

**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 2/18/2016-3/16/2016* FEI NUMBER 3008213711
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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED Paul J. Elmer , President and Owner

FIRM NAME Pharmakon Pharmaceuticals, Inc.	STREET ADDRESS 14450 Getz Rd
CITY, STATE, ZIP CODE, COUNTRY Noblesville, IN 46060-3303	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

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

Specifically,

i. Finished lots of sterile injectable drug products are not tested for potency prior to release and distribution. Morphine Sulfate (PF) 0.5mg/ml in 0.9% Sodium Chloride 1ml fill in a (b) (4) syringe lot #E52418EV11C was processed, released, and distributed on 2/3/16. Potency results were reported as 2460% on 2/10/16, acceptance criteria is (b) (4) %. This lot was recalled by your firm on 2/11/16.

ii. Finished lots of sterile injectable drug products containing preservative are not tested for preservative content, for example, Morphine Sulfate 5mg/ml in 0.9% Sodium Chloride 25ml fill in a (b) (4) syringe lot #E51192DK18C. This lot was processed and shipped on 2/18/16 without such testing.

OBSERVATION 2

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,

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i. Since 4/2014, (b) (4) batches were released prior to receiving potency results that were out of specification. No investigation was conducted into these out of specification test results. Some examples of batches released and shipped include:

Lot #	Active Ingredient	% Potency	Date Made	Date Shipped	Date Tested
E290653A8R	EPINEPHRINE	0	(b) (4)		11/6/2014
E14240A2R	NOREPINEPHRINE	0.4			2/24/2015
E133348.17R	PROMETHAZINE	1.8			1/15/2015
E34082DK8C	MIDAZOLAM	7.1			1/2/2015
E0228143R	PHENYLEPHRINE	25.3			7/29/2014
E09232530R07 E09232530R	PHENYLEPHRINE	25.9			7/25/2014
E40292DK9C	MIDAZOLAM	27.6			6/9/2015
E39250DK31C	MIDAZOLAM	33.8			7/14/2015
E42428DK4C	MIDAZOLAM	34.7			10/20/2015
E40292DK4C	MIDAZOLAM	37.7			5/15/2015
E1106133R	PHENYLEPHRINE	39.4			5/6/2014
E40292DK7C	MIDAZOLAM	44.2			6/1/2015
E083327Z2R	PROMETHAZINE	45.6			5/18/2015
E30152DK5C	FENTANYL CITRATE	52.9			7/14/2014
E39250DK27C	MIDAZOLAM	55.7			6/23/2015
E15058A13R	NOREPINEPHRINE	66			10/26/2015
E34082DK3C	MIDAZOLAM	68.4			7/22/2014
E600949121R	OXYTOCIN	75.6			6/30/2015
E290653A10R	EPINEPHRINE	77.6			11/14/2014
EJKP0412A1R	VECURONIUM	77.6			8/28/2015
E102F0147R	CEFAZOLIN	80.4			9/10/2015

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E60083313R	OXYTOCIN	85.5	(b) (4)	11/14/2014
E06334312R	ATROPINE	85.6		12/31/2014
E16HL01222R	PROPOFOL	86		11/24/2015
E1243458R	PROMETHAZINE	114		11/10/2015
E46342DK6R	BUPIVICAINE	116		8/25/2015
E61055602R	HEPARIN	116		6/3/2015
E43187DK36C	MORPHINE SULFATE	116		11/19/2015
E600949149R	OXYTOCIN	118		8/11/2015
E271353A2R				
E27135A2R	EPINEPHRINE	119.9		4/2/2014
E40292DK10C	MIDAZOLAM	120.9		6/11/2015
E37235DD21C	HYDROMORPHONE	121.6		6/26/2014
E0353613R	PHENYLEPHRINE	124.2		10/13/2015
E02281416R	PHENYLEPHRINE	127.6		9/19/2014
E0643928R	PHENYLEPHRINE	129.1		6/8/2015
E02330736C	MORPHINE SULFATE	207.9		8/15/2014
				1/19/2015
E460953A2R	VANCOMYCIN	0.4		1/23/2015

ii. No investigation was performed into the following test results for drug products already released and distributed:

- Midazolam HCl 1mg/ml in 0.9% Sodium Chloride 2ml fill in a **(b) (4)** syringe lot #EMS3063C tested positive for sterility on 5/20/14.
- Ephedrine Sulfate 5mg/ml in 0.9% Sodium Chloride 5ml fill in a **(b) (4)** syringe lot #E0714148R, Fentanyl Citrate 2mcg/ml and Bupivacaine HCl 0.125% in 0.9% Sodium Chloride 200ml in **(b) (4)** 250ml Bag lot #E45248DK11C, and Ephedrine Sulfate 5mg/ml in 0.9% Sodium Chloride 10ml fill in a **(b) (4)** syringe lot #E0725141R were reported as "Cancelled or Sample Untestable" on 3/02/15, ~~4/16/15~~, and 6/10/15, respectively. No additional test results were provided for these three batches.

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OBSERVATION 3

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

Specifically,

i. The following aseptic practices were observed:

a. Operators were not observed to exhibit slow, deliberate movements while performing aseptic operations in the ISO 5 laminar flow hood. For example, during the filling of HYDROmorphine HCl 0.4 mg/ml in 0.9% Sodium Chloride 30ml fill in a (b) (4) (b) (4) vial lot #E52105DD25C on 2/18/16, an operator was observed to spray gloved hands with sanitizer and wave them around in the laminar flow hood to dry.

b. On 2/19/16, an operator was observed leaving the ISO 5 Suite (b) (4) and performed a (b) (4) (b) (4) in the ISO 6 anteroom using the hand sink. After completion of this task, the operator did not change gloves or sanitize their hands prior to leaving the anteroom and returning to Suite (b) (4) to continue aseptic processing of Fentanyl Citrate 2mcg/ml and Bupivacaine HCl 0.125% in 0.9% Sodium Chloride 200ml in (b) (4) 250ml Bag lot #E3450DK9C-E53450DK9C.

c. Sterile utensils are not always used to handle sterile materials. For example, on 2/23/16, an operator was observed to (b) (4) (b) (4) vials containing Bupivacaine PF (b) (4) mg/ml when (b) (4) (b) (4) (Fentanyl Citrate 2mcg/ml & Bupivacaine 0.125% in 0.9% Sodium Chloride 150ml in a 150ml (b) (4) bag).

d. On 2/25/16, an operator was observed to (b) (4) of Norepinephrine Bitartrate (b) (4) with their gloved hands used in Norepinephrine Bitartrate 8mg added to 5% Dextrose 250ml bag lot #E15229B3R. Additionally, a (b) (4) is used for sterile drug components

(b) (4)
(b) (4) No additional (b) (4) was observed in this process even though the (b) (4) (b) (4). Your firm management stated they were unaware a (b) (4) was not being used during this process.

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e. During the filling of HYDROmorphone HCl 0.4mg/ml in 0.9% Sodium Chloride 30ml fill in a (b) (4)(b) (4) Vial lot #E52105DD45C and Ephedrine Sulfate 5mg/ml in 0.9% Sodium Chloride 10ml fill in a (b) (4) syringe lot #E091305A11R on 3/15/16, both operators were observed to rest their gownned arms and/or elbows on the ISO 5 work surface.

f. During the filling of Cefazolin 2GM added to 100ml 0.9% Sodium Chloride bag lot #E157085.24R on 3/15/16, the operator's gloved hands were observed to block first air while removing (b) (4) Cefazolin with 0.9% Sodium Chloride (b) (4).

