

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

New England District Office
One Montvale Avenue
Stoneham, MA 02180

Tel: (781) 587-7500 Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION

02/04/2013 - 02/19/2013*

FEI NUMBER

3010015551

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Thomas W. Kelsey, Regional Director of Operations

FIRM NAME

Central Admixture Pharmacy Services, Inc.

STREET ADDRESS

27 Village Lane

CITY, STATE AND ZIP CODE

Wallingford, CT 06492

TYPE OF ESTABLISHMENT INSPECTED

Sterile Drug Product Manufacturer

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:

1. The firm performs numerous manual aseptic manipulations in the filling of 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. Between November and December 2012, the firm manufactured approximately (b) batches and (b) only (56%) were tested for sterility. Furthermore, batches tested for sterility are released for patient use before the sterility test is completed (e.g. Potassium phosphate batch 27-144225 and Oxytocin 20 units in Lactated Ringer batch 27-196244).
 - 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.
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 Potassium phosphate batch 27-144225 and Oxytocin 20 units in Lactated Ringer batch 27-196244 which were released for patient use before sterility failure results were obtained.
3. The firm's Quality Unit failed to identify, investigate, and implement permanent corrective actions after events that could impact the quality, safety, efficacy, and purity of sterile injectable drug products manufactured whether or not the batches has been already distributed. For example:
 - a. The firm failed to adequately investigate sterility failures (27-110124-005 dated 01/23/2011; and 27-120328-017 dated 03/27/2012) for Potassium phosphate batch 27-144225 and Oxytocin 20 units in Lactated Ringer batch 27-196244 for the following reasons:
 - i. The investigation into the two sterility failures did not assess for possible root causes of the contamination. It also lacked meaningful corrective or preventive actions to prevent future non-sterility events. At a minimum, corrective actions

SEE
REVERSE
OF THIS
PAGE

EMPLOYEE(S) SIGNATURE

Ramon E. Martinez
Philip Kreiter
Maya M. Davis

EMPLOYEE(S) NAME AND TITLE (Print or Type)

Ramon E. Martinez, Investigator
Philip Kreiter, Investigator
Maya M. Davis, Investigator

DATE ISSUED

02/19/2013

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER New England District Office One Montvale Avenue Stoneham, MA 02180 Tel: (781) 587-7500 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 02/04/2013 - 02/19/2013* FEI NUMBER 3010015551
---	---

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Thomas W. Kelsey, Regional Director of Operations

FIRM NAME Central Admixture Pharmacy Services, Inc.	STREET ADDRESS 27 Village Lane
CITY, STATE AND ZIP CODE Wallingford, CT 06492	TYPE OF ESTABLISHMENT INSPECTED Sterile Drug Product Manufacturer

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.

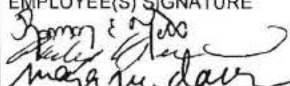
DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

did not include additional cleaning or augmented environmental monitoring as a result of this sterility failure.

- ii. In both occasions the same microorganism *Staphylococcus epidermidis* was responsible for the contamination events. This microorganism has been isolated during routine environmental monitoring in the facility approximately 10 times in 2011 and 2012.
- iii. The firm failed to extend the investigation to all associated batches that may have been manufactured under the same inadequate practices or conditions that led to the microbial contamination of these lots.
- iv. The firm's investigation failed to evaluate all manual operations used in the manufacture of sterile injectable drug product for conditions that allowed an environmental contaminant to reach sterile drug product batches.
- v. The firm released and shipped sterile drug product for patient use before the sterility failure results were complete. As a result of the microbiological contamination, sterile drug product batches were removed from the market. However several units were already used by patients. No health hazard evaluation was conducted by the firm.

The firm continues to manufacturing sterile injectable drug products via numerous manual operations and release for patient use before sterility testing results are available and complete.

