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	1/22/2024-2/2/2024*
	FEI NUMBER 3008461619

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Atul Shastri, President - Operations

FIRM NAME	STREET ADDRESS
Eugia Pharma Specialities Limited	34 To 48 Plot No: 4, Unit - Iii; Tsiic
CITY, STATE, ZIP CODE, COUNTRY Sangareddy, Telangana, 502307 India	TYPE ESTABLISHMENT INSPECTED Sterile Drug Manufacturer

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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 and followed.

During aseptic filling operations, procedure HO-CQA-SOP-229 "Clean Room Practices and Aseptic Behaviour" and line specific intervention procedures were not followed:

1. During set-up and aseptic filling of [(b) (4)] Injection batch [(b) (4)] (US market) on January 20, 2024, the following was observed:

   a. An operator performed an [(b) (4)] intervention at approximately [(b) (4)] for [(b) (4)] tubing adjustment (Intervention C43). The operator was supposed to perform the intervention from [(b) (4)] so they did not need to reach over the fill line, but instead [(b) (4)] which required them to lean over the conveyor. The operator did not first sanitize their hands before entering the filling barrier. The operator leaned over open vials that were still present on the line at the time of the intervention. Not all exposed vials were removed. This intervention was not documented and performing this intervention from [(b) (4)] has not been evaluated in smoke studies or media fills.

   b. An intervention was observed at the stoppering [(b) (4)] that required an [(b) (4)] intervention at approximately 10:14 to clear broken vials. The operator used a forceps brought from the Grade B area into Grade A to clear vials without first sanitizing it. Then

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	Justin A Boyd, Investigator Eileen A Liu, Investigator - Dedicated Drug Cadre Anastasia M Shields, Investigator X Eileen A Liu Investigator - Dedicated Drug Cadre Signed By: 2000427259 Date Signed: 02-02-2024 12:55:16	2/2/2024

the operator directly used their hand on sterile parts of the stoppering (b) (4) and on the conveyor. This intervention was not recorded in the batch record. It had not been previously covered in a smoke study or media fill. No personnel monitoring finger dabs were collected at the end of the intervention.

c. An (b) (4) intervention was performed at approximately 10:17 that included putting a zip tie on the tubing connected to the (b) (4) The operator performed the intervention while reaching over the exposed (b) (4) This intervention was inaccurately recorded in the intervention record as C46 (b) (4) adjustment), which does not include installing zip ties and does not require the operator to work directly above the (b) (4)

d. During interventions at the vial (b) (4) to remove broken or fallen vials, the operator used the RABS (b) (4) directly over open vials that were not subsequently removed. The RABS (b) (4) are removed (b) (4) for (b) (4) but otherwise remain on the line where they are sanitized, but not sterilized. The intervention record under reported the number of times this intervention occurred.

When glass breakage occurred and generated glass particulate during this intervention, the operator did not remove surrounding vials that could have been contaminated with glass particles. Glass breakage was observed during interventions at approximately (b) (4) (b) (4) There were no entries in the intervention record of any glass breakage during filling of the batch.

e. An operator reached the RABS (b) (4) over stoppers and the sterile stopper bowl at approximately 13:34. This intervention (C31) was not recorded in the intervention record.

f. Following set-up and before the start of filling, an operator performed an (b) (4) intervention (C16) to adjust the filling machine at approximately (b) (4) working directly above the exposed (b) (4) The operator unnecessarily left the barrier (b) (4) of the (b) (4) open when going to a different part of the filling room.

g. Liquid was observed below the conveyor near the vial (b) (4) area. The operators did not take action to address the liquid, determine the source, or document the occurrence in the batch record.

2. During set-up and aseptic filling of (b) (4) batch (b) (4) (US market) on January 21-22, 2024, the following was observed:

a. An operator reached a RABS (b) (4) over the (b) (4) and open (b) (4) during interventions at approximately 8:10 and 8:26. The RABS (b) (4) are removed (b) (4) (b) (4) for (b) (4) but otherwise remain on the line where they are sanitized, but not sterilized. The exposed (b) (4) were not removed. This intervention was not established in the smoke studies or media fill.

b. An operator performed an intervention (C11) by reaching the RABS (b) (4) directly over sterile stoppers and the sterile stopper bowl to clear stopper jams. This occurred approximately 16 times during the batch, but was only documented in the intervention record 3 times.

c. During installation of the stopper bowl, the hands of the operator were directly over the sterile stopper bowl.

3. During set-up and aseptic filling of (b) (4) Injection batch (b) (4) (US market) on January

21-22, 2024, the following was observed:

a. During an [redacted] (b) (4) intervention (C38) to remove fallen vials at approximately [redacted] (b) (4) on January 24, 2024, an operator reached over open vials that were not subsequently removed. This intervention was not documented in the intervention record.

b. During set-up activities, the operator had their hands, forearms and head in the Grade A area and directly above the exposed sterile [redacted] (b) (4)

c. During interventions (C3) at the vial [redacted] (b) (4) the operator extended the RABS [redacted] (b) (4) over open vials that were not subsequently removed.

d. During interventions at the stopper bowl (C54), the operator used the RABS [redacted] (b) (4) over exposed sterile stoppers and the surfaces of the stopper bowl.

