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	7/30/2018-8/22/2018* FEI NUMBER 3009590582

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
David L. Cain, Operations Manager

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 WE OBSERVED:

OBSERVATION 1

Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to aseptic processing of drug products.

Specifically,

a) The design of the facility and operations in the main cleanroom result in a cluttered ISO-7 room in which personnel must turn sideways and hold up their arms to pass each other, and which requires aseptic operators to routinely handle paper within the ISO-5 space. For example, in each of (b) (4) bays that comprise the main cleanroom, (b) (4) ISO-5 workbenches are reportedly concurrently in use to produce (b) (4) different batches of iv bags containing (b) (4) ml, with each batch operation requiring a minimum of (b) (4) operation support carts stacked with starter iv bags and other components, and for the transfer of materials, which leaves (b) (4) aisles each approximately (b) (4) feet wide for up to (b) (4) operators, (b) (4) pharmacists, and during monitoring periods, an environmental monitor (EM) and the EM cart to maneuver through the bay.

b) Labeling operations occur in the cleanroom for which paper labels are applied to the finished iv bags produced on the Repeater Pump within the ISO-5 workbench. Additionally, printers located directly beneath the (b) (4) (b) (4) workbenches which require the operator to print and handle the paper batch record for each iv bag unit produced.

c) The component iv bags staged for the next shift and/or next day's production is delivered into the cleanroom during operations and stored in the cleanroom.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Zhongren Wu, Generic Drug User Fee Amendments (GDUFA) Gayle S Lawson, Investigator	X Gayle S Lawson Investigator Signed By: Gayle S. Lawson -S Date Signed: 08-22-2018 10:26:08	8/22/2018

d) The disinfection of iv bags to be used in the production of finished product in the cleanroom, is performed in an open area of the warehouse, which is an uncontrolled area located adjacent to the cleanroom materials entrance. This area of the warehouse has no drain, and (b) (4) solution dripping from the wet iv bags pools on the floor and runs in pools under the staged carts of iv bags and in front of the (b) (4) loading area.

OBSERVATION 2

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

Specifically,

a) procedures for the disinfection and introduction of the diluent and component iv bags into the cleanroom production area does not ensure the firm's established (b) (4) dwell time is achieved, in that the iv bags are immersed for less than (b) (4) in a tote (b) (4) solution and placed on a cart for (b) (4). The process is inadequate in that:

i) the preparation of the (b) (4) solution observed on 7/31/18 did not include mixing of the solution following the addition of (b) (4).

ii) the iv bags were immersed in the (b) (4) solution for less than (b) (4); yet the firm's study for the established (b) (4) dwell time, (b) (4) (b) (4) Summary Report (7/27/17), exposed the test coupons to the disinfectants at (b) (4) minutes.

iii) the firm's study, (b) (4) CAPS Lehigh Valley, PA Summary Report, concludes that the (b) (4) process does not have an impact to the CAPS cleanroom environment, as evidenced by successful environmental monitoring during the study period; yet no evaluation of the microbiological or

particulate load on the iv bags has been performed to demonstrate the impact of the process on the surface and ports of the iv bags.

iv) the firm determined that the (b) (4) solution is acceptable for (b) (4); however there is no monitoring of the (b) (4) solution during the (b) (4) to ensure the acceptability of the (b) (4) throughout the (b) (4), and there has been no assessment of the particulate load in the (b) (4) solution at the end of the (b) (4) period to ensure that the (b) (4) wiping will also adequately remove particulate matter.

b) Operators producing iv bags using the Repeater Pump at the (b) (4) workbenches in Bays (b) (4) retrieve paper labels from the support cart in the ISO-7 area which are introduced into the ISO-5 workbench without changing or sanitizing their gloves, and then label the filled iv bag within the ISO-5 workbench. For example, on 8/03/18, aseptic operator producing Oxytocin (b) (4) units in Lactated Ringers 1000ml Lot 37-410385 at ISO-5 workbench (b) (4) in Bay (b) (4) retrieved labels after each (b) (4) units were finished and placed the labels on the units without sanitizing hands or changing gloves.

c) Sterile connection manipulations made by operators working in the ISO-5 workbenches using (b) (4) (b) (4) were observed to use twist and push motions with both hands while hanging new components and sterile connecting and disconnecting the iv bag, blocking the first pass air with the upper hand. For example, on 8/08/18, aseptic operator producing Trophamine 3% Lot 37-411610 at ISO-5 workbench (b) (4) in Bay (b) (4) blocked HEPA-filtered fist air by placing the hand and twisting above the empty finished product iv bag while connecting it.

d) Sterile connection manipulations made by operators working in the ISO-5 workbenches using Repeater Pumps were observed to inject the active ingredient into iv bags while the (b) (4) iv bags were stacked on the workbench, and not lifting the iv bag thereby blocking first pass air. For example, on

