To: Art Czabaniuk
FDA, Detroit District Office
300 River Place, Suite 5900
Detroit, MI 48207

Cc: Sarah Napier, Investigator
Emily Orban, Investigator

FEI: 3011130315

Re: Response to FDA Form 483 Issued 11/13/2014 following inspection dates 10/29/2014 – 11/13/14

Dear Sir,

Please accept this letter as authorization to post on the FDA Internet website University Compounding Pharmacy's following response to FDA Form 483 Notice of Observations, dated 12/2/2014 as submitted to FDA Detroit District Office, unredacted but without attachments. We understand this response will be posted under the FDA Form 483 Notice of Observations for University Compounding Pharmacy issued on 11/13/2014 by Investigator Napier.

Thank you,

Bradley McCloskey, PharmD (PIC)
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RESPONSE TO FORM 483

We acknowledge FDA's observations below. However, University Compounding Pharmacy (UCP) is a 503A pharmacy duly registered, licensed, practicing, and inspected under state jurisdiction of the Michigan Board of Pharmacy (MIBOP). UCP is compliant with all requirements thereof, including but not limited to USP General Chapter <797> (USP <797>). Furthermore, on October 28, 2014, the day before FDA entered to inspect, UCP passed MIBOP inspection. See Attachment A.

UCP does not compound for office use. UCP compounds only pursuant to individual, named patient prescriptions. Furthermore, UCP has not undertaken voluntary registration as a 503B outsourcing facility, the trigger for FDA oversight under the Compounding Quality Act. Therefore, any Observations describing extra-jurisdictional requirements are not applicable. Nonetheless, in the interest of cooperation and goodwill we permitted your inspectors entry to our facility, and it is in that same spirit we provide you with our responses here.

OBSERVATION 1

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

Specifically,

i. ***Adequate validation of aseptic processing operations, specifically, process simulations (media fills), have not been performed under representative worst case aseptic processing conditions to assure the sterility of drug products Currently, SOP 1.60, Orientation and Training, requires use of a syringe for the filling of two 10ml vials through a 0.22 micron filter This process does not include, for example, worst case lot sizes, vial sizes, and equipment used in normal aseptic operations such as repeater pumps. For example, media fill simulations are not representative of:***

...

ii. ***Non-sterile disposable wipes are used to wipe "ISO 5" laminar flow hoods with sterile 70% ispropyl alcohol. For example, such wipes ere used for cleaning "ISO 5" laminar flow hood #1 prior to the aseptic processing of Selenium 40mcg/ml Injectable lot 10302014@16 on 10/30/2014***

iii. ***The bioburden of non-sterile drug components is not evaluated, and bioburden limits have not been established, for non-sterile bulk formulated products to ensure the***

sterilizing process is adequate to remove the microbiological load For example, non-sterile drug components used in the processing of Hydroxocobalamin 1,200mcg/ml Injectable lot 09052014@66.

iv. ***In situ air pattern analysis has not been performed in the "ISO 5" laminar flow hoods, where sterile drug products are processed and filled, to demonstrate unidirectional airflow over the product during static or dynamic conditions. For example, the "ISO 5" laminar flow hood in which Hydroxocobalamin 1,200mcg/ml Injectable lot 09042014@66 was processed on 9/4/2014. Additionally, such analysis has not been performed in areas classified "ISO 7".***

RESPONSE TO OBSERVATION 1

i. UCP is compliant with its regulatory requirements under the authority of the MIBOP and operates consistent with USP <797> guidance. Because UCP is committed to the highest degree of patient safety and believes in constant process improvement in order to protect consumers, we have implemented a new procedure for media fills and will modify our media fill SOP to take into account:

a. Lot sizes, vial sizes and other worse case conditions
b. use of the repeater pump
c. use of different filters
d. Media fill SOP to be revised to include one media fill per process every 6 months

Target Date for Completion: Revise SOP within 30 days. UCP will keep FDA informed of its progress on this matter and update FDA once complete.

ii. UCP is compliant with its regulatory requirements under the authority of the MIBOP and operates consistent with USP <797> guidance, which states,

> "All cleaning materials, such as wipers, sponges, and mops, shall be nonshedding, preferably composed of synthetic fibers, and dedicated to use in the buffer or clean area, ante-area, and segregated compounding areas and shall not be removed from these areas except for disposal."
> *USP **797** - Pg 16; Section - Cleaning and Disinfecting the Compounding area*

iii. UCP is compliant with its regulatory requirements under the authority of the MIBOP and operates consistent with USP <797> guidance.

iv. UCP is compliant with its regulatory requirements under the authority of the MIBOP and operates consistent with USP <797> guidance. Because UCP is committed to the highest degree of patient safety and believes in constant process improvement in order to protect consumers, we decided to, and have already performed, smoke studies in our ISO 5 hoods. Please see Attachment B for study results.