4. During set-up and aseptic filling of [redacted] (b) (4) Injectable Suspension [redacted] (b) (4) Vial batch [redacted] (b) (4) (US market) on January 17-18, 2024, the following was observed:

a. During an [redacted] (b) (4) intervention (C39) to clear jammed stoppers on the stopper track, the operator reached over exposed stoppers and the sterile surfaces of the stopper track with their hand and arm. A second operator using a RABS [redacted] (b) (4) reached over open, filled vials and moved their hand rapidly near open vials.

b. During interventions (C1) to remove jammed and fallen vials in the incoming vial area, the operator reached the RABS [redacted] (b) (4) over open vials. Exposed vials were not removed. These interventions were not documented in the intervention record.

c.During an intervention to adjust the stopper holder (C32), an operator took a wipe, which had been used to wipe a tool in the Grade B area and was on a cart in the Grade B area, and passed it into the Grade A area. It was then used to wipe the conveyor near open vials.

d.During installation of the stopper bowl, the operator repeatedly touched the sterile contact surfaces of the stopper track that move the stoppers to the fill line.

5.During aseptic filling of (b) (4) Injection batch (b) (4) (Canada market) on January 18, 2024, the following was observed:

a.During an intervention to remove a jammed vial at approximately 8:13, the operator forcefully struck a vial with the forceps, causing it to break. No vials in the area were removed and there was no documentation of the intervention or glass breakage. The RABS (b) (4) were observed directly over other open vials that were not removed during this intervention.

b.During an intervention (C17) for adjustment of the (b) (4) near the stoppering station, the operator placed a black (b) (4) which is sanitized, but not sterilized, on the sterile stoppering (b) (4) This intervention was not documented.

c.Liquid was observed below the conveyor near the vial (b) (4) area. The operators did not take action to address the liquid, determine the source, or document the occurrence in the batch record.

6.During machine setup on Line (b) (4) prior to aseptic filling of batch (b) (4) (b) (4) Solution (b) (4) mL, an operator performed an (b) (4) intervention to install the

stopper (b) (4) in the Grade A area. The operator was using their hands to uncover the (b) (4) bowl and then placed their hands directly inside the (b) (4) where they were observed touching the inside walls and base of the (b) (4) The inside of this (b) (4) comes in direct contact with sterilized (b) (4) stoppers used to seal aseptically filled vials.

OBSERVATION 2

Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

1. The Line (b) (4) contains a total of (b) (4) and integrity testing of all (b) (4) is performed after (b) (4) batch. Review of CCTV video recordings showed (b) (4) integrity testing was not performed on (b) (4) during post fill (b) (4) integrity testing associated with aseptically filled (b) (4) Injection batches (b) (4) and (b) (4) Injection batch (b) (4) (all U.S. batches). However, passing integrity test results were generated for all (b) (4) that were not tested.

   Production personnel stated they repeatedly test the same (b) (4) while assigning (b) (4) IDs from other (b) (4) that are not actually tested. This practice was observed to have occurred following batch (b) (4) (2 out of the (b) (4) were actually tested), batch (b) (4) (4 out of the (b) (4) were actually tested), and batch (b) (4) (10 out of the (b) (4) were actually tested). Production personnel stated not all (b) (4) were tested because some of the (b) (4) would not pass.

   On January 26, 2024, (b) (4) did not pass after three attempts to integrity test it, resulting in a product non-conformance investigation. The Line (b) (4) Assistant Manager for Production stated that no previous (b) (4) integrity failures were reported for Line (b) (4) from November 2019 to date.

2. Environmental monitoring data worksheets for Grade A swab surface monitoring associated with

aseptically filled (b) (4) Injection batches (b) (4) and (b) (4) (b) (4) Injection batch (b) (4) (all U.S. batches), documented collection of samples that were never taken. IPQA personnel confirmed swabbing of Grade A (b) (4) tools and equipment surfaces was not performed. There are a total of (b) (4) swab sampling locations including but not limited to "on the (b) (4) (b) (4) "(b) (4) ", and "on the (b) (4) near (b) (4) IPQA personnel confirmed the unexposed swabs were delivered to the Microbiology QC laboratory for processing, incubation, and enumeration. Results of the swabs were reviewed and released with no reported growth for batches (b) (4) and (b) (4) and (b) (4) despite sampling that did not occur.