- b. The firm failed to adequately investigate and implement permanent corrective actions after ten environmental investigations upon reaching action limits in classified manufacturing areas (e.g. ISO 5 and ISO 7) from personnel, air and surfaces initiated in 2011 and 2012. There is no indication that the firm isolated the cause for the contamination. Also, there is no indication that cleaning was performed after each action events. Several microorganisms such as: *Staphylococcus epidermidis* were isolated as part of the events.
- c. The firm's Quality Unit failed to investigate approximately 241 microbiological isolates sampled from 2011-2012 in critical areas of the clean room, including the ISO 5 environment (e.g. air and surfaces) and personnel (e.g. gloved fingertips and sleeve

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Ramon E. Martinez, Investigator Philip Kreiter, Investigator Maya M. Davis, Investigator	DATE ISSUED 02/19/2013
-----------------------------------	--	--	---------------------------

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER New England District Office One Montvale Avenue Stoneham, MA 02180 Tel: (781) 587-7500 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 02/04/2013 - 02/19/2013*
	FEI NUMBER 3010015551

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Thomas W. Kelsey, Regional Director of Operations

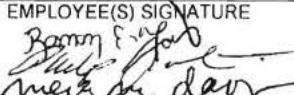
FIRM NAME Central Admixture Pharmacy Services, Inc.	STREET ADDRESS 27 Village Lane
CITY, STATE AND ZIP CODE Wallingford, CT 06492	TYPE OF ESTABLISHMENT INSPECTED Sterile Drug Product Manufacturer

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:

covers). The microbiological isolates were not identified and no impact to product quality by the excursion events was assessed.

- d. The firm's Quality Unit failed to identify and investigate two (2) environmental samples taken the day of 08/29/2011 for personnel gloved fingertips demonstrating microbial growth exceeding action limits (b) (4) (Result = 6 CFUs). The microbiological isolates were not identified; corrective actions were not implemented; and no impact to product quality by the action limit events was assessed. Products including Potassium Phosphate IV (e.g. Batch 27-170886 and Batch 27-170887) were manufactured on 08/29/2011.
 - e. Complaint investigations into bag leaks for TPN (e.g. 27-110118-004, 27-121012-034) and cardioplegic bags (e.g. 27-110425-016), which account for approximately 26/38 (68%) of the complaints received from January 2011-Present, state that the leak was detected prior to administration and that there is no risk; however, the investigation does not include a risk assessment to product sterility for container breach.
4. The sterile technique qualification (media fills) do not represent 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) when the following sizes ranging approximately from 50mL, 250mL, 500mL, 1000mL, bags are used during routine production. Other container closures such as pumps 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: In 2012 (process) Media fills for small volume parenterals used approximately (b) units for the media fills. Right after the validation was completed a

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Ramon E. Martinez, Investigator Philip Kreiter, Investigator Maya M. Davis, Investigator	DATE ISSUED 02/19/2013
-----------------------------------	--	--	---------------------------

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER New England District Office One Montvale Avenue Stoneham, MA 02180 Tel: (781) 587-7500 Industry Information: www.fda.gov/oc/industry		DATE(S) OF INSPECTION 02/04/2013 - 02/19/2013*
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: Thomas W. Kelsey, Regional Director of Operations		FEI NUMBER 3010015551
FIRM NAME Central Admixture Pharmacy Services, Inc.	STREET ADDRESS 27 Village Lane	
CITY, STATE AND ZIP CODE Wallingford, CT 06492	TYPE OF ESTABLISHMENT INSPECTED Sterile Drug Product Manufacturer	

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:

lot of Magnesium Sulfate 2 gm/ 50 mL D5W batch 27-188162 was manufactured with (b) units of sterile injectable drug product.

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

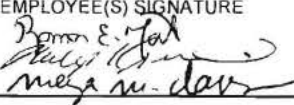
5. Air Flow pattern studies "smoke studies" are inadequate for the following reasons:

- 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.

6. 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 for patient use.

