

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

DISTRICT ADDRESS AND PHONE NUMBER		DATE(S) OF INSPECTION
4040 North Central Expressway, Suite 300 Dallas, TX 75204 (214) 253-5200 Fax: (214) 253-5314 Industry Information: <a href="http://www.fda.gov/oc/industry">www.fda.gov/oc/industry</a>		02/19/2013 - 02/27/2013
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED		FBI NUMBER
TO: Mr. Bruce W. Bagby, General Manager		3000717703
FIRM NAME	STREET ADDRESS	
PharMedium Services, LLC	12620 W Airport Blvd Ste 130	
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED	
Sugar Land, TX 77478-6200	Producer of Sterile Drug Products	

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**

Equipment and utensils are not cleaned and maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically, your firm does not always keep laminar flow hoods visually clean of residue on HEPA filter surfaces and covering grates. Laminar flow hoods are considered an ISO 5 environment where mixing and pooling of sterile injectable drug products occurs.

On 2/19/2013, I observed white and yellow residue (rough or crystalline in appearance) on the HEPA filters and filter manifolds installed on hood (clean bench, model (b) (4) numbers 1, 2, 4, and 5 (four out of (b) (4) laminar flow hoods in the clean room). I observed residue in areas up to approximately eight inches square on the filter and manifold surfaces facing the operator work area where sterile injectable drug products were being pooled and mixed. These laminar air flow hoods are designed to move air through the HEPA filter, through the drug handling space, and out of the hood towards the operator who is handling the drug product and other materials.

I observed the following examples of drugs mixed or pooled in these hoods at the time I observed the residue described above:

- Hood #1 - Oxytocin lot #13050117S - (b) (4) 500mL bags;
- Hood #2 - Heparin lot #13050138S - (b) (4) 500mL bags;
- Hood #4 - Cefazolin lot #13050114S - (b) (4) 100mL bags;
- Hood #5 - Heparin lot #13050169S - (b) (4) 50mL syringes;

Your management stated there is no investigation or corrective action documented for these residues.

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	Stephen D. Brown, Investigator Scott T. Ballard, Investigator	02/27/2013

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TO: Mr. Bruce W. Bagby, General Manager

## FIRM NAME

PharMedium Services, Llc

## STREET ADDRESS

12620 W Airport Blvd Ste 130

## CITY, STATE, ZIP CODE, COUNTRY

Sugar Land, TX 77478-6200

## TYPE ESTABLISHMENT INSPECTED

Producer of Sterile Drug Products

## OBSERVATION 2

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

Specifically, your firm does not use non-shedding foot covers for employees who work in the clean room where sterile injectable drugs are mixed and pooled.

On 2/19/2013, I observed white particles on the floor of the clean room. Particles observed were white and approximately two to three millimeters square.

On 2/20/2013, management stated these particles could be shedding from foot covers. I observed foot covers missing an elastic/rubber type of strip from the surface of the cover that contacts the floor of the clean room while employees are wearing the foot covers.

On 2/21/2013, I observed white particles on the floor of the clean room. I observed particles as follows:

Number of Particles	Adjacent Hood #	Drug in Hood	Lot #
17	3	Norepinephrine	13052095S
7	5	Oxytocin	13052060S
18	14	Oxytocin	13052077S
8	4	Cefazolin Sodium	13052134S
18	2	Oxytocin	13052082S

I observed all particles described above, within a one-foot radius of operators or within one and a half feet of the hood (clean bench) air intake.

