DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
New England District Office One Montvale Avenue Stoneham, MA 02180 Tel: (781) 587-7500 Industry Information: www.fda.gov/oc/industry	01/07/2013 - 01/29/2013* FEI NUMBER 3004407863

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Thomas W. Kelsey, Regional Director of Operations

FIRM NAME	STREET ADDRESS
Central Admixture Pharmacy Services, Inc.	55 6th Road
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Woburn, MA 01801	Sterile Drug Product Manufacturer

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

1. The firm manufactures admixtures from commercially available finished products. The firm performs numerous manual aseptic manipulations in the filling of the sterile injectable drug products intended for patient use. The following conditions were observed:

   a. The firm does not test all finished product batches for sterility. There is no justification for only sending the last batch of the day for sterility testing. From 06/12 to 12/12 the firm manufactured approximately (b) batches and only (b) (20%) were tested for sterility. Furthermore, batches tested for sterility are released for patient use before the sterility test is completed (e.g. continuous renal replacement therapy (CRRT) batch 24-325144 was released for patient use before sterility failure results were obtained on 06/12).

   b. The firm does not test final units for the presence of bacterial endotoxin in finished sterile drug product lots after aseptic manual filling operations.

   c. The firm manufactures Ranitidine 5 mg, 10 mg, 15 mg, and 25 mg yet they have never tested any lots of Ranitidine for sterility.

2. There is a lack of microbial reduction/control steps in the manufacturing process of sterile drug products. For example, the firm has not evaluated the product impact of a lack of microbial reduction filter after numerous manual aseptic manipulations in the filling of sterile injectable drug products intended for patient use.

   Furthermore, the firm manufactured continuous renal replacement therapy (CRRT) batch 24-325144 which was released for patient use before sterility failure results were obtained on 06/12.

3. The following events were inadequately investigated, root cause was not determined and permanent corrective actions not implemented:

   a. On 6/18/12 a sterility failure was reported for lot 24-325144 of continuous renal replacement therapy (CRRT) where (b) bags were made on 6/11/12 and shipped to (b) (4) on 6/12/12. The culture grew *Bacillus lentus* and *Bacillus circulans*. No root cause was determined. There was no additional cleaning or environmental monitoring performed as a result of this sterility failure. The firm did not perform any impact assessment for products made in the same hoods between 6/11/12 and 6/18/12.

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b. On 10/2/12, the firm identified growth on routine air bioburden samples that were taken on 9/27/12. This routine sampling occurred in both clean rooms and there were two positive sites: TPN bench 2 in the clean room 1 and hood 6 which is located in clean room [redacted]. The cultures were identified as *Staphylococcus epidermis* and *Staphylococcus capitis*. The firm did not determine the root cause of the contamination. The firm performed additional testing in clean room 1 only, no additional isolates were recovered. Of note, the investigation only covered clean room 1 and referenced benches B2 and B6 as those in question, yet the isolates were found on bench 2 and hood 6, which is a located in a different clean room. This investigation was reviewed and approved by the Regional QA Manager on 10/30/12.

c. The Quality Unit failed to adequately investigate, and implement permanent corrective actions after approximately 211 environmental microbiological excursions were isolated from critical areas such as personnel fingers and sleeves inside ISO 5 hoods and controlled manufacturing areas during the manufacture of sterile injectable drug products in 2011-2012. There is no documented evidence that suggests that a health hazard evaluation was initiated nor conducted in order to assess the potential quality impact of isolates present during the manufacture of sterile drug products. Furthermore, your firm does not perform identification of the observed microbiological isolates.

d. The firm failed to investigate the potential product impact after a HEPA filter failed certification in 06/12. This HEPA filter is located on top of the ISO 5 bench used in the manufacture of TPNs and Cardioplegia Solution.

