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	11/27/2017-12/15/2017* FEI NUMBER 3007045542

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Ms. April M. Armstrong, General Manager	
FIRM NAME PharMEDium Services, LLC.	STREET ADDRESS 6100 Global Dr
CITY, STATE, ZIP CODE, COUNTRY Memphis, TN 38141-8385	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

The quality control unit lacks authority to review production records to assure that no errors have occurred and fully investigate errors that have occurred.

Specifically,

Your Quality Unit failed to follow the established procedures and conduct an adequate review for the release of final drug products that were found to be out of specifications. In addition, your firm's Quality Supervisor of Operations and Documentation, who is authorized to perform QA final batch record reviews, stated their department does not "verify the validity of the data" contained within the batch records for potency, identity, sterility, and endotoxin prior to QA final release for distribution. During our review of your firm's records, we observed these errors were not identified by your Quality Unit, and were signed as reviewed, and released from your inventory for distribution. For example, but are not limited to:

A. Environmental Monitoring Failures:

1. Several lots were released and distributed that were found to be out of specification for (b) (4) environmental monitoring in the ISO 5 hood where these lots were aseptically produced on the date of failure. For example, but are not limited to:

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	June P Page, Investigator Jennifer L Huntington, Investigator Neda Hamandi, FDA Center Employee or Employee of Other Federal Agencies	X June P Page Investigator Signed By: 2000405709 Date Signed: 12-15-2017 15:56:59	12/15/2017

a. On 01/26/2017, a (b) (4) sample revealed 3 CFU identified as *Bacillus Lichenoformis*, a spore former, in ISO 5 hood (b) (4) On 01/26/2017 (b) (4) lots were produced and distributed on hood (b) (4) resulting in the release of (b) (4) units. For example, but are not limited to:

   i. Lot 170250237M, 100 mcg/mL Phenylephrine HCl (Preservative Free) (Contains Sulfites) in 0.9% Sodium Chloride, resulting in the release of (b) (4) units.

b. On 03/14/2017, a (b) (4) sample revealed 2 CFU identified as *Microbacterium Hydrothermale*, a non-spore former, in ISO 5 hood (b) (4) On 03/14/2017 (b) (4) lots were produced and distributed on hood (b) (4) resulting in the release of (b) (4) units. For example, but are not limited to:

   i. Lot 170730041M, 1 mg/mL Morphine Sulfate (Preservative Free) (Contains Sulfites) in 0.9% Sodium Chloride, resulting in the release of (b) (4) units.

c. On 05/03/2017, a (b) (4) sample revealed 2 CFU identified as *Paenibacillus Vini*, a non-spore former, in ISO 5 hood (b) (4) On 05/03/2017 (b) (4) lots were produced and distributed on hood (b) (4) resulting in the release of (b) (4) units. For example, but are not limited to:

   i. Lot 171220222M, 50 mcg/mL Fentanyl Citrate (Preservative Free) Injection, resulting in the release of (b) (4) units.

d. On 08/10/2017, a (b) (4) sample revealed 2 CFU identified as *Bacillus Lichenoformis*, a spore former, in ISO 5 hood (b) (4) On 05/03/2017 (b) (4) lots were produced and distributed on hood (b) (4) resulting in the release of (b) (4) units. For example, but are not limited to:

   i. Lot 172220122M, 10 mg/mL Methohexital Sodium (Preservative Free) in Sterile Water for Injection, resulting in the release of (b) (4) units.

e. On 08/16/2017, a (b) (4) sample revealed 4 CFU identified as *Penicillium Chrysogenum*, a fungus, in ISO 5 hood (b) (4) On 08/16/2017 (b) (4) lots were produced and distributed on hood (b) (4) resulting in the release of (b) (4) units. For example, but are

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not limited to:

i. Lot 172270189M, 0.4 mg/mL Atropine Sulfate Injection, resulting in the release of (b) (4) units.

