

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

DISTRICT ADDRESS AND PHONE NUMBER 300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax: (313) 393-8139	DATE(S) OF INSPECTION 6/6/2016-6/29/2016*
	FEI NUMBER 3003531601

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED  
Stanley S. Kent , Chief Pharmacy Officer

FIRM NAME University Of Michigan	STREET ADDRESS 1500 E Medical Center Dr
CITY, STATE, ZIP CODE, COUNTRY Ann Arbor, MI 48109-5000	TYPE ESTABLISHMENT INSPECTED 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**

Investigations of a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.

Specifically,

Review of multiple positive sterility test results and associated documentation noted that the investigations were inadequate regarding root cause identification, potential additional product or process impact evaluation, and corrective action.

- i. Bupivacaine 0.125% epidural cassettes Print # (b)(4) with (b)(4) units produced on 5/7/16 with expiry 6/6/16 and recovery of gram positive rods.
- ii. Phenylephrine 1mg/10mL syringes Print # (b)(4) with (b)(4) units produced on 3/30/16 with expiry 4/29/16 and recovery of coagulase negative Staphylococcus species.
- iii. Calcium Gluconate 1g/50mL IV Bags Print # (b)(4) with (b)(4) units produced on 3/2/16 with expiry 4/1/16 and recovery of gram negative rods and coagulase negative Staphylococcus species.
- iv. Calcium Gluconate 1g/50mL IV Bags Print # (b)(4) with (b)(4) units produced on 9/9/15 with expiry 10/8/15 and recovery of Bacillus species.
- v. Calcium Gluconate 2g/50mL IV Bags Print # (b)(4) with (b)(4) units produced on 8/17/15 with expiry 9/16/15 and recovery of Paecilomyces species.
- vi. Bupivacaine 0.25% epidural cassettes Print # (b)(4) with (b)(4) units produced on 8/10/15 with expiry 9/9/15 and recovery of Kocuria species.
- vii. Hydromorphone 15mg/30mL PCA Print # (b)(4) with (b)(4) units produced on 6/23/15 with expiry 7/23/15 and recovery of Bacillus subtilis.

**OBSERVATION 2**

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

Specifically,

- A. The aseptic practices and techniques observed at your facility during aseptic processing of sterile drug products are inadequate. On 6/6/16 in Cleanrooms (b)(4) and on 6/7/16 in Cleanroom (b)(4) the following were observed:
- i. Items such as wrapped syringes, a plastic tub, vials, and IV bags were transferred from the ISO 7 space to the ISO 5 work area without sanitization.
  - ii. Non-sterile gauze wipes were placed directly in the ISO 5 hoods.
  - iii. Operators were observed to contact items within the ISO 5 hoods without sanitizing their gloved hands after contacting items and surfaces in the ISO 7 area.
  - iv. Operators were observed to rest their gloved hands and non-sterile gown sleeves on the ISO 5 work surface.
  - v. Bottles of sterile (b)(4) are hung on the trash can lip in the ISO 7 space. These spray bottles are used for surface and glove sanitization in the ISO 5 work area.
- Example products processed during observation on 6/7/16 include Calcium Chloride 10% Print # (b)(4) and vancomycin 1,500 mg in sodium chloride 0.9% in 290mL Order Med ID (b) (6), (b) (4).
- B. The (b)(4) your Calcium Chloride injectable product from non-sterile bulk ingredients are not (b)(4). For example, on 6/7/16, (b)(4) of Calcium Chloride 10% Print # (b)(4) with expiry 6/10/16 was observed.
- C. Smoke studies performed for (b)(4) are not performed under dynamic conditions to properly evaluate airflow patterns during production activities.

**OBSERVATION 3**

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

Specifically,

- A. Surfaces in the ISO 5 hoods included cracks and seams that are not easily cleanable. For example, Hood (b)(4) in (b)(4) was observed with a small open seam where the work surface and right wall connect. These crevices are not easily cleanable. Processing of Calcium Chloride 10% injectable Print # (b)(4) was observed in Hood (b)(4) on 6/7/16.

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- B. During aseptic processing in the ISO 7 Cleanroom (b)(4) on (b)(4), the following was observed.
- i. At least one ceiling tile was not secure to its frame and moved approximately half an inch when the door opened and closed.
  - ii. The smooth sprinkler covers were not flush with the ceiling tiles with rough edges of the cut ceiling tile visible. These gaps to the unclassified space above the cleanroom were not sealed.
  - iii. Surface damage, including small gouges and peeling, was observed on multiple ceiling tiles creating a not easily cleanable surface.
  - iv. The chairs used by operators were not constructed of easily cleanable materials and surfaces.
  - v. The (b)(4) contacted by the operators were not easily cleanable surfaces.
  - vi. An approximately 3 inch section of a floor seam was bent and damaged resulting in a large crevice and is not an easily cleanable surface.
  - vii. Multiple unnecessary items were located within the room such as a utility ladder and plastic bins stacked on the floor.
  - viii. Rough and rust-colored areas were noted on the side of the cleanroom refrigerator.
- Example products processed in (b)(4) on 6/7/16 include Calcium Chloride 10% injectable Print # (b)(4) and vancomycin 1,500 mg in sodium chloride 0.9% 290mL Order Med ID (b) (6), (b) (4)
- C. The room HEPA filters in the ISO 7 and 8 classified areas of cleanrooms (b)(4) are not leak tested during periodic certification activities.

