DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	July 15-19 and 22-26, 2024
	FEI NUMBER 3003981475

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dwight D. Hanshew, Jr., Chief Quality Officer

FIRM NAME	STREET ADDRESS
Biocon Biologics Limited	B1 B2 B3 Block No, Q13 Of Q1 And W20 & Unit S18
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Bengaluru, Karnataka, 560099, India	Drug Substance and Drug Product Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) 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.

1. Air flow visualization studies for the [redacted] (b) (4) line used to aseptically fill [redacted] (b) (4) for the US market did not meet the acceptance criteria of airflow that is unidirectional and free from turbulence or follow the established execution instructions in the study protocol.

a. In the area where empty [redacted] (b) (4) are opened and exposed to the environment there is a gap between the overhead HEPA filters of approximately [redacted] (b) (4) Raw video footage obtained during the smoke studies of this area show air turbulence and upward flowing air. The raw video footage showing this deficient air flow pattern was not included in the final edited versions of the videos discussed in the validation report.

b. The videos show upward flowing smoke along the RABS barrier near [redacted] (b) (4) inside the filling and stoppering RABS. This area is below an approximately [redacted] (b) (4) gap between the edge of the HEPA filter and the RABS barrier. The validation report did not identify any deficiencies in this area. A similar gap between the RABS barrier and the HEPA filters exists on all [redacted] (b) (4) sides of the RABS filling barrier. The air flow visualization studies have not thoroughly evaluated this gap.

c. The videos show upward flowing and turbulent air flow near a gap between the HEPA filter edge and the barrier [redacted] (b) (4) outside of the filling barrier, near [redacted] (b) (4) There is an approximately [redacted] (b) (4) gap between the edge of the HEPA filter and the RABS barrier. This Grade A classified area is used during [redacted] (b) (4) assembly of the machine, and interventions. The raw video footage showing this deficient air flow pattern was not included in the final versions of the videos discussed in the validation report.

d. The [redacted] (b) (4) barrier used to open and load empty [redacted] (b) (4) has a support for the [redacted] (b) (4) positioned about [redacted] (b) (4)

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below the HEPA filter. The smoke studies did not thoroughly evaluate the impact of this support on the air flow in this area.

e. Protocol (b) (4) QA/AFVP/017 for the (b) (4) line states the smoke needs to be introduced by placing the nozzle with the smoke upwards and the nozzle should be moved to cover the entire area of the filter. Raw video files show the smoke nozzle pointed in downward direction and in fixed locations. The final edited videos did not show the smoke from where it was introduced near the filter to the working location.

2. The (b) (4) vial line is used for aseptic filling and (b) (4) for the US market product (b) (4) For the air flow visualization studies in this area:

a. In the Grade A areas there are gaps between adjacent HEPA filters and between the barrier and the edge of the HEPA filters. These areas have not been thoroughly assessed during airflow pattern studies. Examples include, but are not limited to:

A (b) (4) gap between LAF-14 and LAF-15 located above the stopper bowl and the conveyor where open vials pass. Limited static air flow analysis conducted in June 2024 appeared to show upward flowing smoke in this area.

A (b) (4) gap between LAF-16 and LAF-17 above the conveyor where (b) (4) vials travel to the (b) (4)

b. Smoke studies to support interventions for vial removal on the (b) (4) stopper removal from stopper track and replacement of (b) (4) as per SOP S2/BF/FM/SOP/0158 do not clearly demonstrate good aseptic processing technique. For instance, smoke studies to remove vials from (b) (4) or stoppers from stopper track appear to violate first air principles on remaining container closures and stoppers. In addition, the smoke study to demonstrate that the firm can replace a (b) (4) during production appears to show the (b) (4) glove covering and/or touching tubing that is needed to attach to the (b) (4) aseptically.

c. Smoke studies to demonstrate that personnel, carts, and equipment crossing the Grade A (b) (4) conveyor area to demonstrate unidirectional air flow at critical locations within the fill line or during interventions in the (b) (4) Vial Filling Line were not provided.

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3. For the (b) (4) Vial filling aseptic area, air visualization studies to demonstrate airflow from filling room into B-grade corridor for aseptic filling line located in (b) (4) and airflow from B corridor into entrance and exit change rooms do not effectively provide visualization of air flow patterns during operational conditions. In addition, air visualization for the laminar airflow inside (b) (4) RABS, does not show enough detail or angles to verify laminar airflow in grade A areas.