3. Environmental monitoring data worksheets for Grade A (b) (4) surface monitoring (b) (4) associated with aseptically filled (b) (4) Injection batches (b) (4) and (b) (4) Injection batch (b) (4) (all U.S. batches), documented collection of samples that were never taken. IPQA personnel confirmed that only 10 out of the (b) (4) were sampled for batch (b) (4) None of the (b) (4) were sampled for either batch (b) (4) or batch (b) (4). IPQA personnel stated all (b) (4) media plates (used and not used for sampling) were delivered to the Microbiology QC laboratory for incubation and enumeration. Results for these plates were reviewed and released with no reported growth for batches (b) (4) and (b) (4) and (b) (4) despite sampling that did not occur.

4. (b) (4) non-viable particle counts (NVPC) taken in Grade A and Grade B aseptic processing areas are reported without collecting samples in the documented locations.

   a. Production personnel involved in Line (b) (4) filling (b) (4) Injectable Suspension (b) (4) Vial batch (b) (4) (US market) on January 17-18, 2024, stated (b) (4) Grade A and Grade B non-viable particle count samples are not taken in the fill room at the documented sample locations. Rather, they are taken from an (b) (4) in the aseptic corridor outside of the filling room. These samples are taken after the

corresponding aseptic filling activities have occurred. To get the time and date that appears on the NVPC printout to match, the operators change the time and date on the NVPC instrument by backdating it to when the sample should have been collected.

A production operator stated the samples are taken in the aseptic corridor (b) (4) because the tests do not always pass when taken in the filling room at the designated locations. The operator acknowledged there have been previous failing results that were not reported. These failing printouts were discarded and the tests were repeated in the aseptic corridor (b) (4)

A production supervisor for aseptic filling Lines (b) (4) and (b) (4) stated he was aware of this ongoing practice for the past year. He stated he initially instructed employees to take samples in the aseptic corridor when the NVPC device was not functional because it was not charged. He acknowledged production employees continued the practice.

b. Production personnel involved in Line (b) (4) filling (b) (4) batch (b) (4) (US market) confirmed the (b) (4) Grade A and Grade B nonviable particle count samples were not taken in the filling room. Samples were taken in the aseptic corridor (b) (4) but documents were made to indicate they were taken in the filling room by changing the time and date on the NVPC instrument.

c. Production personnel responsible for (b) (4) NVPC monitoring during the filling of (b) (4) Injection, Batch (b) (4) (US market), on January 18, 2024, stated NVPC samples for the grade B area of Line (b) (4) Block (b) (4) were actually collected in the (b) (4) and not in the filling room in the designated sample locations. The operators changed the time and date on the instrument by backdating it to when the sample should have been collected to get the time and date to match for reporting in the records.

Interviews with production personnel and recordings of previous media fills demonstrate this is an ongoing practice. Media fills performed in September 2022 (Block (b) (4) Line (b) (4) April 2023 (Block (b) (4) Line (b) (4) September 2023 (Block (b) (4) Line (b) (4) November 2023 (Block (b) (4) Line (b) (4) and December 2023 (Block (b) (4) Line (b) (4) similarly showed NVPC samples were not taken at the times and locations documented in the records.

5. (b) (4) non-viable (b) (4) air samples taken in Grade A and Grade B aseptic processing areas are submitted to the microbiology laboratory without exposing the plates at the specified locations. Samples are collected in an aseptic corridor (b) (4) or (b) (4) instead of the specified locations in the filling room. Records are made to appear as if the samples were collected at the specified locations and times in the filling room. For example:

   a. IPQA personnel involved in monitoring during (b) (4) Injectable Suspension (b) (4) Vial batch (b) (4) (US market) on January 17-18, 2024, stated the (b) (4) air sampling documented in the records, including both Grade A and Grade B sample locations, were not exposed in the filling room at the documented locations.

   b. IPQA personnel involved in monitoring during (b) (4) batch (b) (4) (US market) on January 21-22, 2024, confirmed (b) (4) air sampling documented in the records were not exposed in the filling room at the documented locations.

   c. IPQA personnel involved in monitoring during (b) (4) batch (b) (4) (US market) on January 20, 2024, confirmed (b) (4) air sampling documented in the records were not exposed in the filling room at the documented locations.

d. IPQA personnel involved in filling (b) (4) Injection, batch (b) (4) (US market), on January 18, 2024, stated the samples from sampling points (b) (4) (b) (4) in the Grade B area of Block (b) (4) Line (b) (4) were not exposed in the filling room at the documented locations. Instead, these samples were taken in the (b) (4) These samples were submitted to the laboratory and placed on incubation without ever being exposed to the environment in the filling room.

Interviews with IPQA personnel and recordings of previous media fills demonstrate this is an ongoing practice. Media fills performed in September 2022 (Block (b) (4) Line (b) (4) April 2023 (Block (b) (4) Line (b) (4) September 2023 (Block (b) (4) Line (b) (4) November 2023 (Block (b) (4) Line (b) (4) and December 2023 (Block (b) (4) Line (b) (4) similarly showed (b) (4) air samples were not taken at the times and locations documented in the records.

