



BOB FERGUSON

# ATTORNEY GENERAL OF WASHINGTON

University of Washington Division • Box 359475 • Seattle, Washington 98195-9475

August 30, 2016

Ms. Miriam R. Burbach, District Director  
Food and Drug Administration  
22215 26<sup>th</sup> Ave SE, Suite 210  
Bothell, Washington 98021

**RE: University of Washington Medical Center (UWMC) Inpatient Pharmacy Food and Drug Administration (FDA) inspection FEI Number 3012562031**

Ms. Burbach,

On behalf of University of Washington Medical Center (UWMC) Inpatient Pharmacy, I authorize the United States Food and Drug Administration (FDA) to publicly disclose the information described below on the FDA's web site. I understand that the information that is disclosed may contain confidential commercial or financial information or trade secrets within the meaning of 18 U.S.C. § 1905, 21 U.S.C. § 331, and 5 U.S.C. § 552(b)(4) that is exempt from public disclosure under those statutory provisions and/or relevant FDA regulations. I agree to hold the FDA harmless for any injury caused by the FDA's sharing the information with the public.

Information to be disclosed: UWMC's letter dated August 24, 2016 (a copy of which is attached hereto), excluding attachments/exhibits, which responds to the FDA's Form 483 dated August 4, 2016 (FEI No. 3012562031). Authorization is given to the FDA to disclose the above-mentioned information which may include confidential commercial or financial or trade secret information. As indicated by my signature, I am authorized to provide this consent on behalf of UWMC and my full name, title, address, telephone number, and facsimile number are set out below for verification.

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In the event there are any questions regarding the disclosure of such information, I hereby request pre-disclosure notification so that we can address any such questions prior to disclosure of the material.

Thank you.

Sincerely yours,



DAVID M. KERWIN  
Assistant Attorney General  
4333 Brooklyn Avenue NE, 18<sup>th</sup> Floor  
Box 359475  
Seattle, WA 98195  
Office: (206) 543-4150  
Fax: (206) 543-0779

August 31, 2016

Ms. Miriam R. Burbach, District Director  
Food and Drug Administration  
22215 26th Ave SE, Suite 210  
Bothell, Washington 98021

RE: University of Washington Medical Center (UWMC) Inpatient Pharmacy Food and  
Drug Administration (FDA) inspection **FEI Number 3012562031**

Ms. Burbach:

Please be aware that the University of Washington is a State institution and as required by State law, the Washington State Attorney General's Office represents the University of Washington in all legal and regulatory matters. This legal representation includes any and all inspections and/or enforcement actions taken by the FDA concerning any part of the University of Washington, including but not limited to the UWMC Inpatient Pharmacy.

Thank you and please contact me with any questions.

Sincerely,



Shabir Somani  
Chief Pharmacy Officer  
UW Medicine Pharmacy



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August 24, 2016

Ms. Miriam R. Burbach, District Director  
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22215 26<sup>th</sup> Ave SE, Suite 210  
Bothell, Washington 98021

**RE: University of Washington Medical Center (UWMC) Inpatient Pharmacy Food and Drug Administration (FDA) inspection FEI Number 3012562031**

Ms. Burbach,

Per FDA Investigator Gerard De Leon's instructions, this letter comprises UWMC's response to the FDA Form 483 Observations which were issued on August 4<sup>th</sup>, 2016 following an inspection of our inpatient pharmacy.

The UWMC Inpatient pharmacy operates pursuant to the rules and regulations of Washington State, the Washington State Pharmacy Quality Assurance Commission, and relevant United States Pharmacopeia (USP) Chapter 797 standards. As indicated on the Form 483, the UWMC pharmacy is a producer of compounded sterile preparations used for identified patients and produced pursuant to valid orders. Nonetheless, a review of the Observations demonstrates that we were investigated pursuant to the FDA's current Good Manufacturing Practices ("cGMP").