2. Several lots were released and distributed that were found to be out of specification for glove fingertip environmental monitoring in the ISO 5 hood where these lots were aseptically produced on the date of failure. For example, but are not limited to:

a. On 10/30/2017, a fingertip sample revealed 7 CFU identified as *Bacillas Thuringiensis*, a spore former, in ISO 5 hood (b) (4) On 10/30/2017 (b) (4) lots were produced on hood (b) (4) resulting in the distribution of (b) (4) units. For example, but are not limited to:

i. Lot 173020012M 0.4 mg/mL Atropine Sulfate Injection, resulting in the release of (b) (4) units

b. On 10/07/2017, a fingertip sample revealed 3 CFU identified as *Staphylococcus Hominis*, a non-spore former, in ISO 5 hood (b) (4) On 10/07/2017 (b) (4) lots were produced on hood (b) (4) resulting in the distribution (b) (4) units. For example, but are not limited to:

i. Lot 172790055M, 2 mcg/mL Fentanyl Citrate and 0.2% Ropivacaine HCl (Preservative Free) in 0.9% Sodium Chloride, resulting in the release of (b) (4) units.

c. On 09/04/2017, a fingertip sample revealed 2 CFU identified as *Paenibacillus Glucanolyticus*, a spore former, in ISO 5 hood (b) (4) On 09/04/2017, the following lot was produced and distributed on hood (b) (4)

i. Lot 172470026M, 10 mg/mL Rocuronium Bromide (Preservative Free), resulting in the release of (b) (4) units.

d. On 09/25/2017, a fingertip sample revealed 2 CFU identified as *Bacillus Subtilis*, a spore former, in ISO 5 hood (b) (4) On 09/25/2017, (b) (4) lots were produced on hood (b) (4) resulting in the distribution of (b) (4) units. For example, but are not limited to:
   i. Lot 172670179M, 1 mg/mL Morphine Sulfate (Preservative Free) in 0.9% Sodium Chloride, resulting in the release of (b) (4) units.

e. On 10/31/2017, a fingertip sample revealed 2 CFU identified as *Staphylococcus Epidermidis*, a non-spore former, in ISO 5 hood (b) (4) On 10/31/2017 (b) (4) lots were produced on hood (b) (4) resulting in the distribution of (b) (4) units. For example, but are not limited to:
   i. Lot 173030024M, 50 mcg/mL Fentanyl Citrate (Preservative Free) Injection, resulting in the release of (b) (4) units.

B. Sterility Failures:
1. Lot 172040012M and Lot 172040203M, Hydromorphone HCL in Sodium Chloride 0.9%, after a confirmed sterility out-of-specification (OOS) which documented five (5) microbes, resulting in the release (b) (4) units.
2. Lot 172540107M, Neostigmine Methylsulfate, after a confirmed sterility OOS which documented one (1) microbe, resulting in the release of (b) (4) units.

C. Endotoxin Failures:
1. Lot 171690199M, 0.2% Ropivacaine, after a confirmed endotoxin OOS which documented a value of <0.14EU/mL (maximum specification (b) (4)), resulting in the release of (b) (4) units.

D. Potency Failures:
1. Lot #171090051M, 10 mcg/mL Fentanyl Citrate (Preservative Free) in 0.9% Sodium Chloride, was found to be super-potent. This product was released on 05/10/2017, resulting in the distribution of (b) (4) syringes.
2. Lot #170890204M, 2.5 mcg/mL Fentanyl Citrate and 0.1% Bupivacaine HCl

(Preservative Free) in 0.9% Sodium Chloride, was found to be super-potent. This product was released on 04/03/2017, resulting in the distribution of (b) (4) syringes.

3. Lot #170250217M, 5 mcg/mL Fentanyl Citrate (Preservative Free) in 0.9% Sodium Chloride, was found to be sub-potent. This product was released on 04/03/2017, resulting in the distribution (b) (4) syringes.
4. Lot #170180002M, 10 mcg/mL Fentanyl Citrate (Preservative Free) in 0.9% Sodium Chloride, was found to be sub-potent. This product was released on 04/12/2017, resulting in the distribution of (b) (4) syringes.

