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	12/3/2018-12/14/2018* FEI NUMBER 3008461619

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Rajesh Kulkarni , Vice President Quality

FIRM NAME	STREET ADDRESS
Aurobindo Pharma Limited - Unit IV	Plot Nos. 4, 34 To 48, Epip, Tsiic, Ida, Pashamylaram, Patancheru Mandal, Sangareddy
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Medak District, Hyderabad, Telangana, 502307 India	Manufacturer of Human Drug Products

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DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

OBSERVATION 1

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

Specifically,

1) The following conditions were observed after evaluating environmental monitoring procedures (prescribed for filling-line set-up/assembly and filling operations), the execution of smoke studies, and the execution of aseptic filling operations in different filling rooms in the firm's (b) (4) Block:

a) Procedures establish the collection of dynamic air samples in Grade-A areas (within filling line RABS enclosures) and Grade-B areas (external to the filling line RABS enclosures) at the frequency of (b) (4) sample per location per (b) (4). The air sampled volume per location is (b) (4) L ((b) m^3), which takes approximately (b) (4) to collect. There is no assurance on how these active-air sample results are representative of the air quality throughout the filling (b) (4), which endures up to (b) (4).

b) In Filling Line (b) (Filling Room # (b) (4)):

1. No dynamic air samples are collected near the vial stoppering station. Note: a dynamic-air sample is collected near the stopper (b) (4) area, which is physically separated from the vial

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stoppering station by a physical barrier.

2. (b) (4) sample is collected from the (b) (4) surface of the (b) (4) that opens into the (b) (4) conveyor / (b) (4). However, during interventions in which the operators have to go through the (b) (4) conveyor area (from one side of the filling line to the other side), (b) (4) of the enclosure are opened exposing the (b) (4) surface of the (b) (4) to Grade-B conditions (note: during this intervention the (b) (4) go through a Grade-A area). There is no rational to justify the collection of surface samples from the (b) (4) surface of (b) (4) of the (b) (4) opened during the intervention.

c) In Filling Line (b) (Filling Room # (b) (4)), no surface samples are collected from the (b) (4) (b) (4) and from the (b) (4) stopper bowl.

d) In Filling Line (b) (Filling Room # (b) (4)):

1. (b) (4) of the settling plates used for continuous air monitoring in the (b) (4) area and the settling plates used to monitor the filling (b) (4) area ((b) (4) of the filling (b) (4) area) are placed (b) (4) and not at working level, close to the areas intended to be monitored by the plates. In addition, no settling plates are placed near the vial stoppering station and in the area where (b) (4) stoppers are handled (i.e., bag (b) (4) and loading).

2. No dynamic air samples are collected in the LAF enclosure area where (b) (4) stoppers are handled (i.e., bag (b) (4) and loading). In addition, no surface samples are collected from the (b) (4) surface of the LAF enclosure barriers and from the (b) (4) surface of the (b) (4) used to load stoppers into the stopper (b) (4). Note: to load (b) (4) stoppers into the (b) (4), the stopper bag is placed in the LAF enclosure located in front of, but physically separated from the (b) (4). A (b) (4) is used to load the stoppers into the (b) (4). To load the stoppers, the operator opens the (b) (4) of the LAF enclosure (i.e., which opens to a Grade-B area) and introduces (b) (4) into the LAF enclosure to (b) (4) the bag, and load the

stoppers into the stopper (b) (4) .

e) In Filling Line (b) (Filling Room # (b) (4) – used for the filling of syringes):

1. The settling plate and the dynamic-air sampler (used for continuous passive-air and dynamic air monitoring) are placed on the "(b) (4) of the filling machine". This position is not close to the syringe-tub infeed area where constant operator intervention occurs (i.e., syringe-tub loading intervention).

2. No settling plates are used and no dynamic air samples are collected near the syringe filling and stoppering areas.

3. No surface samples are collected from the (b) (4) surface of the LAF enclosure used for (b) (4) (b) (4) loading interventions. Note: (b) (4) stopper bags are introduced into a LAF enclosure located in front of but physically separated from the machine LAF (where the (b) (4) (b) (4) is located). A (b) (4) is used to load the stoppers into the (b) (4) . To introduce the stoppers, the operator opens the (b) (4) of the LAF enclosure (i.e., which opens to a Grade-B area) and (b) (4) the LAF enclosure.

f) In Filling Line (b) (4) (Filling Room # (b) (4) – used for the filling of (b) (4) solutions in (b) (4) containers), no surface samples are collected from the surface of the (b) (4) that surrounds the bottle (b) (4) and which makes contact with operators gowns during (b) (4) loading operations.

g) For (b) (4) filling rooms the passive-air sampling with settling plates is done at (b) (4) Grade-B area locations (i.e., external to the filling line enclosures) at a rate of (b) (4) per location and per (b) (4) . Written procedures do not prescribe the use of these settling plates in a continuous monitoring scheme and do not define when to collect these samples during the filling of the batch (i.e., locations are (b) (4) monitored).

h) No surface samples are collected from the (b) (4) used in the different filling rooms to (b) (4) primary-packaging component bags during component-loading interventions (In most instances, the (b) (4) are handled by the operators using their gloved-hands, not (b) (4)). In addition, no all forceps used during the execution of interventions in critical areas within the filling line enclosures are surface-sampled as part of environmental monitoring procedures.