7. The firm applies expiration dating to all compounded sterile injectable products. The stability program is inadequate as follows:

- a. The firm has performed limited stability testing for their manufactured drug products. For example, studies for the following two products do not evaluate all configurations of diluents, strengths, and packaging:
 - i. Oxytocin is produced as 20 units/ 1000 mL NS, 20 units/1000mL LR, 30 unit/ 500mL LR, 40 unit/1000mL LR. The firm's Stability Study V0212 evaluated Oxytocin 30 units/NS 1000mL, 125units/D10W 250mL, 10units/1000mL D5W/LR, 40 units/500mL D5W/LR. Additionally, this study did not evaluate bacterial endotoxin.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Ramon E. Martinez, Investigator Philip Kreiter, Investigator Maya M. Davis, Investigator	DATE ISSUED 02/19/2013
FORM FDA 483 (9/08) PREVIOUS EDITION OBSOLETE		INSPECTIONAL OBSERVATIONS	Page 4 of 11

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER New England District Office One Montvale Avenue Stoneham, MA 02180 Tel: (781) 587-7500 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 02/04/2013 - 02/19/2013* FEI NUMBER 3010015551
--	---

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

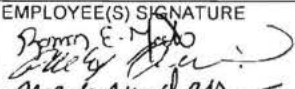
TO: Thomas W. Kelsey, Regional Director of Operations

FIRM NAME Central Admixture Pharmacy Services, Inc.	STREET ADDRESS 27 Village Lane
CITY, STATE AND ZIP CODE Wallingford, CT 06492	TYPE OF ESTABLISHMENT INSPECTED Sterile Drug Product Manufacturer

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:

- ii. Vancomycin is produced in strengths such as 1.25g/250mL D5W/NS, 1.5g/250mL NS, 1.5g/500mL D5W/NS, 750mg/250mL NS. The firm did not perform its own stability studies and the literature paper provided evaluated 1mg/mL in D5W/NS and 5mg/mL in a 60mL disposable silicone balloon infuser. Additionally, this study evaluated only potency and no other attributes such as sterility and bacterial endotoxin.
 - b. The firm manufactures Ropivacaine in a pump with a 30 day expiration date at room temperature storage. The firm did not perform its own stability studies for the pump, and the Technical bulletin provided includes no potency, sterility, and/or bacterial endotoxin data. The bulletin included a summary statement that there was no significant difference between preparation stored in the pump versus a glass vial control.
8. Gowning used to manufacture sterile drug products is inadequate:
- a. Personnel face mask and hair nets are not sterile. In addition sterile gowns can be re-used throughout the day before they are replaced.
 - b. Personnel exposed foreheads were observed as part of their gowning procedures. Operators were observed working inside the ISO 5 work benches in the manufacture of sterile injectable drug products.
9. There is no scientific justification for the selections and frequencies of the environmental monitoring sampling locations currently used at the firm's controlled areas (ISO 5, ISO 7 and ISO 8) where sterile drug products are manufactured. For example:
- a. Production of sterile drug products is performed on a daily basis within ISO 5 laminar flow workbenches; however, the firm conducts environmental monitoring with the following frequencies:
 - i. Particulate matter air samples (non-viable particulate monitoring) are taken on a (b) (4) basis within ISO 5 laminar flow workbenches.
 - ii. Air and surface bioburden samples are taken on a (b) (4) basis within ISO 5 laminar flow workbenches. (b) (4) workbenches were observed in Compounding Room #1, where the production of sterile drug product occurs.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Ramon E. Martinez, Investigator Philip Kreiter, Investigator Maya M. Davis, Investigator	DATE ISSUED 02/19/2013
-----------------------------------	--	--	---------------------------

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

New England District Office
One Montvale Avenue
Stoneham, MA 02180

Tel: (781) 587-7500 Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION

02/04/2013 - 02/19/2013*

FEI NUMBER

3010015551

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Thomas W. Kelsey, Regional Director of Operations

FIRM NAME

Central Admixture Pharmacy Services, Inc.

STREET ADDRESS

27 Village Lane

CITY, STATE AND ZIP CODE

Wallingford, CT 06492

TYPE OF ESTABLISHMENT INSPECTED

Sterile Drug Product Manufacturer

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:

Ultimately, each workbench is sampled (b) (4) for air and surface bioburden.

iii. Personnel gloved fingertips sampling is taken (b) (4) on operators that participate daily in the production of sterile drug products.

iv. Personnel sterile sleeve cover sampling is taken (b) (4) from one (1) of the two (2) sleeve covers of operators that participate in the production of sterile drug products; however, both arms of operators were observed to enter the ISO 5 areas during the production of sterile drug products. Moreover, the personnel monitoring fails to include surface sampling on the operators' facemask, forehead, and chest.

