

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

<small>DISTRICT ADDRESS AND PHONE NUMBER</small> 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: OPFBLAinspection483Responses@fda.hhs.gov		<small>DATE(S) OF INSPECTION</small> 01/07/2025-01/17/2025
		<small>FEI NUMBER</small> 3017231337
<small>NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED</small> Cai Bao, SVP Quality		
<small>FIRM NAME</small> Bio-Thera Solutions, Ltd.	<small>STREET ADDRESS</small> 155 Yaotianhe Street	
<small>CITY, STATE, ZIP CODE, COUNTRY</small> Huangpu District, Guangzhou, Guangdong Province, China 511356	<small>TYPE ESTABLISHMENT INSPECTED</small> Drug substance and 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 WE OBSERVED:**

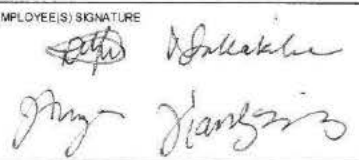
**OBSERVATION 1**

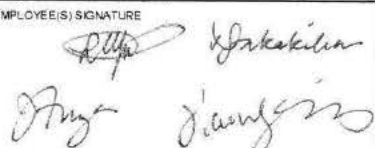
Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not fully established or followed. Specifically,

A. Aseptic techniques aimed at maintaining sterility of sterile items and surfaces are not used at all times.

- 1) Sterile materials are not always handled with sterile tools. For instance,
  - i. During equipment setup for (b)(4) filling operation (b)(4) (b)(4) Batch # (b)(4) 01/09/2025), non-sterile (b)(4) were used to remove (b)(4) covers for the stopper bowl and stopper chute.
  - ii. During equipment setups for (b)(4) and vial filling operations (b)(4) (b)(4) Batch # (b)(4) 01/09/2025 and (b)(4) drug product (b)(4) Vial Batch # (b)(4) 01/10/2025), sterile scissors were placed on the non-sterile surfaces in the RABS. The scissors were subsequently used to cut open (b)(4) bags containing sterile parts such as stoppers and (b)(4). In addition, this was observed during review of dynamic air flow visualization study videos (VR-EV-A-010) of the vial filling line.
- 2) While reviewing approved dynamic air flow visualization study videos (VR-EV-A-150, version 02) of the (b)(4) filling line, the following deficiencies were noted:
  - i. Operator was observed to block first air to the exposed sterile (b)(4) with non-sterile (b)(4) while performing (b)(4) adjustment intervention.

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	<small>FORM FDA 483 (09/08)</small>	<small>PREVIOUS EDITION OBSOLETE</small>	<b>INSPECTIONAL OBSERVATIONS</b>

