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	4/25/2024-5/3/2024*
	FEI NUMBER 3009883410

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Atul Shastri , President Operations

FIRM NAME	STREET ADDRESS
EUGIA Pharma Specialities Limited	Unit - 2, A - 1128 & B - 1127 Bhiwadi
CITY, STATE, ZIP CODE, COUNTRY Riico Industrial Area, Rajasthan, 301019 India	TYPE ESTABLISHMENT INSPECTED Sterile Drug Manufacturing Site

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 and followed.

1. During aseptic filling operations, procedure EP2-PRD-SOP-002, "Personnel Behavior in Aseptic Area" and line specific intervention procedures were not followed:

   a. During aseptic filling of (b) (4) Injection:

      i. On April 16, 2024, for line assembly and filling on your (b) (4) Line, U.S. market batch (b) (4) Injection (b) (4) gram/vial, operators were observed performing an (b) (4) manual intervention where they used (b) (4) to assemble the (b) (4) (Intervention I-1.3) used to (b) (4) dispense (b) (4) of sterile (b) (4) into the empty sterile vial on the filling line. During this step of set up the operator's arms and upper torso were also observed reaching over the line blocking laminar air flow. This practice was consistent with that observed during line assembly for ROW (b) (4) Injection, batches (b) (4) A similar intervention was observed during media fill batch (b) (4) conducted in July of 2022 and determined by investigation APL-AN-PNC-22-0125 to be the root cause of a contaminated vial

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Anastasia M Shields, Investigator Justin A Boyd, Investigator Vaishali J Patel, Investigator	X Vaishali J Patel Investigator Signed By: 2002647361 Date Signed: 05-03-2024 06:56:46	5/3/2024

and subsequent media fill failure.

ii. During aseptic filling on April 17, 2024, [(b) (4)] gram/vial, US batch [(b) (4)] the operator was observed using the non-sterile RABs [(b) (4)] to perform intervention C-3, "Adjustment of fill weight", where [(b) (4)] were placed into and around the [(b) (4)] used to dispense the sterile [(b) (4)] into each vial. This same intervention was observed and performed in the same manner during the filling of ROW [(b) (4)] Injection, batches [(b) (4)]

iii. On April 16, 2024, operators were observed performing an [(b) (4)] intervention to change out the canister of sterile [(b) (4)] from an empty canister to a full canister. This intervention involves numerous manual manipulations where the operator uses [(b) (4)] and where their arms and upper body are over the filling line and stopper track with exposed stoppers. This intervention is performed up to [(b) (4)] times during aseptic filling of [(b) (4)] Operators were also observed using [(b) (4)] to manually wipe spilled [(b) (4)] off the filling line following this intervention.

b. During filling of [(b) (4)] Injection on [(b) (4)] lines [(b) (4)]

i. During intervention C-67 "Removal of Fallen Vial From Conveyor Before [(b) (4)] on [(b) (4)] line [(b) (4)] operators were observed to touch the rim of an open vial with the RABS [(b) (4)] during batch [(b) (4)] The vial was subsequently left on the line and filled. In other instances of this intervention during batches [(b) (4)] the RABS [(b) (4)] closely

passed directly over open vials that were not 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.

ii. During interventions to remove fallen vials at the (b) (4) operators used the RABS (b) (4) directly over open vials that were not subsequently removed. For example, this occurred during aseptic filling of: (b) (4) Injection batches manufactured on (b) (4) line (b) (4) including US market batches (b) (4) and (b) (4) (b) (4) Injection batches manufactured on (b) (4) line (b) (4) including EU market batches (b) (4)

iii. During (b) (4) of stoppers (intervention I-3) and removal of jammed (b) (4) stoppers (intervention C-17) on line (b) (4) the operator was observed to use the RABS (b) (4) directly over sterile stoppers and the surfaces of the sterile stopper bowl. For example, during aseptic filling of (b) (4) Injection US market batches (b) (4)

iv. On April 25, 2024, while observing an operator performing area cleaning in the Grade A and Grade B areas of line (b) (4) where vials are aseptically filled, (b) (4) the operator's donned sterile gowning was observed to have a hole in the back of the gown on the left side.