6. Review of the CCTV footage from Block (b) (4) revealed that on January 18, 2024, operators were observed performing post filling, environmental surface monitoring of the Grade A RABs (b) (4) (b) (4) (b) (4) are to touch the media plate (b) (4) The RABs (b) (4) being sampled were observed to never touch the (b) (4) plate. For example:

   a. Block (b) (4) Line (b) (4) (CCTV CAM2) the RABs (b) (4) was placed just above the surface of the (b) (4) never touching the plate. Monitoring was associated with aseptically filled batch (b) (4) Injection, US market.

   b. Block (b) (4) Line (b) (4) (CCTV CAM3) the RABs (b) (4) was observed over the (b) (4) plate during EM monitoring, the (b) (4) never touching the plate. Monitoring was associated with aseptically filled batch (b) (4) Inj. US market.

7. For surface swabbing SOP E3-QC-MIC-GEN-0014, "The sampling area covered should be

greater than or equal to (b)(4) cm^2 but no larger than (b)(4) cm^2 or sampling shall be done such that it covers the maximum surface of the intended location." Review of the CCTV footage from Block (b)(4) Line (b)(4) CAM3, from January 18, 2024, showed an operator performing Grade A swab sampling on the tweezers used to perform interventions on open sterile unfilled vials that are used to hold the aseptically filled drug product. Post filling of Batch (b)(4) (b)(4) Inj. US market, the operator did not touch the surface of one side of the tweezers with the swab and only touched a small section of the other side of the tweezers with the swab.

8. Production personnel only print the passing (b)(4) integrity testing results. If there are failures, leaks, interrupted tests, or alarms, the results are not printed to be included with the batch record for QA review. For example:

   a. Line (b)(4) post (b)(4) integrity for (b)(4) Injection batch (b)(4) failed to include two failing and two leaking results.

   b. Line (b)(4) post (b)(4) integrity for (b)(4) Injection batch (b)(4) failed to include one failing, four interrupted, and three alarms.

9. During processing of chromatograms, only the final version of the chromatogram is being saved after application of manually entered timed integration events.

OBSERVATION 3

Batch production and control records do not include complete information relating to the production and control of each batch.

1. Production personnel used the "Check List for Verification of Product Contact Parts for Line-(b)(4) to document the (b)(4) stopper (b)(4) bowl (IVFSM-001/S017) and the cap (b)(4) bowl (IVCPM-001/S006) were removed, washed, and (b)(4) before being used in the Grade A

[redacted] for the aseptic filling of [redacted] Injection batches [redacted] and [redacted] Injection batch [redacted] (all U.S. batches). Review of CCTV showed the stopper bowl and cap bowl were not removed from the [redacted] during the disassembling step. Production personnel confirmed they had not performed the bowl disassembly, washing, or sterilization between these batches.

2. Per SOP EP3-PR-SOP-048-00, Block [redacted] Line [redacted] are cleaned [redacted] of [redacted] filling activity. The e-log cleaning records document specific times the [redacted] were cleaned for [redacted] of the aseptically filled batches [redacted] and [redacted] and [redacted] Review of CCTV recordings showed none of the [redacted] were cleaned. Production personnel confirmed they did not clean any of the [redacted] Grade A [redacted] associated with these batches.

3. E-log cleaning records documented cleaning activities including mopping, disinfection, [redacted] rinse, and sanitization for the Block [redacted] Line [redacted] vial filling & stoppering machine (PN-IVFSM-001), and vial sealing machine (PN-IVCPM-001). Review of CCTV recordings associated with aseptically filled batches [redacted] and [redacted] showed most of these cleaning activities were not performed. Production personnel confirmed they did not follow the cleaning SOP for Line [redacted] cleaning and they made up the time spent for each cleaning activity documented in the e-log.

4. Review of the intervention records showed production personnel did not document all interventions or document interventions accurately. Production personnel inside the aseptic filling room do not have records. Intervention records are supposed to be documented by a production operator located outside of the production room continuously watching live activities from the CCTV camera. Production operators stated they may stop watching to perform weight checks or to take bathroom breaks, with no alternative person recording while they are not present. Review of recordings identified the following batches had interventions that were not recorded:

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Atul Shastri, President - Operations

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a. (b) (4) batch (b) (4) (US market). There were 24 interventions not recorded. This included (b) (4) new interventions that would have required a product non-conformance investigation. (b) (4) is the maximum permitted times for intervention (C11), clearing of jammed (b) (4) stoppers. The intervention record only documents (b) (4) occurrences, but the intervention occurred approximately 13 more times that were not documented. This would have exceeded the permitted number of interventions and required a product non-conformance investigation.

b. (b) (4) Injectable Suspension (b) (4) Vial batch (b) (4) (US Market) had 21 interventions that were not recorded. This included six instances of clearing of jammed vials with L(b) (4)PN-GP005, which is a new intervention that would require a product non-conformance investigation.

c. (b) (4) Injection (b) (4) mg/mL batch (b) (4) and batch (b) (4) (US market) had a total of 97 interventions not recorded in filling and (b) (4) record.

d. (b) (4) Injection USP (b) (4) mg/vial, batches (b) (4) and (b) (4) (US market), had a total of 167 interventions not recorded in filling and (b) (4) record.

e. (b) (4) Injection batch (b) (4) (US market) had 12 interventions that were not recorded.

f. (b) (4) Injection batch (b) (4) (US market) had 7 interventions that were not recorded.

