DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
US Customhouse Rm900 200 Chestnut St Philadelphia, PA 19106 (215)597-4390 Ext:4200 Fax:(215)597-0875 ORAPHARM1_RESPONSES@fda.hhs.gov	2/27/2023-3/30/2023* FEI NUMBER 3009590582

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Rachel C. Schwartz, 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	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 OBSERVED:

OBSERVATION 1

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, your firm's investigation into mold and spore-forming micro-organisms identified from environmental monitoring (EM) samples collected in ISO 5 classified clean room areas used in the production of sterile drug products are deficient:

A. Investigation NQE-US58-221214-564 was opened 12/14/2022 and closed 03/27/2023 for all mold recoveries during the month of November 2022. In November 2022, your firm had five EM excursions of 1 CFU/mL (specification: (b) (4) CFU) identified as *Penicillium chrysogenum/ Penicillium species* recovered in four different ISO 5 laminar air flow (LAF) hoods. Your firm released two out of (b) (4) of the affected lots in which 1CFU of *Penicillium chrysogenum* was recovered in (b) (4) different ISO 5 EM surface samples of LAF hoods (b) (4) : Potassium Phosphate 30mmol/500mL NS, Lot#(b) (4) , Exp: 16 Feb 2023 and del Nido formula (Plasmalyte), Lot# (b) (4) , Exp: 16 Jan 2023. Both lots were produced and released into market. Additional recoveries of *Penicillium species* were recovered in a viable air EM sample of ISO 5 LAF hood (b) (4) in which Vancomycin 1.25gram/ 250ml Dextrose, Lot# (b) (4) , Exp: 05/07/2023 was produced. This lot was also released for further distribution. Your firm's investigation failed to determine and implement the appropriate corrective actions.

B. On 11/9/2022, 1CFU/mL of *Nigrospora* species was identified on the right sleeve of an aseptic

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technician's personnel monitoring sample (specification: (b)(4) cfu) during the preparation of Induction 8:1 High Potassium, Lot#(b) (4) , Exp: 24 Dec 2022 and Maintenance 4:1 Low K (20mEq), Lot# (b) (4) , Exp: 24 Dec 2022. Additionally, on 01/31/2023, 1 CFU/mL of *Nigrospora* species was recovered on the right fingertip of an aseptic technician's personnel monitoring sample during the preparation of Oxytocin 30 units/ 500mL NS, Lot#(b) (4) Exp: 01 May 2023. Your firm released all lots for further distribution without a thorough investigation.

C. On 12/23/2022, your firm identified 1CFU/mL of *Chaetomium globosum*, a mold species, on the right finger tip of an aseptic technician's personnel monitoring sample (specification: (b)(4) cfu) during the preparation of Reperfusate NO K, Lot#(b) (4) , Exp: 02/13/2023. Your firm released this lot for further distribution without a thorough investigation.

D. On 02/01/2023, your firm identified 1 CFU/mL of a gram-negative bacteria, *Klebsiella oxytoca*, on the touch screen of your compounding machine (specification: (b)(4) cfu) that is within your ISO 5 LAF hood, where Maintenance 8:1 Low K , Lot# (b) (4) Exp: 18 Mar 2023, was produced. Your firm released this lot for further distribution without a thorough investigation.

OBSERVATION 2

Written records of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications do not always include the conclusions and follow-up.

Specifically, your firm's environmental monitoring (EM) and personnel monitoring (PM) data shows recovery of spore forming microorganisms of 1 CFU/mL in your ISO 5 critical zone areas for approximately 100 instances since November 2022 to March 2023. Despite recovering a significant number of bacteria, yeast, mold, and other spore forming organisms, your firm failed to conduct

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investigations into the root causes or implement adequate corrective and preventative actions to mitigate the risk of mold and spore forming bacteria thereafter. During this same time frame, your firm continued to manufacture and distribute sterile injectable drug products made in the same ISO 5 locations with recovery of micro-organisms. The following are some examples of the drug product(s) batches produced on the same days mold forming bacteria was recovered from their respective ISO 5 areas:

A. On 01/26/2023, 1CFU, identified as *Micrococcus lutecus,* was recovered on the right sleeve (Specification: (b)(4) CFU) of an operator during the production of Norephinephrine 4mg/250mL D5W, Lot# (b) (4) , Exp: 26 April 2023

B. On 02/02/2023, 1CFU, identified as *Brevibacterium* species, was recovered on the right fingertip (Specification (b)(4) CFU) of an operator during the production of Modified St. Thomas Formula Low K (70eQ) 1000mL, Lot# (b) (4) Exp: 19 Mar 2023

C. On 02/14/2023, 1CFU, identified as *Bacillus licheniformis,* was recovered from the surface of a repeater pump in LAF hood (b)(4) (Specification (b)(4) CFU) during the production of Heparin 2,500 units/ 500mL NS, Lot# (b) (4) , Exp: 25 April 2023

D. On 02/15/2023, 1CFU, identified as *Stahylococcus hominis,* was recovered on a surface sample (Specification: (b)(4) CFU) in the ISO 5 LAF hood (b)(4) during the sterility testing of drug product lots produced. Three batches were also compounded in the ISO 5 LAF hood (b)(4) on02/15/2023 were tested and released for distribution: Oxytocin 20 units, Lot# (b) (4) Exp: 16 May 2023; Oxytocin 30 units, Lot# (b) (4) , Exp:16 May 2023; and, Oxytocin 30 units, Lot# (b) (4) , Exp: 16 May 2023.