E. During an interview with your firm's QC Supervisor, it was revealed, that the batches are released from your Memphis facility without adequately reviewing the lab investigations conducted by your other locations to determine if these batches are acceptable for release. For example, but are not limited to:

1. Lot #172750101M, 0.125% Bupivacaine HCl (Preservative Free) in 0.9% Sodium Chloride.
2. Lot #173220027M, 1% Lidocaine HCl (Preservative Free) in 0.9% Sodium Chloride.

F. Non-conformance, MNC-17-1279, addresses your QC department's lack of investigations regarding system suitability failures, the unjustified use of various analytical instruments during an investigation, insufficient data to determine if a confirmed OOS occurred. This non-conformance addresses (b) (4) lots, which resulted in the distribution of (b) (4) units.

OBSERVATION 2

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

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Specifically,

1. Your firm continued processing and released finished products after confirmed media fill failures.
    a. Process PRO028 (100 mL bag) failed media fill on 01/18/17 and on 04/13/17. Your firm continued processing resulting in the production and distribution of at least (b) (4) units.
    b. Process PRO026 (250 mL bag) failed media fill on 06/01/2017. Your firm continued processing resulting in the production and distribution of at least (b) (4) units.
    c. Process PRO042 (250 mL cassette) failed media fill on 06/21/2017. Your firm continued processing resulting in the production and distribution of at least (b) (4) units. For example, but not limited to:
        i. A total of (b) (4) unique batches of 0.1% Bupivacaine HCl (Preservative Free) in 0.9% Sodium Chloride were produced despite the PRO042 (250 mL cassette) failed process validation on 06/21/2017. The total units distributed are: (b) (4) units. For example: Batch 172540226M was produced on 09/14/2017 despite that PRO042 (250 mL cassette) failed process validation on 06/21/2017.
    d. Process PRO032 (150 mL cassette) failed media fill on 06/28/2017. Your firm continued processing resulting in the production and distribution of at least (b) (4) units. For example, but not limited to:
        i. A total of (b) (4) unique batches of 12 mg Dexamethasone Sodium Phosphate (0.24 mg/mL) added to 0.9% Sodium Chloride were produced despite the PRO032 (150 mL cassette) failed process validation on 06/28/2017. The total units distributed are: (b) (4) units. For example: Batch 173160087M was produced on 11/16/2017 despite that PRO032 (150 mL cassette) failed process validation on 06/28/2017.
2. Your firm failed to follow your SOP, CPS-303, Operation of Laminar Air Flow Benches; which states the following: (b) (4)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	June P Page, Investigator Jennifer L Huntington, Investigator Neda Hamandi, FDA Center Employee or Employee of Other Federal Agencies	X June P Page Investigator Signed By: 2006405709 Date Signed: 12-15-2017 15:58:59	12/15/2017

(b) (4)

For example:

a. (b) (4) particle counts performed from 10/01/17 to 10/29/17, which are documented on Form #F-303-002, documents ISO 5 laminar air flow hoods in the ISO 7 Main Clean room and ISO 7 Suites (b) (4) were not (b) (4) as per your SOP-303. All testing performed in October were due to a Critical Work Order (CWR) and were performed under static conditions. No routine (b) (4) monitoring was performed in October 2017. In addition, not all ISO 5 laminar air flow hoods were tested in October as per your procedure CPS-303.

b. (b) (4) particle counts performed November 12, 2017, which are documented on Form #F-303-002, documents ISO 5 laminar air flow hoods and ISO 5 (b) (4) fillers (b) (4) (b) (4) located in ISO 7 Suites (b) (4) were not (b) (4) (b) (4) as per your procedure, CPS-303. All of the forms provided document the sampling was for CWR under static conditions. No routine (b) (4) monitoring was performed in November 2017 for the hoods in the ISO 7 Suites and ISO 5 (b) (4) fillers.

