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From: Dr. James Gilman, Clinical Center CEO

Through: Dr. Majid Tanas, Chief of Pharmacy, Clinical Center

Date: March 27, 2019

Subject: Response to FDA 483, FEI #3011547221

This letter is in response to observations identified in the Food and Drug Administration (FDA) Form 483, dated March 6, 2019 (FEI #3011547221). The National Institutes of Health (NIH) executive leadership takes these 483 observations seriously and is dedicated to maintaining compliance with applicable regulations and ensuring patient safety.

Since the inspection, NIH has been taking steps to thoughtfully correct and prevent the concerns identified in the 483. These actions are comprehensive with targeted completion dates addressed in the included documentation.

NIH will provide the FDA with status updates, until all actions contained herein have been completed.

Sincerely,

Majid Tanas, PharmD, MHA, MS
Chief, Department of Pharmacy
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OBSERVATION 1

Aseptic Manipulations are performed in an area where the unidirectional movement of air in the ISO 5 area is disrupted.

Specifically, smoke studies completed in laminar airflow workbench (Equipment ID: LAFW2) on 10/10/2018 demonstrated that air refluxes around the control panel and where the sterile connections are made on the ExactaMix Compounder. The Compounder is used to prepare total parenteral nutrition (TPN) bags.

NIH Response:
The Baxter ExactaMix Compounder is essential for direct patient care and cannot be removed from operation. Although, NIH had taken steps to include placement of risers and airfoils. Airflow visualization studies from October 2018 identified air reflux around the control panel and scale. The study identified the presence of airflow concerns around connections to the valve block above the compounder.

The NIH Clinical Center Pharmacy Department is in the process of developing an alternative method to aseptically make connections for the TPN compounder by April 30, 2019. The effectiveness of the alternative configuration will be tested via smoke study by May 31, 2019.

Concomitantly, NIH will continue to pursue the previously initiated outsourcing of these products to an FDA-registered outsourcing provider within the calendar year 2019.

OBSERVATION 2

Deficiencies were noted with aseptic processing performed within the ISO 5 areas.

Specifically,

(A) On 2/19/2019, an operator was observed reusing an alcohol prep pad that had come in contact with the ISO 5 biosafety cabinet (Equipment ID: BSC2) workbench surface and the chemotherapy prep mat during the preparation of Tacrolimus Continuous Infusion, 5 mg/ml.

(B) On 2/22/2019, an operator was observed performing aseptic processing in ISO Class 5 Laminar Airflow workbench (Equipment ID: LAFW1) with part of the non-sterile gown around the abdomen area inside the ISO 5 work surface.

(C) On 2/22/2019, an operator was observed resting her gloved hands on the work surface of LAFW1 during preparation of Bone Marrow Pink Syringes (not administered in humans). During the operation, the technician was observed to rest one hand at a time directly on the ISO 5 work surface and use the other hand to hold the barrel of a syringe. The operator's arm was also observed to pass over the open bottle of DMEM (Dulbecco's modified eagle medium).

NIH Response:

(A) The observation involving reuse of a sterile alcohol prep pad is not consistent with SOP CCP-20010 – General Principles for Sterile Assurance. Communication has been sent to the IV room staff to reinforce acceptable behavior, with read and signature receipt due by April 5, 2019.

Additional language will be included in the SOP to clarify that a new pad is required prior to wiping each critical site by April 15, 2019.

Quarterly qualification will highlight the importance of single-use alcohol prep pads and the avoidance of possible contact contamination by adding an evaluation to qualification forms 20010F.1 by June 30, 2019.

Operational and Quality Assurance observation forms will be updated to enforce this behavior by April 15, 2019.

These changes will be incorporated in the 2019 annual training program and will be completed by September 30, 2019.

