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 ORAPHARMInternational483responses@fda.hhs.gov	12/13/2022-12/23/2022
	FEI NUMBER 3010254278

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Sanjay Kumar Jain, Ph.D.

FIRM NAME	STREET ADDRESS
Amneal Pharmaceuticals Private Limited	Plot no. 15, PHARMEZ (Special Economic Zone) Sarkhej-Bavla Highway No.8A, Matoda, Ta: Sanand District
CITY, STATE, ZIP CODE, COUNTRY Ahmedabad, Gujarat 382213, India	TYPE ESTABLISHMENT INSPECTED Pharmaceutical Parenteral 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.

The observations noted in this Form FDA-483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the quality system requirements.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

1. The Personnel behavior and practices in aseptic process area, document number AP-SMC-020, establish the responsibility of the In Process Quality Assurance (IPQA) department, for example, "To verify the practices in aseptic process area as per checklist." This includes to, (b)(4) (b)(4) in aseptic area according to the do's and don'ts checklist" and as confirmed by the Senior General Manager Quality Assurance the visual verification is performed "at least" (b)(4) The IPQA Manager & Senior General Manager QA explained that the visual verification is normally accomplished in about (b)(4) for both the aseptic fill line and the (b)(4) area. There are no documents to describe the rationale to support how and why the (b)(4) "verification" of the aseptic filling process and the separate (b)(4) process, is adequate; and the do's and don'ts verification records do not delineate (b)(4) Grade A areas. In addition,

   a. Mindful of the once (b)(4) QA visual verification of the do's and don'ts checklist, please see the summary table below. The summary table list the number of manufacturing days during the year that were used to manufacture the finished sterile drug products and the number of times that QA performed a visual verification of the aseptic filling process. Excluding the number of visual verifications performed (b)(4) noted in the summary, QA does not routinely observe the aseptic filling process operations for the remaining days of the year.

SEE REVERSE OF THIS PAGE	Thomas J. Arista – Investigator/NE	DATE ISSUED 12/23/2022

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Parenteral Unit	*Floor*	*Year 2021*	*Visual Verifications performed by QA*	*Year 2022*	*Visual verifications performed by QA*
(b) (4)					

2. To perform the requisite aseptic set up operations of the aseptic fill line (b) (4) Parenteral, the production operator accesses the (b) (4) Restricted Access Barrier System ((b) (4) RABS) via the fill equipment access panel [e.g., (b) (4)] that is approximately (b) (4) A production operator was observed having to raise both arms and by turning the entire body sideways was able to enter and exit this specific Grade A area. Due to the size of the access panel opening, it appears that it provides production personnel limited space to perform the required aseptic set up activities.

3. Production operators wear protective eyewear (i.e., goggles) during the aseptic processing of a finished drug product. With the Senior General Manager of Quality Assurance, we observed four production operators wearing goggles during the aseptic processing in the (b) (4) RABs. The goggles were not appropriately worn e.g., there were open spaces observed where the goggle straps are tightened and an open space at the bottom of the goggles such that the face of the operators could be observed.

4. The Summary Report for Disinfectant Qualification, document number AP-QCM-MIS-43-00, dated Aug 23 , 2022, consists of a summation regarding the "obtained results for the execution of the disinfectant validation and to have a documentary evidence and conclude that (b) (4) area capable enough to achieve acceptance criteria mentioned in the approved protocol when microorganisms are challenged with defined contact time and concentration. Shelf-life/hold time is also established and summarized in this summary report." There were various "clean room work surfaces that were used in the study". However, the disinfectant qualification studies did not include the following materials i.e., the (b) (4) cart's (b) (4) wheels, the (b) (4) that is used to seal the (b) (4) the (b) (4) that are used in the (b) (4) RABS, the (b) (4) gowning material, and the specific type of (b) (4) used in the study is not known. In addition,

a. There is a separate Validation study to evaluate the effectiveness of disinfectant for surfaces (b) (4) (b) (4) document number AP-QCM-MIS-039-00, dated 08 Feb 2020. "The purpose of study is to establish the documented evidence to demonstrate the efficacy of disinfectant agents to reduce the microbial load from the surfaces when used at recommended dilutions for the routine disinfection applications." The study did not include all of the clean room surfaces as in the August 2020 disinfection qualification validation studies e.g., (b) (4) (b) (4)

5. The aseptic fill lines in (b) (4) include the use of (b) (4) (b) (4) that assist to diffuse the HEPA filter air into the Grade A (b) (4) of the RABS. The Vice President Sterile Manufacturing & Operations confirmed that the (b) (4) are not cleaned and sanitized.

