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	10/3/2023-10/12/2023*
	FEI NUMBER 3007187282

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Dinesh Singla, Sr. Vice President. Head Corporate Quality & RA

FIRM NAME	STREET ADDRESS
Panacea Biotec Pharma Limited	Malpur, Baddi
CITY, STATE, ZIP CODE, COUNTRY Solan, Himachal Pradesh, 173205 India	TYPE ESTABLISHMENT INSPECTED Sterile and Non-Sterile 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 established, written and followed.

Specifically,

A. Viewing of the aseptic filling area is only available through real time and previously recorded videos. During this inspection reviewed the last aseptic batch recorded on the same line ((b) (4) Injectable Suspension, (b) (4) mg), which uses the same procedures as product for the U.S. market, as well as previously recorded batches of (b) (4) Injection, (b) (4) mg/vial, manufactured from August 28, 2022, to May 31, 2023. The following discrepancies were noted during the review of aseptic practices:

1. Poor aseptic technique was noted during aseptic connection performed during the set-up of equipment for the aseptic filling of (b) (4). The aseptic operator pried off the (b) (4) cover resulting in the forceps contacting the opening of the batch tank. Additionally, during the review of (b) (4) batch (b) (4), a second operator was observed entering the extended LAF area while the aseptic connection was taking place. Having a second person enter the area during the aseptic connection is not address in the smoke studies or media fills.
2. An operator was observed extending the RABs (b) (4) over the running conveyer belt containing open vials during the aseptic filling of (b) (4) Injectable Suspension, (b) (4) mg filled on Sep. 24, 2023. No vials were discarded.
3. Peeling (b) (4) tape was observed being used inside the (b) RAB/RAB for identification of the RAB (b) (4).
4. An operator was seen struggling to open the (b) RAB (b) (4) at (b) (4), prior to setup of filling equipment used during the aseptic filling of (b) (4), lot (b) (4) on Feb. 5, 2023. During An aseptic operator was observed trying to "fix" the seal on the same (b) (4) at 14:31 during set-up of the equipment. This activity is not covered in set-up or any other procedure.
5. Personnel monitoring is performed (b) (4) the *"filling machine parts assembly – open* (b) (4) *"*. During this activity, the operator performed aseptic connections. Prior to being monitored, the operator's gloves are exposed to (b) (4) numerous times.
6. The forceps used to perform interventions at the filling equipment is located directly below the RAB (b) (4) port. The operator

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Sandra A Boyd, Investigator - Dedicated Drug Cadre Muna Algharibeh, Investigator X Sandra A Boyd Investigator - Dedicated Drug Cadre Signed By: 2000367072 Date Signed: 10-12-2023 00:05:02	10/12/2023

needs to extend his hand through the (b) (4) port prior to using the forceps to perform interventions at this location.

7. Aseptic operators tuck the (b) (4) above the mobile LAF when unloading sterile items into the extended Grade A area. Gaps between these (b) (4) were observed during the review of (b) (4) videos.

B. Qualification of aseptic personnel is deficient in that it does not specify activities to be performed during a media fill in order to be qualified.

1. Although (b) (4) operator performs set-up during routine manufacturing, during a media fill, multiple operators divide up this task. Who performs what activities is not documented. This could result in an operator who installs the stopper bowl being qualified to install the filling (b) (4) during routine manufacturing.
2. Qualification of engineers, supervisors or IPQA personnel is not specified in BFI-PD-119 Procedure for Qualification of Person for Working in Aseptic Area (critical Operations), v5, dated 27AUG23.

OBSERVATION 2

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

Specifically,

A. Aseptic processing areas are deficient regarding the system for monitoring environmental conditions. Adequate scientific justification could not be provided for the following:

1. Change control BIC 295/22, dated June 30, 2022, regarded the changing of the NVPC probes located in (b) RAB-(b) (b) RAB-(b):

Probe	Location	Distance from Probe to Location Center	
		From	To
(b) (4)			

The probes were moved to the opposite site of the (b) RABs, away from operator activity and raised approximately (b) (4) higher than their previous location.