ii. Adequate validation of aseptic processing operations, specifically, process simulations (media fills), have not been performed under worst case conditions to assure that sterile processing techniques are adequate to ensure the sterility of drug products. Currently, each operator involved in aseptic processing must perform a "Personal Aseptic Technique Test", in which (b) (4). This process does not include, for example, use of all representative container closure systems, worst case lot sizes (ex: (b) (4) syringes), most complex/difficult aseptic operations, or equipment used in normal aseptic processing such as sterile (b) (4) and repeater pumps.

iii. A (b) (4) was observed in the gowning room (b) (4). This (b) (4) was not in use and operators were observed to walk throughout the room regardless of their garbing attire.

iv. No documentation was provided to support that the (b) (4) used to sterilize (b) (4) used in aseptic filling operations has been adequately validated for its intended use, or that periodic maintenance of such is performed according to the user manual.

(b) (4)

This is a repeat observation of that written on the FDA 483 dated 3/13/2014.

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OBSERVATION 4

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

Specifically,

i. According to SOP PH100 *Environmental Control and Monitoring*, (b) (4)

The (b) (4) has been in place since 1/2015; however, your firm management stated there have been no (b) (4)

a. On 2/19/16, Suite (b) (4) was observed to have a pressure reading of 0.005 inches of water.

b. (b) (4)

(b) (4) Vancomycin HCl 1 (b) (4) GM added to 5% Dextrose in a 250ml (b) (4) bag lot #E442253A1R was processed in Suite (b) (4) on this day.

c. The Pressure (b) (4) Log documents several examples of Suite (b) (4) being outside the specified range. For example, Ceftriaxone 1GM in Sterile Water 10ml fill in a (b) (4) syringe lot E570078M3R was processed on 2/10/16 in Suite (b) (4) the Pressure (b) (4) Log documented the (b) (4) on this day. Your firm management stated these logs were not being reviewed.

No investigation has been conducted into these pressure readings.

ii. The Cleanroom Certification Reports dated (b) (4) both report that (b) (4) is Negative to the (b) (4), respectively. No investigation was conducted.

iii. The (b) (4) for each clean room suite. During the inspection, your firm management became aware that (b) (4) the last time data was (b) (4) in the ISO 5 Suites (b) (4) was

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on 2/3/16, data was last (b) (4) in Suite (b) (4) on 2/4/16. Additionally, Suite (b) (4) does not have a (b) (4) Pressure (b) (4) Log.

iv. Pressure gauges in Suite (b) (4) used to aseptically process Cephalosporin drug products, were not calibrated prior to 2/20/16. Suite (b) (4) has been in use since 6/2/14.

v. The anteroom for Suite (b) (4) was observed to have a pressure reading of zero on 2/19/16. This room is considered ISO 6 and is connected to Suite (b) (4) which is classified ISO 5.

This is a repeat observation of that written on the FDA 483 dated 3/13/2014.

OBSERVATION 5

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

Specifically,

i. Not all sanitizers and cleaning agents used in the classified areas are sterile. For example, (b) (4) are not purported to be sterile. Also, between 4/30/14 and 5/23/14, a mixture of (b) (4) was used to clean Suites (b) (4), all classified ISO 5; these items were also stated by your firm's management not to be sterile.

ii. SOP PH109 *Sanitization (Disinfection)* requires the use of a sporicidal agent (b) (4) to reset microbial resistance. The (b) (4) Sanitization Log for each suite did not document the use of a sporicidal agent:

(b) (4)

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iii. Disinfectant efficacy studies have not been performed to demonstrate that the disinfectants and the application methods used to clean the ISO 5 areas can sufficiently reduce bioburden.

iv. Scientific justification was not provided to support that (b) (4) is an appropriate contact time for all disinfectants used in the sterile suites.