Target Date for Completion: Smoke studies completed on 11/10/2014

OBSERVATION 2

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

Specifically,

Gowning of operators performing aseptic operations in the "ISO 5" laminar flow hoods is inadequate in that protective gowns, face masks, and hair nets worn during aseptic processing are not sterile. Additionally, the current gowning method leaves facial skin exposed, including eyes and forehead. For example, gowning worn as observed during the aseptic processing of Selenium 40mcg/ml Injectable lot 10302014@16 on 10/30/2014.

RESPONSE TO OBSERVATION 2

UCP is compliant with its regulatory requirements under the authority of the MIBOP and operates consistent with USP <797> guidance, which states:

> "After completion of hand washing, a nonshedding gown with sleeves that fit snugly around the wrists and enclosed at the neck is donned. Gowns designated for buffer area use shall be worn, and preferably they should be disposable. If reusable gowns are worn, they should be laundered appropriately for buffer area use."
>
> *USP 797 – Pg 16; Section – Personnel Cleansing and Garbing*

> "Garbing activities considered the dirtiest include donning of dedicated shoes or shoe covers, head and facial hair covers (e.g., beard covers in addition to face masks), and

face masks/eye shields. Eye shields are optional unless working with irritants such as germicidal disinfecting agents or when preparing hazardous drugs."

USP 797 – Pg 16; Section – Personnel Cleansing and Garbing

OBSERVATION 3

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

Specifically,

i. ***Environmental monitoring is not performed at least daily during drug production in the critical areas, to evaluate the quality of the aseptic processing environment and assess whether aseptic conditions are maintained.***
   a. ***Non-viable particulate monitoring is performed in the aseptic processing room once every six months***
   b. ***Viable air monitoring is performed in each laminar flow hood once every six months***
   c. ***Viable surface monitoring is performed in each laminar flow hood once per month***
   d. ***Personnel fingertip monitoring is performed for one operator every two weeks***

ii. ***No data was provided to support that the incubator used to incubate environmental monitoring surface and fingertip samples is qualified for its intended use EnviroTest Media Paddles Directions for Use states, "Incubate at an elevated temperature (USP<797>) 30-35 degrees C for 48 to 72 hours." The temperature of the incubator is checked only daily on business days, and no documentation was provided to support calibration of the unit's temperature probe.***

The above apply to aseptic processing areas used to process and fill all sterile drug products, for example, Hydroxocobalamin 1,200mcg/ml injectable lot 09052014@66 and Selenium 40mcg/ml injectable lot 10302014@16 on 10/30/2014.

RESPONSE TO OBSERVATION 3

i) UCP is compliant with its regulatory requirements under the authority of the MIBOP and operates consistent with USP <797> guidance, which states:

a. Viable and Nonviable Environmental Sampling Testing

"Environmental sampling shall occur as part a comprehensive quality management program and shall occur minimally under any of the following conditions:

- as part of the commissioning and certification of new facilities and equipment
- following any servicing of facilities and equipment
- as part of the re-certification of facilities and equipment (i.e., every 6 months);"

*USP **797** – Pg 13; Section – Viable and Nonviable Environmental Sampling Testing*

b. "Certification procedures such as, those outlined in *Certification Guide for Sterile Compounding Facilities* (CAG-003-2006)$_9$ shall be performed by a qualified individual no less than every 6 months and whenever the device or room is relocated or altered or major service to upstream of the facility is performed."
USP 797 – Pg 13; Section – Viable and Nonviable Environmental Sampling Testing

c. "Surface sampling shall be performed in all ISO classified areas on a periodic basis. Sampling can be accomplished using contact plates or swabs, and it shall be done at the conclusion of compounding."
USP 797 – Pg 18; Section – Surface Cleaning and Disinfection Sampling and Assessment

d. USP <797> requires gloved fingertip sampling prior to initially compounding (3 samples) during an observed competency every six months (2 samples) and on a routine basis.
"After completing the initial gowning and gloving competency evaluation, re-evaluation of all compounding personnel for this competency shall occur at least annually for personnel who compound low- and medium-risk level CSPs and semi-annually for personnel who compound high-risk level CSPs using one or more sample collections during any media-fill test procedure before they are allowed to continue compounding CSPs for human use."
USP 797 – Pg. 17; Section – Gloved Fingertip Sampling

