DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax:(313) 393-8139 Industry Information: www.fda.gov/oc/industry	06/17/2014 - 06/25/2014* FEI NUMBER 1000306306

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
TO: Mr. Glenn J. Pangrazzi, Director of Pharmacy

FIRM NAME	STREET ADDRESS
Central Admixture Pharmacy Services, Inc.	37497 Schoolcraft Rd
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Livonia, MI 48150-1007	Producer of Sterile Drug Products

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

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

Specifically,

A sterility failure with identification of *Aspergillus* species was obtained from the [redacted (b)(4)] samples of Cardioplegia produced on 5/22/14 which resulted in the recall of all [redacted (b)(4)] Cardioplegia units produced on Pump #[redacted (b)(4)] for the day. Investigation 13-140528-009 was opened as a result of this sterility failure and remains in draft form as of 6/19/14. Although no root cause for the sterility failure has yet been identified, your firm continues to produce additional Cardioplegia and Total Parenteral Nutrition units using the same production processes (e.g. the use of the [redacted (b)(4)], aseptic practices, materials handling, and sanitization). Inadequate data was provided to justify limiting the scope of potential impact to only the [redacted (b)(4)] Cardioplegia units.

Products produced by your firm include the following:
Del Nido Cardioplegia with Lidocaine lot 13-920742-0-1
TPN lot 13-920782-0-1 on 5/22/14
TPN lot 13-927687-0-1 on 6/17/14
Cardioplegia lot 13-927584-0-1 on 6/17/14

OBSERVATION 2

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

Specifically,

A. The active viable environmental monitoring (EM) performed at your facility is inadequate in that:
   i. Active viable EM is not performed during every drug production shift in the critical areas. Only one active viable air sample is routinely collected [redacted (b)(4)] [redacted (b)(4)]. However, drug production

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activities at the facility routinely occur [redacted] (b) (4)

ii. Active viable EM is not performed in the ISO 5 workstations under routine processing (dynamic) conditions. Observation of active viable EM performed on 6/19/14 in ISO 5 workstations [redacted] (b) (4) noted that during the air sampling, no operators were nearby and no production activities occurred at the workstations being sampled.

iii. The volume of air sampled for active viable EM and conversion to cfu/m^3 is inappropriate for the specification limit. For each sample, a total of [redacted] (b) (4) of air is sampled over [redacted] (b) (4) per SOP-CAPS-4000172, Environmental Monitoring, which also states an action limit [redacted] (b) (4) For example, active EM sampling on 5/29/14 in ISO 5 hood [redacted] (b) (4) resulted in 1 cfu per 400 L. This translates to 2.5 cfu/m^3, which is an action level excursion. Due to an insufficient sample size and correction factor, this result was recorded as "pass" and no investigation into root cause or potentially affected lots was conducted.

B. The non-viable particulate (NVP) environmental monitoring (EM) performed at your facility is inadequate in that:

i. NVP monitoring is not performed during every drug production shift in the critical area. [redacted] (b) (4) NVP air sample is routinely collected [redacted] (b) (4). However, drug production activities at the facility routinely occur [redacted] (b) (4)

ii. NVP monitoring is not performed continuously during routine processing and the sampled volume of air is inadequate. Each NVP sample taken using the [redacted] (b) (4) particle counter is a [redacted] (b) (4)

iii. The NVP monitoring sample is not taken at a location and orientation to collect meaningful data where there is the most potential risk to the product. An example of NVP monitoring was observed on 6/19/14 in ISO 5 workstation # [redacted] (b) where the probe was held [redacted] (b) (4) This was stated to be indicative of all NVP monitoring performed in each of the ISO 5 workstations and is not representative of routine processing (dynamic) conditions.

C. The personnel monitoring performed at your facility is inadequate in that:

i. Monitoring of each operator's gloves is not performed on a daily basis. Routine personnel monitoring of each operator's sleeves and fingertips is only performed [redacted] (b) (4) However, sterile drug production activities at the facility routinely occur [redacted] (b) (4).

ii. The technique for fingertip monitoring is not optimized to permit the recovery of microorganisms, if present. Three instances of personnel monitoring observed on 6/19/14 noted only very light contact of the media plate with the very tip of the fingers only. Additionally, one operator's gloves appeared to be damp with IPA during the monitoring.