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OBSERVATION 4

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

1. Block-(b) (4) Line (b) (4) re-qualification and (b) (4) exposure were not adequately performed:

   a. During (b) (4) re-qualification, Chemical Indicators (CI) and Biological Indicators (BI) were not placed at the worst case location of each (b) (4) Folds in the (b) (4) sections of the (b) (4) were observed. However, CI and BI were placed only on the smooth surface of each (b) (4) during (b) (4) qualification cycles.

   b. There is no written procedure on how to use (b) (4) appropriately to prepare the (b) (4) for (b) (4) cycles. Partially (b) (4) and folds in the (b) (4) areas were seen receiving (b) (4) prior to commercial manufacturing.

2. The following deficiencies were observed during review of air flow visualization studies (smoke studies):

   a. Smoke studies for Block (b) (4) Line (b) (4) was not conducted under dynamic condition. Although various interventions were performed, the filling line remained static and did not simulate the commercial manufacturing condition. For example, removal a fallen vial was simulated at the (b) (4) location. The operator removed a fallen vial that was staged next to a few standing vials. However, under the true dynamic condition, the (b) (4) would be filled with empty vials and moving.

   b. For the Block (b) (4) Line (b) (4) the operator's activities in (b) (4) sterile (b) (4)

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stoppers obstructed the path of unidirectional flow (first air) by reaching their arm over the [(b) (4)] The operator also created turbulent air when he shook the canister in quick and short motions to release [(b) (4)] stoppers to the [(b) (4)]

c. On filling Line [(b) (4)] the simulation of removing a jammed [(b) (4)] stopper at the [(b) (4)] stopper bowl did not include simulation of reaching into the bowl.

d. Review of the Air Flow Visualization Studies and the Air Flow Visualization Study Protocol E3-UTL-RQ-P-0032, entitled, "Dynamic Air Flow Visualization Studies", for Line [(b) (4)] Block [(b) (4)] used to aseptically fill vials for the U.S. market, revealed that the study failed to assess air flow while the filling machine was running (dynamic condition).

The firm management stated the same smoke study approach applies to all Block [(b) (4)] and Block [(b) (4)] aseptic fill lines.

3. Qualification of the HVAC system for the Line [(b) (4)] machine did not demonstrate it can maintain appropriate air quality for aseptic filling of US market [(b) (4)] and [(b) (4)] products.

   a. The [(b) (4)] of the [(b) (4)] occurs in an area that has been classified Grade C with no overhead HEPA coverage. No NVPC data has been collected in this area to demonstrate appropriate particle control. Smoke studies have not evaluated whether air flow from this area would allow air to ingress into the Grade A filling zone.

   b. Smoke studies of the Grade A filling zone demonstrate turbulence near the area where containers are filled. The smoke studies do not evaluate if air from surrounding areas can ingress into the filling zone. There has been no dynamic NVPC data of the Grade A

filling zone below the filling (b) (4)

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.

1. Investigation Report APL-FU4-PNC-22-0255 was opened when media fill batch (b) (4) (b) (4)mL vial), conducted on Line (b) (4)in Block (b) (4) was found to have 124 contaminated units. These contaminated units were consistently found in vials located throughout trays (b) (4) (out of (b) (4) total trays). The investigation attributed the media fill failure to a vial breakage that caused spilled media at the stoppering station. Per your investigation, the spilled media from the broken (b) (4)ml vial also traveled the entire (b) (4) foot (b) (4) mm) length of the (b) (4) conveyer and generated visible spillage under the conveyer at the (b) (4) tanks. No contaminated units were observed until more than 11 hours after the initial vial breakage and media spill. Surface monitoring of the filling line did not detect any contaminants. The investigation failed to thoroughly assess any other potential sources of the microbial contamination.

   Similar occurrences were observed during commercial batches. Vial breakage at the stoppering station was observed during (b) (4) Injection batch (b) (4) on January 20, 2024. Spillage at this same location under the conveyer at the (b) (4) tanks were observed during (b) (4) Injection batches (b) (4) (January 18, 2024) and (b) (4) (January 20, 2024).

