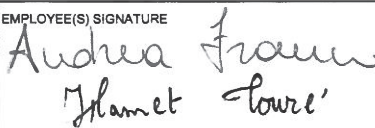
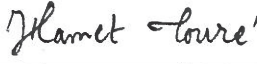
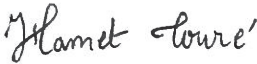


DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DISTRICT ADDRESS AND PHONE NUMBER CDER/OPQ/OPMA/Division of Pharmaceutical Manufacturing Assessment VI 10903 New Hampshire Avenue; White Oak Building 51, Room 2269 Silver Spring, MD 20993 E-mail: opmablainspection483responses@fda.hhs.gov		DATE(S) OF INSPECTION 10/14/2024-10/21/2024	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED James Hamilton, President		FEI NUMBER 3012144557	
FIRM NAME Berkshire Sterile Manufacturing	STREET ADDRESS 480 Pleasant Street		
CITY, STATE, ZIP CODE, COUNTRY Lee, MA 01238	TYPE ESTABLISHMENT INSPECTED Drug Product		
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 microbial contamination of drug products purporting to be sterile are not established, written, or followed. Specifically,			
1. A mousehole in the (b) (4) is used to connect the (b) (4) filling line (Grade A) to the (b) (4) drug product bag held in Clean Room (b) (4) Grade D), opening the (b) (4) to the outside environment. Sufficient air supply and overpressure are not monitored on a continuous basis at this location to ensure that (b) (4) is maintained. In addition, the movement of the tubing in and out of the mousehole also represents a risk of microbial contamination from the surrounding Grade D room into the (b) (4) filling chamber. 2. The sterile cover around the (b) (4) is removed prior to the (b) (4) installation in its resting position. Possible contact between the unprotected (b) (4) and surfaces (b) (4) gloves, tubing, and equipment) or possible blockage of first air above the unprotected (b) (4) poses a risk. 3. The Airflow Visualization Studies (AVS) of the Aseptic Processing Area are incomplete. a. The removal of the sterile cover around the (b) (4) during setup was not simulated. b. The simulation for the replacement of the (b) (4) a permitted critical intervention during filling, did not include the detachment of tubing from the (b) (4) and the attachment of tubing to the (b) (4) c. The simulation for the change of the filling assembly, a permitted critical intervention, was partially simulated. d. The simulation for the (b) (4) stoppering of vials, a permitted non-routine intervention, has not been updated to reflect current procedures. 4. Critical operations are not always performed with sterile tools. a. During the (b) (4) installation in the (b) (4) on October 16, 2024, the operator held the top of the (b) (4) with a sterile tool while holding the (b) (4) tubing with the (b) (4) glove. The			
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proximity of the operator's hand poses a risk of blockage of first air above the (b) (4) or contact with the (b) (4) b. The operator tightened the screw that holds the (b) (4) in the (b) (4) holder several times with the (b) (4) glove first and then with a sterile tool. The operator's gloved hand was observed near the (b) (4) during a critical intervention that could possibly be exclusively performed with a sterile tool. 5. When untying tubing in the filling assembly bag in the (b) (4) the operator was not moving slowly and deliberately. 6. The operator had difficulty removing the sterile (b) (4) creating friction prior to installation of the (b) (4) in its final resting position. 7. Insufficient instructions are provided to (b) (4) operators in the batch record and written procedures to perform the (b) (4) stoppering of vials to avoid blockage of first air over (b) (4) (b) (4) vials while maintaining aseptic technique using a sterile tool. 8. Insufficient instructions are provided to (b) (4) operators in the batch record and written procedures for the removal of the stopper bowl cover to avoid blockage of first air over the stopper bowl and the stopper bowl tracks. 9. Insufficient instructions are provided to (b) (4) operators in the batch record and written procedures for (b) (4) moving vials in (b) (4) from (b) (4) to the (b) (4) to avoid blockage of first air over the open vials. 10. SOP-MFG-005, Personnel/Material/Equipment Flow Into and Out of cGMP Clean Rooms, Revision 22, effective June 26, 2024, indicates that all materials staged for entry into the manufacturing area, must be wiped with (b) (4) sprayed with (b) (4) with a (b) (4) contact time, and then wiped with (b) (4) spray. Disinfectant efficacy studies for this cleaning procedure were only conducted using (b) (4) surfaces (material of (b) (4) of (b) (4) gloves).			
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October 14-21, 2024

