objectionable conditions and practices listed on the front of this form are reported:

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 judgement, 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."