2. Investigation APL-FU4-PNC-23-0499 was opened due to the reject rate of (b) (4)% during 100% (b) (4) analyzer analysis of (b) (4) Injection (b) (4) vials batch (b) (4) exceeding the reject limit of (b) (4)%. No assignable cause was identified, but the probable caused identified (b) (4) stoppers for some vials following the (b) (4) and

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Atul Shastri, President - Operations	
FIRM NAME Eugia Pharma Specialities Limited	STREET ADDRESS 34 To 48 Plot No: 4, Unit - Iii; Tsiic
CITY, STATE, ZIP CODE, COUNTRY Sangareddy, Telangana, 502307 India	TYPE ESTABLISHMENT INSPECTED Sterile Drug Manufacturer

(b) (4)

CAPA APL-FU4-PNC-23-0499-CAPA-1 was opened to monitor the next 30 batches. During this monitoring, additional batches exceeded the (b) (4)% reject limit for (b) (4) analyzer were identified, including US batches (b) (4) Injection batch (b) (4) (b) (4)%), (b) (4) Injection batch (b) (4) (b) (4)%), and (b) (4) Injection batch (b) (4) (b) (4)%). The CAPA did not identify any assignable cause. There were no identified corrective actions or preventive actions implemented.

The investigation was not extended to the other US market (b) (4) products manufactured in the same (b) (4) that do not receive 100% (b) (4) analysis. There was no investigation of whether vials from these batches similarly lack appropriate (b) (4) due to potential ingress of (b) (4) that could negatively impact the quality and stability of the product. The following US market (b) (4) products are not 100% analyzed for (b) (4) (b) (4) Injection, (b) (4) Injection. (b) (4) Injection, (b) (4) Injection, (b) (4) Injection, (b) (4) Injection, (b) (4) Injection, and (b) (4) Injection.

3. OOS investigation 4OOS230142 was opened for (b) (4) Injection batch (b) (4) at the (b) (4) long term stability conditions, when (b) (4) had a result of (b) (4)% compared to a specification of not more than (b) (4)%. The OOS was invalidated based on a literature review that said the impurity could be formed under (b) (4) The conclusion stated the sample may be OOS because of exposure to the environment during sample preparation. The investigation found no abnormalities in sample preparation and no hypothesis testing was performed to determine if environmental exposure could generate an increase in this impurity. The stability data showed an increasing trend from (b) (4)% at time of release to (b) (4)% at the 12-month timepoint tested prior to the OOS result.

This stated root cause was not extended to investigate commercial manufacturing, to evaluate how long vials that have been filled, but not stoppered, can remain on the line when there are line stoppages.

4. Procedure E3-QC-CI-GEN-0009 "Handling of Out of Trends" was not followed to open investigations based on stability testing results.

   a. (b) (4) batch (b) (4) (US market) exceeded the changes from one timepoint to the next that requires an OOT investigations for the three month timepoint (b) (4) six month timepoint (b) (4) nine month timepoint (b) (4) twelve month timepoint (b) (4) and expiration date (b) (4) No OOT investigations were opened.

   b. The on-going stability study (6 months completed) of the process validation batches for (b) (4) Injection (b) (4) mg/vial, (b) (4) and (b) (4) does not follow the expected trend for assay (by HPLC) in comparison with previous stability studies of the same product. Per your procedure outlined in SOP EP3-QC-SOP-032, OOT investigations are required for results which suggest the potential for OOS results to occur (b) (4) within the same stability study. The following data was obtained for the first 6-months of the (b) (4) shelf life (Specification (b) (4) (b) (4) %) and no OOT investigations have been opened:

      Batch # (b) (4) the assay results are (b) (4) % (initial), (b) (4) % (3M), and (b) (4) % (6M)
      Batch # (b) (4) the assay results are (b) (4) % (initial), (b) (4) % (3M), and (b) (4) % (6M)
      Batch # (b) (4) the assay results are (b) (4) % (initial), (b) (4) % (3M) and (b) (4) % (6M)

5. OOS investigation 04OOS220099, was opened when finished product test for (b) (4) (by (b) (4) for

(b) (4) Injection (b) (4) mg/Vial, Batch # (b) (4) was found to be (b) (4)% on test sample #2 (determination-2 of 2), against the specification of not more than (b) (4)%. As part of your OOS procedure, HO-CQC-SOP-029-00, fresh samples were used and two additional investigational tests performed. The investigational test results found test sample #1 to be OOS with a result (b) (4)%. A second investigation test was run with a result of (b) (4)%. Per your investigation, the OOS result was determined to be invalid when these test results were averaged together to obtain a passing result of (b) (4)%. Your firm does not have a procedure that defines when averages are acceptable.

6. There have been four rejected batches of (b) (4) Injection (US market) for exceeding the limit for individual unknown impurity including (b) (4) (May 2023), (b) (4) (May 2023), (b) (4) (February 2020), and (b) (4) (February 2020). The most probable cause in the 2020 failure investigation included dispensed API that was exposed to room temperature for a prolonged period prior to compounding. A similar root cause was identified in the 2023 failure investigations.

   Other batches have similar total time out of refrigeration as the rejected batches, including US market batches (b) (4) and (b) (4) but these were not considered in the investigation.