(B) To avoid the presence of excess garment protrusion away from the body we have incorporated the following process improvements:

- Communication has been sent to the IV room staff regarding leaning into the hood and/or standing against the hood as per SOP CCP-20010 General Principles of Sterility Assurance, with read and signature receipt due by April 5, 2019.
- Sizing guides have been provided to staff for their review.
- Staff will be reassessed for appropriate sizing to ensure the absence of puffing around the chest and abdomen, by April 15, 2019.
- Operational and Quality Assurance observation forms will be updated to enforce this behavior by April 15, 2019.
- By June 30, 2019, additional details will be added to the quarterly garbing and hand hygiene assessment form that specifies the qualifying individual will assess for absence of puffing around the chest and abdomen when personnel don the coverall.

(C) During the review of SOP CCP-20010 General Principles of Sterility Assurance, it was noted that the SOP does not specify personnel contact with ISO 5 surfaces. Additionally, the SOP does not specify passing of hands and forearms above open containers in a laminar flow hood. The following improvements have been identified:

- Communication has been sent to the IV room staff to remind technicians to not contact the ISO 5 surfaces and to not pass hands or forearms over open containers, with read and signature receipt due by April 5, 2019.
- Operational and Quality Assurance observation forms will be updated to enforce this behavior by April 15, 2019.
- SOP CCP-20010 General Principles of Sterility Assurance will be revised to specify that personnel contact with ISO 5 surfaces, including the deck, must be avoided by April 30, 2019. A statement will be included within the SOP that instructs operators to avoid passing hands or forearms above these critical sites.
- The preparation of this bone marrow sample diagnostic solution is being assessed for outsourcing to an FDA-registered outsourcing provider.

OBSERVATION 3

Cleaning pads used in the ISO 5 classified aseptic processing areas were not sterile.

(A) EasyReach Cleaning Pads (Part # MEQT0001) used to clean the interior surfaces of the ISO 5 hoods are not sterile.
(B) On 2/19/2019, re-sealable multi-packs of Prosat® Sterile Presaturated Wipes were found stored with the seal open in the ISO 7 area. The Prosat® Sterile Presaturated Wipes are used in the routine cleaning and disinfection of the ISO 5 hoods. The presaturated wipes are also used to disinfect materials or supplies before introduction into and use in the critical ISO 5 zone.

NIH Response:

(A) Benchmark Products Suite® Reach Tool with Suite-Cover (sterile, single-packaged, disposable pads) have replaced the use of the Contec EasyReach® cleaning tool and cleaning pads. Supplies were ordered on March 18, 2019 and change out will be completed by March 31, 2019.

(B) Communication has been sent to the IV room staff to instruct technicians to aseptically place Prosat® Sterile Presaturated Wipes used for interior hood surface cleaning inside the ISO 5 hoods and close when not in use, with read and signature receipt due by April 5, 2019. SOP CCP 20011 Cleaning and Sanitization of the interim IVAU (I-IVAU) will be updated to reflect the new process by April 30, 2019.

OBSERVATION 4

Media fills were not performed that closely simulate aseptic production operations incorporating, as appropriate, worst case activities and conditions that provide a challenge to aseptic operations.

Specifically, the media fills are performed using the CHEMOTEQ kit, which fails to simulate preparation of the total parenteral nutrition (TPN) bags using the ExactaMix Compounder. TPN preparations represent the largest volume parenteral drug products made at the site.

NIH Response:

NIH media fills are modeled after an example of a medium risk admixture which encompasses the majority of aseptic manipulations conducted in the preparation of medications. These include manipulations typically performed during a TPN preparation.

There is no commercially available product for pharmacy automated compounding devices.

In collaboration with the Department of Laboratory Medicine, a protocol will be developed, validated, and implemented by December 31, 2019. The protocol will include validation in triplicate with QA review for each cycle.

OBSERVATION 5

Your facility design allowed the influx of poor-quality air into a higher classified area.