4. The environmental monitoring and conditions of the aseptic core are deficient for the following reasons:

a. Gowning used to manufacture sterile drug products is inadequate:

i. Personnel face mask and hair nets are not sterile. In addition sterile gowns can be re-used throughout the day before they are replaced.

ii. Personnel exposed foreheads were observed as part of their gowning procedures.

These operators can work inside the open-faced class 100 hoods in the manufacture of sterile injectable drug products.

iii. The firm provides one set of scrubs to all employees that work in the clean room. The firm's procedure: Gowning Requirements, is silent with respect to laundering of these scrubs. A pharmacy technician explained that she uses her scrubs for 5 days each week and brings them home on the weekend to launder.

iv. The firm requires staff that work inside the clean room to keep a pair of "facility shoes" in the locker room. These shoes are used by clean room staff when working in the clean room. There is no requirement for cleaning of these shoes. The shoes were seen stored on a visibly dirty floor inside the locker room.

b. Environmental monitoring of the ISO 5 laminar flow hoods in not performed in association with daily operations. Sterile drug products are aseptically manipulated in these hoods as part of daily operations. However, environmental monitoring for non-viable particulates, surfaces and viable particulates is performed (b) (4) in the ISO 5 hoods.

c. The firm failed to perform environmental monitoring during the manual aseptic connections during the manual filling of sterile injectable drug products.

d. Personnel monitoring is limited to the assessment of the manufacturing technician's fingers and sleeves and this sampling is done only on a (b) (4) basis. Other critical areas such as forehead, forearms, chest and shoulders are not monitored.

5. The firm applies expiration dating to all compounded sterile injectable products. The stability program is inadequate in that:

a. CAPS has performed limited stability testing on some of their manufactured drug products. For example, the firm routinely manufactures Oxytocin in multiple different strengths including Oxytocin 30 units/500ml LR and Oxytocin 25 units/250ml LR. CAPS performed stability testing in 2008 on one lot of Oxytocin 10 units/250ml NS, Oxytocin 30 units/1000ml NS, Oxytocin 10 units/1000ml D5WLR and Oxytocin 40 units /500ml D5WLR.

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b. The firm has not confirmed thru analytical testing all expiry dates for injectable drug products made at this site. For example, the firm applies a 30 day expiry date to Cefazolin 2gm/100ml D5W in the refrigerator and a 60 day expiry to Ranitidine 25mg/25ml D5W when stored in the freezer yet the company has not performed any analytical testing on either of these products.

6. The sterile technique qualification (media fills) do not represent your routine operating conditions and does not evaluate worst-case activities that can provide a challenge to manual aseptic operations. Specifically,

   a. The aseptic process validation does not challenge representative container closure systems currently used at your facility that represents a worst case challenge. For example, your firm performs media fill studies with (b) (4) bags when the following sizes ranging approximately from 50mL, 150mL, 250mL, 500mL, 1000mL, bags are used during routine production. Other container closures such as pumps and syringes were not evaluated.

   b. The media fills do not simulate aseptic manufacturing operations that incorporate worst-case activities and conditions that provide a challenge to aseptic operations. For example: maximum number of personnel and their activities, and an evaluation of critical routine and non-routine interventions (e.g. the continuous entering and exiting of the class 100 hoods used in the manufacture of sterile drug products.)

   c. Filled units used as part of the media fills are not representative of the manufactured batches. For example:

      i. Media fills for small volume parenterals used approximately (b) units for the media fills. Right after the validation was completed a lot of Magnesium Sulfate 2 mg/ 50 mL D5W lot 24-345890 was manufactured with over (b) units of sterile injectable drug product.

      ii. Media fills for large volume parenterals used approximately (b) units for the media fills. However, Cardioplegia Solution batches can range from approximately (b) (4) units per batch.

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d. The firm has not performed media fills to simulate their pooling process. All executed media fills are for an aseptic transfer only.