D. The aseptic practices and techniques observed at your facility are inadequate in that:

i. Numerous instances were observed where an operator's gloved hands were above an exposed sterile connection and in the path of unidirectional ISO 5 airflow. For example, on 6/18/14 during setup of the [redacted] (b) (4), during spiking of many raw material containers, and during replacement of the TPN and Cardioplegia bags. The air flow patterns during these types of manipulations were not specifically evaluated during the smoke studies performed.

ii. Numerous instances were observed where an operator's gloves were not appropriately sanitized with [redacted] (b) (4) [redacted] (b) (4) prior to performing activities in the ISO 5 workstations. For example, on 6/18/14 an operator touched label paper in the ISO 7 space and then immediately reached into ISO 5 workstation # [redacted] (b) (4) to perform a sterile connection

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without sanitizing their gloves.

iii. Numerous instances were observed where non-sterile items are not fully decontaminated when placed into the ISO 5 workstation. For example, on 6/18/14 only the top of a raw material bottle was sprayed with [redacted] when moved from the ISO 7 space to ISO 5 workstation #[redacted]. Additionally, non-sterilized label paper is routinely placed directly into the ISO 5 workstations.

E. The gowning and associated practices at your facility are inadequate in that:

i. The sterile garb worn by operators does not cover all exposed areas. Observation of operators working at the ISO 5 workstations revealed that the gowning hood and mask do not provide adequate facial coverage allowing exposure of the skin around the eyes and forehead. Additionally, on 6/17/14, an operator producing TPN units at workstation #[redacted] was observed with the tops of his shoes including a portion of his shoelaces exposed. The facility-dedicated shoes are also worn in non-classified areas.

ii. On 6/18/14, an operator standing at ISO 5 workstation #[redacted] was observed to be talking while performing a sterile connection within the workstation. The face masks worn by operators state a bacterial filtration efficiency of 94%. Additionally, sterile connections were observed to be performed [redacted]

F. The following materials sanitization and transfer procedures are inadequate in that:

i. Data was not provided to support that the disinfectant efficacy studies performed were equivalent to observed practices. Project [redacted], approved 12/2001, states to [redacted]. However, on 6/19/14, an operator was observed to use a [redacted] to wipe approximately [redacted] consecutively without re-application of the [redacted].

ii. Reused lab coats exposed to the non-classified space are worn by employees who handle materials [redacted] during material transfer operations. On 6/18/14, an employee was observed donning a disposable lab coat that hung in the non-classified hallway. He then sprayed materials that were previously treated with [redacted] with [redacted] in the product room (ISO 8) and wiped and transferred them to a cart for transfer into the cleanroom (ISO 7), for example [redacted]. The lab coats are reportedly replaced [redacted]

iii. Neither material transfer carts nor the cart drapes are sanitized prior to transfer to the cleanroom after loading by employees wearing reused lab coats described above.

G. The [redacted] used in the ISO 5 workstations for the production of sterile drug products are not routinely treated with a sporicidal agent during cleaning, and there is no routine environmental monitoring of the devices.

H. Your firm's aseptic process validation (media fill) program is inadequate in that:

i. Media fills have not been performed for all equipment and workstations where sterile drug production occurs. Media fills have only been performed for in ISO 5 workstations #[redacted] with [redacted] and have not been performed for the [redacted] in workstations #[redacted]

ii. During media fills, positive controls are not conducted to demonstrate the incubated units are capable of supporting growth, if present.

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Lots produced include:
Del Nido Cardioplegia with Lidocaine lot 13-920742-0-1 on 5/22/14
TPN lot 13-920782-0-1 on 5/22/14
Maintenance Cardioplegia lot 13-927689-0-1 on 6/18/14

THIS IS A REPEAT OBSERVATION

OBSERVATION 3

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

Specifically,

The air handling system for the ABX (antibiotic) room where penicillin and cephalosporin drug products are produced also supplies air to the TPN (where other human drugs are produced), Ante, Gowning, and Product rooms. Air from all the rooms exhaust to the common unclassified space where it is re-supplied via the common air handling system to the same rooms listed above. In addition, while the TPN room is typically at a higher pressure than the ABX room, review of the pressure differential gauges on 6/18/14 noted several transient pressure reversals between the TPN and ABX rooms.

Adequate segregation of the personnel and materials relating to penicillin and cephalosporin (antibiotic) drug products from other human drug products is not performed. Entry to the ABX (antibiotic) room can only be made from the TPN room and as such, personnel and materials relating to the production of antibiotic and non-antibiotic drug products are co-mingled during production operations.

Products produced on 6/18/14 include:
Maintenance Cardioplegia lot 13-927689-0-1 in the TPN room
Cefazolin 1gm/10mL lot 13-927354 in the ABX room

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*** DATES OF INSPECTION:**
06/17/2014(Tue), 06/18/2014(Wed), 06/19/2014(Thu), 06/25/2014(Wed)

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