6. The Rationale for Environmental Monitoring dated 14 April 2015, establishes that "A well-defined comprehensive environmental monitoring program is regarded as an essential part of aseptic processing. A good environmental monitoring program will provide evidence that the facility and its equipment are operating under defined controlled conditions. It will provide information on the effectiveness of applied controls measures such as" for example, "aseptic technique, gowning practices, process controls, facility design and maintenance" as well as "cleaning/sanitization procedures." The following are not included in the EM sampling program e.g., (b) (4) (b) (4) for the aseptic fill lines in the (b) (4)

II. In addition,

a. A (b) (4) cart is used when performing the EM sampling in aseptic fill line (b) (4) in Parenteral (b) (4) With the Senior Vice President India Quality Management, we observed the trolley wheels with what appeared to be a build-up of some form of dirt like material. The Senior General Manager of Quality Assurance confirmed that the cart's wheels are not subject to EM sampling.

b. There is an (b) (4) Unit ((b) (4) speaker, (b) (4) , with a semipermeable polyester membrane is used to communicate from the Grade B area, that surrounds the aseptic fill line (Grade A) (b) (4) and the control non-classified (CNC) personnel corridor. With the President of Operations & the Senior Vice President of Quality Management India we observe in the (b) (4) unit's metal interior surface an unknown substance with a dark color, which appeared to have a mold like appearance. It was confirmed that the (b) (4) unit is not subject to any form of EM sampling.

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7. An EM sample is taken from the aseptic fill line (b) (4) (b) (4) the (b) (4) of the access panel is sampled. The EM sampling does not consist of any other area within the confined space of where the production operator was observed raising both arms and turning the entire body sideways to enter and exit this specific Grade A area.

8. The Handling of Microbial Isolates, document number, ACM-QCM-004, dated 15 Jun 2022, the general procedure/requirement establish that the "Microbial identification shall be carried out for data trending purpose and to assist product and facility contamination investigations and in the development of effective countermeasure and to maintain the area/process/system in the state of control." The "Microbial identification of environment isolate aids in the evaluation of cleaning/ sanitization effectiveness, personnel training, deterioration and malfunction of AHU system and facilities." The EM and personnel monitoring samples for the Grade B area is described in the Frequency of Microbial Isolate Exhibit-II i.e., for routine plates observation to (b) (4) (b) (4) (b) (4) The Assistant Manager QC Microbiology explained the EM samples are visually compared to the isolate library, which consist of approximately (b) (4) (b) (4) photographs of previously isolated microorganisms that are (b) (4) media. The Assistant Manager QC Microbiology added, if the microorganisms look like the (b) (4) photograph, then no further microbiological identification is performed. Regarding the (b) (4) sample, is it used to determine, for example, if cleaning is acceptable, evaluate the movement of personnel, if the EM program is recovering the same microbial flora from (b) (4) The identification of the unknown microbial isolates' genus and species are based on the (b) (4) photographs.

9. The Environment Monitoring Program (b) (4) Aseptic Manufacturing Are (b) (4) dated 21 Mar 2017 describes the intent "is to evaluate the potential risk prominent to aseptic areas" and "to capture the potential viable contaminants in the aseptic areas with respect to, Risk identification and justification for environment monitoring location and frequency" and "To evaluate the existing and additional location to identify the worst and representative location". The document lists "Site Justification". The Assistant General Manager QC Microbiology confirmed that there are no written evaluations regarding the EM sample site locations to support the "Site Justification".

10. The 18 Dec 2020 Quality Risk Management – document Environment Monitoring Location at (b) (4) of (b) (4) describes an evaluation was performed "to determine current rationalized sample locations for viable and non-viable monitoring during environmental monitoring programme is adequate."