2. Setting the non-viable particle (NVP) limits to the following:
   - ASSEMBLY OF FILLING/SEALING EQUIPMENT: Non-viable particle (NVP) excursions are not investigated, and an impact assessment is not performed unless >(b), >(b) (4) excursions (minimum of (b) (4)) or unless a minimum (b) successive alarm events within (b) (4) occurs more than (b) times. Assembly of equipment takes approximately (b) to

(b) (4)

- FILLING: NVP excursions are not investigated, an impact assessment is not performed, and exposed vials are not discarded until > (b) (4) NVP monitoring excursions are obtained. BFI-PD-079 Operation of Online Particle Counter procedure states excursions ≤ (b) (4) are not investigated, and the exposed vials are not discarded. NVP excursions are only investigated and vials are discarded if the excursions exceed (b) (4) or a minimum (b successive alarm events in (b) (4) .
- SEALING: NVP excursions ≤ (b) (4) are not investigated, an impact assessment is not performed, and exposed vials are not discarded. Only excursions occurring more than (b times and lasting over (b) (4) (minimum of (b) (4)) or a minimum of (b successive alarm events in (b) (4) occurs more than (b times would trigger an investigation and discarding of the open and exposed vials. Sealing activity lasts approximately (b) (4) .

B. Aseptic personnel working in the Grade A area are held to Grade B gowning standards when leaving the aseptic area. Although the operator performs open (b) (4) set-up of the (b RAB/RAB and stands in the Extended Grade A area throughout filling, these operators are held to grade B gowning specifications of (b CFU/Plate during their gowning personnel monitoring upon (b) (4) the aseptic area.

OBSERVATION 3
Employees engaged in the manufacture and processing of a drug product lack the training required to perform their assigned functions.

Your visual inspection process is inadequate. You depend on this inspection process to reject critical and major defects, including but not limited to units presenting with particles, seal integrity defects and (b) (4) rejects, etc. Your visual inspection process is used to inspect finished products, including (b) (4) injection (b) mg/vial, (b) (4) # (b) (4) , approved (b) (4) ; and (b) (4) (b) (4) injectable suspension (b) (4) mg/vial, (b) (4) # (b) (4) .

Specifically,

A. Your visual inspection qualification kit lacked the defects for fibers, hair, and cosmetic vial defects such as air bubble, (b) (4) defect, and chipped vial which are all included in the list of "Defects and the Rationale for the Kit Preparation", and required per the firm's Protocol, PB1/MI/QA055-07, titled "Preparation of Qualification Kits and Qualification of Visual Inspectors", dated 08 July 2023.

B. Your firm has established (b) (4) visual inspection qualification kit which is used to qualify visual inspection operators during their initial visual inspection qualification and their (b) (4) re-qualification. Using (b) (4) kit repeatedly may allow operators to become familiar with the kit. Your firm reuses this (b) (4) visual inspection defect kit (b) (4) consecutive times, within a (b) (4) period, on (b) (4) (b) (4) .

C. You do not address inspection fatigue during the qualification and requalification of visual inspectors by testing under worst case

conditions.

D. Discrepancies were observed in the qualification records for two visual inspectors. The end of test (b) overlapped with beginning of test (b). For example:
- (b) Visual inspection initial qualification performed on 12 June 2023: The time for the (b) (4) and the (b) (4) test overlapped by (b) (4).
- Visual inspection initial qualification performed on 16 June 2023: The time for the (b) (4) and the (b) (4) test overlapped by (b) (4).

The (b) (4) visual inspectors performed visual inspection for the following two batches of (b) (4) Injection, (b) (4) mg/vial:
- Batch# (b) (4), manufactured on 11 July 2023, and released to the U.S. Market on 25 Aug 2023.
- Batch# (b) (4), manufactured on 20 July 2023, and released to the U.S. Market on 25 Aug 2023.

E. Your process for the qualification of microbiologists for visual inspection of media fills is deficient. On 29 Apr 2023, (b) (4) microbiologists were qualified on (b) (4) during (b) (4) of (b) (4). Each microbiologist was qualified after identifying (b) defect vials in a total of (b) (4) medial fill vials. Per the firm's protocol PB1/MI/QC 204-00, titled "Protocol for Qualification of Personnel for Visual Inspection of Media Fill Containers and Sterility Samples", effective date 22 Apr 2023, "each microbiologist will be able to finish approximately (b) (4) vials in (b) (4) ". The qualification of the (b) microbiologists would take at least (b) (4) rather than (b) (4).