v. On 2/18/16, a white colored residue was observed on the HEPA filter grate of laminar flow hood (b) (4) during the processing of HYDROmorphone HCl 0.4 mg/ml in 0.9% Sodium Chloride 30ml fill in a (b) (4) Vial lot #E52105DD25C. On 3/10/16, white residue was also observed on the HEPA filter grate of laminar flow hoods (b) (4)

vi. No documentation was provided to support that Suite (b) (4) was sanitized (b) (4) from 4/23/14-9/22/14 or that Suite (b) (4) was sanitized (b) (4) from 6/2/14 to 11/5/15, according to SOP PH109 *Sanitization (Disinfection)*. In addition, no documentation was provided to support that Suite (b) (4) was cleaned (b) (4) according to SOP PH108 (b) (4) *Hood/Floor Cleaning* from 6/2/14-11/24/14 and 2/12/15-10/28/15. Cefazolin 1GM in Sterile Water 10ml fill in a (b) (4) syringe lot #E102F00916R was processed in Suite (b) (4) on 8/4/15.

vii. On 3/15/16, residue was observed on the metal surface on top of the following laminar flow hoods in the ISO 5 suites: (b) (4)

This is a repeat observation of that written on the FDA 483 dated 3/13/2014.

OBSERVATION 6

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

Specifically,

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The current gowning method may leave facial skin exposed. For example, on 2/25/16, an operator aseptically processing Norepinephrine Bitartrate 8mg added to 5% Dextrose 250ml bag lot #E15229B3R in the ISO 5 laminar flow hood 1 was observed with several inches of skin on their forehead exposed.

This is a repeat observation of that written on the FDA 483 dated 3/13/2014.

OBSERVATION 7

Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.

Specifically,

On 2/19/16, two ceiling tiles in the Suite (b) (4) processing area were observed to be exposed and not flush with the other ceiling tiles in this room. Your firm classifies this room as ISO 5.

OBSERVATION 8

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

Specifically,

i. Environmental monitoring is not performed at least daily during drug production in the critical areas to evaluate the quality of the aseptic processing environment and assess whether aseptic conditions are maintained.

a. Non-viable particulate monitoring is performed in the aseptic processing areas once every six months.

b. Viable monitoring:

Passive air monitoring is performed (b) (4) but was not observed to occur in the laminar flow hoods where processing occurs. On 2/23/16, during processing of Cefazolin 2GM added to 5% Dextrose 50ml USP lot #E157084.114R in

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Suite ^{(b) (4)} a media plate for viable passive air monitoring was set ^{(b) (4)}, away from the laminar flow hood.

Active air monitoring is performed ^{(b) (4)}. It is also performed ^{(b) (4)}.

ii. On 2/18/16, an operator processing HYDROmorphone HCl 0.4mg/ml in 0.9% Sodium Chloride 30ml fill in a ^{(b) (4)} vial lot #E52105DD25C was observed to spray disinfectant on the laminar flow hood surface and then almost immediately after, a surface sample was collected using ^{(b) (4)} plates in this location.

iii. The frequency of personnel monitoring is inadequate. A ^{(b) (4)} requires ^{(b) (4)}.

a. According to SOP PH100 *Environmental Control and Monitoring*, the action level for personnel monitoring for ^{(b) (4)}. The following are examples of CFUs reported on gloves:

Date	Operator	Hood	Product	CFU
12/8/14	^{(b) (7)(C), (b) (6)}	^{(b) (4)}	Ropivacaine HCl lot#E61080474R Promethazine lot#E143044.113R	5
2/10/15	^{(b) (7)(C), (b) (6)}	^{(b) (4)}	Rocuronium lot#ERT416X4R	4
10/13/15	^{(b) (7)(C), (b) (6)}	^{(b) (4)}	Bupivacaine HCl lot#E50379DK1R HYDROmorphone HCl lot#E47345DD18C	16
10/20/15	^{(b) (7)(C), (b) (6)}	^{(b) (4)}	HYDROmorphone HCl lot#E50055DD33C HYDROmorphone HCl lot#E50055DD32C Ephedrine Sulfate lot#E05141515R Fentanyl Citrate lot#E48234DK31C Fentanyl Citrate/Ropivacaine HCl	14

