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	3/24/2022-4/4/2022*
	FEI NUMBER 3003821988

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Veerappan Subramanian, Ph.D., President & CEO

FIRM NAME	STREET ADDRESS
Somerset Therapeutics Limited	54/1 Bodhihal Village, Nelamangala
CITY, STATE, ZIP CODE, COUNTRY Bangalore, Karnataka, 562123 India	TYPE ESTABLISHMENT INSPECTED 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:
PRODUCTION SYSTEM

OBSERVATION 1

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

Specifically,

a) During the review of the smoke studies (PRO & REP/QA/21/094) for (b) (4) injectable line conducted on (b) (4) - (b) (4), the following inadequate conditions and practices were observed:

1) Laminar air flow was not always visualized as the smoke generator did not consistently follow the operator or the video was stopped too soon when transferring (b) (4) components from the (b) (4) to the mobile LAF, from the mobile LAF to the ISO 5 (b) (4) preparation area, and during some assembly and interventions in the (b) (4) ISO 5 area.
2) (b) (4) tubing is connected to various parts of the filling (b) (4) manifold with gloved hands without the use of a tool. The manifold ports/inlets are facing upwards and the gloved hand can potentially disrupt (b) (4) air. Section 4.1.6 of SOP PDI-006 "Operation of Vial Filling & Plugging Machine (Integrated Line) states "*Fix the* (b) (4) *tube into the* (b) (4) *through sterilized forceps*." It was stated during the inspection that they can't use forceps in this area because it is tight but that they are "practicing"; however, this practice has not been

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implemented.

b) During the filling operation of Exhibit batch (b) (4) (non-commercial) of (b) (4) Solution in (b) (4) on 3/29/22, we observed the following inadequate aseptic practices:

1) Two incidents when the operator removed a jammed bottle from the (b) (4) in the filling area through the (b) (4) port by using forceps. However, we observed that the (b) (4) disrupted (b) (4) air over some open bottles in the conveyor belt and the (b) (4) but these empty bottles were not removed after the intervention and were subsequently filled. SOP PDA-117 "Handling of Interventions during Filling" (New Injectable and (b) (4) line), effective 1/29/21, does not instruct the operators to remove exposed empty bottles or vials during interventions. These filling lines ((b) (4) & (b) (4)) will be used for aseptically filled commercial drug products when approved.
2) During the loading of sterile bottles into the chute through the (b) (4), we observed the operator (b) (4) the bag vigorously and touching it at various points. His movements were not slow and deliberate.
3) During wiping of the open (b) (4) of the bottle chute (b) (4), we observed the operator's back touching and pushing back the (b) (4) creating a temporary gap between the ISO 5 and ISO 7 areas. This working area was tight as there was a cart used as a working surface for wiping and opening bags of sterile bottles.

This is a repeat observation.

LABORATORY CONTROL SYSTEM

OBSERVATION 2

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

Specifically,

a) Your firm failed to establish a robust non-viable particle sampling plan as part of your environmental monitoring program for all critical aseptic manufacturing area on Lines, (b) (4), (b) (4), and the Ampoule (b) (4) Line.

Without a scientifically sound sampling plan and evaluation of the critical manufacturing areas, no representative non-viable particle (NVP) monitoring data supports your ISO-5 classification for the product path from the out-feed (b) (4) to which transfers product filling and sealing/stoppering of bottles, and vials during aseptic processing of finished drug products for (b) (4), (b) (4).

During our inspection, we observed that your continuous NVP probes are placed at unknown distances apart from one another within the critical manufacturing areas where activities, such as, the in-feed/(b) (4) of tips, caps, and stoppers to the process can generate non-viable particles which may contaminate the products manufactured on all manufacturing lines.

The risk assessment from (b) (4) (Manufacturer) for (b) (4) Line fails to include a rationale for the NVPC sampling locations and placement of counters and fails to evaluate the entire critical area of the manufacturing line. For example, the transport line from the outfeed (b) (4) of open vials to product filling, appears to be approximately (b) (4) or more. The transport line in this space includes (b) (4) and (b) (4) ports used for interventions which may cause particle generation and impact the quality of the product. There is no continuous NVP monitoring of this area of the line.

The risk assessment for (b) (4) Filling Lines, (b) (4) Vial (b) (4) Filling Line, and the Ampoule (b) (4) Line critical manufacturing areas where open bottles and vials are processed do not include a CAD/scale drawing of

the lines and rationales for the sampling locations selected. The distance between NVPC counters is also not evaluated to determine if all critical areas are covered with the current location of NVP counters.