4. During smoke studies for all US market aseptic filling lines (b) (4) the smoke generated in the Grade B areas and held over the individuals performing the interventions into Grade A used a (b) (4) based smoke generator. There has been no demonstration to show these particles would demonstrate neutral buoyancy during airflow pattern evaluations.

5. Categorization of defects that have the potential to risk contamination are not adequate. Failure of Media Fill Batch (b) (4) was potentially attributed to both (b) (4) position and/or liquid found in the (b) (4) of the stopper. Neither of these defects is considered a critical defect even though the firms media fill failure investigation has identified them as potential risks to sterility assurance. (b) (4) position is categorized as a minor defect and liquid in the (b) (4) of the stopper is categorized as a major defect during the visual inspection process.

OBSERVATION #2

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

1. On (b) (4) filling line, during aseptic filling of (b) (4) batches (b) (4) (US Market), and (b) (4) batch (b) (4) operators were observed to extend the (b) (4) glove over the sterile stopper bowl and sterile stoppers (b) (4) closure) during interventions to add stoppers.

2. On (b) (4) Vial filling line, during aseptic filling operations, procedure S2/BF/FM/SOP/0076 – "Aseptic Behaviors in the Aseptic Processing Area and Periodic Review" was not followed. During review of aseptic filling of (b) (4) injection lots (b) (4) (US Market), (b) (4) US Market), (b) (4) (b) (4) executed between July 5-13, 2024, the following was observed (the list is non-exhaustive):

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• Operators opened the (b) (4) wrapping of the sterilized (b) (4) gloves outside the RABS barrier.
• Employees did not sanitize hands prior to interventions performed on (b) (4) 17 near vial feed area after touching HMI panel.
• Employees did not stop vial feeding during clearance of fallen vials intervention performed using (b) (4) 17 near the vial feed area.
• Employees crossed the grade A (b) (4) conveyor belt area located in (b) (4) area without sanitizing the (b) (4) RABS (b) (4)
• Employees opened filling areas (b) (4) using their hands and not their elbows.
• Employees did not move slow and deliberate.
• Employees appeared to rest against filling room walls.

3. The (b) (4) Vial Filling Line is not designed to minimize crossing the Grade A laminar flow area through a (b) (4) conveyor as personnel can only enter the rear side of the fill line and must cross the Grade A laminar flow through a (b) (4) conveyor to exit the front side of the fill line. Equipment needed on the rear side of the fill line for operations must enter the front side of the fill line and brought across the Grade A laminar flow area to the rear side of the fill line. Review of this area noted the following:

a. There are no limits to the number of personnel, carts, and equipment that can traverse the Grade A (b) (4) conveyor that is located between the stoppering station and the (b) (4) loading station during both filling line setup and during filling operations. Crossing the laminar flow requires manual dismantling and reassembly of vial (b) (4) and the vial conveyor belt with gloved hands within the fill line in order to allow personnel and cart crossings. Greater than 30 crossings of the Grade A laminar flow area were observed by personnel alone or with a cart during both setup and filling operations on the (b) (4) Vial line during filling of batch (b) (4) of (b) (4) on July 24, 2024. The same filling line and procedures are used during aseptic filling of (b) (4) for the US market. (b) (4) vials traverse this conveyor.

b. Personnel crossings of the Grade A (b) (4) conveyor are not considered an intervention as per SOP S2/BF/FM/SOP/0158 and thus not appropriately documented. In addition, the number of personnel and cart crossings of the Grade A (b) (4) conveyor are not purposely challenged in aseptic process simulations as they are not considered interventions.

c. During filling of (b) (4) batch (b) (4) on July 24, 2024, manufacturing operations began immediately after cleaning was completed of the Grade A (b) (4) conveyor area, which does not adhere to SOP (b) (4) PROD-SOP-0030. The procedure requires a (b) (4) waiting period before production can resume after decontamination.

d. During filling of (b) (4) batch (b) (4) personnel were crossing back and forth through the Grade A (b) (4) conveyor area during an intervention in the fill line where stoppers were being loaded into the stopper (b) (4) The stopper (b) (4) is located adjacent to the Grade A (b) (4) conveyor area.

4. During filling of (b) (4) batch (b) (4) here was an intervention (at (b) (4) where vials were removed from the (b) (4) while reaching over the remaining open container closures that were used in subsequent manufacturing.