c. During aseptic canister filling of bulk (b) (4) batch (b) (4) (EU market):

i. Operators placed forceps and (b) (4) in a (b) (4) in the (b) (4) laminar airflow (LAF) during aseptic sampling of filled containers. The operator reached over the tools and rested their hands directly above the tools before using the (b) (4) to sample sterile product and the forceps to open the sterile canister by contacting the primary closure (b) (4) stopper. Additionally, the operator was observed to place the (b) (4) cap and stopper on the sampling vials or base of the LAF and then reach over it before replacing the product contact stopper on the canister. This sampling of filled containers of (b) (4) bulk occurs approximately (b) (4) times (b) (4) batch during US market batches.

ii. The sterile canisters used for filling bulk (b) (4) (b) (4) were placed on a stool outside of the barrier for opening and closing, rather than on the (b) (4) as specified in procedure EP2-PBA-SOP-065. During (b) (4) and placing of the open canister on the (b) (4) the operator was observed to reach across and disrupt (b) (4) laminar airflow near the open sterile canisters.

d. During aseptic filling of bulk (b) (4) API into sterile canisters:

i. (b) (4) filling, (b) (4) filled canister is opened in a (b) (4) LAF for sampling. The operator places sterile forceps and (b) (4) that contact the product and primary closure in the sampling (b) (4) and leans over these items during operations.

ii. The operator appeared to lean their body near the open container during removal and placing of the (b) (4) stopper and while reaching for the (b) (4) line.

2. Four batches of (b) (4) Injection required corrective interventions to replace (b) (4) (b) (4) after (b) (4) seized due to build up of sterile product leaking from the (b) (4) and drying, causing sticking, following filling line stoppages. Change control CPL-AN-CC-23-0092 (closed June 29, 2023), implemented the spraying of the (b) (4) with sterile (b) (4) throughout the batch whenever the (b) (4) surfaces start to dry. For example, for (b) (4) Injection batches it occurred seven times during US market batch (b) (4) and six times during EU market batch (b) (4)

   The change did not include an assessment to identify an appropriate way to prevent leaking or to apply a lubricant that would not rapidly dry and require repeated interventions during the aseptic filling operations to reapply it. The intervention was approved without evaluating the new intervention in the smoke studies on (b) (4)

   During batches (b) (4) operators did not follow the intervention procedures that require filling to be stopped while performing this intervention of spraying (b) (4) on the (b) (4)

OBSERVATION 2

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

1. In commercial production, sterile (b) (4) API is aseptically filled into canisters, approximately (b) (4) batch. (b) (4) filling, (b) (4) canister is opened and manually sampled by inserting a sampling tool in a (b) (4) LAF. This repetitive manually intensive aseptic intervention for (b) (4) canister is only included in (b) (4) media fill (b) (4)

The filled (b) (4) API canisters are later aseptically dispensed into a (b) (4) (b) (4) The (b) (4) product is filled into approximately (b) (4) canisters (b) (4) batch. (b) (4) canister is opened and manually sampled by inserting a sampling tool in a (b) (4) (b) (4) LAF. This repetitive manually intensive aseptic intervention for (b) (4) canister is only included in (b) (4) media fill (b) (4)

2. Airflow visualization (smoke studies) of Grade A laminar flow do not demonstrate there is appropriate air flow during commercial operations:

   a. During aseptic filling of (b) (4) bulk (b) (4) a (b) (4) laminar airflow unit with (b) (4) flow is placed (b) (4) to the (b) (4) filling area with a (b) (4) laminar flow. Open sterile cannisters are placed near (b) (4) areas. Smoke study evaluations have not thoroughly evaluated this boundary to evaluate any turbulent flow caused by the interaction of the (b) (4) laminar flow units.

   b. The manual opening and aseptic sampling of canisters in a (b) (4) LAF has not been evaluated during smoke studies. This sampling occurs (b) (4) filling bulk (b) (4) API and again (b) (4) filling the (b) (4)

   c. The smoke studies for the areas where filling of API into canisters and for filling of (b) (4) bulk (b) (4) into canisters occurs was not configured the same way as it is used during commercial production. The smoke studies only included (b) (4) canisters, while (b) (4) were typically present in commercial manufacturing. Additionally, a sample (b) (4) and scale are present in commercial

production, but not in the smoke studies. The (b) (4) supply is placed on a (b) (4) in the smoke studies, but was observed to be kept on the (b) (4) LAF during commercial batches.