- b. The procedure "Infection Control – Environmental Monitoring", SOP-CAPS-4000172 is not followed during personnel monitoring (fingers) after manual manipulations in the manufacture of sterile drug products. Fingertips were observed being monitored on the contact plate, in contrast with the procedure, as they were tapped instead of rolled to maximize surface evaluation area.
- c. The firm's environmental monitoring for non-viable particulate is not adequate to assess particulate levels in classified areas. Specifically, on 02/06/2013 we observed an I.V. technician placing the isokinetic probe placed on the surface of a table facing a wall during sampling. There is no data to support that this location will provide representative data of the environment.
- d. There is no scientific justification for not including a phone located in the Compounding Room (manufacturing area) as part of the environmental monitoring program. This phone is used by I.V. technicians on a routine basis during the manufacture of sterile drug products.
- e. No environmental monitoring occurs within the firm's Prep Rooms (ISO 8). The Prep Rooms are utilized as the only route of access to the firm's Gowning Rooms from unclassified areas, and the Prep Rooms are utilized by personnel to wipe down supplies for introduction, via Pass Throughs, to the firm's Compounding Rooms. Firm personnel were observed to enter the Prep Rooms clothed in materials (e.g. non sterile laboratory coats) that were exposed to the conditions of the unclassified areas of the

SEE
REVERSE
OF THIS
PAGE

EMPLOYEE(S) SIGNATURE

Ramon E. Martinez
Philip Kreiter
Maya M. Davis

EMPLOYEE(S) NAME AND TITLE (Print or Type)

Ramon E. Martinez, Investigator
Philip Kreiter, Investigator
Maya M. Davis, Investigator

DATE ISSUED

02/19/2013

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

New England District Office
One Montvale Avenue
Stoneham, MA 02180

Tel: (781) 587-7500 Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION

02/04/2013 - 02/19/2013*

FEI NUMBER

3010015551

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Thomas W. Kelsey, Regional Director of Operations

FIRM NAME

Central Admixture Pharmacy Services, Inc.

STREET ADDRESS

27 Village Lane

CITY, STATE AND ZIP CODE

Wallingford, CT 06492

TYPE OF ESTABLISHMENT INSPECTED

Sterile Drug Product Manufacturer

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:

firm (i.e. warehouse) in order to prepare supplies and access the Gowning Rooms.

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

10. The firm's manufacturing areas design is inadequate to prevent contamination or mix-ups for the following reasons:

- a. Differential pressure is not adequately monitored and controlled between 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.
- b. The (b) (4) barriers separating ISO 5 laminar flow workbenches and surrounding ISO 7 areas are inadequate for preventing operators from accessing ISO 5 areas during the manufacture of sterile drug products. Operators were observed beneath the (b) (4) barriers, with exposed faces (foreheads and eyes), engaging in the manual manipulation of sterile injectable drug products within the ISO 5 areas.
- c. Several aseptic processing rooms at the facility lack adequate space and segregation to prevent contamination and mix-ups. Numerous lots of different products are produced simultaneously in a single room. Aseptic processing and labeling operations occur in very close proximity in an open room. For example, up to (b) personnel generally operate in Compounding Room 1 at the same time. This operation requires products to be produced in separate ISO 5 workbench at the same time, which generally requires (b) (4) per operation.
- d. The facility is not adequately designed and controlled to prevent influx of contamination from lesser controlled areas. Staff enters through the Prep Room (which connects to the gowning room) to initially access the clean room area from an uncontrolled, unclassified hallway. This hallway has many activities and offices, and an insect was observed in this area.
- e. The facility is not adequately designed and controlled (e.g. lack of interlocking doors) to prevent influx of contamination from lesser controlled areas. Doors accessing the Pass Through from Prep Room #1 (ISO 8) and Compounding Room #1 (ISO 7) were observed to

SEE
REVERSE
OF THIS
PAGE

EMPLOYEE(S) SIGNATURE

Ramon E. Martinez
Philip Kreiter
Maya M. Davis

EMPLOYEE(S) NAME AND TITLE (Print or Type)

Ramon E. Martinez, Investigator
Philip Kreiter, Investigator
Maya M. Davis, Investigator

DATE ISSUED

02/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

New England District Office
One Montvale Avenue
Stoneham, MA 02180
Tel: (781) 587-7500 Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION

02/04/2013 - 02/19/2013*

FEI NUMBER

3010015551

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Thomas W. Kelsey, Regional Director of Operations

FIRM NAME

Central Admixture Pharmacy Services, Inc.