7. Air Flow pattern studies "smoke studies" are inadequate for the following reasons:

   a. The air flow pattern video does not present data to adequately assess the requested "downward sweeping airflow pattern" for the ISO 5 aseptic fill zone. The firm failed to evaluate the potential product impact of the turbulence, air eddies observed in the middle of the ISO 5 hoods during dynamic operations.

   b. The smoke study did not include an evaluation of the personnel activities performed in the adjacent ISO 5 hoods to determine that the personnel activities do not negatively affect the air flow patterns within ISO 5 hoods.

   c. The study does not demonstrate critical aseptic connections performed during the assembly of ISO 5 hoods used to fill sterile pharmaceuticals.

8. The firm manufactures admixtures from commercially available finished products. However, the firm does not test the potency of the final drug product after numerous lots are further diluted as part of the manufacturing process of sterile drug products. Complaint 24-110202-002 for Oxytocin lot 24-235156 citing lack of effect in 2 different patients was received in 2011.

9. The following poor aseptic technique was observed for manufacturing personnel during gowning operations before entering the controlled manufacturing areas:

   a. Operator touched the exterior of his sterile suit in multiple locations with bare hands.

   b. Operator wiped the sterile gowning pant legs on the floor.

10. There is no data to support that the firm's processing procedures will not increase the risk of cross-contamination between products. For example: the firm manufactures beta-lactam drug products in a non dedicated facility where sterile injectable drug products are manufactured. The firm's employees can manufacture beta-lactam and non beta-lactam products in any hoods interchangeably. Furthermore, the firm does not test/assess for the presence of beta-lactams in other sterile manufactured drug products.

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11. Differential pressure is not adequately monitored and controlled between in the controlled manufacturing areas. Specifically: there is no continuous monitoring of the pressure differential between ISO 5 areas and lower classification areas. Also, there are no visible or audible alarms when differential pressure problems occur.

12. In 2007, the firm had a large walk in refrigerator installed in the warehouse. This refrigerator is approximately (b) (4) [redacted]. This refrigerator is used to store among other temperature sensitive materials, incoming active drug products, completed drug product orders awaiting shipping, and the back up sterility samples are also stored in this refrigerator. This refrigerator has not yet been qualified and has been used to store drug product since 2007.

13. The Cleaning Procedure requires (b) (4) [redacted] dry mopping in the warehouse and (b) (4) [redacted] cleaning of the refrigerators and incubators.

    a. On 1/7/13, the floors in the warehouse were visibly dirty in and around pallets of material stored in the warehouse. The last (b) (4) [redacted] clean occurred on Thursday 1/4/13 according to the warehouse staff.

    b. On 1/7/13, the self defrosting unit within the large three door refrigerator was visibly dirty and leaking into a bucket. This refrigerator is used to store compounded sterile drug products that are awaiting shipping to customers. The last clean for this refrigerator occurred in 12/12. The date that the cleaning actually occurred is not recorded.

    c. On 1/10/13, the locker room where staff change into their scrubs was seen visibly dirty with many "dust bunnies" on the floor close to staff clean room shoes. The locker room is not included in the cleaning procedure.

14. The loading door in the warehouse is approximately 8 feet by 8 feet 2 inches. The door was not flush with the warehouse floor. A large gap was seen under the warehouse door. In addition, the rubber weather stripping on the top of this door was hanging down about 2 feet from the top of the door and therefore not properly secured within the channel.

15. The firm uses wet lines for their sprinkler system. The firm has covers over all sprinklers in their clean room. The system is deficient in that:

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

a. The firm has not inspected each individual sprinkler in house since the system was originally installed.

b. The as built drawings for the location of the individual sprinklers in the clean room were reviewed. The as-built drawings do not reflect the placement and location of all sprinklers at current day.

***Dates of Inspection:**

01/07/2013 (Mon), 01/08/2013 (Tue), 01/09/2013 (Wed), 01/10/2013 (Thu), 01/11/2013 (Fri), 01/17/2013(Thu), 01/29/2013 (Tue)

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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 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."