3. During our observation of aseptic processing, we observed the following:
   a. On 11/27/2017, Personnel conducted aseptic manipulations in an area that blocked the movement of (b) (4) air around an open unit, either before or after it was filled with sterile product.
   b. On 11/27/2017, we observed employees grasping the syringe plunger during aseptic processing.
   c. On 11/27/2017, personnel moved rapidly in the vicinity of open sterile units, which disrupted the airflow and increased the risk of bringing lesser quality air into the ISO 5 classified aseptic processing area.
   d. On 11/27/2017, personnel touching equipment or other surfaces located outside of the ISO 5 classified aseptic processing area with gloved hands and then engaged in aseptic processing without sanitizing gloves.

e. On 11/28/17, we observed an employee leaning against the wall in main ISO 7 clean room.

OBSERVATION 3

Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable construction and location to facilitate cleaning, maintenance, and proper operations.

Specifically,

Your firm failed to establish an adequate air supply filtered through (b) (4) air filters under positive pressure in the aseptic processing areas.

1. The syringe filling machine (ISO 5) remains open to a Controlled Non-Classified (CNC) area during aseptic production. Furthermore, construction in the NC area occurred from 7/29/17 through 11/19/17 while production was taking place. Approximately (b) (4) aseptically produced lots were made and distributed during this period of time.

2. On 11/28/17, we observed a cracked light cover approximately 6 inches long and 1 inch wide located directly above the compounding area in ISO 5 (b) (4) (b) (4). In addition, we observed light fixture covers lifted creating gaps located directly above the compounding area in (b) (4) operational ISO 5 (b) (4) exposing uncleaned areas to aseptic processing.

3. On 11/28/17, we observed approximately a 2in x4mm gap in between the ceiling tiles above Hood (b) (4).

OBSERVATION 4

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

Specifically,

1. Your firm conducted an efficacy study to support a (b) (4) contact time for (b) (4) (b) (4) however your firm continued to identify spore-forming bacteria in your ISO 5 and ISO 7 zones even though they have been cleaned. Although a disinfectant effectiveness study appears to have demonstrated a (b) (4) contact time was sufficient for the sporicide, the supplier recommends a (b) (4) contact time.
2. Sterile cleaning solutions are prepared in an unclassified area and then transferred into the ISO 7 clean room.
3. Your firm uses (b) (4) in the preparation of (b) (4) sterile (b) (4) solution which is used in the sanitization process as a sporicidal agent for injections sites. This is prepared in an unclassified area prior to being utilized in the ISO 5 and ISO 7 classified areas.

OBSERVATION 5

Drug product production and control records, are not reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed.

Specifically,

1. During the review of your QC lab investigations, we noted potency failures initially ran on your firm's (b) (4) and subsequently passed when re-tested on an (b) (4) instrument. However, your firm failed to establish the use of various instruments during an investigation. This same observation was discovered by your firm on 04/06/2017, under Investigation, 17-TN-117. However, your QC Analysts continue to perform subsequent re-testing on an (b) (4) instrument after a failed (b) (4) result during an investigation to justify the release of final drug products,

without written approval from your firm's Director of Quality Control. In addition, during an interview of your QC Analyst, they stated these (b) (4) failures corresponded to around the same timeframe of a raw material supplier change. For example, but are not limited to:

a. 170920040M: 0.3 mg/mL HYDROmorphone HCl in 0.9% Sodium Chloride
b. 170920299M: 0.5 mg/mL HYDROmorphone HCl in 0.9% Sodium Chloride
c. 172330191M: 1 mg/mL Morphine Sulfate (Preservative Free) (Contains Sulfites) in 5% Dextrose
d. 172700026M: 2 mg/mL HYDROmorphone HCl Injection
e. 170740181M: 0.1 mg/mL HYDROmorphone HCl in 0.9% Sodium Chloride

2. Your firm failed to reject batches with confirmed OOS for endotoxin levels. Lab investigations document OOS endotoxin levels where the original test results were not invalidated. The samples were retested, and passing results are documented in the batch records. Examples include, but are not limited to the following:
   a. Investigation 17TN236 was opened to investigate an Endotoxin failure for Lot 170390046M, Propofol 1% Injectable Emulsion. The sample was retested and passed without justification, resulting in the distribution of (b) (4) units.
   b. Investigation 17TN203 was opened to investigate an Endotoxin failure for Lot 170360013M, Propofol 1% Injectable Emulsion. The sample was retested and passed without justification, resulting in the distribution of (b) (4) units.

