DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
One Montvale Avenue Stoneham, MA 02180 (781)587-7500 Fax:(781)587-7556 ORAPHARM1_RESPONSES@fda.hhs.gov	10/4/2021-10/15/2021* FEI NUMBER 3012144557

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Shawn D. Kinney, President & CEO

FIRM NAME	STREET ADDRESS
Berkshire Sterile Manufacturing, Inc.	480 Pleasant St
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Lee, MA 01238-9265	Sterile Drug Manufacturer

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

Drug product containers were not clean and sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.

Specifically, the firm purchases non-sterile plastic vials that have not been tested for endotoxin level or subvisible particles and sterilizes these plastic vials by (b) (4) without any processing to remove pyrogenic substances. These vials were not tested for endotoxin level prior to use in the manufacturing of (b) (4) hase 3 clinical trial.

OBSERVATION 2

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

Specifically, on 10/14/2021, during observation of aseptic filling operation for (b) (4), Lot (b) (4), for Phase 1 clinical trial, an operator was observed grabbing the tips of the forceps with his gloved hand and used the forceps to grab a stopper and manually place the stopper onto the vial. This corrective intervention was not documented as required by SOP-MFG-055, "Performance of Aseptic Interventions within Aseptic Filling (b) (4)". Similar handling of forceps can be seen in the firm's 2021 smoke study video (File name: (b) (4) Smoke Study 2021 Part 2.mp4), performed under (b) (4), at/around 15:03, 26:30, 27:19, and 28:55 timestamp.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Mindy M Chou, Investigator Daniel L Zheng, Investigator	X Mindy M Chou Investigator Signed By: 2000648922 Date Signed: 10-15-2021 16:28 ST	10/15/2021

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OBSERVATION 3

Certificates of testing of containers and closures are accepted in lieu of testing without establishing the reliability of the supplier's test results through appropriate validation of the test results at appropriate intervals.

Specifically, the firm does not conduct analytical testing on each incoming lot of ready-to-use vials and ready-to-sterilize stoppers for subvisible particles to assure the components are of acceptable quality for use in manufacturing of IND drug products (Phase 1, Phase 2, and Phase 3) such as (b) (4) , (b) (4)) for Phase 1 clinical trial and (b) (4) (Lot # (b) (4)) for Phase 2 clinical trial. The firm did not verify the reliability of all the test results provided by the supplier's certificate of analysis during vendor qualification.

OBSERVATION 4

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

Specifically,

(A) According to the Vice President of Manufacturing and the Manufacturing Manager, the HEPA filter diffuser panels of the (b) (4)) system attached to the (b) (4) located in cleanroom 113 and the (b) (4) system for the (b) (4) located in cleanroom 109 are not included in the cleaning process. The (b) (4) systems are used to transfer materials into the (b) (4) during all drug product production. On 10/8/2021 and 10/13/2021, black streaks were observed on two of the HEPA filter diffuser panels in the (b) (4) system attached to the (b) (4)

(B) Per SOP-MFG-102, (b) (4) is only cleaned with (b) (4) and does not require the use of a sporicidal agent. According to the Vice President of Manufacturing, a sporicidal agent is not used to clean the (b) (4) systems when SOP-MFG-102 became effective on September 15, 2021 and superseded the cleaning procedure outlined in SOP-MFG-069, "Operation & Maintenance of (b) (4) (b) (4) (b) (4)

(C) Residues and stains were observed in the (b) (4) system attached to the (b) (4) and in the (b) (4)

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(b) (4) on 10/8/2021 and 10/13/2021 when the two equipment were in the "clean" state:

i. On 10/13/2021, a brownish stain was observed on the HEPA filter diffuser screen in the (b) (4)
ii. On 10/13/2021, white residues were observed on the IV hanging bar in the (b) (4) White residues were seen on the front glass panel of the (b) (4).
iii. On 10/13/2021, off-white residues were observed around one of the air exchange holes on the removable work tray installed in the left side of the (b) (4) Visible scratches were also observed on the surface of the removable work tray near the door to the (b) (4)
iv. On 10/8/2021 and 10/13/2021, white residues were observed around the frame of the door in the (b) (4) system attached to the (b) (4) The door leads into the (b) (4).

OBSERVATION 5

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

Specifically, the firm did not complete performance qualification for (b) (4)) Device Serial # (b) (4) to ensure that the test device is capable of consistently and reliably detect any leaks in the (b) (4) Device Serial # (b) (4), (b) (4) were used to perform (b) (4) integrity testing for (b) (4) (b) (4) ; Phase 3 clinical trial) on 5/23/2021 and (b) (4) Device Seria (b) (4) was used for the production of (b) (4) (Lot # (b) (4) (b) (4); Phase 3 clinical trial) on 6/30/2021.

OBSERVATION 6

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically,

(A) On 10/05/2021, we observed analyst (b) (6) performing sub-visible particulate testing of the 3-month

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	Mindy M Chou, Investigator Daniel L Zheng, Investigator X Mindy M Chou Investigator Signed By: 2000648922 Date Signed: 10-15-2021 16:28 ST	10/15/2021

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stability sample for Client (b) (4) as per test method TM-QCA-009, "Test Method for Analysis and Evaluation of Particulate Matter in Liquid Samples Using (b) (4) ". The analyst pooled (b) (4) vials of the stability samples into a (b) (4) (b) (4) without first inverting each sample vial to ensure any particles that might be dislodged in the stopper are suspended properly. Instead, the analyst inverted the pooled solution (b) (4) times. TM-QCA-009 is also used in the finished product release testing of vialed IND drug products to include (b) (4)) for Phase 2 clinical trial and (b) (4) (b) (4) (Lot # (b) (4) for Phase 3 clinical trial.

(B) On 10/5/2021, we observed analyst (b) (6) performing visual appearance testing of the 3-month stability sample for Client (b) (4) Lot # (b) (4) , as per SOP-QCA-023, "Visual Appearance Testing". The analyst did not invert the amber vial before transferring the sample into a (b) (4) to perform the testing. SOP-QCA-023 is also used in the finished product release testing of vialed IND drug products to include (b) (4) g (Lot # (b) (4) for Phase 1 clinical trial.

***DATES OF INSPECTION**

10/04/2021(Mon), 10/05/2021(Tue), 10/06/2021(Wed), 10/07/2021(Thu), 10/08/2021(Fri), 10/11/2021(Mon), 10/12/2021(Tue), 10/13/2021(Wed), 10/14/2021(Thu), 10/15/2021(Fri)

X Daniel L Zheng
Investigator
Signed By: Daniel L. Zheng -S
Date Signed: 10-15-2021 16:29:39

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Mindy M Chou, Investigator Daniel L Zheng, Investigator X Mindy M Chou Investigator Signed By: 2000648922 Date Signed: 10-15-2021 16:28:51	10/15/2021

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."