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<p>ii. Operator was observed to adjust (b)(4) with (b)(4). The non-sterile (b)(4) were in direct proximity of the exposed sterile (b)(4) and appeared to have made contact with the (b)(4) opening of the (b)(4).</p> <p>3) Inadequate aseptic techniques were observed during approved media fill studies.</p> <p>i. While performing non-routine interventions in media fill study VR-PV-A-002 Revalidation Report of Media Fill in Building (b)(4) Filling Line – (b)(4) operator was observed leaning his/her head, upper body, and elbow inside the RABS in close proximity to the exposed (b)(4). Operator was also observed to handle sterile items inside the RABS using non-sterile (b)(4) hands.</p> <p>ii. Reviewing the video recording of non-routine interventions during media fill study VR-PV-A-002) revealed up to (b)(4) operators gathering and speaking together for periods of up to (b)(4) at a time in the (b)(4) filling room. In addition, Deviation DE2023527, opened 10/06/2023 and closed 10/24/2023, was initiated because of a TNTC (too numerous to count) environmental monitoring sample result. The likely root cause was operators were observed to be talking animatedly in the Grade C compounding room.</p> <p>4) Operator movement and activities inside the RABS used for vial filling as well as the outer Grade B area and Grade C areas did not minimize risk to sterility. Specifically, on 01/10/2025 during equipment setup for vial filling operation (b)(4) Vial Batch # (b)(4) operator's movements inside the RABS were not slow and deliberate.</p> <p>5) Sanitization of the RABS (b)(4) do not always use a new side of the wipe at new wiping locations. Instead, operators were observed to use the side having contacted (b)(4) hands.</p> <p>B. The aseptic processing system is not designed to prevent potential microbiological contamination.</p> <p>1) On 01/14/2025, the (b)(4) used for compounding the drug product was observed to be (b)(4) exposing the (b)(4) to surrounding grade C air before it was (b)(4) the drug product under Grade A air.</p> <p>2) The manufacturing areas are not under control for mold. Specifically,</p>			
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DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
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<p>i. There is an unacceptably high number of mold recoveries in the classified rooms used for manufacture of (b)(4) drug substance and drug product. In the most recently available (b)(4) trend report of microbial identification (b)(4) 2-SOP-QC-04-048-R08(1.0), there were 70 recoveries of mold in Grade C and D areas. The (b)(4) HVAC system report from (b)(4) that only reviews investigated mold recoveries, 2-SMP-(b)(4) 015-R07 (3.0), includes a mold recovery in the grade B area outside the Grade A (b)(4) filling line area and a mold recovery in the grade B area outside the Grade A vial filling area.</p> <p>ii. Trend reports of microbial identification are on a (b)(4) and it took approximately (b)(4) before the review of the (b)(4) trend report of microbial identification for the period of (b)(4) 2-SOP-QC-04-048-R08 (1.0), was completed, signed by QA in (b)(4).</p> <p>iii. In the Alert Limit and Action Limit Management Procedure, 2-SMP-(b)(4) 015-R08 (1.0), mold is only investigated if there is greater than a (b)(4) recovery of (b)(4) CFU in Grade C and D areas.</p> <p>iv. Documentation of mold recoveries is not controlled.</p> <p>a. The SOP for colony counting of bioburden and environmental monitoring plates, 2-SOP-QC-04-139 (8.0), does not include instructions for reporting mold recoveries. In addition, the colony counting record sheet does not include entry locations documenting the recovery of mold.</p> <p>b. Mold identification to the species level is not required for mold detected in process (b)(4) tests, environmental monitoring, and the tests for raw materials and excipients according to the SOP for microbial identification, 2-SOP-QC-04-048 (4.0). Instead, it can be identified to the genus level.</p> <p>3) (b)(4) are introduced into the (b)(4) filling and stoppering RABS (Grade A area) without decontamination. Prior to the introduction of the (b)(4) the package (b)(4) (b)(4) was wiped in Grade C area and sent to (b)(4) under Grade B environment) for (b)(4) One wipe sprayed</p>			
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FORM FDA 483 (09/08)	PREVIOUS EDITION OBSOLETE	INSPECTIONAL OBSERVATIONS	Page 3 OF 9

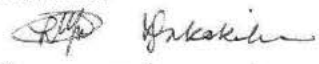

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with (b)(4) was used to wipe down multiple (b)(4) packages, and no inspections of package for seal integrity or potential leak were performed. There is no assurance that the (b)(4) was free of contamination prior to entering the RABS grade A area.

- 4) An electrical outlet located approximately one (1) foot above floor level was used for power supply to a (b)(4) conveyor belt in the (b)(4) filling room. During (b)(4) filling operation for (b)(4) Batch # (b)(4) 01/14/2025, operators were observed to crouch down to connect and disconnect power multiple times during the operation, posing an unreasonable contamination risk to the gown control.
  - 5) During the (b)(4) filling operation for (b)(4) product Batch # (b)(4) 01/09/2025, operators were observed to wear goggles with small breathing holes exposed to air without protection or covers.
  - 6) Personnel monitoring after the (b)(4) RABS (b)(4) setup operation was performed by only taking surface samples of operator (b)(4). No surface sampling of other locations of the gown was performed. During (b)(4) filling operation for (b)(4) Batch # (b)(4) 01/14/2025, an operator was observed to return to grade B filling area after personnel monitoring – post surface sampling of (b)(4) gown – had been performed.
  - 7) According to the drug product manufacturing floor manager, environmental monitoring (EM) of the drug product compounding area (grade C compounding room) is not always performed contemporaneously with batch production.
- C. The Media Fill program is not adequately performed to validate the aseptic operations for (b)(4) vial drug product (DP) manufacturing.
- 1) Unfilled and sterilized media left in the (b)(4) bags were not always incubated for growth during process simulation studies.
  - 2) Media fills are performed with dedicated (b)(4) that are not used in routine production.