OBSERVATION 6

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.

THIS IS A REPEAT OBSERVATION

Specifically,

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1. Your firm failed to investigate and appropriately determine if batches can be released for Potency, Identity, Endotoxin, and Sterility final release out-of-specifications. For example, but are not limited to:

   a. Your firm released (b) (4) batches that were under investigation and identified to have confirmed final release specification failures, resulting in the distribution of (b) (4) units.

   b. Your firm released (b) (4) batches that were under investigation and identified to have "Insufficient Data to Assess"; resulting in the distribution of (b) (4) units.

   c. Your firm failed to provide the original lab investigation for investigation 17TN927 for a sterility failure for (b) (4) for the following lots. Your firm recreated the investigation on 12/06/17 and provided a Memo dated 12/06/17 with the intent to recreate the investigation.

      i. 171500154M: 2 mcg/mL Fentanyl Citrate and 0.125% Bupivacaine HCl (Preservative Free); resulting in the release of (b) (4) units.
      ii. 171500246M: 2 mcg/mL Fentanyl Citrate and 0.0625% Bupivacaine HCl (Preservative Free); resulting in the release of (b) (4) units.
      iii. 171500117M: 2 mcg/mL Fentanyl Citrate and 0.0625% Bupivacaine HCl (Preservative Free); resulting in the release of (b) (4) units.

   d. Investigation STER-TN-17-003 was opened on 09/19/17 to investigate a confirmed Sterility failure for Lots 172610078M, 172610098M, 172610099M, and 172610231M, Midazolam. There has been no investigation as to the root cause of the sterility failure and there has been no assessment of other batches that may have been impacted by the sterility failure.

e. Investigation STER-TN-17-001 was opened on 08/29/17 to investigate a confirmed Sterility failure for Lots 172390034M and 172390170M, Verconium Bromide. There has been no investigation as to the root cause of the sterility failure and there has been no assessment of other batches that may have been impacted by the sterility failure.

f. Investigation END-TN-17-012 was opened on 08/31/17 to investigate a confirmed endotoxin failure for Lot 172410236M, Phenylephrine. There has been no investigation as to the root cause of the endotoxin failure and there has been no assessment of other batches that may have been impacted by the endotoxin failure.

g. Investigation END-TN-17-050 was opened on 10/04/17 to investigate a confirmed endotoxin failure for Lot 172760171M, Ropivacaine. There has been no investigation as to the root cause of the endotoxin failure and there has been no assessment of other batches that may have been impacted by the endotoxin failure.

2. Your firm failed to perform an adequate review of extraneous peaks due to a (b) (4) resulting in the distribution of product. On 04/08/2017, your firm's Investigation Plan ID, 17TN544-IP08Apr2017A, indicated three extraneous peaks were detected in the (b) (4) analysis of Fentanyl. The result of the experiment indicated that the third extraneous peak is likely a (b) (4) . Approximately, (b) (4) lots of fentanyl were documented in your firm's lab investigations for this issue; these lots were released. For example but not limited to:

   a. Lot 170890053M, 10 mcg/mL Fentanyl Citrate (Preservative Free) in 0.9% Sodium Chloride, resulting in the release of (b) (4) units.
   b. Lot 170930174M, 10 mcg/mL Fentanyl Citrate (Preservative Free) in 0.9% Sodium Chloride, resulting in the release of (b) (4) units.
   c. Lot 170890050M, 5 mcg/mL Fentanyl Citrate (Preservative Free) in 0.9% Sodium

Chloride, resulting in the release of (b) (4) units.

OBSERVATION 7

Input to and output from the computer, related systems of formulas and records or data are not checked for accuracy.

Specifically,

1. Quality Control laboratory release specification for Sterility, Endotoxin, Potency, and Identity are accessible for unlimited printing, without any means of reconciliation (i.e. no date/time-stamp) by non-QC personnel.

    a. For example, during our review of your firm's records, we observed multiple copies for QC final specification result sheets with varying results (ex. a failing result was observed in your investigation reports and a passing result was observed in your batch records for the same lot).