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
## EMPLOYEE(S) SIGNATURE



Stephen D. Brown, Investigator  
Scott T. Ballard, Investigator

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<h3 style="margin: 0;">OBSERVATION 3</h3> <p>Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established.</p> <p>Specifically,</p> <p>A) Your firm does not perform environmental sampling of personnel gowning other than finger-tip contact plates and finger-tip contact plates are only taken from (b) (4) employees (b) (4). I observed up to six operators working in the clean room on 2/21/2013 within a one-hour period. One operator at each hood was performing mixing or pooling operations.</p> <p>Other areas of personnel gowns are not sampled as part of environmental monitoring efforts. Between 2/19-21/2013, I observed operators mixing and pooling drugs within laminar flow hoods. Gown sleeves and surfaces on the front side of the gown come into contact with hood edges, and drug vials. The operator's gloves and sleeves move in the operating space occupied by sterile injectable drugs during mixing and pooling operations performed by the operator.</p> <p>Additionally, your management stated there is no monitoring of viable airborne particles for every lot or shift. Only (b) (4) room air and (b) (4) hood air samples are collected according to SOP #CPS-707, dated 9/17/2012. Also, there is no monitoring of non-viable particles for every lot or shift. Only (b) (4) hood samples (SOP #CPS-303, dated 1/31/2006), and (b) (4) room samples (SOP #CPS-307, dated 6/14/2011) are collected.</p> <p>B) Your SOP #CPS-719 entitled, "Processing Equipment Validation and Re-Validation" (Effective date: 4/30/12) documents, in part, that a total of (b) (4) (b) (4). In this case, a total of (b) (4) Media Fill Units were utilized, or a total of (b) (4) vial changes (b) (4).</p> <p>However, observation of pooling operations on 2/20/13 for the product, Norepinephrine Bitartrate 16 mg Added to 250ml 0.9% Sodium Chloride Injection, USP, lot #13051130S, revealed that your firm was using a total of (b) (4) vials of drug product which exceeds the (b) (4) vial maximum documented in the equipment validation.</p>			
<h3 style="margin: 0;">OBSERVATION 4</h3> <p>Each batch of drug product required to be free of objectionable microorganisms is not tested through appropriate laboratory testing.</p> <p>Specifically, your firm has not conducted sterility testing for the majority of the lots of drug products</p>			
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<p>manufactured and distributed. For example, between 1/3/12 and 1/24/13 your firm manufactured and distributed approximately (b) (4) lots of drug product (Different formulations/container closures) and conducted sterility testing on 61 lots. For example,</p> <ul style="list-style-type: none"> <li>The drug product, Heparin 2,000 Units per 1,000 ml (2 Units/ml) added to 0.9% Sodium Chloride Injection, USP, lot #13016002S (Expiration date: 3/22/13) was manufactured on 1/15/13 and shipped to a consignee on 1/16/13 without sterility testing.</li> <li>The drug product, Magnesium Sulfate 1 g Added to 50ml 5% Dextrose Injection, USP, lot #13016004S (Expiration date: 3/2/13) was manufactured on 1/15/13 and shipped to a consignee on 1/16/13 without sterility testing.</li> <li>The drug product, Calcium Gluconate 1g (10mg/ml) in 0.9% Sodium Chloride 100ml Fill in a IntraVia Bag, lot #13016003S (Expiration date: 3/2/13) was manufactured on 1/15/13 and shipped to a consignee on 1/16/13 without sterility testing.</li> </ul>			
<b>OBSERVATION 5</b>			
<p>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.</p> <p>Specifically, your firm has not conducted potency testing for the majority of the lots of drug products manufactured and distributed. For example, between 1/3/12 and 1/24/13 your firm manufactured and distributed approximately (b) (4) lots of drug product (Different formulations/container closures) and conducted potency testing on 20 lots. For example,</p> <ul style="list-style-type: none"> <li>The drug product, Heparin 2,000 Units per 1,000 ml (2 Units/ml) added to 0.9% Sodium Chloride Injection, USP, lot #13016002S (Expiration date: 3/22/13) was manufactured on 1/15/13 and shipped to a consignee on 1/16/13 without potency testing.</li> <li>The drug product, Magnesium Sulfate 1 g Added to 50ml 5% Dextrose Injection, USP, lot #13016004S (Expiration date: 3/2/13) was manufactured on 1/15/13 and shipped to a consignee on 1/16/13 without potency testing.</li> </ul>			
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<p>1/16/13 without potency testing.</p> <ul style="list-style-type: none"> <li>The drug product, Calcium Gluconate 1g (10mg/ml) in 0.9% Sodium Chloride 100ml Fill in an IntraVia Bag, lot #13016003S (Expiration date: 3/2/13) was manufactured on 1/15/13 and shipped to a consignee on 1/16/13 without potency testing.</li> </ul>			
<p><b>OBSERVATION 6</b></p> <p>Drug products do not bear an expiration date determined by appropriate stability data to assure they meet applicable standards of identity, strength, quality and purity at the time of use.</p> <p>Specifically,</p> <p>A) Review of "Stability Report" dated 7/16/09 for Norepinephrine, lot #1330720 and Sodium Chloride, lot #C769000 (Date of compounding: 5/8/09) under test sample designation 21 (Expiration date: 58 days) revealed assay results for the following days:</p> <ul style="list-style-type: none"> <li>Time 0: Passed            %LC: 107.3, 107.6, and 106.8 (Specification: (b) (4))</li> <li>Day 15: Passed            %LC: 108.0, 108.0, and 106.0 (Specification: (b) (4))</li> <li>Day 30: Passed            %LC: 95.8, 97.7, and 97.2 (Specification: (b) (4))</li> <li>Day 46: Passed            %LC: 94.5, 92.3, and 92.7 (Specification: (b) (4))</li> <li>Day 61: Failed            1) Three samples            %LC: 86.7, 92.6, and 92.5 (Specification: (b) (4))            2) Two samples (re-injection)</li> </ul>			
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%LC: 85.7 and 87.2