5. The (b) (4) line is proposed used for aseptic filling of the (b) (4)

a. During aseptic filling on the (b) (4) line for (b) (4) batch (b) (4) an operator performed an (b) (4) intervention to add stoppers. The operator was observed to use their hands and arm over the sterile stoppers and stopper bowl during addition of the stoppers. The operator then held their hand over the stopper bowl between addition of stoppers bags.

b. After personnel monitoring of hands and forearms conducted at the end of an (b) (4) intervention during (b) (4) batch (b) (4) an operator did not immediately change their gloves and subsequently touched the filling machine HMI screen.

OBSERVATION #3
Laboratory test procedures and controls are not established and followed.

1. Test procedures are not followed for integration of chromatograms. During (b) (4) testing for (b) (4) analysts initially applied a standard processing method that resulted in integration that appeared consistent with the reference chromatogram in the standard test procedure, integration during analytical method validation, and approved integration during previous stability timepoints. This initial processing resulted in OOS results for long

term stability samples for the percentage of basic variants. Without adequate justification, analysts were permitted to reprocess chromatograms, which reduced the area integrated for the percentage of basic variants. This changed the result from out of specification to within specification (≤ (b) (4) %). For example:

(b) (4) 24-month, Initial: (b) (4) % Reprocessed: (b) (4) %, Stability samples for this batch were confirmed OOS at 36 and 48 months.

(b) (4) 48-month. Initial: (b) (4) % Reprocessed: (b) (4) %

(b) (4) 36-month. Initial (b) (4) % Reprocessed (b) (4) %

Additionally, permissions assigned to analysts in the Empower chromatography software include the ability to view quantitation peak fields in review. This allows the analyst to see area counts and results before deciding whether to save the reprocessed chromatogram or enter additional integration parameters. Standard test procedure QC/Q8/ SPEC/FP/170-01 requires any changes to the processing to be done by changing one parameter at a time. However, the analysts do not save the result after each parameter is changed, only the final chromatogram is saved.

2. Written testing procedures are inadequate to ensure appropriate quality control of (b) (4) drug substance and drug product for purity and impurity determination by RP-HPLC. Specifically, one of the system suitability criteria of this analytical method is "post peak to the main peak at a relative retention time (RRT) range of (b) (4) should be observed". According to the method validation results, the first peak post to the main peak (i.e., (b) (4) was selected for the system suitability evaluation. However, after reviewing the chromatograms of historical system suitability samples over the past two years, we observed that different post-peaks were eluted within the RRT range of (b) (4) and thus the analysts inconsistently selected a peak for system suitability evaluation other than (b) (4) A retrospective evaluation of system suitability samples over the past two years showed a RRT range of (b) (4) for (b) (4) peak. If (b) (4) peak was uniformly selected for system suitability evaluation, about 35% of the reported assays results which passed system suitability criteria should have been considered as invalid results. The RRT of (b) (4) peak is critical because RRT is taken consideration into the integration procedure.

3. The [(b) (4)] Standard Test Procedure requires electropherograms generated during the purity by NR CE-SDS be integrated first using a standard processing method. If this does not provide appropriate integration, the procedure allows modifications to optimize the processing method by making changes one at a time. Only if the method cannot be optimized, the procedure allows analysts to request to use manual integration.

Review of electropherograms found no meaningful attempt was being made to optimize processing methods before manual integration. A NR CE-SDS analyst stated manual integration is being used [(b) (4)]%" of the time.

4. There have been no procedures established to identify and investigate out of trend (OOT) or unexpected results during stability testing. For example:

a. The percent basic variants has a specification of ≤ [(b) (4)]% during [(b) (4)] bulk stability testing and the basic variants is expected to increase during the shelf life. Results prior to the [(b) (4)] expiration date included batch [(b) (4)] at the 36-month timepoint with a result of [(b) (4)]%. No limits have been established to open investigations until after an out of specification result has been reached.

b. Unexpected results are not investigated. For example, during [(b) (4)] bulk stability CE-SDS non-reducing, [(b) (4)] has a limit of ≤ [(b) (4)]% and is expected to increase over time.

Batch [(b) (4)] had a [(b) (4)] result for [(b) (4)]% at the 12-month timepoint and decreased to [(b) (4)]% at the 24-month timepoint.

Batch [(b) (4)] had a [(b) (4)] result of [(b) (4)]% at the 3-month timepoint and decreased to [(b) (4)]% at the 24-month timepoint.

