DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	6/5/2023-6/13/2023*
	FEI NUMBER 3009864467

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Colin Mackey, Chief Executive Officer

FIRM NAME	STREET ADDRESS
Symbiosis Pharmaceutical Services Limited	Unit 10, Scion House, Stirling University Innovation Park
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Stirling, FK9 4NF United Kingdom	Sterile Drug Product 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 I OBSERVED:

OBSERVATION 1

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

Specifically,

A. During the review of video footage of your Process Performance Qualification (PPQ) batch (b) (4) (filing batches), manufacturing date 08 Jul 2022, I observed the manufacturing activities documented in Batch Manufacturing Record (BMR) are not contemporaneous and reflective of the actual activities performed. For example,

1)For (b) (4) – Step no. (b) (4) "Record the time at (b) (4) of compounding" is documented in the BMR as 13:38. Whereas according to the video footage, this activity was completed on 13:48
2)For Bioburden and (b) (4) Sampling – Step no. (b) (4), Specification section for "Record time of sampling" is documented in the BMR as 13:48. Whereas according to the video footage, this activity was completed on 13:56.

B. During the review of video footages of batch (b) (4), I observed four (4) production operators working inside a small Grade B and Grade C rooms and two (2) production operators working inside a very small Grade A area (separated by (b) (4) from Grade B) moving rapidly from one area to other areas within the room potentially creating a lot of air turbulence. Additionally, these operators were observed bending down, moving objects from one corner to another inside Grade B and Grade C areas

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Pratik S Upadhyay, Investigator	X Pratik S Upadhyay Investigator Signed By: Pratik S. Upadhyay -S Date Signed: 06-13-2023 11:32:20	6/13/2023

(conventional and containment suits). I also observed that one of the operators sat down on the floor inside Grade A for about 1:20 minutes to fix the wheels of a rolling trolly while the other operator was standing very close to him in a very small area in front of the (b) (4). This operator then stood up and touched the trolly and pushed it back against the wall inside Grade A in front of (b) (4). As such on multiple occasions, operators were seen not sanitizing their hand gloves as they moved from Grade B to Grade A areas and vice versa. These behaviors of your operators are in deviation with your SOP: MAN-1, Titled: Cleanroom Behavior, Revision: 9 in sections: 10.10., 10.14., 10.24., 10.29., and 10.32.

In addition, I observed one of the operators tumble and lost his balance due to a (b) (4) in his way. The operator then managed his balance by holding the LAF (b) (4) RABS (Grade A). This operator then rapidly kicked the (b) (4) to push it away.

The rapid movement of your production operators along with touching objects inside the room and moving roller cart rapidly was consistent even when your firm facilitated simulation of product manufacturing for (b) (4) from (b) (4). These behaviors and movements can generate air turbulence inside the aseptic manufacturing areas potentially leading to product contamination.

C. There are no smoke studies performed inside the LAF (b) (4) (Grade A) for area cleaning activities upon vial spillage (low to medium risk intervention) of (b) (4) Injection (b) (4) mg/ml) and other products manufactured by your firm.

D. There is no assurance over the reliability of microbiological tests results pertaining to finger touch plate. for example,

On 09-Jun-2023 during the review of video footage of your (b) (4) – PPQ batch (b) (4) that took place on 08-Jul-2022, I observed two (2) production operators provided finger touch plate samples by slightly touching fingertip to contact plate for (b) (4) and less whereas according to your procedure

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	6/5/2023-6/13/2023*
	FEI NUMBER 3009864467

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Colin Mackey, Chief Executive Officer

FIRM NAME	STREET ADDRESS
Symbiosis Pharmaceutical Services Limited	Unit 10, Scion House, Stirling University Innovation Park
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Stirling, FK9 4NF United Kingdom	Sterile Drug Product Manufacturer

SOP: Q-24, Revision: 31, Titled: Environmental Monitoring In Operation, section 10.2.17.2 it has to been done for a minimum of (b) (4). The detail of operator's fingertip contact point are as follows:

Fingertip contact (Start Time)
09:36:54
(b) (4)

