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	4/18/2016-5/6/2016* FEI NUMBER 3012248018

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Jason E. Prokopik , Chief Operating Officer

FIRM NAME	STREET ADDRESS
Pharmakon Compounding Pharmacy, Inc.	14460 Getz Rd Ste 300
CITY, STATE, ZIP CODE, COUNTRY Noblesville, IN 46060-3303	TYPE ESTABLISHMENT INSPECTED Compounder of sterile drugs

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

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.

Specifically,

i. Adequate validation of aseptic process simulations (media fills) has not been performed under worst-case conditions/scenarios to assure that sterile processing techniques are maintained throughout the process, thus ensuring sterility of drug products. Currently, personnel performing aseptic processing must demonstrate good aseptic technique using the [redacted (b)(4)] This process does not include, for example, use of [redacted (b)(4)] worst-case lot sizes (e.g. [redacted (b)(4)] units), and representative container closure systems (e.g. eye droppers) used in typical and often routine aseptic processing operations.

Individuals performing aseptic processes have not been validated for proper technique via a media fill test. Batch records covering the following lots of sterile products indicate that they were produced by an individual without a documented media fill test, as evidenced by the personal aseptic technique test log:

- Epinephrine 1 mg/ml in 2 ml vial, lot #C16723159, [redacted (b)(4)] units produced on 04/05/2016 by technician

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- Epinephrine 1 mg/ml in 2 ml vial, lot #C16723160, (b)(4) units produced on 04/12/2016 by pharmacist (b) (7)(C), (b) (6)
- Cefuroxime 10 mg/ml in balanced salt solution 0.5 ml in 1 ml slip tip syringe, lot #146025.204, (b)(4) units produced on 03/21/2016 by technician (b) (7)(C), (b) (6)

ii. "In Situ" smoke studies performed by (b)(4) in (b)(4) for qualification/certification of the (b)(4) (b)(4) (ISO 5), suggest that (b)(4) A comment in the certification report states, "(b)(4) . Moreover, there was no documentation stating that these studies were performed under dynamic conditions simulating aseptic processing to show a sweeping action over and away from the critical processing area.

OBSERVATION 2

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

Specifically, during the production of epinephrine 1 mg/mL, lot #C16723161 on 04/19/2016 and phenylephrine 2.5%/tropicamide 1%, lot #125441/B59 on 04/20/2016 we observed:

i. Syringes containing non-sterile product within (b)(4) used for (b)(4) not sanitized before being (b)(4) (b)(4) The inside of the (b)(4) containing the syringes is not sterile and is not sanitized prior to (b)(4) .

ii. Airflow appears to be obstructed by the rack of supplies placed on the (b)(4) Top of rack is approximately 8-10 inches from the HEPA filter, and boxes of syringes were placed on the higher shelves. Buildup of wrappers/waste in the (b)(4) during processing of epinephrine was also observed.

iii. (b)(4) are infrequently replaced. (b)(4) are replaced with new, sterile (b)(4) are not checked for (b)(4) before use.

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OBSERVATION 3

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

Specifically,

i. The (b)(4) (ISO 5), used in aseptic processing of sterile drug products, are located in an unclassified room/area:

- (b)(4) serial number (b)(4), with (b)(4) used for (b)(4) drugs
- (b)(4) serial number (b)(4), used for (b)(4) drugs only

ii. According to the (b)(4) testing reports for qualification/certification of the (b)(4) (b)(4)), performed on (b)(4) a failure in (b)(4) occurred when the (b)(4) (b)(4) Since the (b)(4) are located within an unclassified room, the potential for (b)(4) microbial contamination is increased; especially, when considering that personnel frequently (b)(4) (b)(4) activities are performed during the course of aseptic processing, environmental monitoring, or cleaning/sanitizing operations, as necessary. For example, observed during production of the following lots:

- Epinephrine 1 mg/mL (EPI01), lot #C16723161, (b)(4) units produced on 04/19/2016
- Phenylephrine 2.5%/Tropicamide 1% (PT002), lot #125441/B59, (b)(4) units produced on 04/20/2016

The (b)(4) are equipped with (b)(4) s for (b)(4) are checked (b)(4) under static conditions and (b)(4) This frequency is not justified and it is not clear whether (b)(4) can be detected.

iii. The (b)(4), used for sterilization of the following has not been adequately qualified (not (b)(4)), nor is periodic maintenance being performed on (b)(4), as reported.