OBSERVATION #4

Computerized systems lack controls and review of electronic data to prevent omissions in data.

1. The electronic data for the [(b) (4)] non-viable particle F2-APC-05 showed results that failed to meet acceptance criteria, which had not been reported in the paper records. Operators are supposed to transcribe results into paper logbooks and attach printouts, which are reviewed. There is no review of the source electronic data to ensure all

data is reported. Examples of unreported data for tests that stopped before the [(b) (4)] sample collection time observed in the electronic data included:

Point [(b) (4)] LAF-09- [(b) (4)] Unloading (Grade A) on July 4, 2024, 14:42. The [(b) (4)] micron particle limit of not more than [(b) (4)] had already been exceeded with a result of 57 when the test stopped.

Point [(b) (4)] LAF-09- [(b) (4)] Unloading (Grade A) on June 18, 2024, [(b) (4)] The [(b) (4)] micron particle limit of not more than [(b) (4)] had already been exceeded with a result of 53 when the test stopped.

[(b) (4)] zone (Grade A) on June 17, 2024, [(b) (4)] The [(b) (4)] micron particle limit of not more than [(b) (4)] had already been exceeded with a result of [(b) (4)] when the test stopped.

[(b) (4)] zone (Grade A) on June 18, 2024, [(b) (4)] The [(b) (4)] micron count had a count of [(b) (4)] particle compared to a limit of [(b) (4)] when the [(b) (4)] test was stopped after 2 minutes and 58 seconds.

Review of data older than April 25, 2024, was not possible because data is not being backed up and had been overwritten. Similar NVPC tests that were stopped before completion were observed on [(b) (4)] NVPC F2-APC-01.

A risk assessment dated June 28, 2024, was performed by the data governance group and identified the potential for not reporting data in these systems. However, the assessment resulted in no action to review the source electronic data, rather it allowed the reliance on print outs. The assessment did not evaluate the need to back-up the electronic data.

2. CE-SDS testing for [(b) (4)] is performed for release testing and occasional stability testing on instruments QC-Q8-AI-877 and QC-Q8-AI-876 that utilize 32 Karat Software. Neither instrument has been configured to save all electropherogram results. Only the final result is saved as the analyst changes the processing method and uses manual integration.

Deviation investigation #29510 was initiated May 24, 2021, when electronic data did not match the submitted printout during CE-SDS analysis on instrument QC-Q17-AI-364 and the same 32 Karat Software. The

investigation found the system had not been configured to save all results and was updated with this configuration. This investigation was not extended to evaluate all instruments and ensure they had been configured to save all data.

Additionally, a gap assessment by the data governance group was approved February 12, 2024, for the 32 Karat software. The failure to save all data was not identified during the gap assessment.

3. Production supervisors are given access to delete results in the (b) (4) integrity testing equipment. A gap assessment dated February 10, 2024, was performed by the data governance group did not address the delete privilege granted to production supervisors.

4. Audit trail review procedures for production software are general and do not contain instructions specific to the different softwares to ensure a thorough review of raw data. In addition, audit trail reviews for (b) (4) software are done on the printout copies and do not evaluate the source electronic data.

5. Investigation #151029 into the loss of data time points during (b) (4) cycles data for (b) (4) software notes that this was the only occurrence for the loss of data observed. However, review of work orders records shows that this incident had occurred at least eight (8) times prior to the opening of this investigation. During deviation investigations there is no evaluation of work orders when considering whether an event is recurring. The corrective action for the lost data was to open change control #155447 which requires an upgrade of the software but the change control does not contain information associated with a mitigation strategy to prevent data loss until the new software can be obtained.

6. Raw data video files for smoke studies conducted to qualify filling line for US commercial products located in building (b) (4) were not available.

OBSERVATION #5

Investigations of an unexplained discrepancy or a failure to meet a specification were not thorough and did not extend to other batches that may have been associated with the discrepancy or failure.

1. Investigation PR #134741 was not thorough and expanded to assess the full scope of the discrepancies. The

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investigation found personnel had inappropriately changed set points for instruments that impacted the monitoring and alarms for differential pressure, temperature, and relative humidity in building (b) (4) used to aseptically manufacture US market (b) (4) drug product. The investigation found these inappropriate changes were made as a quick fix instead of addressing frequent maintenance issues. The investigation also found the calibration records generated by a third party vendor that should have detected these discrepancies did not report accurate data.

