DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
404 BNA Dr., Bldg. 200, Ste 500 Nashville, TN 37217-2597 Phone: (615) 366-7801 Fax: (615) 366-7802 Industry Information: www.fda.gov/oc/industry	11/27/2017-01/05/2018
	FEI NUMBER 3004153061

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Brenda L. Womack, General Manager

FIRM NAME	STREET ADDRESS
PharMEDium Services, LLC.	913 N. Davis Ave.
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Cleveland, MS 38732-2106	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) (WE) OBSERVED:

OBSERVATION #1

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

****THIS IS A REPEAT OBSERVATION FROM THE 2013 & 2015 INSPECTIONS****

Specifically,

1) On 11/27/2017 and 11/28/2017, we observed the firm's technicians preforming aseptic processing for sterile drug products and the following significant aseptic technique deficiencies were observed, which were also deviations from the firm's SOP CPS-313, titled "ASEPTIC TECHNIQUE AND CLASSIFIED AREA MANAGEMENT", Version 4 Effective Date: 02/28/17:

a) We observed compromise of the ISO 5 work areas by technicians leaning and over-reaching into the hoods to retrieve material that had been placed behind the product being filled on several occasions. This action placed the technician's arm in front of the laminar air flow allowing for turbulence to occur above the product.

b) We observed technicians not sanitizing hands/wrist with sterile (b) (4) prior to entering/re-entering ISO 5 work areas on numerous occasions.

c) We observed technicians to have continuous rapid movements in the ISO 5 hood work areas during aseptic processing especially while observing for particulate matter after filling plastic IV bags.

2) A review of the firm's security surveillance video, ((b) (4)) regarding 3 mcg/mL Fentanyl Citrate and 0.05% Bupivacaine HCL in Sodium Chloride 0.9% Lot #172760060C dated 10/04/2017 that failed endotoxin

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Marvin D. Jones	Marvin D. Jones, Investigator Saundrea A. Munroe, Investigator	01/05/2018

testing, noted the following significant aseptic technique deviations, which were also deviations from the firm's SOP CPS-313, entitled "ASEPTIC TECHNIQUE AND CLASSIFIED AREA MANAGEMENT" Version 4 Effective Date: 02/28/17:

a) The technician did not sanitize their gloves upon re-entering the ISO 5 hood work area at least 41 times during processing of this lot.

b) The technician was observed leaning and over-reaching into the ISO 5 hood work area at least 19 times during processing of this lot.

c) The technician was observed touching items in the trash container on 3 occasions and then re-entering the ISO 5 hood work area without sanitizing/changing their gloves during processing of this lot.

d) The return airflow to the ISO 5 hood was observed to be blocked by the technician and equipment at least 6 times during processing of this lot.

e) The technician used the (b) (4) in the ISO 5 hood work area without sanitizing the unit at least 4 times during processing of this lot.

f) The technician placed an electronic weigh scale into the ISO 5 hood work area without sanitizing the unit during processing of this lot.

OBSERVATION #2

Control procedures are not established which validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Specifically,

Your firm has been experiencing potency (over and under) failures with combo drug families such as; Fentanyl/ Bupivacaine and Fentanyl/Ropivacaine from the 2 mcg/mL to 7 mcg/mL concentration. Also, your firm has been

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experiencing potency failures with non-combo drug families such as; Hydromorphone with the concentrations of 0.04 mg/mL to 2 mg/mL and Morphine with the concentrations of 1mg/mL to 10mg/mL. Per the firm's CAPA #055 dated 07/13/2017, the firm has had a total of 152 Total Confirmed Potency Failures from 01/16/2017 to 10/26/2017.

The (b) (4) deliver the quantity of each active drug ingredient and the diluent for the (b) (4) per specification for each drug product. As of 11/07/2017, the (b) (4) are no longer utilized for drug product lots that require active drug ingredients of (b) (4). Drug lots that require (b) (4) (b) (4) are currently (b) (4) by (b) (4). This change was based on an analysis of failure results where a majority of the failures were (b) (4) of the active drug ingredient delivered by the (b) (4) The equipment manual for the (b) (4) declares "Acceptable volume ranges between (b) (4)."