Specifically, materials are transferred into and out of the ISO 7 Sterile IV Prep Room (1C166A5B) using two cart pass-throughs. On 2/22/2019, it was observed that the door to the pass-through (labeled 'IN' in room 1C166A5B) would move when the door to the second pass through (labeled 'OUT' in room 1C166A5B) was forcefully shut in the ISO 8 IV Prep Anteroom (1C166A5A). On 2/25/2019, the door sweeps on the cart pass through doors in the ISO 8 IV Prep Anteroom (1C166A5A) showed signs of damage and were secured to the door using cleanroom tape.

NIH Response:
NIH has identified that the interlock mechanism within the pass-through requires adjustments. Staff have been forcefully shutting the doors to engage the interlock mechanisms. Adjustments to the door to address the interlock mechanism will be completed by April 15, 2019.

All door sweeps were inspected for wear and tear damage. The identified door sweep was replaced on March 16, 2019.

A preventative maintenance program for the pass-through will be developed, which will consist of time-based activities, monitoring and response to trouble calls by May 24, 2019.

OBSERVATION 6

The material of construction of the cleanroom walls is not suitable for the intended use.

Specifically, on February 19, 2019, several pieces of tape were observed on the walls or ceiling of the ISO 7 Sterile Hazardous Prep Room (1C166A7B), the ISO 7 Immunotherapy Prep Room (1C166A7D), and the ISO 7 Sterile IV Prep Room (1C166A5B). The tape is used to identify areas where the paint is flaking or pain bubbles or other damage to the walls, doors, or other surfaces. According to management, structural damage to the facility is repaired approximately every two to four weeks.

Between January 18, 2019 and February 25, 2019, 66 locations were identified by the pharmacy staff that required repair. Sixty-four of the identified locations were in the ISO classified rooms of the I-IVAU.

NIH Response:

The interim IVAU is constructed in accordance with USP <797>, which permits the use of gypsum board and epoxy paint. In addition to daily cleaning, NIH performs weekly cleaning of the ceiling, walls, and floors by utilizing both sporicide and disinfectants on a rotating basis. Investigation has revealed that the epoxy paint is insufficient to withstand the cleaning regimen and daily operational activities. Sporicide and disinfectant utilization cannot be decreased at this time in order to maintain a state of control.

As a result of lessons learned, we have concluded that the current materials should not be used in future facilities. Therefore, the expansion IVAU and the permanent IVAU will not be composed of

epoxy coated gypsum board. NIH will be evaluating other materials of construction which may include, but is not limited to, fiberglass resin panel, modular cleanroom panels, stainless steel, and glass paneling. Once in the expansion IVAU, the interim IVAU will be decommissioned and remediated with the aforementioned material.

NIH CC pharmacy supports patient care that is 24/7. Cleanroom tape, that can withstand the cleaning regimen, is applied to entomb areas of concern while work plans are developed to minimize impact to patient care and safety. The majority of these areas of concern are the size of a quarter or less. The cleanroom tape completely covers the area of concern, as well as the surrounding area, to allow regular cleaning and operations to continue in an aseptic manner. Immediate shut down would occur for emergency repairs that compromise the state of control in the facility.

Scheduled downtime for repairs alternate between the 1C166A7 and 1C166A5 suites. The 66 areas of concern, that were covered with cleanroom tape, included damage identified by DFOM and Pharmacy that occurred since the last scheduled down time for repairs on November 30, 2018 – December 1, 2018 in the 1C166A7 Suite and January 10, 2019 – January 11, 2019 in the 1C166A5 Suite.

Pharmacy and DFOM completed a walkthrough on January 18, 2019 and February 6, 2019 (Pharmacy only) in order to document areas of concern for the next scheduled downtime which was to be completed on March 1, 2019. A final list was compiled on February 14, 2019. As a result, the log reflected the damage in total that occurred between December 1, 2018 and February 25, 2019.

A plan was informally adopted in early 2019 to remediate areas of concern that coincide with the twice monthly sporicide cleanings of the ceiling, walls, and floor. Effective March 31, 2019, we will target remediation/repair cycles twice monthly.

OBSERVATION 7

Your facility was designed and/or operated in a way that permits poor flow of personnel.