d. Your airflow visualization study conducted on the (b) (4) Line used to fill (b) (4) Protocol # E2-MIS-VSP-0073, effective June 13, 2023, performed under dynamic conditions, was not representative of commercial production for intervention C3, "Adjustment of fill weight" (C-13 in the smoke study protocol). During our review of commercial production for US batch (b) (4) and ROW batches (b) (4) (b) (4) an operator was observed performing this intervention multiple times where they used the RABs (b) (4) and reached their entire arm across the filling line to manually manipulate and adjust the fill weight and (b) (4) In your smoke study, this intervention was performed using forceps, in lieu of the operator's arm, to reach across the line and simulate this intervention. Your media fill study conducted in November 2023 per protocol E2-(b) (4)-APSP-0001, shows this same intervention, C-3, being performed through the RABs (b) (4) using a small tool, where the operator has minimal contact with the (b) (4)

OBSERVATION 3

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

1. Investigation APL-AN-PNC-22-0125 was opened when one turbid vial in (b) (4) #64, produced during the aseptic process simulation for the (b) (4) Line, performed in July 2022, was found on (b) (4) (b) (4) of incubation. The organism was identified as *Staphylococcus haemolyticus*. This line is used to aseptically fill the U.S. marketed drug product, (b) (4) gram and (b) (4) mg vials. Your

investigation references the time frame of 13:43 to 14:39 when you believe the (b) (4) containing the turbid vial was filled. Your investigation documented that 14 of the 15 interventions performed during that time frame were (b) (4) interventions. It attributes the root cause to be (b) (4) intervention C-37, "Replacement of the (b) (4) using the rational that this is a non-routine intervention. In your investigation you did not fully assess the other 13 (b) (4) interventions performed during that time frame. You also did not address the risk to commercial product as this intervention was observed in the media fill recording to include the same manual manipulations as those observed while reviewing commercial production, machine assembly, specifically intervention I-1.3 "Assembly of the (b) (4) Your corrective action was elimination of the intervention, "Replacement of the (b) (4) but it failed to include an assessment of the current interventions that are performed during set up and filling, which require the same or similar manual manipulations, including ways to augment those similar inventions to reduce risk to the product.

2. On October 07, 2023, OOS Investigation ANOOS230014 was opened when the following results for (b) (4) content, by ICP-OES, for (b) (4) Sterile Bulk (b) (4) were obtained against the specification of (b) (4) %:

   Batch (b) (4) %
   Batch %
   Batch %

   Your firm's laboratory investigation attributed the OOS results to be due to (b) (4) (b) (4) in the sample container resulting in the test sample containing (b) (4)

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On March 24, 2023, OOS Investigation ANOOS230004 was opened when the Assay result (by HPLC) for (b) (4) Sterile Bulk (b) (4) was found to be (b) (4) % on an (b) (4) basis against the specification of (b) (4) % and (b) (4) % on a (b) (4) basis against the specification of (b) (4) %. Your investigation conclusion determined that the OOS result was due to minor (b) (4) (b) (4) (potential (b) (4) of API), within the sample.

This bulk (b) (4) is filled into canisters up to (b) (4) in size, in which it is allowed to sit for an undefined length of time prior to being filled into individual vials. Each of these investigations and the associated manufacturing investigations failed to assess the length of time the bulk containers (b) (4) remained in storage prior to sampling. The investigations were not extended to establish whether similar (b) (4) occurs in the commercial containers.

Additionally, your firm has not established bulk (b) (4) hold times, supported by bulk hold studies, for your (b) (4) to show that the (b) (4) does not (b) (4) degrade over time to an extent that adversely impacts the quality of the finished sterile drug product.

For example, (b) (4) bulk lot # (b) (4) were permitted to sit for up to 7 months as a bulk (b) (4) in (b) (4) canisters before being filled into vials. The following finished drug product batches for (b) (4) gram/vial were filled using this bulk (b) (4) and distributed to the U.S. market: (b) (4) (b) (4)

OBSERVATION 4

Separate or defined areas to prevent contamination or mix-ups are deficient regarding the manufacturing and processing operations.

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1. Your firm's containment control and monitoring programs are inadequate to address the possibility of cross contamination of (b) (4) pharmaceutical products (i.e. (b) (4) APIs and finished dosage forms) with the (b) (4) and vice versa. Prior to introducing (b) (4) on site on (b) (4) and beginning manufacturing operations for (b) (4) in (b) (4) on November 28, 2023, the following controls were not established:

    a. Your firm did not develop and implement an analytical method capable of detecting cross contamination of (b) (4) in the (b) (4) products.

    b. Your firm did not develop and implement an analytical method capable of detecting the presence of cross contamination of (b) (4) in the (b) (4) manufacturing facilities (b) (4) nor have you identified appropriate monitoring locations to assess for potential cross contamination.

    c. Your firm did not establish/validate a deactivation agent for decontamination of the (b) (4) product or a contingency (corrective action) procedure that will be implemented if contamination is found which exceeds established acceptable limits in the manufacturing blocks or other common areas.