The investigation did not include attempts to interview the third party calibration employees that generated calibration records that shows criteria was met, but which should have detected the unauthorized changes.

The investigation did not identify the full scope of the work performed by the third party calibration vendor at this site and any potential impact to other work performed.

The investigation identified a lack of oversight of the third party calibration work by onsite engineering personnel. The investigation did not expand to evaluate work performed by other third parties performing calibration and qualification activities under the inadequate oversight of engineering personnel.

The investigation identified IT personnel had an inadequate GMP understanding and provided administrator access to make changes that had not been approved by quality. There was no assessment of the work requests made to IT, from all departments, to determine if other requests had been granted by IT personnel to provide administrative access to make changes without quality approval.

2. The environmental monitoring trending program for (b) (4) does not include evaluation of route of ingress into the aseptic areas grades A and B for recovered fungi/mold and gram-negative organisms. In addition, prior to approximately February 2024, the site would not conduct investigations when (b) (4) trends revealed recovery rates or action limit excursions rates which exceeded acceptance levels.

3. Deviations 177060, 129067, and 131819 are related to drug product spilling into the fill line through an air vent filter. The investigation did not thoroughly assess the risk of microbial ingress due to the wetting of the vent filter when deciding to release the associated drug product batches.

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4. Deviations 170836, 180034, and 193440 initiated in January-May 2024, describe forceps used in (b) (4) vial filling line that released discolored particles into a solution upon swabbing the forceps to assess microbial growth during post-batch environmental monitoring in the Grade A fill line. The identity of the particles has not been analytically identified. When a (b) (4) wipe was used to clean the forceps a (b) (4) noticeably (b) (4) stain was left on the (b) (4) wipe. Forceps are used throughout the (b) (4) Vial Filling Area performing a number of critical aseptic functions including manipulation with product contact stopper equipment.

5. There are multiple deviations (>10) regarding exceeding hold times in drug product manufacturing. In Deviations 171146, 172572, and 179602 the quality unit released the drug product based on limited data that covered the excursion, typically a single batch. Quality has not implemented appropriate preventive controls to prevent recurrence or conducted studies to justify extending hold times.

6. There is no process to routinely identify visible particulate rejects during visual inspection in order to identify and minimize particulate sources in the aseptic filling areas.

7. (b) (4) NVPC data associated with batch (b) (4) showed "Error" in numerous instances where the continuous monitoring probes did not provide a result. The personnel that had reviewed and approved the data did not know what these "Error" meant or its impact. The record was approved by QA without comment or actions to investigate the cause and impact for the repeated errors.

8. There has been no investigation for the repeated (b) (4) measurements at multiple (b) (4) drug substance (b) (4) steps where (b) (4) measurements were out of batch manufacturing record (BMR) defined ranges. There is no assurance the (b) (4) results obtained from (b) (4) measurement are consistent for use during the subsequent manufacturing process. Specifically, during the (b) (4) process, the BMR describes that in case (b) (4) of the (b) (4) solution measured (b) (4) is not in the BMR range, the result(s) is allowed to be verified using (b) (4) instrument on sample(s) collected from (b) (4) of the (b) (4) system. However, when (b) (4) of the (b) (4) solution measurements are within the BMR ranges, (b) (4) verification is not performed. For instance,

a. Batch No (b) (4) at (b) (4) step: (b) (4) of (b) (4) for (b) (4) check before Lot- (b) (4) was (b) (4) which is out of the BMR range (b) (4) was measured as (b) (4) and the (b) (4) result was

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accepted.

b. Batch No (b) (4) at (b) (4) step: (b) (4) of (b) (4) of was (b) (4) which is out of the BMR range of (b) (4) was measured as (b) (4) and the (b) (4) result was accepted.

c. Batch No (b) (4) Lot (b) at the (b) (4) step: (b) (4) of (b) (4) for (b) (4) was (b) (4) which is out of the BMR range of (b) (4) was measured as (b) (4) and the (b) (4) result was accepted. However, Batch No (b) (4) Lot (b) (4) and Lot (b) (4) at the (b) (4) step: (b) (4) (b) (4) of (b) (4) for (b) (4) were (b) (4) which were within the BMR range and the (b) (4) results were accepted without (b) (4) confirmation.

d. Batch No (b) (4) Lot (b) (4) at (b) (4) step: (b) (4) of (b) (4) for (b) (4) was (b) (4) (b) (4) respectively, out of BMR range of (b) (4) was measured as (b) (4) respectively. All (b) (4) results were accepted.