"† After completing the initial gowning and gloving competency evaluation, re-evaluation of all compounding personnel shall occur at least annually for low-

and medium-risk level CSPs and semiannually for high-risk level CSPs before being allowed to continue compounding CSPs."

USP 797 – Pg.33; Section – Gloved Fingertip Sampling

iii. UCP is compliant with its regulatory requirements under the authority of the MIBOP and operates consistent with USP <797> guidance, which makes no statement about calibrating incubators. Furthermore, UCP has been in contact with the manufacturer of the incubator, who confirmed UCP is using the incubator in accordance with its instructions for use. There is no reference to calibrating the temperature probe in the manual, and the company confirms that users cannot calibrate the temperature gauge. See Attachment C.

OBSERVATION 4

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

Specifically,

The monitoring frequency of pressure differentials between the aseptic processing areas and surrounding areas of lower air quality is not justified. Currently, such pressure differentials are checked and documented by operators once per day on each day of use according to SOP 1.40, Compounding Area Requirements (Sterile). Assurance was not provided to support that a temporary loss in differential pressure during filling operations would be detected and appropriately handled. For example, the aseptic processing areas in which all sterile drug products are processed and filled, including but not limited to Hydroxocobalamin 1,200mcg/ml Injectable lot 09052014@66 and Selenium 40mcg/ml Injectable lot 10302014@16 on 10/30/2014.

RESPONSE TO OBSERVATION 4

Observation 4

UCP is compliant with its regulatory requirements under the authority of the MIBOP and operates consistent with USP <797> guidance, which states:

"A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the buffer area and the ante-area and between the ante-area and the general environment outside the compounding area. The results shall be reviewed and documented on a log at least every work shift (minimum frequency shall be at least daily) or by a continuous recording device. The pressure between the ISO Class 7 (see Table 1) and the general pharmacy area shall not be less than 5 Pa (0.02 inch water column). In facilities where low- and medium-risk level CSPs are prepared, differential airflow shall maintain a minimum velocity of 0.2 meters per second (40 feet per minute) between buffer area and ante-area."

USP 797 – Pg. 13; Section – Differential Pressure Monitoring

OBSERVATION 5

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

Specifically,

i. ***Beyond use dates assigned to sterile drug products are not always supported by sterility testing over the labeled shelf life in representative container closure systems, for example:***

   -...

ii. ***For drug products containing a preservative, testing has not been performed to support that the preservative system retains antimicrobial effectiveness over the labeled shelf life of the drug product. For example, Hydroxocobalamin 1,200mcg/ml Injectable lot 09052014@66.***

RESPONSE TO OBSERVATION 5

i. UCP is compliant with its regulatory requirements under the authority of the MIBOP and operates consistent with USP <797> guidance. Because UCP is committed to the highest degree of patient safety and believes in constant process improvement in order to protect consumers, we will modify our SOP to perform a sterility test at the end of our potency testing to verify sterility over the entire life of the beyond use date.

ii. UCP is compliant with its regulatory requirements under the authority of the MIBOP and operates consistent with USP <797> guidance. Because UCP is committed to the highest degree of patient safety and believes in constant process improvement in order to protect consumers, we will modify our SOP to perform a sterility test at the end of our potency testing to verify the preservative still has microbial effectiveness over the entire life of the beyond use date.

Target Date for Completion: Revise SOP within 30 days. UCP will keep FDA informed of its progress on this matter and update FDA once complete.

OBSERVATION 6

Container closure systems do not provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

Specifically,

Adequate container closure integrity testing has not been performed for any sterile product container closure systems. Specifically, vials are filled through insertion of a needle through the rubber vial closure, and data was not provided to support that this closure will prevent the ingress of microbial contamination post puncture. For example, the container closure system used to package Hydroxocobalamin 1,200mcg/ml Injectable lot 09052014@66.