Your firm has been using (b) (4) since 2013 for the (b) (4), which contain active drug ingredients and the diluent.

A review of numerous opened and closed Nonconformance Reports (NCR), noted that it appears that your (b) (4) are not capable of consistently delivering the proper amount of active drug ingredients or diluent to ensure that finished drug products are within acceptable specifications. Therefore, your firm is relying solely on finished drug product testing to release drug products for distribution. The NCRs reviewed noted the following:

a) NCR #CNC-17-322 dated 10/03/2017 regarding the over potency testing results for Lot #172750002C and Lot #172750004C.

Per this investigation, based on the potency result of 0.225 mg/ml for Lot #172750002C, the (b) (4) of hydromorphone HCL 10 mg/ml delivered to the (b) (4) (b) (4) was (b) (4). This was (b) (4) (b) (4) than the recipe amount (b) (4) The (b) (4) of diluent delivered was (b) (4) (b) (4) which amounted to an under-delivery of (b) (4).

Per this investigation, based on the potency result of 0.214 mg/ml for Lot #172750004C, the (b) (4) of hydromorphone HCL 10 mg/ml delivered to the (b) (4) was (b) (4). This was (b) (4)

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(b) (4) than the recipe amount (b) (4) The (b) (4) of diluent delivered was (b) (4) which amounted to an under-delivery of (b) (4)

b) NCR #CNC-17-324 dated 10/04/2017 regarding the over potency testing results for Lot #172760009C.

Per this investigation, based on the potency result of 0.211 mg/ml for Lot #172760009C, the (b) (4) of hydromorphone HCL 10 mg/ml delivered to the (b) (4) was (b) (4) . This was (b) (4) (b) (4) than the recipe amount (b) (4) The (b) (4) of diluent delivered was (b) (4) which amounted to an under-delivery of (b) (4).

c) NCR #CNC-17-327 dated 10/05/2017 regarding the over potency testing results for Lot #172770003C.

Per this investigation, based on the potency result of 0.215 mg/ml for Lot #172770003C, the (b) (4) of hydromorphone HCL 10 mg/ml delivered to the (b) (4) was (b) (4) . This was (b) (4) (b) (4) than the recipe amount (b) (4) The (b) (4) of diluent delivered was (b) (4) which amounted to an under-delivery of (b) (4) .

d) NCR #CNC-17-383 dated 10/10/2017 regarding the under-potency testing results for Lot #172830001C.

Per this investigation, the under-delivery of drug solution, coupled with the over-delivery of diluent could possibly explain the out-of-limit (OOL). A procedural change to CPS-606 has been submitted and approved for implementation on 11/05/2017 to (b) (4) CAPA-055 will be closed, and a new CAPA (corporate-wide) will continue to monitor the effectiveness of this change by noting any effect on the number and rate of potency OOL's. It should be noted that the above NCRs for over/under potency drug products used the firm's (b) (4) for delivery of (b) (4) of the active drug ingredients to (b) (4) .

OBSERVATION #3

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

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****THIS IS A REPEAT OBSERVATION FROM THE 2013 INSPECTION****

Specifically,

During a walk-through of your facility on 11/27/17 and 11/28/17, we observed the following objectionable conditions during compounding operations in your ISO 5 and 7 environments:

a) Rusted metal hinges on plastic totes used to store in-process and finished drug products in your ISO 7 cleanroom

b) White film residue on wall surfaces of three of your ISO 5 hoods

c) Chipped paint on floor surface of your ISO 7 cleanroom

d) Gray paint residue on walls in your ISO 7 cleanroom

e) Foreign material residue on rubber wheels, located on your metal carts used to transport materials through-out your ISO 7 cleanroom