STREET ADDRESS

27 Village Lane

CITY, STATE AND ZIP CODE

Wallingford, CT 06492

TYPE OF ESTABLISHMENT INSPECTED

Sterile Drug Product Manufacturer

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:

be opened simultaneously. Materials prepared within Prep Room #1 (ISO 8) for use in Compounding Room #1 (ISO 7) are staged in the Pass Through, located between the rooms. Access to Prep Room #1 (ISO 8) occurs from unclassified areas of the firm, and manipulation of sterile drug product occurs in Compounding Room #1 (ISO 7).

- f. There is no separate degowning room for I.V. technicians. I.V. technicians perform gowning and degowning operations in the same room. The firm has not evaluated the microbiological impact of performing both operations within the same room.

11. The firm's cleaning procedures and practices are inadequate to control microbial population in the controlled areas used to manufacture sterile drug products. For example:

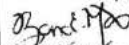

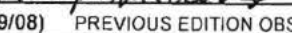
- a. The firm has not evaluated if their current cleaning and sanitizing methods/practices are effective against in-house isolates such as *Gardnerella vaginalis* isolated during routine environmental monitoring in classified areas involved in the manufacture of sterile drug products.
- b. There is no rationale to support the establishment of the cleaning and sanitation frequency used for controlled manufacturing areas.
- c. Effectiveness Study of (b) (4) as a wipedown disinfectant did not include representatives of all surfaces of the controlled manufacturing areas.
- d. There is no assurance that the current cleaning practices are effective against the control of microbial populations in the classified areas. There is no evidence that the firm allows for the validated (b) minutes contact time during all their routine cleaning practices.

12. The firm failed to qualify the reproducibility and accuracy (b) (4) pumps used in the production of total parenteral nutrition (TPN) and cardioplegic drugs and the following was observed:

- a. From January 2012-Present, there have been approximately 94 failures in pumps dispensing the appropriate weight of material. Reason of failure was recorded in only 8 of these failures.

SEE
REVERSE
OF THIS
PAGE

EMPLOYEE(S) SIGNATURE

EMPLOYEE(S) NAME AND TITLE (Print or Type)

Ramon E. Martinez, Investigator
Philip Kreiter, Investigator
Maya M. Davis, Investigator

DATE ISSUED

02/19/2013

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER New England District Office One Montvale Avenue Stoneham, MA 02180 Tel: (781) 587-7500 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 02/04/2013 - 02/19/2013* FEI NUMBER 3010015551
--	---

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Thomas W. Kelsey, Regional Director of Operations

FIRM NAME Central Admixture Pharmacy Services, Inc.	STREET ADDRESS 27 Village Lane
CITY, STATE AND ZIP CODE Wallingford, CT 06492	TYPE OF ESTABLISHMENT INSPECTED Sterile Drug Product Manufacturer

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:

- b. The firm performs a (b) (4) weight verification of the attached scale with a (b) (4) weight and the weight of TPN bags ranges from 200-4000g.
- c. The pump reproducibility is always tested using port (b) and other ports are not evaluated.
- d. The maintenance record lacks documentation of repairs and maintenance performed such that product impact can be evaluated.

Additionally, the firm received reports of hypoglycemia in two infant patients who received TPN (ICARs 27-1202223-009 and 27-130104-001) and investigations determined there was "no issue."