The transferring of open vials and bottles along transport lines without NVP monitoring may increase contamination hazards. Your firm lacks adequate environmental monitoring for this portion of the operation and scientifically based justification that includes areas where container closures of product are exposed to the environment, and at greater risk of contamination.

b) SOP QCB-050 "Environmental Monitoring Programme" effective 3/15/22 does not require surface sampling of portable equipment such as carts that are brought into the ISO 5 filling area and that may come in contact with (b) (4) bags of components.

c) SOP PDA-019 "Monitoring of Differential Pressure in Production Areas" effective 12/26/20, requires recording of differential pressure in (b) (4) injectable line (b) (4) but does not require recording of differential pressure at the (b) (4) of filling operations. For example, filling operations for (b) (4) Injection USP (b) (4) mg/mL, lot (b) (4), ended at (b) (4) on 2/24/22 but differential pressure readings were taken approximately (b) (4) prior (b) (4) on 2/24/22) and (b) (4) later ((b) (4) on 2/25/22) after filling ended.

QUALITY SYSTEM

OBSERVATION 3

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,

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a) Laboratory investigations LI/21/089 and LI/21/091were opened on 4/16/21 & 4/17/21, respectively, to investigate the following bulk solution and finished product assay results for (b) (4) Solution (b) (4) % (b) (4) mL) that fell below the release specification of NLT (b) (4) %:

Bulk (b) (4) (b) (4) %	Bulk (b) (4) (b) (4) %	(b) (4) (b) (4) %	(b) (4) (b) (4) %	(b) (4) (b) (4) %	(b) (4) (b) (4) %

Manufacturing Investigation IR/LI/21/091-PD was opened on 4/20/21 and concluded that no definitive root cause was identified but the API lot used in these batches may have had variation in dissolution rate and some API particles may have settled at the bottom of the compounding tank. These four (b) (4) batches were rejected but the investigation was not extended to other batches that may have been impacted.

b) Manufacturing Investigation IR/LI/21/137-PD was opened on 7/12/21 to investigate OOS high assay results of (b) (4) % (release spec: (b) (4) - (b) (4) %) for (b) (4) Solution (b) (4) % (b) (4) mL), lot (b) (4) . The root cause analysis was not adequate and it concluded the following: "*there were no definitive root cause identified, however the following probable cause cannot be ruled out considering the process design and material nature, the API might not have* (b) (4) *throughout the bulk solution*." It did not investigate the specific lot of API used in this batch and the investigation was not extended to other batches that may have been impacted before the API supplier was subsequently changed in July 2021, and the compounding process was changed and re-validated in Oct/Nov 2021. This batch was rejected but the investigation was not closed until 6 months later on 1/13/22.

c) Investigations of consumer complaints of (b) (4) /(b) (4) and (b) (4) Solutions reporting low fill volume (product contents don't last (b) (4)), empty bottles, and drops that are too large have not extended to the supplier of the bottle nozzles to rule out packaging component variability even though the complaint trending reports for 2020 and 2021 identified these complaints as the most common. In addition, each investigation does not trend type of complaint by product and lot number to identify trends in a timely manner.

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This is a repeat observation.

OBSERVATION 4

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

Specifically,

a) Changes to manufacturing processes are not fully evaluated by your Quality Unit as per SOP QAD-003 "Change Control" to ensure all requirements are completed prior to the implementation of the change. Some examples include:

1) Temporary Change Control TCC/PD/21030 was opened on 4/22/21 to modify the compounding process of (b) (4) Solution (b) (4) % (b) (4) mL) by adding a manual (b) (4) step (b) (4)) during the mixing of the API due to assay failures. According to the change control, validation and qualification requirements were "NA". (b) (4) batches (b) (4) were manufactured with this modified process and released. This change was permanently incorporated into the MBR under Change Control PCC/PD/21094 (6/14/21) which also stated that validation and qualification was not required but a scientific rationale was not documented.

2) Change Control PCC/QA/2107 was opened on 10/26/21 to revise the Master Batch Record for (b) (4) Solution (b) (4) % (b) (4) mL) for the change in manufacturing process (compounding) and increase in batch size from (b) (4) to (b) (4). This major process change required re-validation of the manufacturing process and conduct of stability studies but it did not specify number of

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validation batches and storage conditions that would be required to be placed on stability. Only (b) (4) out of (b) (4) validation batches was placed on long-term stability (2-8°C) without a documented scientific rationale. Also, no validation batch was placed on accelerated stability (25°C/60% R.H.) to support the labeling storage condition of (b) (4) at room temperature.

***DATES OF INSPECTION**

3/24/2022(Thu), 3/25/2022(Fri), 3/28/2022(Mon), 3/29/2022(Tue), 3/30/2022(Wed), 3/31/2022(Thu), 4/01/2022(Fri), 4/04/2022(Mon)

X Kellia N Hicks
Office of Global Policy and Strategy Employee
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Annotations to Observations

Observation 1: Not annotated

Observation 2: Not annotated

Observation 3: Not annotated

Observation 4: Not annotated

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