DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
One Montvale Avenue Stoneham, MA 02180 (781) 587-7500 Fax:(781) 587-7556 Industry Information: www.fda.gov/oc/industry	02/03/2014 - 02/20/2014* FEI NUMBER 3004407863

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Thomas W. Kelsey, Regional Director of Pharmacy

FIRM NAME	STREET ADDRESS
Central Admixture Pharmacy Services, Inc.	55 Sixth Rd
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Woburn, MA 01801-1767	Producer of Sterile Drugs

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

Specifically, the following practices and conditions were observed which increase the risk of cross contamination of compounded sterile preparations made in your facility with β-Lactam drugs and contamination of cephalosporin drugs with penicillin:

1. Your firm does not provide adequate separation of β-Lactam drugs from other drug products for human use. Penicillin G Potassium and cephalosporin drugs; Cefazoline, Ceftazidime, and Ceftriaxone are compounded in Laminar Air Flow (LAF) Hood (b)(4) located in Antibiotic Compounding Room (b) adjacent to LAF Hood (b)(4) which is used to compound Cardioplegia Solution and Total Parenteral Nutritionals (TPN); LAF Hood (b)(4) which is used to compound Continuous Renal Replacement Therapy (CRRT) solutions; and LAF Hood (b)(4) also used to compound CRRT solutions. Compounding operations involving these products and equipment may be conducted simultaneously. For example: On 02/06/2014, two Pharmacy Technicians and one Pharmacist were observed simultaneously compounding Penicillin G Potassium, 2.5 MU, Lot # 24-439407 in LAF Hood (b)(4) and CRRT - CITRATE Solution, Lot # 24-439574 in LAF Hood (b)(4) within Antibiotic Compounding Room (b)

2. Your firm does not provide adequate separation of penicillin and cephalosporin drugs. Penicillin G Potassium and cephalosporin drugs; Cefazoline, Ceftazidime, and Ceftriaxone are compounded in Laminar Air Flow (LAF) Hood (b)(4) located in Antibiotic Compounding Room (b) sometimes on the same day. For example:

   a. On 12/24/2013 the following compounding sequence was conducted in LAF Hood (b)(4)
      - At (b)(4) - Compounding Penicillin GK 5MU/250 ml NS, CAPS Rx # 24-431746
      - At (b)(4) - Compounding Penicillin GK 2.5MU/250 ml NS, CAPS Rx # 24-431747
      - At (b)(4) - Compounding Cefazolin 750 mg/30 ml D5W, CAPS Rx # 24-431738

   b. On 02/06/2014 the following compounding sequence was conducted in LAF Hood (b)(4)
      - At (b)(4) - Compounding Penicillin GK 5MU/250 ml NS, CAPS Rx # 24-439406
      - At (b)(4) - Compounding Penicillin GK 2.5MU/250 ml NS, CAPS Rx # 24-439407
      - At (b)(4) - Compounding Cefazolin 500 mg/50 ml D5W, CAPS Rx # 24-439400

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3. Personnel, equipment, and component movement through your cleanroom facilities is not adequately designed, controlled, and operated to separate β-Lactam drugs from other drug products for human use. For example:

   a. Your central Anteroom is accessed by personnel from TPN Compounding Room (b), Antibiotic Compounding Room (b), Gowning Room, and Product Entry Room during multiple product operations. Personnel were observed moving from compounding rooms to the Anteroom and returning during compounding operations. On 02/06/2014, a technician was observed compounding CRRT - CITRATE Solution in Antibiotic Compounding Room (b) while Penicillin G Potassium was compounded in an adjacent LAF hood then leaving the room and performing TPN compounding operations in TPN Compounding Room (b).

   b. The pressure differential and (b) (4) from Antibiotic Compounding Room (b) to the central Anteroom is not adequately controlled to continuously meet your firm's specification (b) (4). On 02/06/2014, during compounding of Penicillin G Potassium, 2.5 MU, Lot # 24-439407 in LAF Hood (b) and CRRT - CITRATE Solution, Lot # 24-439574 in LAF Hood (b) within Antibiotic Compounding Room (b) the differential pressure said to be measured from the compounding room to the anteroom, read on a magnehelic gauge, was observed at least five times to fall below the specification to a minimum of (b) (4) with recovery taking from 20 seconds to one minute.

   c. The doors between the Anteroom; TPN Compounding Room (b), Antibiotic Compounding Room (b), Gowning Room; and Product Entry Room are not designed for hands free opening and are not interlocked to prevent opening at the same time.