Specifically, sinks located in the ISO 8 IV Prep Anteroom (1C166A5A) and the ISO 8 Gowning Room (1C166A7A) were operated in a manner that allowed water to pool along the sink or on the floor adjacent to the sink.

(A) On 2/19/2019 during the facility walkthrough, a puddle of what appeared to be water (approximately 10 centimeters in diameter) was observed on the floor of the ISO 8 IV Prep Anteroom (1C166A5A) adjacent to the sink. Furthermore, on 2/19/2019, a pharmacist was observed scrubbing in at the sink in ISO 8 IV Prep Anteroom (1C166A5A) then donned the gown which contacted the ISO 7 IV Prep Gowning Room (1C166A5A1) floor.

(B) On 2/22/2019, standing water was observed under a piece of tape on the backsplash panel of the sink located in the ISO 8 IV Prep Anteroom (1C166A5A). Water also appeared to be pooled beneath a bottle of hand sanitizer and nail cleaners placed on the ledge above sink.

(C) On 2/19/2019 and 2/22/2019, standing water was observed to have pooled along the right side of the sink in the ISO 8 Gowning Room (1C166A7A). Water was also seen beneath a bottle of nail cleaners, and the Hibiclens bottle next to the faucet.

NIH Response:

(A) Water identified on the floor was a result of the distance to materials used for the drying of hands. Immediately after observation, supplies were relocated closer to the sink in 1C166A5A. Further remediation is identified in response (C) below.

The SOP CCP-20013 – Gowning in the Interim Intravenous Admixture Unit indicates that gowns are not to touch the floor. Communication has been sent to the IV room staff to reinforce acceptable behavior, with read and receipt due by April 5, 2019.

We will include clarifying language in this SOP for how a gown should be donned so as not to touch the floor by April 30, 2019.

Quarterly qualification will highlight the importance of donning a gown without touching the floor by adding specific evaluation to qualification forms 20010F.1 by June 30, 2019.

Operational and Quality Assurance observation forms will be updated to enforce this behavior by April 15, 2019.

In addition, these changes will be incorporated in the 2019 annual training program and will be completed by September 30, 2019.

(B) As a result of hand hygiene, water pooled around the sink and staff were identified to be washing above the bowl in order to activate the touchless water sensor. Unnecessary supplies were also identified around the sink.

Corrective actions are as follows, (1) staff have been instructed to dry the sink prior to conducting hand hygiene or upon exit of the facility, (2) signs have been posted to create awareness of new procedure, (3) staff have been instructed to wash their hands lower in the sink basin, (4) staff have been reminded to use slower motion in activating the sensor as to not splash water and (5) supplies, not immediately in use, have been removed. Communication was sent out to the IV room staff regarding handwashing technique, with read and signature receipt due by April 5, 2019.

The sink faucet in 1C166A5A is being replaced to allow for an adjustable run time after sensor activation to allow staff to perform hand washing deeper in the bowl and eliminate the need to repeatedly activate the sensor. This is to be completed by May 30, 2019.

Future expansion IVAU plans will be evaluated for dry gowning.

(C) As a result of hand hygiene, water pooled around the sink. In addition, staff were identified to be washing above the bowl in order to activate the touchless water sensor. Sink faucet is short for the basin and requires a longer neck. Additional supplies were also identified around the sink. USP <800> does not allow removal of the sink from the anteroom.

Additional corrective actions are as follows, (1) Staff have been instructed to dry the sink prior to conducting hand hygiene or upon exit of the facility, (2) signs of have been posted to create awareness of new procedure, (3) Staff have been instructed to wash their hands

lower in the sink basin, (4) sensors have been adjusted to run for 90 seconds to prevent staff from constantly trying to reactivate the sensor and inadvertently splashing water and (5) supplies, not immediately in use, have been removed.

The sink faucet in 1C166A7A was replaced on March 16, 2019 with a longer neck and adjustable run time after sensor activation to allow staff to perform hand washing deeper in the bowl and eliminate the need to repeatedly activate the sensor.