OBSERVATION #4

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

Specifically,

Environmental monitoring for non-viable particulates is not performed at sufficient frequencies to represent routine production conditions within the ISO 5 and ISO 7 areas of your cleanroom. According to CPS-707, Microbiological and Environmental Testing, Version 23, Effective Date: 10/06/17, your firm performs non-viable monitoring in the ISO 5 areas on a (b) (4) basis. You stated your ISO 7 cleanroom area also follows this same monitoring schedule.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Marvin D. Jones	Marvin D. Jones, Investigator Saundrea A. Munroe, Investigator	01/05/2018

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Cleveland, MS 38732-2106	Outsourcing Facility

OBSERVATION #5

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

Specifically,

a) Your firm had the ISO 7 compounding room (cleanroom) floor resurfaced on two occasions, from 09/01/2017 to 09/04/2017 and from 09/14/2017 to 09/17/2017 by an outside contractor. Prior to this resurfacing on both occasions, all (b) (4) of the ISO 5 LAFHs and other processing equipment were covered with plastic and moved to an unclassified area for storage during this timeframe. After completion of resurfacing on both occasions, the ISO 5 hoods were moved back into the ISO 7 compounding room. Sterile drug processing began in these hoods on 09/05/2017 after the first resurfacing and on 09/17/2017 after the second resurfacing. The ISO 5 hoods were not recertified until 09/22/2017 and the ISO 7 compounding room was not recertified until 09/23/2017. Your firm failed to recertify the ISO 7 cleanroom and ISO 5 LAFHs prior to processing sterile drug products to ensure that the hoods and compounding room were operating within acceptable specification.

b) The certification of your ISO 5 Laminar Airflow Hoods, which is performed and documented every (b) (4), indicates repairs for HEPA Filter Leaks in the following Hoods:

- Hood (b) (4) (b) (4) 2017 documented HEPA Filter Leaks)
- Hood (b) (4) (b) (4) 2017 documented HEPA Filter Leaks)
- Hood (b) (4) (b) (4) 2017 documented HEPA Filter Leaks)
- Hood (b) (4) September 2017 documented HEPA Filter Leak)
- Hood # (b) (4) ((b) (4) 2017 documented HEPA Filter Leaks)
- Hood # (b) (4) ((b) (4) 2017 documented HEPA Filter Leaks)
- Hood # (b) (4) (September 2017 documented HEPA Filter Leak)
- Hood # (b) (4) (March 2017 documented HEPA Filter Leak)
- Hood # (b) (4) (September 2017 documented HEPA Filter Leak)
- Hood # (b) (4) ((b) (4) 2017 documented HEPA Filter Leaks)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Marvin D. Jones	Marvin D. Jones, Investigator Saundrea A. Munroe, Investigator	01/05/2018

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CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Cleveland, MS 38732-2106	Outsourcing Facility

• Hood # (b)(4) ((b) (4) 2017 documented HEPA Filter Leaks)

Hood #'s (b) (4) had documented HEPA Filter Leaks during both the (b) (4) and (b) (4) 2017 certifications. Your firm failed to take corrective actions regarding sterile drug products processed, inside the above listed ISO 5 Hoods, between documented repairs for HEPA Filter Leaks.

OBSERVATION #6

Samples taken of drug products for determination of conformance to written specifications are not representative.

Specifically,

A review of processing records noted concerns with your firm's current sampling methods for sterile injectable finished drug products. For example, your firm is only pulling (b) (4) for sterility/endotoxin (sample pulled needs to be (b) (4) for testing) and (b) (4) for potency/ID (sample pulled needs to be (b) (4) for testing) testing. Per management, the largest finished batch size processed at this facility is approximately (b) (4) (b) (4) units of finished sterile drug product. These samples are pulled only on a (b) (4) basis which is not representative of the entire batch manufacturing process (beginning, middle, and end).