OBSERVATION 2

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

Specifically, your sterility testing program does not include samples representative of each compounded preparation and process on each operational day. During the period 12/02/2013 to 01/30/2014 your records of compounding activity in LAF Hood (b) show that on at least eight days samples were not taken from the (b) (4) for each ISO 5 LAF Hood used for used for anticipatory compounded sterile preparations with beyond use date exceeding parameters stated in your procedure, TP-CAPS-4000037, Sterility Testing Using (b) (4), Effective: 11/27/2013. For example the following compounded preparations were not sampled for sterility testing:

- Cardioplegia Solution Lot # 24-437716, Compounded on 01/27/2014
- Oxytocin Lot # 24-435788, Compounded on 01/15/2014
- Magnesium Sulfate Lot # 24-430520, Compounded on 12/18/2013
- Norepinephrine Lot # 24-430704, Compounded on 12/09/2013

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OBSERVATION 3

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

Specifically, your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing and support areas as follows:

1. Total Particulate Count and Active Air sampling is not performed each operational shift in critical zones including ISO 5 classified laminar air flow (LAF) hoods and TPN work zones and Surface Monitoring is not performed at the end of daily operations in critical zones. Compounded sterile preparations are aseptically manipulated in these areas as part of daily operations; however, environmental monitoring for total airborne particulates, surfaces, viable airborne particulates, and personnel is performed [redacted] (b) (4).
2. Personnel performing Total Airborne Particulate monitoring in the ISO 5 and ISO 7 classified spaces of TPN Compounding Room [redacted] on 02/05/2014 was observed holding the handheld [redacted] (b) (4) particle counter collection tube in a horizontal to 10-15 degree downward orientation during sampling. The mouth of the sample collection tube did not appear to be directed into the expected air stream during this observation.
3. Personnel monitoring is limited to the assessment of compounding personnel's fingers and sleeves and other critical areas to include the forehead, chest, and shoulders are not monitored.
4. Your environmental monitoring program does not include sampling for bioburden on surfaces frequently contacted by personnel performing aseptic operations. For example:
    a. The [redacted] (b) (4) located in ISO 5 classified TPN work zones.
    b. The handles of portable carts used to move compounding components and other supplies and the amino acid storage shelf cover.
5. You do not perform environmental microbial monitoring of any floor surfaces in the cleanroom facilities and directly adjacent areas as part of a comprehensive monitoring program to evaluate the bioburden in areas used to support and compound sterile preparations.
6. Your environmental monitoring procedures do not call for the identification of any viable colony recovered by surface sampling in ISO 5 critical sites.
7. Your environmental monitoring procedures do not call for the identification of any viable colony recovered by active air sampling in ISO 5 critical sites.
8. Your firm does not perform growth promotion testing on each lot of ready-prepared medium used in testing for environmental bioburden in classified cleanroom areas.

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OBSERVATION 4

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

Specifically, the following conditions were observed which increase the risk of introduction of objectionable bioburden and other contaminants to compounded preparations during processing and elevated bioburden in the compounding environment:

1. The unclassified space surrounding the cleanroom unit is contiguous with the warehouse and shipping / receiving area and is not adequately protected from the outdoor environment when the shipping / receiving overhead door is opened. Insect carcasses were observed in the unclassified space immediately adjacent to the cleanroom exterior.
2. The exit pass through with [redacted] (b) (4) from the ISO 7 classified TPN Compounding Room [redacted] passes directly to the unclassified space for discharge of finished sterile preparations. Your air flow pattern analysis (smoke study), performed on 03/22/2013, fails to evaluate the air flow patterns in the area of this exit pass through when the [redacted] (b) (4) is in place and in use.
3. Your video of the air flow pattern analysis (smoke study), performed on 03/22/2013, in the TPN Compounding Room [redacted] critical zone appears to display an objectionable air flow pattern over ISO 5 classified TPN Compounding Bench [redacted] (b). The indicator "smoke" was observed to be carried downward from the point of introduction then back upward inside the front of the partial enclosure before returning down to discharge at the front of the enclosure. This air flow pattern may be expected to come in contact with compounding personnel arms before flowing upward and returning to the area where aseptic connections are made. During the inspection Pharmacy Technicians were observed making aseptic connections of drug components and receiving bags with the [redacted] (b) (4) pump for production of sterile compounded preparations including TPN within the region of the recorded objectionable air flow. The report of the air flow pattern analysis (smoke study), performed on 03/22/2013, titled "Smoke Study of Class 5 Zone" was approved as "passed" with no deviations documented by your facilities management and final approval by your Quality Unit on 04/16/2013.
4. Water was observed seeping from under loose sheet flooring in the Utility Room at a seam directly in the walkway of personnel who access cleanroom cleaning and sanitization supplies stored in the room. Water was also observed on the Utility Room floor in the area of the lift pump which collects drainage from the utility sink for discharge to the sanitary drain. The corridor outside the Utility Room passes the cleanroom personnel hand wash station and leads directly to the cleanroom Gowning Room and Product Entry Room. Cleanroom personnel wearing plant dedicated footwear and warehouse personnel, administrative personnel, and visitors wearing outdoor footwear were all observed to use this common corridor.
5. A floor drain located in the unclassified area outside the cleanroom facility adjacent to the Compounding Rooms, Employee Locker Room, Employee Bathrooms, Utility Room, and cleanroom personnel hand wash station was observed to have an open perforated cover. According to management the drain is unused and is not on any sanitization program.
6. The employee locker room and changing area used to store plant uniforms and dedicated shoes was not adequately cleaned. A buildup of dust, hair, and other debris was observed on the floor and the tops of lockers were visibly dusty.