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	7/30/2018-8/22/2018* FEI NUMBER 3009590582

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
David L. Cain, Operations Manager	
FIRM NAME Central Admixture Pharmacy Services, Inc.	STREET ADDRESS 6580 Snowdrift Rd Ste 100
CITY, STATE, ZIP CODE, COUNTRY Allentown, PA 18106-9331	TYPE ESTABLISHMENT INSPECTED Outsourcing Facility

8/03/18, aseptic operator producing Oxytocin(b)(4) units in Lactated Ringers 1000ml Lot 37-410385 at ISO-5 workbench (b)(4) in Bay(b)(4) blocked HEPA-filtered first air while injecting the iv bags.

e) the procedures, such as SOP-CAPS-4000062: Compounding Room and ISO Class 5 Certification Specifications, are deficient in that in sections 9.11.1 and 9.11.2 states that the air in the ISO-5 workbenches in the cleanroom (b) (4) and is (b) (4); however the air patterns observed in smoke studies (2016, June 2018, July 2018) revealed that the HEPA air drops (b) (4), where the airflow breaks (b) (4) and as it passes the critical manipulations area, it is at approximately a(b)(4) angle, (b) (4) to (b) (4) hits the workbench surface. Additionally, the Smoke Study Summary Reports do not accurately describe the airflow patterns observed in the smoke study videos and an accurate description of the airflow patterns has reportedly not been provided to the aseptic operators.

OBSERVATION 3

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

Specifically, Environmental Monitoring is not adequate to assure the appropriate cleanroom conditions are met during operations.

a) Sampling is not conducted to be representative of conditions in the cleanroom and aseptic (b) (4) processing (b) (4) Suite).

i) EM is conducted only during the (b) (4) in a cleanroom that is producing drug products on (b) (4) shifts in a facility operating (b) (4).

ii) Viable particulates monitoring of the ISO-5 workbenches is not always sampled (b) (4) of the critical manipulations zone per written procedure, SOP-CAPS-4000582: Environmental Monitoring- (b) (4), which states (6.2.2.A) viable air bioburden sample will be taken (b) (4) of the critical exposure; however for viable air bioburden samples collected in Bay(b)(4) on 8/03/18 (Repeater Pump operations), the (b) (4) unit

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Zhongren Wu, Generic Drug User Fee Amendments (GDUFA) Gayle S Lawson, Investigator	X Gayle S Lawson Investigator Signed By: Gayle S. Lawson -S Date Signed: 08-22-2018 10:26:06	DATE ISSUED 8/22/2018

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	7/30/2018-8/22/2018* FEI NUMBER 3009590582

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
David L. Cain, Operations Manager	
FIRM NAME Central Admixture Pharmacy Services, Inc.	STREET ADDRESS 6580 Snowdrift Rd Ste 100
CITY, STATE, ZIP CODE, COUNTRY Allentown, PA 18106-9331	TYPE ESTABLISHMENT INSPECTED Outsourcing Facility

was placed approximately (b) (4) of the workbench. Additionally, the (b) (4) units, including the plate holder and plate cover, are sprayed with sterile (b) (4) (b) (4) in the ISO-5 workbench. The operator wipes the cover with a cleanroom wipe; however the procedures do not ensure that the cover is dry prior to the start of sampling.

iii) Non-viable particulates monitoring of the ISO-5 workbenches is not always sampled within the critical manipulations zone per written procedure, SOP-CAPS-4000582: Environmental Monitoring- (b) (4) which states (6.4.4) particulate matter counts will be taken within each ISO 5 workspace (b) (4) (b) (4) at the workspace and samples will be taken (b) (4) of the exposure or aseptic manipulation site; however for non-viable particulate air samples collected in Bay (b) (4) on 8/03/18 (Repeater Pump operations), the probe was placed approximately (b) (4) of the workbench at a height of approximately (b) (4) (b) (4) and needle punctures occur (b) (4) of the workbench at or (b) (4) of the work surface.

iv) Non-viable particulates monitoring of the ISO-5 workbench is limited tc (b) (4) samples, and is not always performed while operator is performing operations within the ISO-5 workbench. If initia (b) (4) (b) (4) samples are not within specification, (b) (4) samples are taken. Hard-copy raw data is not retained after the batch is released. Electronic data is not maintained, but may be retrievable for approximately (b) (4) or until over-written, as the internal data held in the unit is reportedly limited tc (b) (4) samples.

v) Non-viable particulates monitoring of the ISO-7 cleanroom area is limited to a rotational schedule, defined in Work Instruction JA-CAPS-400056, in the (b) (4) cleanroom Bays, whereby each Bay with room dimensions of (b) (4) (b) (4) is sampled in one of (b) (4) ocations underneath a HEPA Filter, (b) (4). The aseptic filtration suite (b) (4) suite) is sampled the mixing room and the filling room in one location in each room (b) (4) (b) (4) observed to be sampled under HEPA Filters.