Also, the largest (b) (4) batch size is approximately (b) (4) (b) (4) of finished drug product. The firm does not sample (b) (4) for potency. Per the firm's CAPA #055 dated 07/13/2017, the firm has been having quantity delivery concerns with the (b) (4) delivering the required amount of active drug ingredients and diluent, which has a direct impact on potency.

OBSERVATION #7

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

****THIS IS A REPEAT OBSERVATION FROM THE 2015 INSPECTION****

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Specifically,

1. Your firm conducted an efficacy study to support a (b) (4) time for (b) (4). Your 2017 microbial/environmental logs document, on numerous occasions, spore-forming bacteria in your ISO 5 and ISO 7 zones despite cleaning efforts. Although a disinfectant effectiveness study appears to have demonstrated that a (b) (4) (b) (4) time was sufficient for the sporicide, the supplier recommends a (b) (4) time.

2. Sterile cleaning solutions are compounded and assembled (if not ready to use) in an unclassified area and then transferred into the ISO 7 and ISO 5 environments for use.

3. Your firm uses unfiltered, non-sterile (b) (4) in the preparation of an (b) (4) solution, which is used in the sanitization process as a sporicidal agent for the cleaning of injection sites (vial stoppers and IV ports) prior to aseptic processing. This solution is also prepared in an unclassified area prior to being utilized in the ISO 5 classified area.

4. According to your firm's SOP CPS-310, entitled "SANITATION OF VIAL STOPPERS AND BAG INJECTION PORTS INCLUDING PREPARATION OF SANITIZATION SOLUTION" Version 5, Effective Date: 05/22/17,(b) (4) However, your firm has not conducted any studies supporting the (b) (4) documented in your SOP.

OBSERVATION #8

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

****THIS IS A REPEAT OBSERVATION FROM THE 2015 INSPECTION****

Specifically,

Your firm has had several media fill failures, which indicate that your aseptic techniques are not properly performed. During 2016 and 2017, your firm had a total of 9 media fill failures. Your firm's investigations do not

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properly address the products that were processed by the technicians that failed the media fills.

For example: Per CNC-17-075 dated 02/20/2017, the technician ((b) (6)) had two media fill failures on 02/15/~~201.~~ 2017 nos. The failed test results, regarding the two media fills, were not obtained until 02/20/2017. The investigation concluded that the video footage provided substantial evidence that the processing technician ((b) (6)) had multiple procedural violations relating to improper sanitizations during aseptic processing per CPS-313. Your firm did not perform any type of corrective actions/investigations as to the sterile drug products that were produced by the technician ((b) (6)) on the 02/15/2017, 02/16/2017, 02/17/2017, and 02/20/2017, which included Lot #'s 170450032C, 170460041C, 170460048C, 170460026C, 170480001C, 170470015C, 170470038C, 170500024C, 170500032C, and 170500034C. These Lots were released for distribution.

OBSERVATION #9

The production area air supply lacks an appropriate air filtration system.

****THIS IS A REPEAT OBSERVATION FROM THE 2013 INSPECTION****

Specifically,

A review of the firm's dynamic smoke study videos, dated March 2017 of the ISO 7 cleanroom environment certification, indicated that the pressure differential (airflow) between the cleanroom and ante rooms appeared neutral. According to the smoke study report, signed by QA on 04/03/17, "(b) (6) recommends that an (b) (4) (b) (4) (b) (4) ."

OBSERVATION #10

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

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****THIS IS A REPEAT OBSERVATION FROM THE 2015 INSPECTION****

Specifically,

a) Your firm uses a (b) (4) to remove particulate matter during the (b) (4) process of all finished sterile drug products except Ephedrine drug products. Your firm has not validated the use of these (b) (4) to determine the compatibility of the (b) (4) with the products nor is the (b) (4) use/lot number documented in the batch record.