The QRM assessment document is silent with respect to providing language that instructs to observe the classified manufacturing areas and the aseptic processing operations. The lack of observing the aseptic filling process provides a limitation with respect to performing a comprehensive trend analysis of the EM sample locations. The Senior Manager of IPQA confirmed that the QRM assessment consisted of reviewing the 21 Mar 2017 Environmental Monitoring Program (b) (4) Aseptic Manufacturing Area (b) (4) document.

11. The Non-viable particle monitoring is cleanrooms of (b) (4) facility, document number AP-QCM-087 describe the frequency of monitoring the Unidirectional air flow (UAF) Grade A, (b) (4) Grade A clean air stations. However, as confirmed by Senior Manager of IPQA, the NVP monitoring does not include obtaining particle measurements during the aseptic filling process e.g., when production personnel are performing the various manual activities in an "In Operation" (dynamic) state. Please note for the aseptic fill line in the (b) (4) there are (b) (4) (b) (4) and for the aseptic fill line in the (b) (4) (b) (4) there are (b) (4) (b) (4) that are used during the aseptic filling processes. In addition,

    a. There are (b) (4) UAF units (Grade A) that are used in the aforementioned aseptic processing filling lines. The Senior Manager of IPQA confirmed there is no NVP monitoring of UAF Grade A areas during the dynamic operations e.g., when production personnel perform their respective responsibilities.

    b. There is no record to document the location & height of where the NVP monitoring is performed for the Grade A (b) (4) area to assure that the particle measurements are near the critical aseptic operations that are performed during the (b) (4) process.

    c. Regarding the location and distance of the (b) (4) for aseptic fill line in (b) (4) and for the (b) (4) aseptic fill line there is an (b) (4) located near the (b) (4) station and an (b) (4) located at the capping station. The distance between the (b) (4) (b) (4) is approximately (b) (4) cm and (b) (4) cm, respectively. There is no (b) (4) within the (b) (4) in order to monitor for the presence of particles, which precludes the company from assuring that Grade A conditions are maintained and to assure that the finished drug products are in a state of control prior to the glass vials being sealed.

    d. There are (b) (4) (b) (4) that are used, for example, to transfer (b) (4) material, fill room equipment parts from the (b) (4) Grade A) area to the aseptic fill lines in the (b) (4) (b) (4) manufacturing operations. The Senior Manager of IPQA

confirmed there is no NVP monitoring performed of the (b) (4) Grade A (b) (4) during dynamic operations.

12. The Air Flow Visualization Study & Recovery Study, document number AP-SM-MIS-05-04, describes the purpose for the air flow, for example (b) (4) The Air Flow Visualization Study, document number AP-SM-MIS-01-07, objective is to (b) (4) (b) (4) (b) (4) The acceptance criteria include for example, (b) (4)

The airflow visualization studies (video) document numerous instances where the unidirectional airflow and the personnel's manual operations impact upon the airflow that could not be observed due to either the angle and position of the video camera, or due to an obstructed view caused by the filling equipment and/or due to a lack of smoke over the production personnel's manual arms & hands operations. The concern is applicable for the aseptic process fill lines for (b) (4) The following are examples of the (b) (4) aseptic fill line (please note this is not intended to be an all-inclusive list of examples),

a. During the machine breakdown & maintenance work, the video documents airflow (b) (4) and the creation of (b) (4).
b. During the assembling of vial sealing machine, there are (b) (4) on the (b) (4) of the (b) (4) (b) (4) equipment base.
c. In the capping station there are (b) (4) at the (b) (4) of the (b) (4) shaped structure that is (b) (4) box.
d. Regarding the Grade A (b) (4) that are used during the aseptic filling process, there were no "In Operation" (dynamic operations) personnel activities performed to demonstrate that the manual operations do not negatively impact upon the unidirectional flow of air.
e. During the sterile API from dispensing containers to (b) (4), unable to observe the manual activities performed by production personnel to assure and verify that the unidirectional airflow is maintained.
f. During the aseptic connection & transfer of (b) (4) unable to observe the aseptic manual operations performed by production personnel to assure and verify that the unidirectional airflow is maintained.