2. Your firm does not have written procedures in place describing the review of analytical data used for final release testing of finished drug products. Currently, your firm uses (b) (4) , (b) (4) , and (b) (4) for potency and/or identification testing. Your firm does not conduct a review of the electronic data to ensure (b) (4) integrations are not conducted, audit trails are not routinely reviewed to ensure your product has undergone unauthorized retesting or whether data has been otherwise manipulated.

3. The use of uncontrolled spreadsheets is used during the electronic review of final release specifications for potency by your firm's chemical analytical laboratory. Your analyst demonstrated the final release potency limits on this spreadsheet are unprotected and can be altered.

4. Electronic logs of Quality System reports or files are maintained on uncontrolled spreadsheets. These uses of these spreadsheets are not referenced in any written procedure and do not have an audit trail function to track manipulations. For example, your QC department has provided us with multiple spreadsheets to track laboratory investigations. In addition, we have observed the use of uncontrolled spreadsheets to track Notice of Events (NOE) reports; Non-Conformance Reports (NCRs); Customer Complaints; and Laboratory Out-of-Specifications.

OBSERVATION 8

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

Specifically,
Your firm failed to conduct adequate investigations and institute appropriate corrective actions for customer complaints. Some examples include, but are not limited to the following:

1. Complaint #30030, reported on 10/04/17, documents the non-therapeutic effect of 10 mg/mL Methohexital Sodium (Preservative Free) in Sterile Water for Injection 5 mL in 5 mL BD Syringe, Lot 172390024M. This complaint investigation documents the testing of five (5) samples returned by the customer which were tested by your contract laboratory, (b) (4) (b) (4) According to your contract lab, intact units passed identity and potency testing within product limits however we observed they did not pass for potency per your firm's specifications.

   In addition, no other lots were reviewed during this investigation to assess for trends with the Methohexital drug product. We observed four additional customer complaints for non-therapeutic effect or potency issues for 10 mg/mL Methohexital Sodium (Preservative Free) in Sterile Water for Injection.

2. Complaint #25598, reported on 2/24/17, documents an adverse event due to the use of 1mg/mL Morphine Sulfate (Preservative Free) in 0.9% Sodium Chloride 2mL in 3mL BD Syringe, Lot

170190048M. PharMedium Complaint Investigation #25598 recorded the Patient Outcome as: "A life threatening adverse drug experience". The patient had seizure-like activity and loss of consciousness and had assistance through ventilation. The investigation stated this was an expected adverse event for Morphine sulfate. No other investigation as to the root cause was performed. In addition, per your firm's procedure, CPS-009, Incident/Complaint Handling Procedure, a life threatening adverse drug experience is considered a serious adverse drug experience and is to be reported to the FDA within 15 calendar days. This serious adverse event was not reported to the FDA.

3. Complaint #28538, reported on 7/28/17, documents multiple under-filled syringes for 5mg/mL Ephedrine Sulfate (Preservative Free) in 0.9% Sodium Chloride, Lot 171780037M. The investigation determined two (2) other complaints for the same lot (Complaint #28853 and Complaint #28185). The under-filled syringes were confirmed upon inspection of returned samples. Your investigation determined there were no production-related issues, however there is no documentation of the manufacturing investigation. I observed that the batch record does not include documentation of a visual inspection for this lot which was manufactured on (b) (4) (b) (4) The root cause documents the only way this could have occurred would be due to (b) (4) (b) (4) t. The firm reported this potential root cause to the manufacturer of the (b) (4) (b) (4) There was no evaluation by the Quality Unit as to the impact of (b) (4) for this lot and no investigation was performed into other batches to assess the impact of the lot of (b) (4) used in the production of Lot 171780037M.

4. Complaint #30676, dated 10/26/17, reports 23 leaking units for 25mcg/mL Fentanyl Citrate (Preservative Free) in 0.9% Sodium Chloride 100mL in 100mL Medication Cassette Reservoir, Lot 172910051M. The investigation reports four other incidents for this lot (Complaint #30551, dated 10/23/17; Complaint #30565, dated 10/23/17; Complaint #30575, dated 10/23/17; and Complaint #30671, dated 10/26/17). The investigations reveal clamps were not engaged and, in some cases, caps were completely off. There is no manufacturing investigation documented and no root cause has been identified. In addition, there has been no assessment by your Quality Unit

as to the disposition of this lot and the potential effects on other similar batches.