In addition,

2) Non-viable particulate (NVP) monitoring samples are neither collected continuously (i.e., batch-related) nor collected in the following Grade-A areas within the filling line enclosures in the following aseptic filling rooms:

a) In Filling Line (b (4) (Filling Room # (b) (4)), the (b) (4) stopper loading and the (b) (4) conveyor areas (where continuous operator's activity occurs) in only collected on a (b) (4) basis. Note: the (b) (4) conveyor area is used for the operators to pass back-and-forth from one side of the filling line to the other (note: during this intervention the (b) (4) goes through the Grade-A area within the filling line enclosure).

b) In Filling Line (b (4) (Filling Room # (b) (4)), no NVP monitoring/sampling is performed at the (b) (4) stopper loading area (where continuous operator's activity occurs). In addition, NVP samples are only collected on a (b) (4) basis at the (b) (4) conveyor area, which is an area of continuous operator's activity used for the operators to pass back-and-forth from one side of the filling line to the other (note: during this intervention the (b) (4) goes through the Grade-A area within the filling line enclosure).

c) In Filling Line (b (4) (Filling Room # (b) (4)), no NVP monitoring/sampling is performed at the (b) (4) stopper loading area (where continuous operator's activity occurs).

d) In Filling Line (b (4) (Filling Room # (b) (4)), (b) (4) NVP sampling is done close to the (b) (4) stopper loading area. No NVP monitoring/sampling is performed at the (b) (4) conveyor area (where continuous

operator's activity occurs). Note: the (b) (4) conveyor area is used for the operators to pass back-and-forth from one side of the filling line to the other (note: during this intervention the (b) (4) goes through the Grade-A area within the filling line enclosure).

e) In Filling Line (b) (4) (Filling Room # (b) (4) – used for the filling of (b) (4) solutions in (b) (4) containers), NVP samples at the (b) (4) loading and the bottle loading areas (where continuous operator's activity occurs) are only collected on a (b) (4) basis.

f) In (b) (4) Block Suite (b) (4) (Filling Room # (b) (4)), NVP samples at area near the (b) (4) stopper bowl and the (b) (4) conveyor area (where continuous operator's activity occurs) are only collected on a (b) (4) basis. Note: the (b) (4) conveyor area is used for the operators to pass back-and-forth from one side of the filling line to the other (note: during this intervention the (b) (4) goes through the Grade-A area within the filling line enclosure).

In addition,

3) The following conditions were observed during the review of the video clips for the smoke studies conducted in the following filling lines during simulation of filling-line assembly (set-up) and aseptic filling activities:

a) In Filling Line (b) (4) (Filling Room # (b) (4)):

1. The video recording for the simulation of the introduction of the stopper bag and its loading into the (b) (4) does not show the airflow (smoke) pattern when the operator removes and transfers the (b) (4) stopper bag from the mobile LAF cart into the (b) (4) area within the filling line enclosure. Smoke pattern is shown only when the operator loads the stopper bag into the (b) (4) . Note: the (b) (4) stopper bag is removed from the LAF cart (Grade-A area), exposed to Grade-B conditions, and introduced into the (b) (4) area within the filling line enclosure (Grade-A area).

2. The video recording for the simulation of the introduction of the (b) (4) and bowl into the filling line enclosure (as part of line assembly operations) does not show the airflow (smoke) pattern when the operator removes and transfers the (b) (4) stopper bowl from the mobile LAF cart to the filling line enclosure. Smoke pattern is shown only when the operator introduces the stopper bowl in the filling line enclosure. Note: the (b) (4) and bowl are removed from the LAF cart (Grade-A area), exposed to Grade-B conditions, and introduced into the filling line enclosure (Grade-A area).

3. The video recording for the simulation of the operator passing from one side of the filling line to the other side through the (b) (4) conveyor area is not representative of the conditions observed during aseptic filling operations. The video shows (b) (4) operator going through the (b) (4) conveyor area while in current operation conditions the operators can go through the area with a mobile LAF cart or a cart with environmental monitoring equipment and media plates. In addition, the smoke generating device is fixed and does not move along with the operator. The smoke pattern can't be assessed during the execution of the whole intervention (i.e., passage through the Grade-A area within the filling line enclosure). Note: during this intervention the (b) (4) goes through the Grade-A area within the filling line enclosure.

b) In the video for the simulation of the (b) (4) stopper loading in Filling Line (b) (Filling Room # (b) (4)), it is not shown the airflow pattern when the stopper is transferred from the mobile LAF cart into the LAF enclosure (i.e., stopper bag is staged (b) (4) and loaded into the (b) (4) through this area). In addition, the video does not clearly show the smoke pattern when the stopper bag is loaded into the (b) (4).

c) In Filling Line (b) (Filling Room # (b) (4)):

1. The video recording for the simulation of the introduction of the (b) (4) bowl into the filling line enclosure (as part of line assembly operations) does not show the airflow (smoke) pattern when the operator removes and transfers the (b) (4) stopper bowl from the mobile LAF cart to the filling line enclosure. Smoke pattern is shown only when the operator installs the

stopper bowl. Note: the (b) (4) and bowl are removed from the LAF cart (Grade-A area), exposed to Grade-B conditions, and introduced into the filling line enclosure (Grade-A area). The video does not show the introduction of the stopper (b) (4) into the filling line enclosure.