Section 503A of the Federal Food, Drug and Cosmetic Act states:

"(a) In General.--Sections 501(a)(2)(B), 502(f)(1), and 505 shall not apply to a drug product if the drug product is compounded for an identified individual patient based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient, ... ." This language was intended to remove facilities such as the UWMC inpatient pharmacy from the requirements of the cGMP. While it may well be the case, as laid out in the FDA's recent draft guidance, "Insanitary Conditions at Compounding Facilities," that all facilities, whether regulated under section 503A or not, are subject to the requirements of section 501(a)(2)(A), we

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respectfully take that position that section 501(a)(2)(A) cannot be used to effectively nullify section 503A(a) and one of its intended purposes.

As such, we believe the Observations are, in part, an incorrect application of standards. Regardless, UWMC Pharmacy appreciates the thorough investigation by FDA inspector De Leon and has made and will continue to make improvements in our processes as described below. Whatever the standard applied, we believe the following actions will fully satisfy any and all FDA concerns.

## **OBSERVATION 1**

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

Specifically,

A) On July 11, 2016 during the production of Epinephrine 5mg in D5W 250mL (20mcg/mL. Lot: OG1116A and Nicardipine 25mg in NS 250mL (0.1mg/mL), Lot: OG1116B inside the Small Clean Room:

- 1) Non-sterile TX 612 TechniCloth Nonwoven Wipers sprayed with sterile 70% isopropyl alcohol were used to clean and wipe down the surface of the Baker ISO 5 horizontal laminar flow hood (LFH), S/N 107347.

## **RESPONSE**

USP Chapter 797 indicates that low shedding wipes shall be used when cleaning and disinfecting compounding surfaces. There is no mention of the need to use sterile wipes.

Per USP 797 standards: "Cleaning and disinfecting shall occur before compounding is performed. Items shall be removed from all areas to be cleaned, and surfaces shall be cleaned by removing loose material and residue from spills; for example, water-soluble solid residues are removed with sterile water (for injection or irrigation) and low-shedding wipes. This shall be followed by wiping with a residue-free disinfecting agent such as sterile 70% IPA, which is allowed to dry before compounding begins."

We will standardize our process to use sterile 70% alcohol pre-saturated non-shedding wipes when disinfecting in the ISO 5 environment. Pharmacy staff will be trained to the standard process in September, 2016.

B) On July 11, 2016 apparent white debris was observed on the metal filter grate of the Baker ISO 5 horizontal LFH, S/N 116386 located inside the Small Clean Room.

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## **RESPONSE**

The Baker ISO 5 horizontal LFH, S/N 116386 ISO 5 environment was tested by an outside contractor on March 22<sup>nd</sup>, 2016 and passed all viable and nonviable environmental monitoring as required by USP Chapter 797. UWMC Pharmacy follows USP 797 standards when cleaning and disinfecting the LFHs. Baker, the manufacturer of the LFH, was contacted for guidance on how to best clean the metal filter grates to avoid damaging the HEPA filter. Currently there are no established recommendations from the manufacturer on how to routinely clean the grates. We will work with the manufacturer to develop a best practice for cleaning and disinfecting of the metal filter grates. As an improvement to our cleaning process of the metal filter grates, we submitted a purchase order on August 22<sup>nd</sup>, 2016 for replacement metal filter grates to allow for cleaning based on monthly inspection of the LFH. Pharmacy Staff will also be trained in September 2016 on how to identify and immediately notify a manager if they detect any apparent debris on any metal filter grate.

## **OBSERVATION 2**

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

Specifically,

- A) Apparent pitting was observed on the main workbench and apparent pitting and black scratches were observed on the bottom of the metal filter grate of the Baker ISO 5 horizontal LFH, S/N 107347 located in the Small Clean Room.

## **RESPONSE**

The LFH passed all viable and nonviable environmental monitoring as required by USP Chapter 797 on March 22<sup>nd</sup>, 2016. The area in question will be visually inspected each month for signs of discoloration and monitored monthly via surface sampling. The LFH will be monitored semi-annually for viable and nonviable particles as per USP Chapter 797.