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OBSERVATION 2			
The (b) (4) formulation process is not adequately controlled or designed to minimize the contamination risk of upstream drug product manufacturing steps. Specifically, (b) (4) of the (b) (4) bulk drug substance (BDS) are performed as a (b) (4) process in one of (b) (4) formulation rooms (Clean Rooms) (b) (4) in the Grade C area. During lot (b) (4) on October 15, 2024, (b) (4) BDS bottles were (b) (4) in a (b) (4) sterile liner placed in a tank with a (b) (4) centimeter diameter in Clean Room (b) (4). The following risks have been identified with the current process: 1. While placing the sterile (b) (4) liner in the tank, the operator touched the interior of the liner within the tank with gloved hands. There is no assurance that the product was not poured over the area touched by the operator during (b) (4). 2. While facing the tank, the operator was observed sanitizing his hands with a disinfectant spray in the direction of the liner and tank. There is no barrier over the tank to prevent the ingress of particles and contaminants. 3. The storage conditions of the tank used for formulation pose a risk. The tanks used to hold the liner are stored in an area of the facility that is not controlled. During a walkthrough of this area, two tanks were observed without a lid. The tanks were stored next to a barrel that was not clean. The tanks may be reused; one larger tank that was not covered had 2021 inscribed on it. Material parts that are brought into the manufacturing area undergo sanitization with (b) (4) with a (b) (4) contact time, and (b) (4). Efficacy studies have not included the material of construction of the tank (b) (4) used in formulation. 4. There is a risk of microbial ingress during the (b) (4) process. Mold recoveries have occurred in Clean Room (b) (4) and Clean Room (b) (4) two of (b) (4) rooms used for (b) (4) formulation: • Clean Room (b) (4) One recovery on August 22, 2024, and one recovery in four different locations of the room (four total recoveries) on August 26, 2024 • Clean Room (b) (4) One recovery on September 20, 2024. 5. Pests pose an additional risk to the (b) (4) product. A live insect was recovered in the manufacturing area (Clean Room (b) (4) on June 6, 2024, and a live bug (centipede) was recovered in Clean Room (b) (4) on June 14, 2024.			
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FOOD AND DRUG ADMINISTRATION

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OBSERVATION 3

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

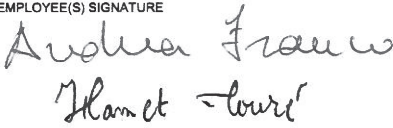
1. Glove monitoring is not adequate. For example, on October 16, 2024, during filling line setup and filling activities in Clean Room (b) (4) some (b) (4) gloves were used ambidextrously (the same glove used with both the left and right hands of the operators). During environmental monitoring of the (b) (4) the gloves that were used ambidextrously were not monitored (finger dab) ambidextrously. In addition, the environmental monitoring of (b) (4) gloves did not allow sufficient contact time. The QC Micro operator was observed touching the contact plate with each digit and immediately removing it after approximately a second; each digit was not gently rolled on the contact plate.
2. There is (b) (4) viable passive settling plate in the filling chamber of the (b) (4). The location of the settling plate for viable passive monitoring is above the working surface and located (b) (4) above the (b) (4) table where vials are filled.
3. Insufficient instructions are provided to the QC Micro operator in SOP-QCM-030, Environmental Monitoring of the (b) (4) and Formulation Rooms at Berkshire Sterile Manufacturing, Revision 21, August 7, 2024, to perform post-fill monitoring of the (b) (4). The QC Micro operator was observed sampling the (b) (4) during post-fill monitoring. The sides of the (b) (4) were not sampled and, therefore, not all portions of the (b) (4) were sampled.
4. The stopper bowl tracks, which are indirect product contact surfaces, are not sampled as part of post-fill monitoring.
5. The QC Micro operator was observed sampling the bottom of the stopper bowl. However, this is not described adequately in SOP-QCM-030, which mentions that the interior of the stopper bowl should be sampled.