In each of the above instances these finished sterile injectable products were released for distribution.

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OBSERVATION 3

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

Specifically,

A. According to your firm's procedure, TP- CAPS-4000040, *Sterility Testing Using* (b) (4) (b) (4), step 2.6.3A states to collect a (b) (4) aliquot to test the sterility of your sterile drug products using an alternative sterility test method via the (b) (4) (b) (4) Your firm lacks supporting data or scientific rationale demonstrating that a reduced sample volume relative to the volume recommended in USP<71> is at least equivalent to the USP method, For example, for your firm's drug product, Oxytocin 30 units/ 500mL NS, Lot (b) (4), Exp: 01 May 2023, only (b) (4) was tested from each of the containers collected, which is only (b) (4) of your fill volume. Your firm provided no data to support the adequacy of conducting sterility testing with sample size volumes that are less than those required by the USP <71> sterility testing method. Since microbial contamination may not be uniformly distributed throughout a drug product unit, reduced sample volumes could potentially cause false negative sterility test results and inappropriate release of finished sterile injectable products into the market.

Your firm uses the (b) (4) sterility test method with a maximum sample size of (b) (4) to conduct sterility testing on all finished sterile injectable products produced and distributed and this observation impacts all lots of sterile drug product currently released and within expiry.

B. Your firm incubates sterility test samples of drug products from (b) (4) days. The incubation period performed for the method suitability studies allowed samples of bacteria to be incubated for (b) (4) days and samples of fungi to be incubated for (b) (4) days. Your firm's method suitability studies examined growth from days (b) (4) (in USP<71> an incubation period of 14 days is required). Your firm does not have any scientific justification for (b) (4) the incubation period used for sterile drug products using this alternative sterility

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method. This observation applies to sterility testing of all finished sterile drug products that your firm produces.

OBSERVATION 4

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

Specifically, there is no scientific rationale or data to support the use of a reduced sample size of (b) (4) used by your firm in the alternate sterility testing system, (b) (4), which has a maximum sample size capacity of (b) (4). For example, the firm's sterility test sample size for the total parenteral nutrition (TPN) product, Trophamine 2% / Dextrose 10% product, filled to (b) (4) mL, is (b) (4) (b) (4) of the product volume, which is tested for sterility using the (b) (4). However, USP <71> requires a minimum sample size of 10% of the total volume (b) (4) mL for the TPN example). Your firm uses this (b) (4) sterility test method to conduct sterility testing on all finished sterile injectable products produced and distributed and this observation impacts all lots of sterile drug product currently released and within expiry.

THIS OBSERVATION WAS PREVIOUSLY CITED IN 2015 AND 2018.

OBSERVATION 5

Procedures designed to prevent objectionable microorganisms in drug products not required to be sterile are not established and followed.

Specifically,

A. On 03/01/2023, during the production of Micro Del Nido, Lot#(b) (4), Exp: 16 Apr 2023, which was performed in the vertical Laminar Air Flow (LAF) hood (b) (4) a (b) (4) was used to fill approximately (b) (4) syringes. During the production process, I observed an employee block the critical areas from receiving first pass air flow from the (b) (4) ISO 5 LAF hood when connecting and

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removing the syringes from the product (b) (4). The operator was also observed inverting the syringe filled with sterile Micro Del Nido, Lot# (b) (4), pointing the open end straight down which blocked first pass ISO 5 air to cap the filled syringe.

B. On 02/28/2023, during the filling process of Sodium Phosphate Lot (b) (4) Exp: 29 May 2023, your quality control technician was observed performing a finger-tip PM sample on an IV technician immediately after the IV technician sprayed their gloved hands with sterile (b) (4) while producing drug product in the ISO 5 LAF hood.

OBSERVATION 6

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

Specifically, on 03/01/2023, I observed that a quality control chemist was able to change the time, time zone and date and save these changes on the Ultra Performance Liquid Chromatography (UPLC) systems which is used to determined potency. The time, time zone, and date for your firm's (b) (4) UPLC systems can be changed by the user with no requirement of administrative privileges thereby allowing for the altering of real-time records and data collection. Controls are not established to prevent changes to the set the time, date, and time zone of the UPLC systems.

***DATES OF INSPECTION**

2/27/2023(Mon), 2/28/2023(Tue), 3/01/2023(Wed), 3/02/2023(Thu), 3/03/2023(Fri), 3/28/2023(Tue), 3/29/2023(Wed), 3/30/2023(Thu)

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."