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			lot#E48234DK32C	
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The following are examples of CFUs reported on gowns:

Date	Operator	Hood	Product	CFU
7/30/14	(b) (7)(C), (b) (6)	(b) (4)	HYDROmorphone HCl lot#E37235DD24C Ketamine lot#E121005A21C Fentanyl Citrate/Ropivacaine HCl lot#E32266DK16C Fentanyl Citrate lot#E32266DK15C	TMTC
12/31/14	(b) (7)(C), (b) (6)	(b) (4)	Oxytocin lot#E60087905R	23
1/13/15	(b) (7)(C), (b) (6)	(b) (4)	Succinylcholine Chloride lot#E44378EV2R	TMTC
3/18/15	(b) (7)(C), (b) (6)	(b) (4)	Morphine Sulfate lot#E44152DK1C Fentanyl Citrate lot#E45078DK2C	TMTC
7/21/15	(b) (7)(C), (b) (6)	(b) (4)	Ceftriaxone lot# E4900208M3R E490208M3R Cefazolin lot#E102F0079R Cefazolin lot#E15702311R Provocholine lot#EP5032H4R	20
10/22/15 10/20/15	(b) (7)(C), (b) (6)	(b) (4)	Sufentanil Citrate/Bupivacaine lot#E10134417C HYDROmorphone HCl lot #E50055DD33C HYDROmorphone HCl lot #E50055DD32C Ephedrine Sulfate lot #E05141515R	105 (b) (4) ; 37 (b) (4)

No investigation has been conducted into these results, nor has any identification been performed on the microorganisms.

AMENDMENT 1

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	X Emily J Orban Emily J Orban Investigator Signed by: Emily J. Orban -S	

**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 2/18/2016-3/16/2016*
		FEI NUMBER 3008213711
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED Paul J. Elmer , President and Owner		
FIRM NAME Pharmakon Pharmaceuticals, Inc.	STREET ADDRESS 14450 Getz Rd	
CITY, STATE, ZIP CODE, COUNTRY Noblesville, IN 46060-3303	TYPE ESTABLISHMENT INSPECTED Outsourcing Facility	

iv. No documentation was provided to support that media plates used for operator glove monitoring contain disinfectant neutralizers to assure microbial contamination can be detected.

v. On 2/15/16, the white colored residue observed on the HEPA filter grate of laminar flow hood was analyzed and 1 CFU was recovered from a swab sample. No investigation has been conducted nor has identification been performed on the microorganism.

This is a repeat observation of that written on the FDA 483 dated 3/13/2014.

OBSERVATION 9

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

Specifically,

Given the observed inadequate environmental controls, testing is deficient in that aseptically filled sterile injectable drug products are released and distributed prior to receiving laboratory results for sterility.

i. Morphine Sulfate (PF) 0.5 mg/ml in 0.9% Sodium Chloride 1ml fill in a (b) (4) syringe lot #E0833054C was not sent for sterility testing. This batch was processed on 9/24/14 and distributed on 9/25/14.

ii. Morphine Sulfate (PF) 0.5 mg/ml in 0.9% Sodium Chloride 1ml fill in a (b) (4) syringe lot #E08330552C was sent for sterility testing but results were not received. This lot was processed on 8/19/15 and distributed on 8/19/15.

This is a repeat observation of that written on the FDA 483 dated 3/13/2014.

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OBSERVATION 10

The operations relating to the processing of penicillin are not performed in facilities separate from those used for other drug products for human use.