- Day 91: Failed

1) Three samples: 90.1, 89.0, and 88.3 (Specification: (b) (4))

B) Review of "Stability Report" dated 5/09 for Norepinephrine, lot #1330720 and Dextrose, lot #C764068 (Date of compounding: 5/8/09) under test sample designation 22 (Expiration date: 58 days) revealed assay results for the following days:

- Time 0: Passed (Re-Preparation)

%LC: 94.6, 95.1, and 95.6 (Specification: (b) (4))

- Day 15: Passed

%LC: 104.5, 101.8, and 103.6 (Specification: (b) (4))

- Day 30: Passed

%LC: 98.0, 96.8, and 95.3 (Specification: (b) (4))

- Day 46: Passed

%LC: 94.6, 94.5, and 92.3 (Specification: (b) (4))

- Day 61: Failed

1) Three samples

%LC: 89.9, 88.6, and 93.8 (Specification: (b) (4))

2) Two samples (re-injection)

%LC: 89.1 and 85.3



- Day 91: Failed

1) Three samples: 87.3, 86.5, and 86.2 (Specification: (b) (4))

In each case, the OOS results were confirmed as valid by your contract laboratory. However, your firm failed to identify a

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<p>root cause or implement corrective action.</p> <p>Your firm indicated that statistical rationale was used to support the 58 day expiration date. However, there is no assurance that your firm has generated substantive data to support the 58 day expiration date.</p>		
<p><b>OBSERVATION 7</b></p> <p>There is no written testing program designed to assess the stability characteristics of drug products.</p> <p>Specifically,</p> <p>A) Your firm's stability testing program failed to include requirements for anti-microbial effectiveness testing to determine whether preservatives such as (b) (4) effectively inhibit microbial growth in your sterile injectable drug products through their Beyond Use Date period. These preservatives are used in the manufacture of approximately (b) (4) different sterile drug product formulations. Some examples consist of the following:</p> <ul style="list-style-type: none"> <li>• Heparin Sodium 1,000 Units (2 units/ml) added to 0.9% Sodium Chloride Injection USP</li> <li>• 230 Units Oxytocin added to Lacated Ringer's Injection USP</li> </ul> <p>B) Your firm has never conducted sterility testing on stability samples for any product formulations.</p>		
<p><b>OBSERVATION 8</b></p> <p>The accuracy and sensitivity of test methods have not been established.</p> <p>Specifically, your firm does not have data to show that microbial enumeration test methods used for environmental monitoring are capable of recovering and detecting the presence of microorganisms on the surfaces of laminar air flow hoods (clean bench, model (b) (4)).</p> <p>On 2/21/2013, I reviewed air and surface environmental testing results for January, March and August 2012. During this time, zero colonies were recovered for both surface and air samples collected inside laminar air flow hoods according to the (b) (4) Environmental Micro Reports (F-707-23). During this time, each of (b) (4) hoods (in January and March) and (b) (4) hoods (in August) was sampled up to (b) (4).</p>		
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On 2/22/2013, I observed your employees collecting samples for environmental monitoring of hood surfaces and hood air samples. Hood surfaces were sampled by (b) (4) of the laminar air flow hood. However, prior to using the (b) (4) on each of the samples observed, the operator who mixed or pooled drug product in the hood, sanitized the stainless steel surface with (b) (4). There was no work performed in the hood between the time the surface was sanitized and the environmental sample was collected. I observed this practice for five of five samples collected.

**OBSERVATION 9**

Reserve samples for drug products are not retained for one year after the expiration date of the drug product.

Specifically, your firm does not maintain retention samples for any drug products. For example,

- Heparin Sodium 25,000 Units (100 units/ml) added to 0.45% Sodium Chloride Injection USP
- 2 g Cefazolin Sodium in Sterile Water for Injection USP
- 40 g Magnesium Sulfate added to Lactated Ringer's Injection USP

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