   Investigations have not collected data to demonstrate this is the root cause and determine an appropriate limit for the maximum amount of time out of refrigeration before compounding. No time limits have been established in the batch records.

7. 04OOS220227 was initiated on December 1, 2022, for (b) (4) Injection, USP (b) (4) mg/mL, (b) (4) mL (b) (4) Vial) batch (b) (4) Osmolality OOS result. The obtained result was (b) (4) mOsmol/kg and the release specification was between (b) (4) and (b) (4) mOsmol/kg. Phase I investigation identified no obvious laboratory errors. Phase IIa manufacturing

investigation found all stages under the state of control. Phase IIb hypothesis testing did not identify any assignable root cause. The investigation suspected the root cause might be due to improper cleaning of sample (b) (4) hence recommended re-testing. However, the suspicion of dirty sample (b) (4) being the root cause was not confirmed by hypothesis analysis. To note, a total of 31 samples were tested on the same date. Only Batch (b) (4) was found OOS. Your firm's investigation lacked scientific justification or confirming information to support the conclusion that the use of dirty sample (b) (4) was the root cause thus allow to re-test. Nonetheless, on January 10, 2023, a new sample was used for the re-test analysis. Results obtained from the re-test found meeting specification and the original OOS result was invalidated. Batch (b) (4) (Mfg. 11/2022, Exp. (b) (4) units) was dispatched to the U.S. market on (b) (4)

8. 04OOS220186 was initiated on September 29, 2022, for (b) (4) and (b) (4) solution USP (b) (4) batch (b) (4) 3 months long term condition stability study OOS result for Particulate Matter by light obscuration method. The obtained result was (b) (4) particles/mL and the release specification was not more than (b) (4) particles/mL (for > or = (b) (4) µm). Phase Ia investigation identified no obvious laboratory errors. Re-measurement of the original samples was also OOS. Phase Ib investigation found a wet glass measuring cylinder was the probable root cause. During the Phase Ib hypothesis analysis, higher but still within acceptance particle counts were obtained when a wet glass measuring cylinder was used. Based on the hypothesis outcome, the usage of wet measuring cylinder was identified as the root cause. The Phase IIa manufacturing investigation yielded no discrepancies. On October 8, 2022, re-test analysis was initiated and found result within acceptance. The original OOS result was thus invalidated. Your firm's investigation was inadequate in that the Phase Ib hypothesis outcome only suggested but did not confirm the wet glass cylinder was the definitive root cause. Nonetheless, the original OOS result was invalidated. A different sample was used for re-test and the result was found within acceptance. Batch (b) (4) (Mfg. 06/2022, Exp. (b) (4) units) was dispatched to the U.S. market on (b) (4) .

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	1/22/2024-2/2/2024* FEI NUMBER 3008461619

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OBSERVATION 6

Your firm failed to establish adequate written procedures for production and process controls designed to assure that the drug products have the identity, strength, purity, and quality that they are purported or represented to possess.

1. Process performance qualification studies for the US market products do not include evaluation of intra-batch or inter-batch variability. Without acceptance criteria for variability, process performance qualification studies were approved without evaluating sources of potential variation. For example:

   a. During process validation of (b) (4) Injection (b) (4) mg for Block (b) (4)

      i. During assay testing of the filled vials (specification (b) (4) %), the (b) (4) samples of batch (b) (4) were OOS with a result of (b) (4) %. The associated OOS investigation identified no root cause.

      Batch (b) (4) showed intra-batch variability with the (b) (4) sample at (b) (4) % and the (b) (4) sample being (b) (4) %.

      There appeared to inter-batch variability with batches (b) (4) having higher assay values (b) (4) %- (b) (4) %) compared to batch (b) (4) %- (b) (4) %).

      ii. The finished product testing for (b) (4) content varied from (b) (4) % (b) (4) to (b) (4) % (b) (4) compared to a specification of not more than (b) (4) %.

      iii. The (b) (4) impurity varied from (b) (4) % (b) (4) to (b) (4) % (b) (4) compared to a specification of not more than (b) (4) %.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Justin A Boyd, Investigator Eileen A Liu, Investigator - Dedicated Drug Cadre Anastasia M Shields, Investigator X Eileen A Liu Investigator - Dedicated Drug Cadre Signed By: 2000427259 Date Signed: 02-02-2024 12:55:16	2/2/2024

b. During process validation of (b) (4) Injection (b) (4) mg for Block (b) (4) Assay testing (b) (4) was not taken from different points to allow for evaluation of intra-batch variability. Sampling was done randomly with a single reported result for each batch. These assay results appeared to show inter-batch variability with batch (b) (4) at (b) (4)% and batch (b) (4) with a result of (b) (4)%, compared to a specification of (b) (4)%-(b) (4)%.