OBSERVATION #6

Equipment used in the manufacture, processing, packing or holding of drug products are not maintained in a manner to prevent malfunctions that would alter the drug product quality.

1. During review of BMS data for the years 2022-2024 I observed too numerous to count excursions of DP below (b) (4) Pa. In addition, there were also too numerous to count alarms documented for excursions of temperature and humidity throughout building (b) (4) areas. Your firm does not evaluate numerical raw data reports for the noted parameters, instead employees only review the trend graph. In addition, although excursions of high differential pressures have caused reverse airflow from (b) (4) room to (b) (4) area in (b) (4) no upper limit value has been defined for alert or action limits.

2. On July 15, 2024, the differential pressures in the women's entry change room into grade C corridor was below the limit of (b) (4) Pa and the door would not close. During the walkthrough differential pressure values below the limit of NLT (b) (4) Pa were observed for instrument ID F2-AHU-15, F2-41B.

3. During review of equipment, there were at least 40 work orders opened for aseptic area equipment repairs

which extended over 100 days in the (b) (4) aseptic area. For example, work order 2000110406 for (b) (4) leakage of (b) (4) -1) shows that it was opened for 130 days.

4. Equipment work orders also revealed recurring issues such as (b) (4) leak test failures, (b) (4) leakages of (b) (4) and data loss. For example, (b) (4) leak test for batch (b) (4) was repeated five times in 2022. This caused process time extension which caused that the site returned the (b) (4) bulk drug substance to freezing conditions to be thawed on a different day. The batch was ultimately rejected after filling. The equipment logs also showed that the (b) (4) leak tests for batch (b) (4) was repeated three times in 2023, and (b) (4) leak test for batch (b) (4) was repeated two times in 2024.

5. On July 17, 2024, there was leaking (b) (4) in the technical area near (b) (4) #1 in (b) (4) building. The (b) (4) was first observed at approximately 1:20pm. Upon return at approximately (b) (4) the leak was still occurring with standing (b) (4) below the (b) (4) Although there were employees working in this area, no notification had been made to maintenance personnel to address the issue.

6. Preventive maintenance records for (b) (4) and LAF for (b) (4) 01 located in the filling area for (b) (4) do not identify the instruments used for verifying laminar flow and pressures, thus they cannot be traced to ensure that they calibrated and suitable.

OBSERVATION #7

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

1. There is no non-viable particle count (NVPC) monitoring of the (b) (4) barrier where (b) (4) are opened and loaded onto the (b) (4) filling line. This area has frequent operator intervention and open (b) (4) are present in this area.

2. The (b) (4) NVPC data associated with (b) (4) is taken outside of the barrier used to perform aseptic connections on the (b) (4) filling line.

OBSERVATION #8

Aseptic processing areas are deficient regarding the system for disinfecting the equipment to produce aseptic

conditions.

Review of disinfection of the aseptic filling rooms and equipment used to aseptically fill US market products noted the following:

1. In the (b) (4) filling room the (b) (4) barriers used for (b) (4) and opening the empty (b) (4) were moved into the Grade B area of the room during floor mopping and during disinfection. When they are returned to the Grade A area, they are not disinfected in Grade A before beginning aseptic filling operations.

2. During disinfection of the (b) (4) barrier in the (b) (4) line, an operator was observed to use the same wipe on the outer surfaces (Grade B side) and then inside (Grade A side). The cleaning procedure does not specify any order for the disinfection of surfaces. Moving between Grade B and Grade A areas with the same wiping tool was also observed during disinfection in the (b) (4) vial line.

OBSERVATION #9

There are no written procedures for production and process controls designed to assure that the drug products have the quality, and purity they purport or are represented to possess.

Your firm qualifies employees who perform 100% manual visual inspection of sterile products using separate kits for particles of known sizes and other defects. The kits used to evaluate the employee's ability to detect different particles of known sizes are not representative of the visual inspection process that would be performed during batch evaluation as they do not challenge the ability of employees to identify particles among other defects.

OBSERVATION #10

Labeling of cGMP materials is not adequate to identify labeled material.

On July 17, 2024, frozen sampling bags were observed in (b) (4) C freezer (QC- (b) (4) in QC testing lab (b) (4) located in Building (b) (4) These samples were (b) (4) bulk harvests reserved for adventitious agents and mycoplasma testing. The print on the labels were illegible due to low temperature storage.