- Finished drug product batches of hydroxyprogesterone (17HP/17HPS), (b)(4)
- (b)(4) glycerin (b)(4)) used in glycerin 48%/lidocaine 1%/epinephrine 1:100,000, (b)(4) (b)(4)

a. The (b)(4)

b. The (b)(4) when the sterilization (b)(4) for the product to be sterilized is (b)(4); however, there is no indication/record that the required (b)(4) are not recorded during (b)(4), as reported.

iv. The (b)(4), used to sterilize glass vials, rubber stoppers, and aluminum lids for production of hydroxyprogesterone (17HPS/17HP), has not been adequately qualified (not (b)(4)

v. The (b)(4) incubators, (b)(4) used to incubate media for sterility testing, media fills, and environmental monitoring, have not been adequately qualified (temperature mapped). Thermometers used in (b)(4) incubators have not been calibrated, as reported. Additionally, there is no record of the date when media is visually examined so as to assure that the required incubation time period has been met; only the (b)(4) in the corresponding logs. For example:

- (b)(4) incubation (b)(4) on 02/16/16
- (b)(4) incubation (b)(4) on 02/18/16

OBSERVATION 4

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

Specifically,

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i. Environmental sampling listed below is not performed at least daily during production in the processing areas, to evaluate the quality of the aseptic processing environment and assess whether aseptic conditions are maintained.

a. Non-viable particulate monitoring of the (b)(4) (ISO 5) is performed (b)(4) .

b. Passive air monitoring of the (b)(4) (ISO 5) is performed (b)(4) (b)(4) (b)(4) , (b)(4) using (b)(4)). In addition, (b)(4) in which the (b)(4) are located.

c. Active air monitoring of the (b)(4) (ISO 5) is performed (b)(4) monitoring is not performed under dynamic aseptic processing conditions. Active air monitoring is not performed for the room in which the (b)(4) are located.

ii (b)(4) fingertip sampling and viable surface sampling is performed (b)(4) as reported. Glove fingertip sampling is also performed for (b)(4)

iii. Media plates used for surface and fingertip sampling prior to February 2016 did not contain disinfectant neutralizers to assure microbial contamination can be detected, as reported.

OBSERVATION 5

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

Specifically, the suitability, efficacy, and limitations of cleaning equipment and disinfecting agents have not been appropriately assessed to ensure potential contaminants are adequately removed from surfaces in the (b)(4) (ISO 5).

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Disinfectant efficacy studies have not been performed to demonstrate that (b)(4) and its application method, including contact time and worst-case locations/objects, used to sterilize the (b)(4) can sufficiently reduce bioburden. (b)(4) via (b)(4) is used (b)(4) to sterilize the (b)(4) (b)(4) . Also sterilized (b)(4) are the (b)(4) , in addition to supplies to be used for the next week such as sterile, packaged syringes, vials, caps, etc., which are (b)(4)

OBSERVATION 6

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

Specifically,

During the production of epinephrine 1 mg/mL, lot #C16723161 on 04/19/2016 and phenylephrine 2.5%/tropicamide 1%, lot #125441/B59 on 04/20/2016 we observed:

i. Not all garb worn into (b)(4) is sterile. Examples include hair nets, beard nets, cotton gloves ((b)(4)), and street clothes and shoes not covered by sterile garb.
ii. Exposed skin (hands, forehead) in (b)(4) .
iii. Street clothes and shoes are worn into (b)(4) and are not completely covered by sterile garb. Sterile gown is open in back, leaving non-sterile street clothes partially uncovered.

OBSERVATION 7

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release.

Specifically,

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i. Aseptically processed sterile drug products are released and distributed without having been tested for potency, as reported. For example:

- Epinephrine 1 mg/mL (EPI01), lot #C16723161, produced on 04/19/2016
- Phenylephrine 2.5%/Tropicamide 1% (PT002), lot #125441/B59, produced on 04/20/2016
- Lidocaine 4%/Epinephrine 0.18%/Tetracaine 0.5% (LET01), lot #5C95A12, produced on 03/03/2016. This product is (b)(4).

ii. Finished lots of sterile drug products containing preservative are not tested for preservative content. Examples include:

- Cyclopentolate 1%/Phenylephrine 2.5% (CP001), contains (b)(4) as a preservative, refrigerated
- Phenylephrine 2.5%/Tropicamide 1%/Ketoraolac 0.5% (PTK002), contains (b)(4) as a preservative, refrigerated
- Lidocaine 4%/Epinephrine 0.18%/Tetracaine 0.5% (LET01), (b)(4), refrigerated

OBSERVATION 8

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

Specifically,

i. No method suitability studies using the required organisms and appropriate testing media (TSB and FTM), as per USP <71> *Sterility Tests*, have been performed in support of the following sterility (b)(4) used by your firm when determining sterility results for finished drug product batches produced: (b)(4). For example:

- Epinephrine 1 mg/mL (EPI01), lot #C16723161, produced on 04/19/2016, (b)(4)
- Phenylephrine 2.5%/Tropicamide 1% (PT002), lot #125441/B59, produced on 04/20/2016, (b)(4) (b)(4)
- Hydroxyprogesterone (17HPS), lot #126199/C04, produced on 02/17/16, (b)(4)

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ii. Aseptically processed sterile injectable drug products produced from non-sterile ingredients are released and distributed without having been tested for endotoxins, as reported. For example:

- Epinephrine 1 mg/mL (EPI01), lot #C16723159, (b)(4) units produced on 04/04/2016
- Epinephrine 1 mg/mL (EPI01), lot #C16723161, (b)(4) units produced on 04/19/2016
- Phenylephrine 2.5%/Tropicamide 1% (PT002), lot #125441/B59(b)(4) units produced on 04/20/2016

OBSERVATION 9

There is no written testing program designed to assess the stability characteristics of drug products.

Specifically,

i. Potency and sterility testing has not been performed in support of assigned Beyond Use Dates (BUDs) for several sterile drug products that are aseptically prepared. Unless stability studies have been performed, BUDs are, by default, 7 or 14 days for refrigerated sterile drug products with no preservatives and 14 days for sterile drug products containing preservatives stored at ambient temperature, as reported. Examples include:

- Lidocaine 1%/Bupivacain 0.75%/Hylenex 150U/mL (b)(4) no preservative, refrigerated, BUD 7 days; pertains to all (b)(4) products.
- Mitomycin 1mg/mL (MIT01), no preservative, refrigerated, BUD 14 days
- Fluorouracil 1mL (5FU01), no preservative, ambient storage, BUD 14 days

ii. Testing results provided by the contract laboratory in support of BUDs for the following sterile drug products were purported to have used analytical methods that are not considered validated or have not met all the requirements for sampling and/or method suitability:

- Hydroxyprogesterone Caproate (sesame oil) 250 mg/mL (17HPS), no preservative, ambient storage, BUD 45 days (tested for potency and particulate matter)
- Epinephrine HCL 1 mg/mL (EPI01), no preservative, refrigerated, BUD 14 days (tested for potency a (b)(4))
- Vancomycin 10 mg/mL (Vanc1), no preservative, refrigerated, BUD 30 days (tested for potency)

- Phenylephrine HCL 10%/tropicamide 1%/ketorolac 0.5% (PTK001), (b)(4) as a preservative, refrigerated, BUD 30 days (tested for potency, sterility, endotoxins, and particulate matter)
- Phenylephrine 2.5%/tropicamide 1%/ketorolac 0.5% (PTK002), (b)(4) as a preservative, refrigerated, BUD 30 days (tested for potency and sterility at (b)(4))
- Cyclopentolate 1%/phenylephrine 2.5% (CP001), (b)(4) as a preservative, refrigerated, BUD 30 days (tested for potency at (b)(4) and sterility at (b)(4))

CoAs for the following products carried a notation that methods for potency testing are not considered validated: 17HPS, EPI01, Vanc1, CP001, and PTK002

CoAs for the following products carried a notation that sterility testing does not meet all requirements for sampling and/or method suitability specified in USP<71> *Sterility Tests*: PTK001, CP001, and PTK002

OBSERVATION 10

Routine calibration of equipment is not performed according to a written program designed to assure proper performance.

Specifically, equipment used for confirmation/assurance of sterility is not calibrated, as reported. For example, the (b)(4) used in the production of epinephrine 1 mg/ml lot #C16723161 produced on 04/19/2016 and phenylephrine 2.5%/tropicamide 1% lot #125441/B59 produced on 04/20/2016.

OBSERVATION 11

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,

No evidence was provided that sterile (b)(4) would be effective in mitigating beta-lactam residues on contact surfaces should a spill occur in the (b)(4) (ISO 5) during aseptic

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processing. Cefuroxime 10 mg/mL (0.5mL in 1 mL syringes) is routinely aseptically processed in the (b)(4) (ISO 5) that are also used for non-beta lactam products. Following production of a beta-lactam product, a sporicidal agent is not used before a non-beta-lactam product is produced in the same (b)(4), as reported.

***DATES OF INSPECTION**

4/18/2016(Mon),4/19/2016(Tue),4/20/2016(Wed),4/21/2016(Thu),4/22/2016(Fri),5/05/2016(Thu),5/06/2016(Fri)

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X Charles L Zhou

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