2. Prior to introducing (b) (4) your firm did not establish thorough containment practices regarding the handling and movement of personnel, equipment, and materials, through common areas. For example:

    a. Your firm also did not restrict personnel working in the (b) (4) manufacturing block (b) (4) from entering the (b) (4) manufacturing blocks on the same

day, and vice versa. Your firm did not have dedicated personnel for each facility.

Your procedure, EP2-PLC-SOP-001-01, "Plant Entry and Exit", does not state that personnel working in one block cannot enter the other.

b. The QC and microbiology laboratories are shared between the (b) (4) facilities. The microbiology laboratory is located in the (b) (4) block where (b) (4) is manufactured. Microbiology samples (EM, bioburden, (b) (4) etc.) taken in the (b) (4) (b) (4) block are incubated and read using shared incubators and laboratory areas with the (b) (4) block. Personnel entering in the laboratory are not restricted from entering production buildings and common areas used be production employees.

c. Paper batch production and control records and environmental monitoring records for (b) (4) products were moved from their respective manufacturing blocks through the campus to the administration building for storage. New documents issued to the respective manufacturing blocks are issued from this shared document control area. Personnel working in the administrative and document control area are not restricted from entering production buildings and common areas used by production employees.

d. Tools such as hammers, wrenches, screwdrivers, etc. which are used to perform general maintenance and repairs throughout the campus and all manufacturing blocks are not dedicated to (b) (4) areas. Maintenance personnel working in the area where tools are stored are not dedicated and are not restricted from entering production buildings.

e. There are separate canteens for workers to use for meal breaks; however, the entrances to these canteens have no controls to prevent workers in the (b) (4) block from using

the same canteen as those working in the (b) (4) blocks, and vice versa.

f. Your firm constructed a new manufacturing/filling block (b) (4) for filling the product (b) (4) injection. This (b) (4) manufacturing block and the manufacturing block for (b) (4) are separated by (b) (4) The warehouse entrances for receiving material are located (b) (4) (b) (4)

g. Personnel working in the (b) (4) production areas pass through a common plant entry and exit area.

h. Facility meeting and conference rooms are common areas between employees that have been in (b) (4) areas. Personnel that have been in these common areas are not restricted from entering production areas.

OBSERVATION 5

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. Appropriate statistical sampling plans that would permit evaluation of intra-batch variability have not been used during process performance qualification studies. (b) (4) data points are taken from (b) (4) without justifying whether this sampling plan could detect variability for (b) (4) Injection from different points on the (b) (4) or from different (b) (4)

2. Your process validation study for (b) (4) Protocol E2-PPQ-P-0031, (b) (4) Injection used (b) (4) sample from the (b) (4) consisting of (b) (4) vial, to assess the (b) (4) content (b) (4) test) of the product. Your sampling plan was not statistically derived where intra batch variability could be evaluated and detected throughout the batch.

OBSERVATION 6

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the equipment to produce aseptic conditions.

On April 29, 2024, (b) (4) cleaning wipes packaged and ready to be used for (b) (4) aseptic cleaning in the Grade A area of the (b) (4) Injection (b) (4) filling line (b) (4) had loose threads and fibers on them. The same wipes are also used for (b) (4) cleaning in the (b) (4) Injection manufacturing lines (b) (4) Upon receiving, the wipes are not inspected for the presence of loose threads and fibers.

OBSERVATION 7

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

Surface monitoring of the filling and stoppering machine is not performed in a timely manner following the completion of aseptic filling operations to ensure the data is representative of the environmental conditions at the time of filling. For example:

1. Following the end of filling for (b) (4) Injection batch (b) (4) at 9:55 on April 20, 2024, the surface monitoring of the filling machine did not start until (b) (4) on April 21, 2024.

2. Following the end of filling for (b) (4) Injection batch (b) (4) at (b) (4) on March 12,

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2024, the surface monitoring of the filling machine did not start until 15:46 on March 13, 2024.

***DATES OF INSPECTION**

4/25/2024(Thu), 4/26/2024(Fri), 4/29/2024(Mon), 4/30/2024(Tue), 5/01/2024(Wed), 5/02/2024(Thu), 5/03/2024(Fri)

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