b) Your firm uses a (b) (4) in the processing of sterile Ephedrine drug products ((b) (4) different item codes) during the (b) (4) process. Your firm has not validated the use of this (b) (4) to determine the compatibility of the (b) (4) with the product nor is the (b) (4) use/lot number documented in the batch record. Also, the firm does not perform a (b) (4) after use of this (b) (4)

c) Your firm has not validated the process for manufacturing sterile finished drug products contained in 250 mL (b) (4) Bags ((b) (4) product codes), 250 mL Blue Cassettes ((b) (4) product codes), 250 mL Yellow Cassettes ((b) (4) product codes), and 250 mL White cassettes ((b) (4) product codes).

d) Your firm does not perform daily checks on scales ((b) (4) total scales) prior to use. These scales are (b) (4) (b) (4) depending upon usage. The scales are used for weighing (b) (4) (b) (4) of active ingredient, (b) (4) (b) (4) containing diluent and active ingredient, and finished product containers. Per management, these scales are calibrated in house every (b) (4).

OBSERVATION #11

Containers and closures are not tested for conformance with all appropriate written procedures.

****THIS IS A REPEAT OBSERVATION FROM THE 2013 INSPECTION****

Specifically,

Your firm does not conduct any sampling/testing upon receipt of sterile finished injectable drug ingredients,

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	Marvin D. Jones	Marvin D. Jones, Investigator Saundrea A. Munroe, Investigator	01/05/2018

MDJ 1/5/18

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product containers or closures; they are approved/released by Quality Assurance without testing. Since raw materials are not tested upon receipt to your facility, potentially defective products are released by your quality unit and utilized in compounding operations. On 11/28/17, your firm initiated a supplier corrective action request (SCAR) for missing graduations on syringes used to produce lot 173310013C HYDROmorphone HCl 1mg/mL on 11/28/17. Since initiation of the SCAR, your firm continued to use this lot of syringes to compound eight (8) additional lots of finished product (173340014C, 173340016C, 173340017C, 173340018C, 173340019C, 173340020C, 173340021C, 173340022C). All products listed have been released by your QA department without resolution of this investigation.

OBSERVATION #12

Container closure systems do not provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

****THIS IS A REPEAT OBSERVATION FROM THE 2013 INSPECTION****

Specifically,

On 11/27/17 during a walk-through of your facility, we observed the storage of two (2) clear in-process containers filled with 10 mcg/ml Fentanyl Citrate in Sodium Chloride 0.9% Lot# 173300032C contained in plastic IV bags, which was awaiting labeling in the staging area. Additionally, we observed one (1) opaque container of Morphine Sulfate 1mg/mL Lot# 173250006C located in the finished product vault. The lid to the storage container was left ajar, allowing light to contact the product. According to labeling on both raw ingredients and compounded products, both are light sensitive and specify to "protect from light." Your SOP, CPS-013, "Storage and Handling of Inventory" Version 13, Effective Date: 06/29/17 also states, "(b) (4) ."

OBSERVATION #13

Batch production and control records do not include complete labeling control records, including specimens or copies of all labeling used for each batch of drug product produced.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
	Marvin D. Jones	Marvin D. Jones, Investigator Saundrea A. Munroe, Investigator	01/05/2018

MDJ 1/5/18

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	FEI NUMBER 3004153061

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Brenda L. Womack, General Manager

FIRM NAME	STREET ADDRESS
PharMEDium Services, LLC.	913 N. Davis Ave.
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Cleveland, MS 38732-2106	Outsourcing Facility

Specifically,

A review of several batch records revealed that these records do not contain samples of the original approved primary, secondary, and case labels applied to the finished drug product.

OBSERVATION #14

Procedures describing the handling of all written and oral complaints regarding a drug product are not followed.

Specifically,

On 09/11/17, your firm performed a recall (RE-17-017) that originated from a consumer complaint regarding illegible expiration date on product label. Per your SOP CPS-007, Recall Procedure, Version 8 Effective Date: 05/04/17, you "will remove the product from the field and then notify the appropriate FDA District office." Your firm did not notify the FDA until inquiry during this inspection.