OBSERVATION 4

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

Specifically,

A. Smoke studies are inadequate in that they do not demonstrate unidirectional air flow in the following instances:
1. The "smoke" is not always positioned above the intervention taking place.
2. The camera angles and distance from activity is not appropriate to thoroughly evaluate the air flow patterns during interventions.
3. The firm tucks the (b) (4) above the mobile LAF when unloading sterile items into the extended Grade A area. A smoke study was not performed to show that this activity does not allow Grade B air to enter the extended Grade A area.

B. Media Fills are not representative of routine production.
1. During the review of approximately 2 hours of filling activities for (b) (4) Injectable Suspension, (b) (4) mg, lot (b) (4), (b) (4) excursions into the (b) RABs unit, using the RAB (b) (4), were not document for:
- Adjustment of the tubing around the filler.

- Extension of the operator's arm into a RAB (b)(4). The operator did not perform an intervention.

2. RAB (b)(4) interventions performed in (b) RAB (b), (loading of the (b)(4)) are not documented. This would include picking up fallen vials or wiping up a spill.

3. PB1/MI/PR019-00 Validation Protocol for (b)(4) of (b) RAB/RAB with (b)(4) Disinfectant Solution Report, dated May 14, 2022, was discrepant in that:
   a. The location of the (b)(4) was not documented during execution of this protocol. The location specified in the Annexure-3 of this protocol for RAB (b) is not feasibly possible as a partition is at that location.
   b. The location of the BIs is not based on the hardest to reach locations. There is no risk assessment performed for the location of the BIs.
   c. BF1-PD-075 Operation and Cleaning of (b) RAB/RAB procedure states to *"ensure that the (b) RAB and RAB (b)(4) are exposed manually or with the help of (b)(4) towards (b)(4) for complete disinfection"*. It is unknown which activity took place during the validation as this condition is not documented. If manual exposure was executed, the duration and how the manual exposure was performed was not documented.

4. The firm does not trend interventions for individual batches.
   a. A summary of interventions is performed (b)(4). This summary only specifies the batches which have the highest frequency for each specific intervention. The trending of individual number and type of interventions occurring for each batch, to support this summary, is not retained.
   b. Only the previous (b)(4) ' worth of data is used in determining the number of interventions to perform in a media fill. This can result in the number of interventions performed during a media fill being less than the number of interventions seen in batches for the previous year.
   c. Run speed, length of filling and hold time prior to filling is not tracked. These activities are represented in the media fill.

OBSERVATION 5
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, non-viable monitoring excursions obtained during machine parts assembly of more than (b)(4) or (b)(4) successive events within (b)(4) were obtained during machines parts assembly in the following batches:

(b)(4) Injection (b)(4) mg/vial

Lot #	Date of Filling	Number of Excursions

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		> (b) (4)	(b) (4) events in (b) (4)
(b) (4)		1	0
		1	0
		1	1
		1	0
		2	0
		1	0
		2	0
		3	0

(b) (4) Injectable Suspension (b) (4) mg

Lot #	Date of Filling	Number of Excursions	
		> (b) (4)	(b) (4) events in (b) (4)
(b) (4)		2	0
		1	0
		1	0

None of these excursions have been investigated as a result of the firm updating BFI-PD-079 Operation of Online Particle Counter procedure for machine parts assembly from: (requiring a deviation if the excursion > (b) (4) or (b) (4) successive events with a duration of (b) (4) in (b) (4)) to (requiring a deviation if excursions of the NVPC particles occur more than (b) (4) events).

OBSERVATION 6

Procedures for the cleaning and maintenance of equipment are deficient regarding sufficient detail of the methods, equipment, and materials used in the cleaning and maintenance operation, and the methods of disassembly and reassembling equipment as necessary to assure proper cleaning and maintenance.

Specifically, cleaning procedures for the cleaning of (b) (4) RAB/RAB and the aseptic area do not contain enough detail to ensure reproducibility between operators.

A. The aseptic filling area consists of (b) (4) RAB (b) (4) through (b) (4) RAB (b) (4), as well as RAB (b) (4) and RAB (b) (4) and the surrounding Grade B area. The associated cleaning procedures do not specify instructions for cleaning/disinfecting from clean to dirty areas, moving from inside to outside when cleaning equipment or the order in which to clean the (b) (4) RAB/RAB units. During the review of cleaning practices performed on Oct. 8, 2023, I observed the operators varying the order of cleaning inside a specific RABs unit as well as

operators cleaning the aseptic area, switching to cleaning the RABs/RAB unit, then back to cleaning of the aseptic area.