RESPONSE TO OBSERVATION 6

UCP is compliant with its regulatory requirements under the authority of the MIBOP and operates consistent with USP <797> guidance.

OBSERVATION 7

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

Specifically,

Aseptically filled sterile injectable drug products are released and distributed prior to receiving final laboratory results for sterility and endotoxins. For example, Hydroxocobalamin 1,200mcg/ml Injectable lot 09052014@66 was made on 9/5/2014 and distributed on 9/10/2014. On 9/18/2014, investigations into a suspected sterility failure commenced at the firm and contract laboratory, resulting in the recall of this drug.

RESPONSE TO OBSERVATION 7

At the outset of this response, we note that UCP dispenses, not distributes, its compounded drug products.

UCP is compliant with its regulatory requirements under the authority of the MIBOP and operates consistent with USP <797> guidance. Because UCP is committed to the highest degree of patient safety and believes in constant process improvement in order to protect consumers, we will modify our SOP to quarantine product until sterility testing is complete. Certain exceptions may be built into the SOP, for example, where patient access would be restricted due to BUDs of 30 days or less. USP<797> permits pre-testing dispensing using the following procedure, which UCP has followed and will continue to follow:

> "When high-risk level CSPs are dispensed before receiving the results of their sterility tests, there shall be a written procedure requiring daily observation of the incubating test specimens and immediate recall of the dispensed CSPs when there is any evidence of microbial growth in the test specimens. In addition, the patient and the physician of the patient to whom a potentially contaminated CSP was administered are notified of the potential risk."
>
> *USP 797 – Pg. 21; Section – Sterility Testing*

Target Date for Completion: Revise SOP within 30 days. UCP will keep FDA informed of its progress on this matter and update FDA once complete.

OBSERVATION 8

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

Specifically,

A 100% visual inspection for contamination is not performed on each lot of sterile drug products prior to release and distribution. Currently, one or two vials from each finished lot of sterile drug product are examined visually for contamination; such examinations are not documented. For example, Dimercaptopropane Sulphonate 50mg/ml Injectable lot 10302014@6.

RESPONSE TO OBSERVATION 8

UCP respectfully disagrees with Observation 8. The responsibilities and procedures applicable to the quality control unit are indeed in writing. SOP 6.10 3.4.2.3 specifically provides that:

Visually inspect for:

3.4.2.3.1 Container leaks
3.4.2.3.2 Integrity
3.4.2.3.3 Cloudiness or separation
3.4.2.3.4 Appropriate color, odor
3.4.2.3.5 Appropriate volume, viscosity
3.4.2.3.6 Particles (swirl against light/dark)

What the inspectors witnessed was the failure of a staff member to visually inspect a vial on a single occasion. To make sure this does not happen again, on 12/2/2014 we retrained our sterile technicians on precisely how to follow our current SOP and inspect every vial for contamination. Following inspection they will initial the appropriate line listed on the master formula to verify all vials have clarity and are particle free. Please see Attachment D for the line that indicates the vials have been inspected for contamination on the master formula.

Target date for completion: Re-training of staff completed on 12/2/2014

OBSERVATION 9

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,

Procedures have not been established for the separation of tasks and segregation of personnel handling beta-lactam drug products from those for all other human drug products. For example, Amoxicillin/Clavulonic Acid (4.5 capsules = 500mg-125mg) lot 10302014@43 was processed in a containment hood in the non-sterile laboratory area on 10/30/2014, and subsequently, Estradiol 1.2mg/gm HRT Cream lot 10302014@69 and Progesterone Slow

Release 50mg Veggie Capsule lot 10302014@62 were compounded in the same laboratory area on that same day.

RESPONSE TO OBSERVATION 9

UCP is compliant with its regulatory requirements under the authority of the MIBOP and operates consistent with USP <797> guidance. Because UCP is committed to the highest degree of patient safety and believes in constant process improvement in order to protect consumers, we will modify our SOP to only compound beta-lactam drug products for human use in dedicated work stations.

> **Target Date for Completion: Revise SOP within 30 days. UCP will keep FDA informed of its progress on this matter and update FDA once complete.**

Thank you very much.