OBSERVATION 2

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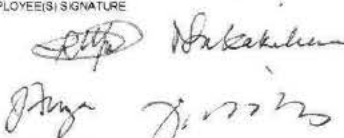
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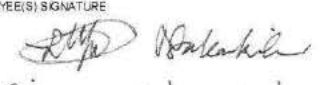

There is a lack of assurance that your manufacturing operations in the drug substance production area are appropriately designed to ensure the prevention of contamination of equipment or product by environmental and processing conditions that would be expected to have an adverse effect on product quality. Specifically, on 01/08/2025, during (b)(4) of the drug substance, the (b)(4) part of the (b)(4) was observed to be exposed to the surrounding Grade C air during (b)(4)

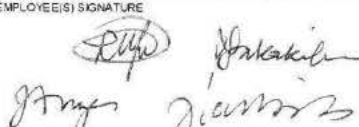
**OBSERVATION 3**

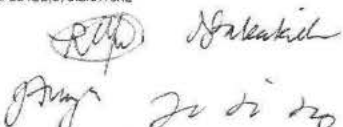
Written procedures for production and process controls designed to assure that the drug product has the identity, strength, purity, and quality that they are purported or represented to possess are not fully established or followed. Specifically,

- A. (b)(4) are performed for (b)(4) drug product (b)(4) manufacturing. According the PPQ batch records, for example, (b)(4) mg (b)(4) mL, Batch size (b)(4) and (b)(4) mg (b)(4) mL, Batch size (b)(4) (b)(4) were taken for (b)(4) and testing samples were taken from the (b)(4) stages of the batch productions. The current (b)(4) sampling plan including the number of samples do not provide a statistically sound representation of the (b)(4) filled in the batch productions.
- B. Appropriate visual inspection (VI) procedures designed to assure batches of (b)(4) product meet appropriate specifications and statistical quality control criteria are not established.
  - 1) 100% visual inspection of (b)(4) and the acceptance testing (AQL testing) are performed in the packaging room next to packaging and labeling machinery equipment with loud background noise, and without dimmed ambient lighting. During (b)(4) filling operation for (b)(4) Batch # (b)(4) 01/14/2025, it was observed that in addition to the (b)(4) visual inspection inspectors and (b)(4) AQL inspector, (b)(4) production and QC personnel were also present in close proximity performing packaging, labeling, and QC sampling activities.

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<p>There is no assurance that the visual inspection and AQL testing can be adequately performed without distraction.</p> <p>2) QA inspector was observed to take (b)(4) at a time to perform AQL while the 100% visual inspection is still ongoing. According to your QA manager, AQL sampling is performed at the (b)(4) of the 100% visual inspection process. Such plan does not provide assurance that the AQL testing is statistically valid, and the sampling provides a true representation of all (b)(4) in the batch production.</p> <p>3) Objects such as liquid observed (b)(4) or liquid observed (b)(4) are classified as Minor Defect. Defects such as particles observed (b)(4) are not defined. Any object (particle or liquid) identified (b)(4) or liquid (b)(4) may indicate stopper seal breach leading to microbial ingress and compromised sterility.</p> <p>4) (b)(4) inspectors were observed to share one (1) visual inspection booth. To perform visual inspection simultaneously the (b)(4) inspectors were observed to seat closely together in cramped positions. The inspectors are not under optimal conditions to perform the visual inspection.</p> <p>5) During the (b)(4) visual inspection swirl and inversion of the (b)(4) were not performed. Enough time, that is, inspecting each (b)(4) for (b)(4) against (b)(4) (b)(4) backgrounds, was not provided to allow for a thorough inspection of each (b)(4).</p> <p>6) (b)(4) were used to conduct the 100% visual inspection.</p> <p>7) Visual inspection testing kit sample units do not represent the real drug unit in which each testing sample has a QR code label on top of the vial while the real drug unit does not have such label.</p>			
<b>OBSERVATION 4</b>			
Adequate procedural controls were not established to protect the electronic data acquisition and process control systems used for the manufacturing of (b)(4) DS and DP in your manufacturing facility. Specifically,			
A. Reviews of electronic data including audit trail information are not performed by the Quality Assurance (QA) unit for manufacturing equipment prior to the final approval of manufacturing batch			
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FORM FDA 483 (09/08)	PREVIOUS EDITION OBSOLETE	INSPECTIONAL OBSERVATIONS	Page 6 OF 9