OBSERVATION 9

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.

Specifically,
The Expiration Date is exceeding the time frame supported by your firm's stability study data. For example:

1. Methohexital samples tested in your stability study were stable for 31 days. However, your firm's current expiration date for 10 mg/mL Methohexital Sodium (Preservative Free) in Sterile Water for Injection is 42 days.

2. Remifentanil samples tested in your stability study were stable for 15 days. However, your firm's current expiration date is 27 days for 50 mcg/mL Remifentanil HCl (Preservative Free) in 0.9% Sodium Chloride.

OBSERVATION 10

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

Specifically,

1. Regardless of batch size, (b) (4) is pulled for sterility and endotoxin testing of all batches. According to your procedure, CPS 790, Using (b) (4) for Sterility Testing of Compounded Sterile Preparations, a volume between (b) (4) is the minimum sample volume for drug products tested at your firm. For example:
    a. Ephedrine Sulfate 5mg/ml in 5mL BD syringes, Lot 171780037M, was produced on 06/28/17 and filled on the (b) (4) syringe filling line (b) (4) This batch was

compounded into (b) (4) (b) (4) (b) (4) which were then filled into (b) (4) 5mL BD syringes. A (b) (4) unit was collected for sterility testing.

2. Your firm does not perform 100% visual inspection of finished sterile drug products against a contrasting background with adequate lighting for product contamination prior to distribution.

OBSERVATION 11

Written procedures are not followed that describe the tests and examinations to be conducted on appropriate samples of in-process materials of each batch.

Specifically,

Your firm failed to notify your customers regarding the recall for the following Endotoxin failure:

Lot 171770059M, 0.2% Ropivacaine HCl in 0.9% Sodium Chloride, was released and distributed on 06/27/2017. The Endotoxin test results were documented in the batch records as less than 0.15 EU/mL and indicated as Pass. The actual Endotixin results were 0.19 EU/mL. The specifications are (b) (4).

OBSERVATION 12

Employees engaged in the manufacture, processing, packing and holding of a drug product lack the training required to perform their assigned functions.

Specifically,

Out of (b) (4) employees, only (b) (4) have access to your firm's Standard Operating Procedures (SOP). Your firm maintains the "read-only" copies of its SOPs in the program (b) (4). Only (b) (4) employees have

access and have been trained to use this program. Per your Senior Operations Manager, employees must obtain SOPs from a supervisor in order to review or reference.

OBSERVATION 13

The labels of your outsourcing facility's drug products are deficient.

Specifically,

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

1. The date that the drug was compounded.
2. 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:

- Fentanyl 2 mcg per mL and Bupivicaine 0.1% in 0.9% Sodium Chloride Injection, 100 mL Cassette
- Fentanyl 10 mcg per mL in 0.9% Sodium Chloride Injection, 2.5 mL
- Hydromorphone 1 mg per mL in 0.9% Sodium Chloride Injection, 50 mL Intravia Bag

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***DATES OF INSPECTION**

11/27/2017(Mon), 11/28/2017(Tue), 11/29/2017(Wed), 11/30/2017(Thu), 12/01/2017(Fri), 12/04/2017(Mon), 12/05/2017(Tue), 12/06/2017(Wed), 12/07/2017(Thu), 12/08/2017(Fri), 12/11/2017(Mon), 12/12/2017(Tue), 12/13/2017(Wed), 12/15/2017(Fri)

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	11/27/2017-12/15/2017* FEI NUMBER 3007045542

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Ms. April M. Armstrong, General Manager

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

X Neda Hamandi
FDA Center Employee or Employee of Other Federal Agencies
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Date Signed: 12-15-2017 15:57:36

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Investigator
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SEE REVERSE OF THIS PAGE

EMPLOYEE(S) SIGNATURE
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DATE ISSUED
12/15/2017