- B) A door installed in the Small Clean Room, between the ISO 8 anteroom and ISO 7 buffer room, is composed of a sealed, wooden material.

## **RESPONSE**

A work order has been placed to purchase and install new metal doors between the ISO 8 anteroom and the ISO 7 buffer room. In addition, the wooden door between the work

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room and the anteroom will also be replaced with an estimated installation date of mid-October.

## **OBSERVATION 3**

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

Specifically,

- A) Sterilized containers, closures, and utensils that are used in sterile drug production are stored in their original sterilization pouch on a cart in the unclassified Drug Services Laboratory and they are used within three to six months of sterilization. This hold time has not been validated to ensure the sterility of the containers, closures, and utensils.

## **RESPONSE**

Validation of the hold time is being conducted to determine the sterility of containers, closures and utensils stored in their original sterilization pouch for 30 days. Results of the studies are expected by November 1<sup>st</sup>, 2016. Once the 30 day hold time has been validated, the Drug Services policy will be updated.

- B) Your practice to “depyrogenate” glass beakers and stir bars used in sterile drug production is inadequate in that they are rinsed with sterile water-for-injection and wiped with a non-sterile TX 612 TechniCloth Nonwoven Wipers prior to use. The outside of the glass beaker is also not wiped with a sterile wipe and sterile 70% isopropyl alcohol prior to introduction into the ISO 5 LFH.

## **RESPONSE**

Sterility and pyrogen testing performed on high risk compounded preparations demonstrates sterility, however sterile wipes have been implemented as a process improvement when wiping glass beakers and stir bars during the high risk compounding process. In addition, the outside of glass beakers are wiped down with a sterile 70% alcohol pre-saturated non-shedding wipe prior to introduction into the ISO 5 environment.

- C) Your practice of wiping down components, containers and closures prior to introduction into the ISO 7 buffer room and the ISO 5 LFH is inadequate in that it is performed with a

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non-sterile TX 612 TechniCloth Nonwoven Wiper sprayed with sterile 70% isopropyl alcohol.

## RESPONSE

Per USP 797 guidelines: "Supplies and equipment removed from shipping cartons shall be wiped with a suitable disinfecting agent (e.g. sterile 70% IPA) delivered from a spray bottle or other suitable delivery method. After the disinfectant is sprayed or wiped on a surface to be disinfected, the disinfectant shall be allowed to dry, during which time the item shall not be used for compounding purposes."

As a process improvement, prior to introduction into the ISO 7 and ISO 5 environments, we will be using sterile 70% alcohol pre-saturated non-shedding wipes or sterile 70% isopropyl alcohol spray bottle.

- D) On May 26<sup>th</sup>, 2016, the Baker S/N # 118435 ISO 5 horizontal LFH and the Baker S/N # 118436 ISO 5 horizontal LFH in the Large Clean Room were certified under at rest/static conditions. The Baker S/N # 118435 ISO 5 horizontal LFH was observed in use during the production of Magnesium Sulfate/Dextrose 5% 8mEq/52mL IVPB Once 208 mL/hr on July 11, 2016.

## RESPONSE

The testing on May 26<sup>th</sup>, 2016 was conducted by an outside contractor to certify the new Large Clean Room and LFH's prior to use. This room and LFH's were not in use at the time of testing. In the future, any new clean rooms will be certified under simulated dynamic conditions before use. The LFHs were retested for viable and non-viable sampling on August 22<sup>nd</sup>, 2016 under dynamic conditions.

- E) An in situ air pattern analysis (smoke study) of the following has not been conducted to demonstrate unidirectional airflow and sweeping action over and away from sterile drug products under dynamic conditions:
- 1) The Baker S/N # 116386 ISO 5 horizontal LFH, Baker S/N # 107347 ISO 5 horizontal LFH, and ISO 7 buffer room in the Small Clean Room
  - 2) The Baker S/N # 165579101014 ISO 5 compounding aseptic isolator, Baker S/N # 118435 ISO 5 horizontal LFH, Baker S/N # 118436 ISO 5 horizontal LFH, and ISO 7 buffer room in the Large Clean Room.