Fingertip contact (End Time)
(b) (4)
(b) (4)

OBSERVATION 2
The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

Specifically,

Your Quality Unit lacks an adequate oversight on the control and management of GMP documents that are critical to ensure the sterile drug products manufactured at the site for the US market are safe and effective. For example, but not limited to:

A. On 06/08/2023, I inspected one (1) out of four (4) lock and key access controlled Shred-it bins maintained by your firm. I observed your manufacturing department employees destroyed "GMP documents" pertaining to original records and raw data by disposing inside an access controlled "Shred-it" bin located in your manufacturing area's write-up and printing section. This section is used by your production operators to print controlled GMP documents and complete documentation activities related to manufacturing and sampling. Many of the documents recovered from this Shred-it bin were signed under "Reviewed by" and "Quality Approved by" sections and dated. The following are some examples of the original controlled GMP documents found inside the Shred-it bin:

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	6/5/2023-6/13/2023*
	FEI NUMBER 3009864467

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Colin Mackey, Chief Executive Officer

FIRM NAME	STREET ADDRESS
Symbiosis Pharmaceutical Services Limited	Unit 10, Scion House, Stirling University Innovation Park
CITY, STATE, ZIP CODE, COUNTRY Stirling, FK9 4NF United Kingdom	TYPE ESTABLISHMENT INSPECTED Sterile Drug Product Manufacturer

1. Form: FRM-108, Label control forms. About 17 original (each document two sided) documents of which one set of documents was signed under Quality Approval (Initial/Date section) whereas other documents were partially completed with initial and date of production operators. Most of these forms were affixed with original product labels and some were missing labels along with details such as pertaining to type of samples, sampling timepoint, testing requirement, line clearance, etc.
2. Form: FRM-340, Vial Inventory Form, Batch Number: (b) (4). Original one set of 24 pages document that was printed by the product operator.
3. Form: FRM-388, Revision: 1, Aliquoting of (b) (4) for Filter Integrity Testing. Original one set of two-sided documents that was partially completed, signed and dated under "Material Required" section by production operator.
4. Torn and crumpled pieces of Form: FRM-273, Visual Inspection Label Control Form. About 30 original documents (each document two sided) were observed of which one (1) document was partially completed. This document was initialed and dated under "QA Approved By" section of "Label Approval" section.
5. Hundreds of unused original labels pertaining to the products manufactured by the firm including labels of (b) (4), Lot: (b) (4), DOM: 01JUN2023
6. Torn pieces of document titled: "Finished Product Sampling Plan and Sampling (with remaining page missing)***", Batch Number: (b) (4). One original partially completed documents with operators initial and date was found inside Shred-it bin. This document was stamped "COPY" and has handwritten information that was changed in "Quantity Sampled" column for "Reference" from 1 by changing number to look like 2. Additionally, details under "Confirm Quantity & Allocated Units are correct" column was crossed-out for details T2 B4 and entered "Y".
7. Form: FRM-68, Finished Product Sampling Plan and Sampling Record, Batch Number: (b) (4). This document completed and QA/QC signed and dated documented did not have a "COPY" stamp on it but the firm considered the document being a photocopy of the original document.
8. Torn and crumpled pieces of form: FRM-72, Material Requisition, Allocation and Return Form. About 18 original unused (blank) controlled GMP forms printed by production operators.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Pratik S Upadhyay, Investigator	X Pratik S Upadhyay Investigator Signed By: Pratik S. Upadhyay -S Date Signed: 06-13-2023 11:32:20	6/13/2023

9. LogType: Logtype-24, In-process and Finished Product QC Sample Logbook.

B. Your employees documented manufacturing activities on a photocopy of the actual document stamped with "COPY" in red ink. It was confirmed that these photocopies are not meant to record GMP activities. For example,
Document titled: "Component Preparation", Batch Number: (b) (4) had employees handwritten sections for "(b) (4) No. Used" and "Qty (Actual)". This document was found inside Shred-it bin.

C. Your employees' hand recorded GMP activities on white uncontrolled blank pages and disposed these pages by tearing into pieces inside "Shred-it" bin.