vi) Personnel fingertip monitoring is not always sampled as appropriate and/or according to written procedure, SOP-CAPS-4000582: Environmental Monitoring- (b) (4) which states (6.6.1.A) that gloves must be dry and not sampled immediately after sanitization with (b) (4). Fingertip sampling was observed on several occasions to be done immediately following (b) (4) glove sanitization, after which the operator held their hands for approximately (b) (4) under the HEPA-filtered air, such as at workbench (b) (4) in Bay (b) (4) on 8/08/18 and in the (b) (4) Filling Room at the (b) (4) ISO-5 workbench on 8/10/18. The contact plate is used tc (b) (4) (b) (4), rather than firmly place each fingertip in contact with the (b) (4) plate.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Zhongren Wu, Generic Drug User Fee Amendments (GDUFA) Gayle S Lawson, Investigator	X Gayle S Lawson Investigator Signed By: Gayle S. Lawson -S Date Signed: 08-22-2018 10:26:06	8/22/2018

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	7/30/2018-8/22/2018* FEI NUMBER 3009590582

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
David L. Cain, Operations Manager	
FIRM NAME Central Admixture Pharmacy Services, Inc.	STREET ADDRESS 6580 Snowdrift Rd Ste 100
CITY, STATE, ZIP CODE, COUNTRY Allentown, PA 18106-9331	TYPE ESTABLISHMENT INSPECTED Outsourcing Facility

vii) On 8/10/18, the operator performing (b) (4) and filling for Sodium Chloride Lot SCC37180810-01, on the (b) (4) workbench, sprayed and wiped the ISO-5 workbench in the critical manipulation area with sterile (b) (4) immediately after which the EM monitoring operator performed the surface sampling on that workbench in the freshly-cleaned area.

b) investigations into out-of-trend (OOT) and out-of-specification (OOS) EM data are not always conducted, per the firm's written procedures, such as SOP-CAPS-4000693: Notification of Quality Event (NQE), which states (5.1.4) that EM deviations (alert, action, atypical organisms) will be handled through the initiation of an NQE. For example, no investigation was initiated to investigate the non-viable particulate count in the filling room ISO-5 workbench (b) (4) on 5/27/18 that exceeded the action limit with counts of (b) (4) and (b) (4) where the alert and action limits are (b) (4) and (b) (4), respectively. The batch (Sodium Chloride Concentrate 23.4% Lot SCC37180527-01) was dispositioned as rejected under NQE-US58-180618-108 (6/18/18), for the technician's failure to obtain a subsequent non-viable particulate count on that workbench.

OBSERVATION 4

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 investigation into the sterility failure of Heparin (b) (4) units in 0.9% Sodium Chloride Lot 37-369839 produced on 3/19/18 was deficient in that:

a) no root cause was determined.

b) the investigation revealed that the pharmacy technician performing the aseptic addition of Heparin Sodium Injection Lot 6015404 into Normal Saline 1000ml Excel Lot J7S009 via the Repeater Pump observed a black residue on the entry ports of approximately (b) (4) Normal Saline bags, and used these bags following spraying with sterile (b) (4) and wiping the ports; yet the investigation did not include an evaluation of the external surface of the iv bags or the process by which (b) (4) of iv bags are introduced into the cleanroom on a daily basis. The Appendix on pages 16-18 of 20 of the investigation indicates that (b) (4) batches with a total yield of (b) (4) units were produced on 3/19/18. Additionally, the investigation did not reference a deviation for this operator's non-compliance.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Zhongren Wu, Generic Drug User Fee Amendments (GDUFA) Gayle S Lawson, Investigator	X Gayle S Lawson Investigator Signed By: Gayle S. Lawson -S Date Signed: 08-22-2018 10:26:06	DATE ISSUED 8/22/2018

c) the investigation revealed that the pharmacy technician performing the aseptic addition for the subject batch cleaned black residue from approximately (b) (4) Normal Saline bags and reported interviewing the product introduction personnel; yet failed to discuss if pharmacy technician aseptic processing personnel were interviewed about their practices pertaining to observed residues. Per the investigation, the firm conducted "a site-wide classroom-type aseptic training" on 4/02/18 to 4/04/18; yet did not reference a Corrective and Preventive Action record, required per SOP-CAPS-4000251: Corrective/Preventive Actions.