B. The (b) RAB (b) and (b) RAB (b) units are located approximately (b) (4) off the floor. During the review of the cleaning which took place on Oct. 8, 2022, the operators did not clean below this area.

C. The RAB (b) (4) were manually manipulated during the (b) (4) of the (b) RAB/RAB unit performed on Oct. 8, 2022. The procedure states to *"ensure that the (b) RAB and RAB (b) (4) are exposed manually or with the help of (b) (4) towards (b) (4) for complete disinfection"*. Details for duration or how to manipulate the (b) (4) during (b) (4) is not included in the procedure and it is unclear how the inconsistent manual manipulations could affect the disinfectant.

D. Cleaning operators were observed standing on (b) (4) during cleaning. These same (b) (4) are used to hold (b) (4) bottles, wipes, environmental monitoring plates and off-line NVP counters during aseptic filling. (b) (4), dated Feb. 15, 2023, failed due to the operator touching the (b) (4) and not sanitizing his gloves during filtration.

OBSERVATION 7

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, sampling plans and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically,

A. Your firm does not perform supplemental destructive testing to ensure the products are essentially free of visible particulates for (b) (4) products including (b) (4) Injection, (b) (4) mg/vial.

B. During a walk-through inspection on 4OCT23, what appeared to be dried (b) (4) contact plates, (lot (b) (4)), were observed as having their media pulled away from the wall of the plate (dehydrated). These plates were used in the following analysis:
   - Surface monitoring for the microbiology laboratory: (b) out of (b) plates were dehydrated.
   - QB1/RQ/BSC/001-06 Viable Particle Monitoring Test Report (Surface Monitoring) for Biosafety Cabinet EO/QC/060, EO/QC/061: Three out of (b) (4) plates read were dehydrated.
   - Routine surface monitoring of the Biosafety Cabinet/3 Way DPB: (b) out of (b) plates were dehydrated.

C. There is no scientific justification for setting the rejection limit for critical, major, and minor defects for (b) (4) products during the 100% manual visual inspection of (b) (4) Injection, (b) (4) mg/vial.

D. Each receiving of sterile gloves, used in the aseptic manufacturing of (b) (4) Injection, (b) (4) mg/vial, is tested for sterility using a method which has yet to be qualified.

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E. Procedure AF-QC-007 Chromatographic Analysis and Documentation Practices procedure requires prior approval from the Head-QC/Designee as well as a justification written on the respective chromatogram for manual integration. This practice is not followed if an analyst manually enters timed integration events to force the specific integration of a peak (such as set touchdown or inhibit integration) for individual samples in a sequence during related substances analysis.

F. Analysts are given permissions within the Empower software to view numerical results in the review window, allowing them to see area counts of peaks while changing the processing methods, without requiring the chromatograms to be saved.

OBSERVATION 8
The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

Specifically, Quality oversight is inadequate in that the aseptic processing areas are not designed to permit viewing through windows to allow the quality unit to provide adequate oversight of the aseptic processing operations. Real time viewing of cameras by Quality, and IPQA personnel located inside the aseptic core evaluate the aseptic practices during filling. These measures are not used to view end of batch environmental monitoring, cleaning of the (b) RAB/RAB or cleaning of the aseptic area.

OBSERVATION 9
Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design and suitably located to facilitate operations for its intended use and cleaning and maintenance.

Specifically, inside the aseptic area used in the manufacture of (b) (4) Injection, (b) (4) mg/vial, a box (approximately (b) (4)), is outlined on the floor of the aseptic area with a (b) (4) paint to mark the placement of the product transfer vessel. This marking is located in both the extended Grade A and Grade B area, directly outside of the (b) RAB/RAB unit. The paint was observed to be flaking off and, in some locations, completely missing. The repainting of this marking last took place February 3, 2022.

***DATES OF INSPECTION**
10/03/2023(Tue), 10/04/2023(Wed), 10/05/2023(Thu), 10/06/2023(Fri), 10/09/2023(Mon), 10/10/2023(Tue), 10/11/2023(Wed), 10/12/2023(Thu)

X Muna Algharibeh
Investigator
Signed By: Muna Algharibeh -S
Date Signed: 10-12-2023 00:09:42

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	Sandra A Boyd, Investigator - Dedicated Drug Cadre Muna Algharibeh, Investigator	X Sandra A Boyd Investigator - Dedica ed Drug Cadre Signed By: 2000367072 Date Signed: 10-12-2023 00:09:02	10/12/2023