2. Per process validation protocol E3-PPQ-P-0131 and report E3-PPQ-R-0148 and the prior protocol FU4-SIAT-PQP-006 and report FU4-PPQ-R-0021, for (b) (4) Injection, (b) (4) mg/(b) (4) mL, your firm failed to validate the (b) (4) allowable time limit for line stoppage during vial filling where filled, open vials are exposed to the surrounding air and the affect this exposure has on product degradation.

The following are examples where the line was stopped with exposed unstoppered vials of (b) (4) Injection, batch, # (b) (4) (US market):

(b) (4) Conveyer Closed.
(b) (4) IPQA person went towards filling HMI side.
(b) (4) IPQA plates taken.

OBSERVATION 7

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

1. There are no controls to prevent operators from changing the date and time on the Climet non-viable particle count equipment. Operators stated they had changed the date and time to back date printouts. Additionally, the instrument is capable of storing and backing-up electronic data,

but the function is not used.

2. CAPA APL-FU4-PNC-23-1089-CAPA-4 was opened August 17, 2023, following a product non-conformance investigation that identified the wrong date on printouts from (b) (4) for in process checks. The investigation identified the (b) (4) and dissolved oxygen meters lacked controls to prevent operators from changing the time and date. The CAPA identified the need to upgrade the instruments to improve data security. But no upgrades have been completed as of February 1, 2024, and no interim controls were implemented.

   Additionally, the Oxi 7310 Dissolved Oxygen Meter allows automatic saving of electronic data that can be backed up to a USB or transferred through a connected computer, but these capabilities are not being used.

OBSERVATION 8

Changes to written procedures are not drafted, reviewed and approved by the appropriate organizational unit.

1. Change Control, APL-FU4-CC-21-0673 for (b) (4) Injection, (b) (4) mg/(b) (4) mL, implemented visual inspection for color change, in the filled and sealed vials, (b) (4) (b) (4) sterilization. As part of recall investigation, APLUnit 04/INV/651/20-00, for this same product, which included color change from clear to (b) (4) (indicative of (b) (4) degradation), you performed a review of your control sample visual inspection results. Per this review, color change was not observed in any vials until the (b) (4) Yet, based on this review, you chose (b) (4) as your inspection time point when reviewing the batch for color change prior to batch release.

   The following are examples of complaints submitted for color change from clear to (b) (4) (b) (4) which were received following the implement of the aforementioned change

control:

a.APL/FU4/2022-USA-PCM-00141
b.APL/FU4/2022-USA-PCM-00152
c.APL/FU4/2022-USA-PCM-00158

2.Prior to June 30, 2022, CCTV recording review for aseptic manufacturing operations was part of the batch record review and disposition decision for each batch. Change control APL-FU4-CC-22-0128 eliminated this review for each batch with no documented justification, evaluation of historical data, or assessment of the impact of this change.

Change control CCP-EP-CQA-23-0023 further implemented changes to the CCTV recording process by changing procedure CQA-SOP-GEN-026 on May 4, 2023, that reduced the amount of time video recordings of production activities is saved to permit review from (b) (4) to (b) (4) The justification stated: "For better compliance", but no explanation could be provided to explain how this change would result in better compliance.

OBSERVATION 9

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Your firm's sterility test method suitability and routine test method for the release of (b) (4) drug product (DP) is deficient in that the products are not appropriately (b) (4) for testing. Examples include but are not limited to the followings (b) (4) products:

1. (b) (4) Injection, (b) (4) mg/vial is (b) (4)

instead of (b) (4) as indicated in the finished product Certificate of Analysis (COA). Per COA (b) (4) (b) (4)

2. (b) (4) Injection, (b) (4) mg/vial is (b) (4) instead of (b) (4) (b) (4) as indicated in the COA. Per COA (b) (4) (b) (4)

3. (b) (4) Injection, (b) (4) g/vial is (b) (4) instead of (b) (4) (b) (4) as indicated in the COA. Per COA (b) (4) (b) (4)

Your firm lacked justification for using (b) (4) other than the ones that have been validated through the manufacturing process and represents patient use. You do not have studies to show that (b) (4) (b) (4) is a suitable (b) (4) that can adequately (b) (4) within a validated timeframe.

(b) (4) was used in the original sterility method suitability. However, without knowing its ability to complete (b) (4) the respective (b) (4) drug product, one cannot rule out the possibility that a lower (b) (4) product concentration instead of the intended concentration was tested for inhibition of microorganisms.

***DATES OF INSPECTION**

1/22/2024(Mon), 1/23/2024(Tue), 1/24/2024(Wed), 1/25/2024(Thu), 1/29/2024(Mon), 1/30/2024(Tue), 1/31/2024(Wed), 2/01/2024(Thu), 2/02/2024(Fri)

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	1/22/2024-2/2/2024*
	FEI NUMBER 3008461619

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Atul Shastri, President - Operations

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Anastasia M Shields, Investigator

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DATE ISSUED
2/2/2024