OBSERVATION 5

The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

Specifically,

a) deviations (notification of quality events (NQE) are not always initiated, as required by SOP-CAPS-4000693: Notification of Quality Event., SOP-CAPS-4000693: Notification of Quality Event (NQE), which states (5.1) that deviations will be documented, reviewed, and investigated. For example, an NQE was not initiated when an EM operator did not have a negative control for viable surface sampling performed on 5/27/18. Instead, the operator submitted a (b) (4) plate later obtained from storage which was not representative of the EM sampling performed that day.

b) (b) (4) alarms for monitoring the pressure differentials for the cleanroom are not handled according to the firm's written procedure, SOP-CAPS-4000648: (b) (4) (b) (4) which states that all alarms must be responded to (section 6.8) and medium and high risk alarms will be documented on form, FRM-CAPS-4000256 for Out of Tolerance Record of Temperature, Pressure, and Humidity Monitored Equipment. Alarms reviewed for the time period from 5/6/18 to 8/09/18 show approximately (b) (4) alarms greater than (b) (4), which are classified as medium and high. No Form 256 were created and no Notification of Quality Events (NQE) were initiated to document the reasons for reclassifying the alarms to low risk. Additionally, approximately (b) (4) alarms occurring from 5/20/18 to 8/09/18 were not responded to in the (b) (4) system, reportedly because the response was entered on a subsequent day.

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	7/30/2018-8/22/2018* FEI NUMBER 3009590582

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
David L. Cain, Operations Manager	
FIRM NAME Central Admixture Pharmacy Services, Inc.	STREET ADDRESS 6580 Snowdrift Rd Ste 100
CITY, STATE, ZIP CODE, COUNTRY Allentown, PA 18106-9331	TYPE ESTABLISHMENT INSPECTED Outsourcing Facility

OBSERVATION 6

Buildings used in the manufacture, processing, packing or holding of drug products are not maintained in a clean and sanitary condition and free of infestation by rodents, birds insects, and other vermin.

Specifically, on 7/30/18, a dead insect was observed on the white baseboard in the room adjacent to the sterile mixing and filling rooms, just beneath the viewing window into the aseptic processing rooms (b) (4) Suite). Additionally, dirt and dust was observed in the rooms adjacent to the (b) (4) suite and main cleanroom bays, where finished product is sent through (b) (4) directly from the cleanroom and sorted by batch.

OBSERVATION 7

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

Specifically, there is no justification for the (b) (4) sterility sample size used by the firm in the alternate sterility testing system, (b) (4), which has a (b) (4) sample capacity. For example, the sterility test sample for Oxytocin products in 1000ml size, is (b) (4) of the product volume, which is sampled for sterility testing using the (b) (4) compared to the 10% (100ml) or more of the product content that is specified in USP<71> Sterility Test.

OBSERVATION 8

Procedures for the preparation of master production and control records are not described in a written procedure.

Specifically, there are no procedures to define the issuance and control of the master batch production records (MBR) to ensure that a complete and accurate copy of the record is provided to production, that it is signed and dated that it has been reviewed for accuracy and that a second person has also reviewed the record, and to preclude unauthorized printing in whole or part. For example, the MBR for the production of Magnesium Sulfate

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Zhongren Wu, Generic Drug User Fee Amendments (GDUFA) Gayle S Lawson, Investigator	X Gayle S Lawson Investigator Signed By: Gayle S. Lawson -S Date Signed: 08-22-2018 10:26:06	8/22/2018

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	7/30/2018-8/22/2018*
	FEI NUMBER 3009590582

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
David L. Cain, Operations Manager	
FIRM NAME Central Admixture Pharmacy Services, Inc.	STREET ADDRESS 6580 Snowdrift Rd Ste 100
CITY, STATE, ZIP CODE, COUNTRY Allentown, PA 18106-9331	TYPE ESTABLISHMENT INSPECTED Outsourcing Facility

50% lot MAG37180628-01, produced 6/28/18 was reportedly printed by production on the (b) (4) system, for which all users log in with a shared password, and there is no requirement for and no record that the document was checked or signed and that a second person has also reviewed the record. There are reportedly no controls in place to prevent printing and reprinting of the MBR. Although the firm provided SOP-CAPS-4000643: Documentation- Hold, Test, Release Policy 503B Facilities-(b) (4), this procedure does not contain instructions for the handling of master batch records.

***DATES OF INSPECTION**

7/30/2018(Mon), 7/31/2018(Tue), 8/01/2018(Wed), 8/02/2018(Thu), 8/03/2018(Fri), 8/06/2018(Mon), 8/07/2018(Tue), 8/08/2018(Wed), 8/09/2018(Thu), 8/10/2018(Fri), 8/20/2018(Mon), 8/21/2018(Tue), 8/22/2018(Wed)

	EMPLOYEE(S) SIGNATURE		DATE ISSUED
SEE REVERSE OF THIS PAGE	Zhongren Wu, Generic Drug User Fee Amendments (GDUFA) Gayle S Lawson, Investigator	X Gayle S Lawson Investigator Signed By: Gayle S. Lawson -S Date Signed: 08-22-2018 10:28:06	8/22/2018