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## **RESPONSE**

We are in discussions with our environmental testing contractor, Technical Safety Services, Inc., as well as a sterile compounding consultant to identify the appropriate in situ air pattern analysis (smoke study) to perform in the LFH and ISO 7 buffer rooms under dynamic conditions. Plan to implement no later than December 31, 2016.

## **OBSERVATION 4**

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

Specifically, On July 11, 2016 the side of an operator's non-sterile gown was observed coming into direct contact with the inner liner of a receptacle container that was stored adjacent to the ISO 5 horizontal LFH in the Large Clean Room. The operator then proceeded to work in the Baker S/N # 118435 ISO 5 horizontal LFH with the front parts of the non-sterile gown exposed inside and in direct contact with the ISO 5 LFH work surface.

## **RESPONSE**

New, higher quality, tighter fitting gowns have been purchased and implemented for personnel working in the clean rooms. Positioning of the receptacle containers in respect to location of the LFH's is being evaluated. Pharmacy staff will be educated in September of 2016 on how to position the receptacle containers to avoid direct contact with their non-sterile-gowns.

## **OBSERVATION 5**

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

On June 25, 2016 an air handling unit that supplied air to the ISO 7 buffer room and ISO 8 anteroom located in the Small Clean Room was shut off for approximately five hours. The air supplied to the ISO 7 buffer room and ISO 8 anteroom was not recertified to verify the classification of the room and environmental monitoring of the room was not performed prior to resuming sterile drug production on June 25, 2016.

## **RESPONSE**

While the supply air was turned off for 5 hours on June 25<sup>th</sup>, 2016, the Small Clean Room exhaust system remained fully operational. It was confirmed that the Small Clean Room maintained above 0.2 pressure differential resulting in a positive pressure environment during the approximate 5 hours. Based on these results we do not believe that the Small

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Clean Room environment was compromised during this time period. Standard operating procedures have been updated to require that significant disruptions to room air supply systems necessitate environmental monitoring to be performed before use.

## **OBSERVATION 6**

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

- A) The following sterile drug products that undergo sterility testing are not held under quarantine (pending sterility testing results) and are released for distribution:
- Fentanyl PCA 1250 mcg/25mL, BUD 30 days refrigerated
  - Hydromorphone PCA 25mg/25mL, BUD 30 days refrigerated
  - Morphine PCA 125mg/25mL, BUD 30 days refrigerated

## **RESPONSE**

According to USP 797, "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."

USP 797 does not require CSPs to be quarantined prior to sterility testing results. The above products are medium risk sterile to sterile drug preparations which do not require terminal sterilization and are not considered high risk level CSPs. As a process improvement, the above products will no longer be produced by UWMC Inpatient Pharmacy and will be outsourced to a 503-B compounding facility by September 30<sup>th</sup>, 2016.

- B) Endotoxin testing is not performed on each finished batch or representative finished batches of finished sterile drug products. For example, endotoxin testing is not performed on batches of the following sterile drug products:
- Fentanyl PCA 1250 mcg/25mL, BUD 30 days refrigerated
  - Hydromorphone PCA 25mg/25mL, BUD 30 days refrigerated
  - Morphine PCA 125mg/25mL, BUD 30 days refrigerated

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## RESPONSE

The above products are medium-risk sterile to sterile drug preparations which do not require terminal sterilization and are not considered high-risk level CSPs and therefore endotoxin testing is not required.

As a process improvement, the above products will no longer be produced by UWMC Inpatient Pharmacy and will be outsourced to a 503-B compounding facility by September 30<sup>th</sup>, 2016.