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
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<p>records. According to your QA reviewer, comprehensive batch record review by QA – prior to final approval of such record – is limited to paper review of the manufacturing record and verification of QC study reports. QA does not independently review and verify critical raw data including audit trails to ensure completeness and accuracy of critical process parameters. In addition, your QA unit failed to observe and identify poor aseptic techniques during the review of aseptic process simulation (media fill) study reports. Production operators were approved to perform routine and non-routine filling operation interventions despite inadequate aseptic behaviors.</p> <p>B. Data management for the Empower 3 Chromatography Data System (CDS) is deficient. Analytical methods used for (b)(4) drug product release and stability testing in the Empower 3 system can be stored in more than one project folder, for example, the same method can be stored in the (b)(4) project folder for testing and in “Method Development” project folder for training and method development purpose. QC review of release testing data only checks data in the (b)(4) project folder and does not cross check the data in the “Method Development” project folder. There is no assurance that all sequences or injections are reconciled and accounted for in the different project folders.</p> <p>C. Permissions assigned to Analysts and Engineers in the Empower 3 CDS include the ability to “calibrate and quantitate data in review” and “view quantitation fields in the review” in review window mode. This allows the analysts to see area counts and results before deciding whether to save the processed chromatogram or enter additional integration parameters. The allowed practice is a gap in your analytical data management in QC labs.</p> <p>D. Appropriate controls are not exercised over QC testing system to assure that testing and control records are only instituted by authorized personnel. A pH meter Asset ID D4-C77 located in QC chemistry lab (b)(4) appeared to be in a ready-to-use screen and was not user and password protected. The same pH meter was used for (b)(4) PPQ batch release and stability testing.</p>			
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<b>OBSERVATION 5</b>			
The responsibilities and procedures applicable to the Quality Unit are inadequate:			
A. The Quality Unit failed to follow the deviation management SOP, 2-SMP- (b)(4)-080 (5.0), by not including the recordable event RE2024011 in media fill report VR-PV-A-009 (03).			
B. The Alert Limit and Action Limit Management Procedure SOP, 2-SMP- (b)(4)-015 (8.0), allows alert limits to be adjusted with a CAPA that does not require a risk assessment. CAPA 2-SMP- (b)(4)-077-R02 (4.0) was approved for loosening the requirement to investigate mold from (b)(4) CFU (b)(4) (b)(4) recovery to greater than (b)(4) CFU (b)(4) recovery in Grade C and D areas.			
C. The deviation management procedure, 2-SMP- (b)(4)-080 (5.0), is inadequate:			
1) It does not require a CAPA for excursions for which "the cause is clear". For example, a CAPA was not opened for recordable event RE2024011 when the particle counter exceeded the acceptance criteria inside the filling machine for vials during media fill run VR-PV-A-009 (03).			
2) Abnormal events and abnormal material events are not required to be listed in validation reports. For example,			
i. In the (b)(4) drug substance batch record for preparation for (b)(4) (b)(4) the failure of the (b)(4) machine was classified as an abnormal event and was not included in the drug substance process validation report.			
ii. In the (b)(4) drug substance batch record for (b)(4) foreign particles were discovered in a flask before use; however, this event was classified as an abnormal material and not included in the drug substance validation report.			
<b>OBSERVATION 6:</b>			
Laboratory controls do not include the establishment of scientifically sound and appropriate standards designed to assure that components and in-process materials conform to appropriate standards of identity, strength, quality, and purity:			
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- A. The bioburden sample hold time study, VR-OV-D-012(04), is inadequate because there were no system suitability controls to demonstrate the lack of interference on growth promotion.
- B. The endotoxin sample hold time of (b) (4) in the endotoxin method, 2-SOP-QC-03-184, was not validated.

*[Handwritten signature]*

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE <i>[Signature]</i>	EMPLOYEE(S) NAME AND TITLE (Print or Type) Yiwei Li, Ph.D., Supervisory Chemist Jeanne Fringer, Ph.D., Chemist Nozomi Sakakibara, Ph.D. Senior Research Scientist Jiangsong Jiang, Ph.D. Pharmaceutical Scientist	DATE ISSUED 01/17/2025
	<i>[Signature]</i>		