D. Your employees have deviated from the following sections of your procedure and policy by destroying and disposing GMP documents:

1. SOP: Q-5, Revision: 11, Titled: "Recording of Raw Data (Good Documentation), sections: 10.4, 10.6, 10.7, 10.15, 10.26, and 12.2.
2. Policy: SP-6, Revision: 5, Titled: "Data Integrity and Electronic Access Management Policy", sections: 4.3.2 to 4.3.6.

OBSERVATION 3
The written stability program does not assure testing of the drug product in the same container-closure system as that in which the drug product is marketed.

Specifically,

(b) (4) samples charged on stability at a contractor are not "labeled and packaged" (L&P) and are not stored inside materials that are consistent with the product L&P. Based on the pictures of stability samples stored inside chambers, I observed about (b) (4) vials charged on stability were inside a closed thick

(b) (4) box. There is not a temperature or humidity sensor inside the box. The vials were stored in a tight space inside this (b) (4) box which would prevent the vials from full exposure at stability conditions (25°C/60%RH and 40°C/75%RH).

Additionally, you have proposed (b) (4) shelf life for (b) (4) based on the stability studies conducted on lots manufactured by the innovator of the drug product which is different than the (b) (4) holder. There are some significant differences in the manufacturing conditions, equipment and materials used by the innovator of the product and the (b) (4) holder.

There is no assurance over the proposed shelf life of (b) (4) for (b) (4) considering significant differences in manufacturing of drug product at your firm.

OBSERVATION 4

The retention period for drug product reserve samples (except those described in 211.170(b)(2) and (3)) is deficient in that they are not retained for one year after the expiration date of the drug product.

Specifically,

Your procedures Q-27 (Reference and Retention samples) and Q-40 (Commercial Product Quality Review) are deficient in that there is no mention of storing retention samples at conditions that is consistent with the product labeling. There is no mention of examining retention samples visually at least once a year for the evidence of deterioration. Additionally, your Quality Agreement with (b) (4) holder is deficient in that there is no mention of responsibilities pertaining to the handling and annual verification of retention samples. During the current inspection, I observed that no retention samples are stored and that your firm has no dedicated area, or a room maintained at required conditions consistent with the product labeling conditions for the storage and handling of retention samples.

OBSERVATION 5

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	6/5/2023-6/13/2023*
	FEI NUMBER 3009864467

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Colin Mackey, Chief Executive Officer

FIRM NAME	STREET ADDRESS
Symbiosis Pharmaceutical Services Limited	Unit 10, Scion House, Stirling University Innovation Park
CITY, STATE, ZIP CODE, COUNTRY Stirling, FK9 4NF United Kingdom	TYPE ESTABLISHMENT INSPECTED Sterile Drug Product Manufacturer

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

Specifically,

The (b) (4) generated at the firm does not ensure the suitability of (b) (4) for its use in (b) (4), cleaning utensils, to (b) (4) that are used in the manufacturing of sterile injectable drug products for the US market.

A. Your firm has not sanitized (b) (4) since year 2018 and as such has no validated procedure for sanitization of the tank holding (b) (4).

B. On 09-Jun-2023, I observed leakage on the (b) (4) system. As a result of this leakage and the other existing leakage nearby on a pipe joint, a wet floor and (b) (4) pool was observed during the walk through inspection of the area throughout the inspection. Even though the issue was discussed with the management, the (b) (4) was seen leaking from the (b) (4) during the inspection, and the firm continued using the (b) (4)

For the existing leakage, your firm simply logged-in an Engineering Request No.: ER-1603 on 01/25/2023 but has not acted upon and resolved the reported (b) (4) leakage issue.