- C) Samples submitted for testing to a third-party laboratory are pooled together and analyzed as one sample. For example,
- 1) 4 out of 42 vials (20mL each) of PBS 0.05M Sterile Injection Solution 20mL, DS Lot # 7105 were submitted for potency, sterility, endotoxin, and fungi testing.
  - 2) 3 out of 25 vials (10mL each) of Phenol Aqueous 5% Sterile Injection 10mL, DS Lot#7258 were submitted for potency, sterility, endotoxin, and fungi testing

## RESPONSE

Samples sent to third-party laboratories are no longer pooled. PBS Solution has been outsourced to a 503-B compounding facility and will no longer be prepared by UWMC Pharmacy.

## OBSERVATION 7

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

Specifically, your firm does not have a stability program or any stability data to support the beyond use date (BUD) assigned to the following sterile drug products that are produced in anticipation of use:

- Fentanyl PCA 1250 mcg/25mL, BUD 30 days refrigerated
- Hydromorphone PCA 25mg/25mL, BUD 30 days refrigerated
- Morphine PCA 125mg/25mL, BUD 30 days refrigerated

## RESPONSE

UWMC Pharmacy determines BUD for compounded sterile products based on manufacturer's recommendations and available published literature consistent with the USP 797 standards.

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As a process improvement, the above products will no longer be produced by UWMC Inpatient Pharmacy and will be outsourced to a 503-B compounding facility by September 30<sup>th</sup> 2016.

## **OBSERVATION 8**

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

Specifically, the non-sterile attire worn by the operators on July 11, 2016 during the production of Magnesium Sulfate/Dextrose 5% 8mEq/52mL IVPB Once 208mL/hr in the Large Clean Room and during the production of Epinephrine 5mg in D5W 250mL (20mcg/mL), Lot: OG1116A and Nicardipine 25mg in NS 250mL (0.1mg/mL), Lot: OF1116B in the Small Clean Room was inadequate as follows:

- A) Operators producing sterile drug products in the Baker S/N # 118435 ISO 5 horizontal LFH (Large Clean Room) and Baker S/N # 107347 ISO 5 horizontal LFH (Small Clean Room) were observed wearing a disposable non-sterile head cover, non-sterile surgical mask, non-sterile gown, and non-sterile shoe covers.
- B) The disposable non-sterile surgical mask and non-sterile head cover worn by the operators in the Large Clean Room and Small Clean Room did not provide adequate coverage to the forehead, neck, or face. Both operators were also not wearing protective eyewear and the operator in the Small Clean Room was observed to be wearing eye makeup.

## **RESPONSE**

UWMC Pharmacy Policy and Procedures requires cleanroom staff to wear shoe covers, bouffant cap, facial hair cover, face mask, gown and sterile gloves. The clean room staff wear appropriate garb for the duties they perform, based on USP 797 standards. USP 797 has no requirement for sterile garb other than gloves. As an improvement to our garbing process, pharmacy technicians working in sterile compounding areas will wear hospital supplied scrubs under the non-shedding gown as of October 2016.

The staff member observed to be wearing eye makeup was not scheduled to work in a sterile compounding area, but was asked to demonstrate sterile compounding for the

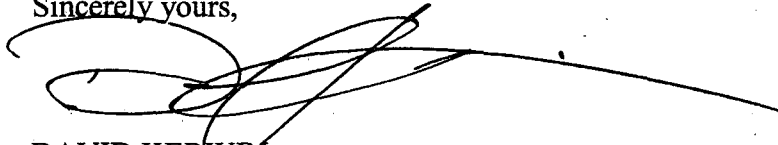
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inspector. All compounding staff will be reeducated in September 2016 regarding the removal of facial cosmetics before entering the IV admixture area.

Thank you for giving us the opportunity to respond to the observations noted during the FDA inspection. We respectfully request that this letter of response be publicly posted when the FDA form 483 observations are posted on the FDA website.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'DAVID KERWIN', with a long horizontal flourish extending to the right.

DAVID KERWIN  
Assistant Attorney General