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OBSERVATION 5

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

Specifically, the following practices and conditions were observed which could contribute objectionable bioburden and other contaminants to compounded preparations during processing and bioburden of the compounding environment:

1. The following poor aseptic technique was observed: A Pharmacy Technician was observed compounding CRRT - CITRATE Solution in Antibiotic Compounding Room (b) (4) LAF Hood (b) (4), repeatedly lifting (b) (4) bottles (b) (4) from a cart in the room to (b) (6) shoulder (making shoulder contact) to loosen the bottle closure before placing each bottle into the ISO 5 classified LAF hood. Additionally, the technician did not sanitize the exterior of the bottles immediately before placement in the ISO 5 classified critical zone.
2. Personnel were observed entering the ISO 8 Classified Product Entry Room directly from the unclassified spaces adjacent to the cleanrooms wearing street footwear. One (b) (6) employee was observed entering the same area without donning a protective cover over (b) (6). The personnel and equipment traffic pattern includes all common spaces traveled by cleanroom personnel wearing plant dedicated footwear and warehouse personnel, administrative personnel, and visitors wearing outdoor footwear and outer clothing.
3. Wheels of equipment and component carts brought into the "grey side" of the ISO 8 Classified Product Entry Room directly from the unclassified spaces adjacent to the cleanrooms are either not sanitized or particulate dirt is not removed before the application of sanitizing solutions.

OBSERVATION 6

Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically, your firm failed to ensure that compounding personnel wear clothing appropriate to protect drug product from contamination. For example:

1. Personnel were observed working in ISO 7 classified cleanroom areas including TPN Compounding Room (b) (4), Antibiotic Compounding Room (b) (4), and the central Anteroom areas having exposed skin from the bridge of the nose to the top of the forehead. Personnel were observed reaching into the ISO 5 Classified TPN Work Zone (b) (4), while compounding TPN, breaking the plane of the ISO 5 enclosure with the exposed facial area.

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OBSERVATION 7

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

Specifically, your firm uses a component of inappropriate quality, [redacted] (b) (4), to compound CRRT - CITRATE Solution, a human drug intended for infusion. According to the batch record for CRRT - CITRATE Solution, Lot # 24-439574-0-1, Exp: 03/08/2014, [redacted] (b) (4), made up [redacted] (b) (4) ml of the total [redacted] (b) (4) ml formulation.

OBSERVATION 8

Each lot of components was not appropriately identified as to its status in terms of being quarantined, approved or rejected.

Specifically, you do not adequately control and identify the status of raw material components and store these components according to their status as quarantined, approved, or rejected. For example:

1. Your procedure, SOP-CAPS-4000157, Material Receiving Handling and Storage, said to include requirements for Quality Control (QC) disposition of raw material components for compounding of sterile preparations, identifies raw material components such as [redacted] (b) (4) as requiring QC control but you do not provide adequate justification for excluding raw material components such as [redacted] (b) (4) and [redacted] (b) (4) from any requirement to be controlled by QC prior to use in compounding drugs for human use.

2. Raw material components such as [redacted] (b) (4) and [redacted] (b) (4) observed stored in the warehouse and said to be in "released status" do not have any indication of status and are not segregated from quarantined and rejected components.

3. [redacted] (b) (4) observed in the quarantine area on 02/03/2014 and said to be available for use was not released by QC as required by SOP-CAPS-4000157, Material Receiving Handling and Storage.

OBSERVATION 9

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

Specifically, your Investigation # 24-130424-010 regarding precipitation observed in TPN did not seek to identify the precipitate as part of a thorough root cause analysis or health hazard evaluation. The complaint investigation concluded only that: "The cause of the TPN precipitation cannot be determined by this investigation."

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OBSERVATION 10

Written distribution procedures are not followed.

Specifically, your procedure SOP-CAPS-4000188, Storage and Delivery of Compounded Sterile Preparations, requires [redacted] for shipping refrigerated preparations. Cardioplegia Solution, Lot # 24-439055, packaged and awaiting shipping on 02/03/2014, was observed to be packed in a format outside the validated conditions stated in procedure SOP-CAPS-4000188. The packaging format calls for [redacted] in each standard insulated corrugated box. [redacted] of the shipping boxes for Cardioplegia Solution, Lot # 24-439055 were observed to contain only [redacted] each and [redacted] shipping box contained only [redacted].

*** DATES OF INSPECTION:**
02/03/2014(Mon), 02/04/2014(Tue), 02/05/2014(Wed), 02/06/2014(Thu), 02/07/2014(Fri), 02/20/2014(Thu)

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 judgement, 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."