DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
US Customhouse, Rm 900 2nd & Chestnut St Philadelphia, PA 19106 (215) 597-4390 Fax:(215) 597-0875 Industry Information: www.fda.gov/oc/industry	02/03/2015 - 02/11/2015* FEI NUMBER 3009590582

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Robert M. Kelly, Director of Pharmacy

FIRM NAME	STREET ADDRESS
Central Admixture Pharmacy Services, Inc.	6580 Snowdrift Rd Ste 100
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Allentown, PA 18106-9331	Drug Compounding 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:

PRODUCTION SYSTEM

OBSERVATION 1

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

Specifically, there is no validation data to assure that (b) (4) used to compound Oxytocin products can maintain sterility for the duration of the batch. (b) (4) can be used to compound more than (b) (4) units of Oxytocin. Over (b) (4) lots of Oxytocin products were produced during the month of January 2015.

OBSERVATION 2

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

Specifically, gowning qualification program to qualify the compounding operators working in the ISO5/ISO7 areas is inadequate, as specified in the procedure# SOP-CAPS-4000516, entitled, *Gowning Requirements -LHV*, version 7.0, in that surface monitoring sites on personnel do not challenge all potential sites that may come into contact with ISO 5 production areas. On 2/5/2015, I observed an operator leaning into the ISO 5 hoods several times during production with body parts, including head, shoulder, upper arm, that were not monitored during the gown qualification.

LABORATORY CONTROL SYSTEM

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	Vlada Matusovsky, PAI Manager Kendra L. Brooks, Investigator Junho Pak, Investigator MICHAEL L. CASNER, INVESTIGATOR	02/11/2015

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OBSERVATION 3

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

Specifically,

a) Alternate Sterility testing method used for product release testing, (b) (4) , is inadequate to detect low level microbial contamination from the final product (b) (4) sterility method has a maximum test sample capacity of (b) (4) For the 1000ml Oxytocin products (b) (4) of the product content is sampled for sterility testing using (b) (4) compared to 10% (b) (4) or more of the product content that is specified in USP <71> Sterility Test. Furthermore, inadequate representative of the produced lot is placed on sterility test. For lot size of 100 units or more, 10 units need to be tested for sterility. Over (b) (4) Oxytocin lots were produced and released in Jan 2015, using (b) (4) sterility testing method.

b) (b) (4) sterility testing method has not been proven to show equivalency to USP <71> Sterility Testing to capture low levels contamination from actual product packaging. Validation failed to evaluate the inherent product dilution effects from the product volumes up to 1000ml. Low sample test volume of (b) (4) for (b) (4) has not been evaluated against the higher sample volume (b) (4) or more) specified in USP <71>Sterility Testing.

QUALITY SYSTEM

OBSERVATION 4

There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

a) Investigation # 37-150122-013 initiated on 1/22/15 following a sterility failure (with subsequent recovery of *Bacillus lentus*) obtained on testing of Oxytocin 20u in 1000 ml Normal Saline, lot 37-81641, compounded on bench #(b) (4) on 1/19/15 and subsequently quarantined is inadequate in that:

   i) The decision to invalidate the result as well as the conclusions that the failure was caused by an inadequate "sterility testing procedure" and/or by "Inadvertent lapse in proper material introduction" are not substantiated by appropriate data and/or evidence.

   ii) Not all products and/or lots that possibly could have been affected by the incident have been evaluated as part of the investigation. For example, multiple lots of Oxytocin and other products have been compounded on

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various days utilizing the same raw materials that are not tested by the firm to verify their sterility. There is no evaluation of the impact on Oxytocin 20 u in 1000 ml D5W LR lot 37-81640 that was compounded on the same day (1/19/15), on the same bench (# (b) (4) using the same (b) (4) . In addition, there was no in-depth evaluation of the Oxytocin raw material lot (b) (4) used in compounding of Oxytocin 20u in 1000 ml Normal Saline, lot 37-81641, although the lot is reportedly is still on hand and is being used in compounding of other lots.

iii) The investigation is silent as to the occurrence of another sterility failure and recovery of bacillus species (*Bacillus pumilus*) from TPN (Total Parenteral Nutrition) Starter Bag, lot 37-74816, compounded on bench # (b) (4) (b) (4) on 12/15/14 and a possible relation between the two failures. In fact, the investigation documents that only the results of the 2015 lots were considered as part of the historical data evaluation.

b) Investigation # 37-141217-0190 initiated on 12/17/14 following a sterility failure (with subsequent recovery of *Bacillus pumilus*) obtained on testing of TPN (Total Parenteral Nutrition) Starter Bag, lot 37-74816, compounded on bench # (b) (4) on 12/15/14 and subsequently recalled is inadequate in that:

i) The decision to invalidate the result as well as the conclusions that the failure was possibly caused by a "temporary lapse in proper material introduction" and/or "lapse in aseptic technique during sampling or sterility testing" are not substantiated by appropriate data and/or evidence.
ii) Not all products and/or lots that possibly could have been affected by the incident have been evaluated as part of the investigation. For example, there was no evaluation of multiple lots of TPN and other products that were compounded on 12/15/14 on the benches adjacent to bench #(b) (4)

OBSERVATION 5

Batch production and control records for each batch of drug product produced do not include an accurate reproduction of the appropriate master production or control record which was checked for accuracy, dated and signed.

Specifically, the firm's reconciliation of rejected/awaiting destruction and accepted units is not always accurate. For example,

a) There is a discrepancy in the accountability of the reserve units for Oxytocin 20u in 1000 ml Normal Saline, lot 37-81641, compounded on 1/19/15 shipped to the CAPS, Irvine CA site on 1/22/15. The Irvine CA site received only [b] reserve units while the CAPS Sample Submission Form documented that [b] were sent. The discrepancy was not noticed until 1/26/15 when the Irvine CA site contacted the Allentown site to report the issue. The investigation into the event was initiated on 1/28/15 and is still in-progress. Reportedly the missing reserve unit was destroyed by the pharmacist on 1/19/15 due to leakage. There was no documentation of this event. In addition, there is a discrepancy in the accountability of the units accepted ((b) (4) units) documented in the batch record for Oxytocin 20u in 1000 ml Normal Saline, lot 37-81641 and the total number of units ((b) (4)

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units) shipped to/received by the CAPS, Irvine CA site as documented on the CAPS Sample Submission Form.

b) There is a discrepancy in the accountability of the units rejected ([redacted] units) documented in the batch record for Oxytocin 20u in 1000 ml Normal Saline, lot 37-81641, compounded on 1/19/15 and the total number of rejected units awaiting destruction ([redacted] units) as documented on the Compounded Preparation Destruction Log. The rejected units were reportedly found in the warehouse reject area by the firm's employee(s) on 1/28-29/15 after the discrepancy was discovered.

OBSERVATION 6

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

Specifically, in the ISO 8 gowning airlock, two operators on two separate days (2/3/2015 and 2/5/2015) were observed to repeatedly contact the outer surfaces of their sterile gowns with the bare skin of their arms. The firm experienced an action level excursion during environmental monitoring conducted during compounding operations on 12/1/14; the investigation concluded that the most probable cause of the excursion, which involved a human skin organism, was improper aseptic technique.

*** DATES OF INSPECTION:**
02/03/2015(Tue), 02/04/2015(Wed), 02/05/2015(Thu), 02/11/2015(Wed)

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