Specifically,

Procedures have not been established for the separation of tasks and segregation of personnel handling cephalosporin drug products from those for all other human drug products. For example, on 2/13/15, Cefazolin 2GM added to 5% Dextrose 50ml USP lot #E102E0232R was processed in Suite (b) (4) ISO 5 laminar flow hood (b) (4) followed by (b) (4) (Brevital Sodium) 10mg/ml 10ml syringe lot #E6929448C. Suite (b) (4) is dedicated to processing cephalosporin drug products; however, Suite (b) (4) is also used to process these products, as recently as 2/10/16 for Ceftriaxone 1GM in Sterile Water 10ml fill in a (b) (4) syringe lot #E570078M3R.

This is a repeat observation of that written on the FDA 483 dated 3/13/2014.

OBSERVATION 11

Drug product containers and closures were not sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.

Specifically,

i. No documentation was provided to support that drug product containers and closures are always received with a Certificate of Conformance or are tested for sterility and endotoxin levels prior to use. These containers and closures are evaluated by (b) (4) (b) (4). For example, (b) (4) 30ml vials lot (b) (4) was used to package HYDROmorphone HCl 0.4mg/ml in 0.9% Sodium Chloride 30ml fill in a (b) (4) vial lot

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0.9% Sodium Chloride 1ml fill in a (b) (4) syringe lot #E52418EV11C with the wrong active ingredient.

This same SOP requires an operator (b) (4). On 2/3/16, an employee who was not a pharmacist, nor the QC, reviewed these items for Morphine Sulfate (PF) 0.5mg/ml in 0.9% Sodium Chloride 1ml fill in a (b) (4) syringe lot #E52418EV11C. This employee signed off as a (b) (4) and did not notice the wrong active ingredient had been selected.

This batch of Morphine Sulfate (PF) 0.5mg/ml in 0.9% Sodium Chloride 1ml fill in a (b) (4) syringe lot #E52418EV11C was recalled on 2/11/16 by your firm due to potency results of 2460% received on 2/10/16.

OBSERVATION 12

OBSERVATION 13

The labeling of your outsourcing facility's drug products does not include information required by sections 503B(a)(10)(A) and (B).

Specifically,

The following information is not found on your drug product labeling:

- Information to facilitate adverse event reporting: www.fda.gov/medwatch and 1800-FDA-1088.

Examples of drug products that do not contain this information:

- Adenosine 1mg/ml
- Bupivacaine HCL 0.125%
- Promethazine HCL 25mg
- Heparin 25,000 USP Units

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OBSERVATION 13

OBSERVATION 14

Your outsourcing facility has not submitted a complete report to FDA identifying all products compounded at your facility during the previous six months as required by section 503B(b)(2)(A). Specifically,

~~The following~~ **Some examples of products that you stated to have** ~~were~~ compounded ~~and~~ were not identified on your report dated December 11, 2015:

- Sodium Citrate 4% injection
- Tetracaine 0.5% injection
- Nalbuphine 10mg/ml injection
- ~~Norepinephrine Bitartrate 8mg injection~~
- Norepinephrine Bitartrate 16mg injection
- Morphine Sulfate Oral Solution 1mg liquid
- Ropivacaine HCL 0.5% injection
- Sodium Phosphate 15mMOL injection
- Sodium Phosphate 3mMOL injection
- Labetalol 5mg/ml
- ~~Norepinephrine Bitartrate 4mg (16 mcg/ml) injection~~
- Phenylephrine HCL 400mcg
- Nitroglycerin 50mcg/ml injection
- Neostigmine 1mg/ml injection
- Sufentanil Citrate/Bupivacaine 0.4mcg/0.1% injection

***DATES OF INSPECTION**

2/18/2016(Thu),2/19/2016(Fri),2/22/2016(Mon),2/23/2016(Tue),2/24/2016(Wed),2/25/2016(Thu),2/26/2016(Fri),3/09/2016(Wed),3/10/2016(Thu),3/11/2016(Fri),3/15/2016(Tue),3/16/2016(Wed)

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3/21/2016

X Emilie Kahn

Emilie Kahn
Investigator
Signed by: Emilie E. Kahn -S

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