Additionally, there were 6 recalls performed in 2015 in which zero (0) of them were reported to the FDA. Three (3) (HHE-15-017, HHE-15-020, HH-15-023) were potency related due to stability failures. HHE-015-002 was initiated due to broken syringe caps, HHE-15-022 was initiated due to a cut off expiry date, and HHE-015-026 was initiated due to syringe discoloration. All recalls listed, except for identified stability failures, originated from consumer complaints.

OBSERVATION #15

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

****THIS IS A REPEAT OBSERVATION FROM THE 2013 INSPECTION****

Specifically,

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Marvin D. Jones	Marvin D. Jones, Investigator Saundrea A. Munroe, Investigator	01/05/2018

MDJ
1/5/18

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a) All but 20 of the drug products manufactured by your firm contain preservatives. Your firm does not perform preservative testing on finished sterile injectable drug products that contain preservatives to ensure the concentration is within acceptable specification.

b) Your firm does not test the pH for finished sterile injectable drug products.

c) Your firm does not perform negative controls during the microbial testing of environmental monitoring samples.

OBSERVATION #16

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 your drug product labels:

a) The date that the drug was compounded.
b) A list of active and inactive ingredients, identified by established name and the quantity or proportion of each ingredient.

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

- Morphine Sulfate 1 mg per mL in 0.9% Sodium Chloride Injection (55 mL in 60 mL BD syringe)
- Morphine Sulfate 1 mg per mL Injection (2 mL in BD syringe)
- Fentanyl Citrate 2 mcg per mL and Bupivacaine HCl 0.125% in Sodium Chloride 0.9% Injection (100 mL, 250 mL)
- Morphine Sulfate 5 mg per mL in 0.9% Sodium Chloride Injection (30 mL in 35 mL Monoject Barrel, 50 mL Cassette Reservoir)

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PharMEDium Services, LLC.	913 N. Davis Ave.
CITY, STATE AND ZIP CODE Cleveland, MS 38732-2106	TYPE OF ESTABLISHMENT INSPECTED Outsourcing Facility

- Fentanyl Citrate 20 mcg per mL in Sodium Chloride 0.9% (100 mL)
- Fentanyl Citrate 2 mcg per mL and Ropivacaine HCl 0.2% in Sodium Chloride 0.9% Injection (100 mL)
- Fentanyl Citrate 10 mcg per mL in Sodium Chloride 0.9% (250 mL)
- HYDROmorphone HCl 1 mg/mL in Sodium Chloride 0.9% (30 mL)
- Lidocaine HCl 2% 20 mg per mL (10 mL)
- Midazolam HCl 2 mg per mL in Sodium Chloride 0.9% (50 mL)
- Rocuronium Bromide 10 mg per mL Injection (5 mL)
- Ropivacaine HCl 0.2% in Sodium Chloride 0.9% (100 mL yellow cassette reservoir)

~~OBSERVATION #17~~ Observation Deleted. MDJ 1/5/2018

~~Your outsourcing facility has not submitted a report to FDA identifying a product compounded during the December 1, 2016, through May 31, 2017, reporting period as required by section 503B(b)(2)(A).~~

~~Specifically,~~

~~The following combination drug products were compounded and not identified on your June 2017 report:~~

- ~~Sufentanil Citrate and Bupivacaine HCl in 0.9% Sodium Chloride~~
- ~~Sufentanil Citrate and Ropivacaine HCl in 0.9% Sodium Chloride~~
- ~~Fentanyl Citrate and Bupivacaine HCl in 0.9% Sodium Chloride~~
- ~~Fentanyl Citrate and Ropivacaine HCl in 0.9% Sodium Chloride~~
- ~~Hydromorphone HCl and Bupivacaine HCl in 0.9% Sodium Chloride~~
- ~~Hydromorphone HCl and Ropivacaine HCl in 0.9% Sodium Chloride~~ MDJ 1/5/2018

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