C. There is a corrosion inside all (b) (4) tanks.

OBSERVATION 6

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Pratik S Upadhyay, Investigator X Pratik S Upadhyay Investigator Signed By: Pratik S. Upadhyay -S Date Signed: 06-13-2023 11:32:20	6/13/2023

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	6/5/2023-6/13/2023*
	FEI NUMBER 3009864467

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Colin Mackey, Chief Executive Officer

FIRM NAME	STREET ADDRESS
Symbiosis Pharmaceutical Services Limited	Unit 10, Scion House, Stirling University Innovation Park
CITY, STATE, ZIP CODE, COUNTRY Stirling, FK9 4NF United Kingdom	TYPE ESTABLISHMENT INSPECTED Sterile Drug Product Manufacturer

Your procedure SOP: Q-26 for Environment monitoring excursion (EME) investigation is deficient. According to section 10.3.7. Phase 1 manufacturing investigation, "Camera footage review" is stated as "(where applicable)". Your firm has not defined the determining factor for the video footage applicability in the SOP. Your EME investigations are biased in that you have concluded majority of investigations based on the review of video footages as one of the investigational tools to determine the root cause for EME. However, in the event when video footage was not available, your firm simply concluded the investigation based on the document review. For example,

EME Investigation: EME-512, Batch Number: (b) (4) Product code: (b) (4) was found to have (b) cfu in Grade B (Action limit: (b) cfu) for right hand dab (RHD) at 11:56 hours for the samples taken on 08-Jan-2023. Your firm concluded the investigation without video footage which appeared to have not been recorded. However, your "Environment Monitoring Submission Form R11 in Operation" confirmed to have video footage set-up and path created. This video footage was later reported to be not found on 02-Feb-2023 during EME investigation. Your firm simply referred to section 10.3.7 of SOP: Q-26 stating, "No camera footage is available for the time concerned".

OBSERVATION 7
Buildings used in the manufacturing of a drug product are not maintained in a good state of repair.

Specifically,

A. On 06-Jun-2023, I observed two (2) brown color objects (about 1.5 to 2 cm in length) inside a transparent ceiling light cover from the viewing window of Grade B room of conventional suite that has Grade A area separated by (b) (4) and (b) (4) LAF (b) (4) controlled at Grade A. On 12-Jun-2023 upon my requests, your firm unscrewed the light cover that revealed the following issues:

1. Two (2) dead inspects resembling butterflies along with a gap of about 1 to 1.5 cm on interior of the

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Pratik S Upadhyay, Investigator	X Pratik S Upadhyay Investigator Signed By: Pratik S. Upadhyay -S Date Signed: 06-13-2023 11:32:20	6/13/2023

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	6/5/2023-6/13/2023*
	FEI NUMBER 3009864467

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Colin Mackey, Chief Executive Officer

FIRM NAME	STREET ADDRESS
Symbiosis Pharmaceutical Services Limited	Unit 10, Scion House, Stirling University Innovation Park
CITY, STATE, ZIP CODE, COUNTRY Stirling, FK9 4NF United Kingdom	TYPE ESTABLISHMENT INSPECTED Sterile Drug Product Manufacturer

panel opening towards ceiling of the room.
2. Metal screws of the light panel pointing towards Grade B area were corroded.

Your firm has no procedure in place for the pest control activities in Grade A, Grade B and Grade C areas. Additionally, this issue was not found and reported by your operators during routine line clearance. This light panel was last accessed for fixture as per Engineering Request number ER- 359 on 12-Dec-2018.

B. The LAF inlet (b) (4) inside Grade B room has corrosion and missing peeled-off paint on multiple areas across the panel.

C. Inside Grade B rooms, an air extraction/exhaust vents were observed blocked with a mobile cart holding a (b) (4) pump on top of it and blocked by LAF (b) (4).

D. On 06/06/2023, I observed a live insect, multiple spider webs, settlement of debris in corners along with gaps underneath the door in controlled and non-classified area of the firm.

***DATES OF INSPECTION**
6/05/2023(Mon), 6/06/2023(Tue), 6/07/2023(Wed), 6/08/2023(Thu), 6/09/2023(Fri), 6/12/2023(Mon), 6/13/2023(Tue)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Pratik S Upadhyay, Investigator X Pratik S Upadhyay Investigator Signed By: Pratik S. Upadhyay -S Date Signed: 06-13-2023 11:32:20	6/13/2023