**OBSERVATION 4**

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the equipment to produce aseptic conditions.

Specifically,

Non-sterile wipes are routinely used in cleanrooms (b)(4) on the ISO 5 work surfaces. For example, non-sterile wipes sprayed with sterile (b)(4) are used in the following instances:

- i. To periodically sanitize the ISO 5 work surface during sterile drug processing activities.
- ii. To remove (b)(4) residues from the ISO 5 work surfaces after use of (b)(4) wipes which are applied (b)(4)

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For example, on 6/7/16, (b)(4) Cefazolin 10gm syringes Print # (b)(4) and (b)(4) mini-bags in cleanroom (b)(4) hood (b)(4) an operator was observed to sanitize the interior ISO 5 hood work surface with a non-sterile wipe sprayed with sterile (b)(4)

**OBSERVATION 5**

Clothing of personnel engaged in the processing of drug products is not appropriate for the duties they perform.

Specifically,

Gowning components such as the protective gown, face mask, shoe covers, and hair net donned by aseptic processing personnel for use in cleanrooms (b)(4) are non-sterile. The current gowning method of operators performing aseptic operations provides incomplete coverage with exposure of facial and neck skin. The gown used by operators extends down to knee height only and is open in the back exposing the hospital scrubs which are worn in unclassified areas to the cleanroom environment.

For example, aseptic processing of Calcium Chloride 10% Print # (b)(4) and Cefazolin 10 gm syringes Print # (b)(4) was observed on 6/7/16 in (b)(4)

**OBSERVATION 6**

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

Specifically,

- A. The environmental and personnel monitoring program for your facility cleanrooms (b)(4) is inadequate in that:
  - i. Viable environmental monitoring is not performed during each production shift in the critical areas. Active viable air samples are taken in the (b)(4) approximately every (b)(4).
  - ii. Viable surface monitoring is not performed during each production shift in critical areas such as the ISO 5 work surfaces. Surface samples are collected approximately every (b)(4) in the (b)(4)
  - iii. Non-viable particulate (NVP) monitoring is not performed during each sterile drug production shift in the critical areas. NVP monitoring is performed approximately every (b)(4) of the (b)(4)

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- (b)(4)
- iv. Personnel glove fingertip monitoring is not performed during each production shift for each sterile drug technician. Currently, fingertip monitoring for (b)(4) is performed (b)(4). Sterile drug processing occurs (b)(4) cleanrooms.
- B. Adequate investigations including root cause assessment, product and process impact, and associated corrective and preventative actions were not conducted for the following environmental monitoring results:
- i. On 12/10/15 in Cleanroom (b)(4), an air sample taken (b)(4) resulted in 1 cfu, a surface sample of the (b)(4) resulted in 1 cfu, and a surface sample of the (b)(4) resulted in 9 cfu.
  - ii. On 11/15/15 in Cleanroom (b)(4), an air sample taken (b)(4) resulted in >10 cfu, and a surface sample taken (b)(4) resulted in 7 cfu.
  - iii. On 10/1/15 in Cleanroom (b)(4), (b)(4) of (b)(4) air samples in the (b)(4) resulted in 10 cfu.
  - iv. On 7/7/15 in Cleanroom (b)(4), an air sample in the (b)(4) resulted in 11 cfu, an air sample in the (b)(4) resulted in 12 cfu, and a surface sample of the (b)(4) resulted in 8 cfu.
  - v. On 6/8/15 in Cleanroom (b)(4), (b)(4) air samples resulted in >20 cfu while (b)(4) samples resulted in 11 cfu in the (b)(4)
- C. The pressure differential monitoring systems for your cleanrooms (b)(4) are not designed to notify your staff of any transient pressure reversals that may occur between areas of differing air classification. An alarm currently only occurs if the set limit is exceeded for (b)(4). For example, a pressure differential limit of (b)(4) is set between the ISO 7 to ISO 8 areas.

**OBSERVATION 7**

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

Specifically,

The sterility testing performed in-house is not scientifically sound in that:

- D. No method suitability studies using the required organisms in the presence of product have been performed for any of the tested formulations.
- E. There is inadequate justification for the sample size (minimum quantity to be used for each medium) for testing via the (b)(4) method. For example, for Phenylephrine Print # (b)(4) consisting of (b)(4) units of 10 mL syringes, (b)(4) of product from each of (b)(4) units was tested in (b)(4) and (b)(4) of product from each of (b)(4) units was tested in (b)(4)

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Sterility testing is limited only to (b)(4) which include, but are not limited to (b)(4)

**OBSERVATION 8**

Drug product containers were not sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.

Specifically,

The in-process (b)(4) used to formulate Calcium Chloride 10% for (b)(4) are not appropriately sterilized and depyrogenated prior to use. Currently these (b)(4) are washed using a (b)(4) prior to use. For example, Calcium Chloride 10% Print # (b)(4) processed on 6/7/16.

**\*DATES OF INSPECTION**

6/06/2016(Mon),6/07/2016(Tue),6/08/2016(Wed),6/09/2016(Thu),6/10/2016(Fri),6/23/2016(Thu),6/29/2016(Wed)

6/29/2016

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