OBSERVATION 4

The program for the visual inspection (VI) of sterile injectable drug products does not provide adequate assurance that finished products manufactured at the facility possess their purported quality attributes, including that they are free from particulate matter and critical defects. Specifically,

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1. The training kit includes (b) (4) vials with products that are clear. It does not include products that are of the same color (b) (4) or size (b) (4) as the (b) (4) DP. 2. The percentage of defective units in the current training and qualification kit is (b) (4) %. 3. The (b) (4) VI training kit is also used for qualification of operators. Each vial is identified with a visible 6-digit number. Therefore, operators are not masked during their qualification. OBSERVATION 5 Standard operating procedures and protocols are not followed, established, or adequate. Specifically, 1. The percentages of SOP training that were overdue in 2023 are as follows: 19% for manufacturing, 17% for Mechanical Engineering/Facilities, 18% for QA – Compliance/Validation, 22% for QA – Shop Floor, 14% for Quality Control – Analytical, 9% for Visual Inspection, and 16% for Warehouse. 2. There is no periodic review of Logbook LBK-WH007, BSC Cleaning Log of (b) (4) Cleanroom (b) (4) (b) (4) Issued Logbook 0022, for the Warehouse dispensary. The logbook was issued on November 21, 2022. However, there has been no supervisory or QA periodic review of this logbook. 3. Personnel limit in the corridor (Clean Room (b) (4)) of the manufacturing area in Grade D is (b) (4). However, operators proceeded in the corridor without awareness of this limit during the walkthrough inspection of the manufacturing area and the limit was exceeded. Clean Room (b) (4) is L-shaped and operators may not have visibility into the presence of other operators in a different part of the corridor. OBSERVATION 6 Written records of investigations into unexplained discrepancies do not always include appropriate documentation, conclusions, and follow-up. Specifically, Deviation DEV-2024-0126 was initiated on June 26, 2024, for the presence of metal like particles between the stopper and the vial in three units of clinical batch (b) (4). The particles were identified as damaged (b) (4) parts and metal particulates found under the (b) (4). Based on the risk of the adverse impact on product quality, the Material Review Board determined the material			
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acceptable for release. The deviation report noted that it is believed that metal particles did not enter the vial or solution during (b) (4). The SME noted that the probable root cause was the landing of the metal particles on the stoppers. The risk assessment of the impact on product quality failed to evaluate whether the contact of the particles with the stoppers could have an impact on product sterility. - The Pest and Rodent Control Program SOP, SOP-EHS-008, does not contain criteria to open a deviation for pest recoveries in clean rooms and (b) (4) that are connected to the manufacturing area. SOP-EHS-008 also does not contain criteria to open a deviation for pest recoveries in other GMP areas: warehouse, temperature controlled units, and the laboratory. Pest limits are defined in terms of recoveries in the indoor traps. Heavy activity in the inner light traps or a non-insect activity in the indoor traps triggers a quality event (SOP-QA-011). Any pest activity discovered in clean rooms requires a Disruption to Controlled Environments Form (SOP-GEN-23); there is no requirement to investigate pest excursions in the manufacturing area. - Pest recoveries in the clean rooms are documented in the Pest Sighting Log logbook. A total of 10 pest recoveries in the cleanrooms and connected CNC areas were documented in this logbook in 2024: February 9, 2024 (CR (b) (4)), March 5, 2024 (CR (b) (4)), March 13, 2024 (CR (b) (4)), May 19, 2024 (CR (b) (4)), May 28, 2024 (CR (b) (4)), May 29, 2024 (CR (b) (4)), June 6, 2024 (CR (b) (4)), June 14, 2024 (CR (b) (4)), July 9, 2024 (CR (b) (4)), and July 10, 2024 (CR (b) (4)). Three events were opened. None of the recoveries were investigated with a deviation during this period.			
OBSERVATION 7			
The facility is not adequately maintained. Specifically, as observed in unclassified areas,			
- An oil spill was observed next to a bottle of (b) (4) and its funnel. - Corrosion was observed on the (b) (4) pump in the Dock 2 area. - Insulation in the walls near Dock 2 was torn. Insulation was visible in the area above the (b) (4). - Panels that line the facility walls were dislodged near Dock 2. - A small hole was observed in the wall of the facility. - The wall in Clean Room (b) (4) (Room) has multiple corners which are not smooth and show a small accumulation of debris by the (b) (4).			
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OBSERVATION 8			
There are discrepancies between the manufacturing process described in (b) (4) and the manufacturing process at the facility. Specifically, (b) (4)			
The commercial Master Batch Record for (b) (4) does not include a process parameter for (b) (4) which is listed in (b) (4). In addition, the commercial Master Batch Record indicates that the acceptable range for the number of vials filled is (b) (4) - (b) (4) units. However, (b) (4) indicates that acceptable range for the number of vials filled is (b) (4) - (b) (4).			
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