13. The firm failed to exclude the ingress of pests into the facility as follows:

- a. During the inspection, a live insect (~1" in length) was observed crawling along the surface of a workbench, abutting the exterior of the firm's Compounding Room #1, where the production of sterile drug product occurs. The workbench was observed to be located within approximately 18 feet of an open, warehouse door (dimensions ~6'10" wide by ~8'5" high) and approximately 14 feet from the gapped, Back Ante Room door accessing the clean room. The warehouse door was observed to be open daily.
- b. Pests were found, during monthly inspections, at trap sites within the facility approximately 221 times from 2011-2012. For example, pests were found in approximately 29 of 38 trap sites (~76%) on 06/23/2011. The pest control records were reviewed and approved by the firm without identifying or quantifying the pests. Furthermore, the firm failed to conduct investigations into the pest activity as potential infestations.
- c. During the inspection, at least 75 winged insects were observed trapped within the firm's flylight, located along the rear wall of the facility, within proximity of the firm's compounding rooms and warehouse door (dimensions ~6'10" wide by ~8'5" high). Moreover, gaps were observed along the doors of the firm's Back Ante Room and Prep Room #1, both accessing the firm's clean room. The warehouse where the flylight is located is used to store sterile drug products.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE   	EMPLOYEE(S) NAME AND TITLE (Print or Type) Ramon E. Martinez, Investigator Philip Kreiter, Investigator Maya M. Davis, Investigator	DATE ISSUED 02/19/2013
-----------------------------------	--	--	---------------------------

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

New England District Office
One Montvale Avenue
Stoneham, MA 02180
Tel: (781) 587-7500 Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION
02/04/2013 - 02/19/2013*

FEI NUMBER
3010015551

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Thomas W. Kelsey, Regional Director of Operations

FIRM NAME

Central Admixture Pharmacy Services, Inc.

STREET ADDRESS

27 Village Lane

CITY, STATE AND ZIP CODE

Wallingford, CT 06492

TYPE OF ESTABLISHMENT INSPECTED

Sterile Drug Product Manufacturer

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:

14. The firm's Quality Unit failed to evaluate and perform a risk assessment and implement applicable corrective actions for approximately 17 supplier recall notifications received January-September 2012. For example, recall notification (reference number RC 12-085) dated July-August 2012 reported breach in sterile bags containing 5% Dextrose Solution, Lactated Ringers, and 0.9% Sodium Chloride. The firm uses commercially available sterile bags in the manufacture of different sterile drug products such as Magnesium Sulfate and Oxytocin in Lactated Ringers.
15. The firm's practices for microbial identification do not provide information related to the microbiological populations found in manufacturing areas where sterile drug products are manufactured. For example, microorganisms are randomly selected and sent for identification on a (b) (4) basis and when an investigation occurred. In 2011 and 2012 the firm isolated approximately 241 microbiological excursions in critical areas such as ISO 5 and personnel during routine personnel monitoring. However the majority of this isolates were not identified.

Also, there is no indication the firm evaluates the potential impact of new microbial species found in the classified areas such as: *Gardnerella vaginalis* isolated from a pass through and *Streptococcus ovis* found in the back ante room adjacent to the controlled manufacturing areas in 2012.

SEE
REVERSE
OF THIS
PAGE

EMPLOYEE(S) SIGNATURE

Ramon E. Martinez
Philip Kreiter
Maya M. Davis

EMPLOYEE(S) NAME AND TITLE (Print or Type)

Ramon E. Martinez, Investigator
Philip Kreiter, Investigator
Maya M. Davis, Investigator

DATE ISSUED
02/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

New England District Office
One Montvale Avenue
Stoneham, MA 02180

Tel: (781) 587-7500 Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION

02/04/2013 - 02/19/2013*

FEI NUMBER

3010015551

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Thomas W. Kelsey, Regional Director of Operations

FIRM NAME

Central Admixture Pharmacy Services, Inc.

STREET ADDRESS

27 Village Lane

CITY, STATE AND ZIP CODE

Wallingford, CT 06492

TYPE OF ESTABLISHMENT INSPECTED

Sterile Drug Product Manufacturer

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.

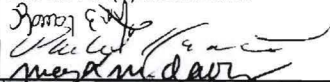
DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

***Dates of Inspection:**

02/04/2013 (Mon), 02/05/2013 (Tue), 02/06/2013 (Wed), 02/7/2013 (Thu), 02/19/2013 (Tue)

SEE
REVERSE
OF THIS
PAGE

EMPLOYEE(S) SIGNATURE



EMPLOYEE(S) NAME AND TITLE (Print or Type)

Ramon E. Martinez, Investigator
Philip Kreiter, Investigator
Maya M. Davis, Investigator

DATE ISSUED

02/19/2013

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."