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g. There is an air flow evaluation to demonstrate that air exits & moves from a positive air pressure area toward a less positive air pressure area. However, the evaluation did not include a simulation of a routine operations e.g., (b) (4) to allow the entry of production personnel and entry of a (b) (4) Rather the air flow visualization consisted of (b) (4) by about (b) (4)

13. There are individual Air Flow Visualization Study & Recovery Studies performed for the aseptic fill lines, the UAF units, (b) (4) and the microbiology sterility tests areas in (b) (4) (b) (4) that have been reviewed and approved by personnel from IPQA, Maintenance, Production and Validation Departments. However, as confirmed by the individuals who reviewed and approved the air flow visualization studies there are no written evaluations regarding the above departments' assessments.

14. There is a (b) (4) in aseptic fill line (b) (4) that is used by personnel to move from the fill room to the (b) (4) area and capping station. The Intervention Trend Report for Vial Filling Line (b) (4) (b) (4) from 01 Feb 2022 to 31 Jul 2022, dated 16 Sep 2022, document that the minimum & maximum number of intervention occurrences consisted of 07 and 37 times, respectively during the manufacturing processes. The Intervention Trend Report for Vial Filling Line (b) (4) (b) (4) from Jan 2022 to Jun 2022, dated 16 Aug 2022, document that the minimum & maximum number of intervention occurrences consisted of NIL and 22 times, respectively during the manufacturing processes. The intend of the intervention trend reports is "To evaluate the actual executed interventions in the GMP batches with respect to allowed or permitted maximum number of interventions" and that the "Evaluation helps to control on the actual requirement of interventions or to identify any new interventions." Notwithstanding the above considerations, there is no airflow evaluation performed for the (b) (4) to demonstrate that the unidirectional air flow is acceptable and that the air flow is not compromised within the Grade A area.

15. As previously reported in the preceding observation, production personnel access the aseptic fill line (b) (4) (b) (4) via the (b) (4) RABS access panel [e.g., (b) (4) that is approximately (b) (4) (b) (4). The body movements performed by the production operator to enter and exit the Grade A environment have a direct impact upon the unidirectional air flow. There is no air flow evaluation regarding the above production personnel activity to assure that the air flow is unidirectional and to assure that there are no (b) (4) and/or air turbulence created by the body movements while in the Grade A area.

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16. As confirmed by the Assistant General Manager Project & Engineering Department, there are no Architectural Layouts (As Build) engineering diagrams for the HVAC units in (b) (4) manufacturing facilities. In addition,

    a. There is not Architectural Layouts for the (b) (4) Restricted Access Barrier System ((b) (4) RABS) that is used to aseptically manufacture (b) (4) finished drug products in the (b) (4) aseptic fill line in (b) (4) or for the (b) (4) RABS aseptic fill lines in (b) (4)

    b. There is a Piping & Instrumentation Diagram (P&ID), identified as PR-2612496 4026295 – Amneal (b) (4) dated 19 April 2016, regarding the (b) (4) RABS in the (b) (4) The Senior General Manager of Quality Assurance confirmed that the Original Equipment Manufacture's (OEM) 2016 P&ID has not been reviewed and approved by the Quality Unit.

    c. Change Control document number CC-AMN-21-2316, dated 1 Nov 21, required that the (b) (4) (b) (4) Which included a change of (b) (4) (b) (4) (b) (4) The above AHUs are used in the aseptic fill room on the (b) (4) (b) (4) As confirmed the Assistant General Manager Project & Engineering Department, there are no engineering diagrams regarding the changes that were made.

    d. Regarding engineering diagrams of the manufacturing facility and production equipment e.g., Architectural Layout (As Built) or P&ID diagrams, the Assistant General Manager and Vice President Project & Engineering confirmed that there is no document/standard procedure (e.g., good engineering practices) to describe and establish basic & fundamental engineering requirements.

***DATES OF INSPECTION**
12/13/22, 12/14/22, 12/15/22, 12/16/22, 12/17/22, 12/19/22, 12/20/22, 12/21/22, 12/22/22, 12/23/22

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."