2. In the video for the simulation of the (b) (4) stopper loading, there is no recording of the airflow pattern when the stopper bag is removed from the mobile LAF cart and transferred to the (b) (4) stopper loading LAF enclosure (i.e., stopper bag is staged (b) (4) and loaded into the (b) (4) through this area). In addition, the video does not clearly show the smoke pattern when the stopper bag is loaded into the (b) (4). Note: the (b) (4) stopper bag is staged in the LAF enclosure (located in front of but physically separated from (b) (4)). A (b) (4) (b) (4) is used to load the stoppers into the (b) (4). To load the stoppers, the operator opens the (b) (4) of the LAF enclosure (i.e., which opens to a Grade-B area) and introduces (b) (4) into this LAF enclosure to (b) (4), handle and load the stoppers into the stopper (b) (4).

d) The firm has not a smoke study video recording to evaluate if (b) (4) bags that, during aseptic filling operations, are placed within the LAF enclosure used to load (b) (4) stoppers into the stopper (b) (4) of the Suite (b) filling line, cause blockage of the air flowing down from the HEPA filters within the LAF enclosure. On 12/5/18, during the filling of (b) (4) Injection, batch # (b) (4), in Suite (b), the LAF enclosure used to load (b) (4) stoppers into the stopper (b) (4) of the filling line was observed with numerous (b) (4) stopper bags staged on (b) (4) of the LAF's (b) (4). As part of routine aseptic filling operations the bags are kept staged and the stopper loaded upon need.

e) Smoke study clips recording simulations of filling line assembly operations and environmental monitoring procedures, not always demonstrate the execution of proper aseptic practices. Conditions observed on the smoke study clips included: operators inadequately gowned with skin exposed to the environment, (b) (4) filling-line equipment parts (i.e., (b) (4), stopper (b) (4), stopper bowls), broken and/or teared equipment-part (b) (4), inadequate removal of equipment part (b) (4), operators touching primary-packaging-component contact surface with no sanitization of

the surface touched by the operator, and opening of filling line enclosure (b) (4) with no sanitization of the (b) (4) surface of the (b) (4) after these surfaces get exposed to Grade-B conditions.

In addition,

4) There is no assurance that the interventions simulated during media-fill runs are always representative of the interventions observed during routine aseptic filling operations (in terms of frequency and duration). The following conditions were observed during the review of media fill records, routine-aseptic-filling intervention records, and media-fill intervention records:

a) Intervention records do not define through which (b) (4) of the line the routine and non-routine interventions are executed. As it can be seen during the observation of aseptic filling operations, several interventions are done thru the RABS (b) (4) by opening (b) (4) even if these (b) (4) are equipped with (b) (4) (i.e., interventions to set and replace settling plates used for environmental monitoring).

b) During routine filling operations the passing of operators thru the (b) (4) conveyors area (in the different filling lines equipped with (b) (4) conveyors) is not documented with duration time. Only (b) (4) times are reported: (b) (4) . During this intervention, the operators have to open the filling line enclosure (b) (4) and pass thru the Grade-A area within the filling line enclosure. The opening and closing back of the (b) (4) during the "entry" and the "exit" interventions is documented with (b) (4) time, (b) (4) .

c) As per procedures, the non-routine maintenance (i.e., equipment breakdown) interventions denoted "NR5" is always simulated by (b) (4) the filling line for (b) (4) . During this time period, mechanical interventions are simulated. In the media-fill intervention records, the intervention is documented as "NR5" with no further details about the mechanical interventions simulated (i.e., what was specifically simulated during the mechanical intervention, in which area of the filling line the intervention was simulated, which (b) (4) or (b) (4) were opened during the simulation, and for how long the (b) (4) of the

filling line enclosure were opened during the simulation of the interventions). In instances whenever a real equipment breakdown occurs during the execution of the media fill, the intervention is considered the NR5 intervention. However, the non-routine intervention resulting from the equipment breakdown is only documented with time duration and with no indication as to which (b) (4) of the line enclosure were opened and for how long (the same way an equipment breakdown intervention would be documented during aseptic filling operations). There is no way to assure that the same challenge the aseptic environment (Grade-A) and equipment within the enclosure faces during the execution of aseptic filling operations is represented during the challenges the aseptic environment and equipment faces during the execution of media fills when real equipment breakdowns occur (classified by the firm as "simulations" and coded as "NR5" interventions) or when no equipment breakdowns occur and for which the above-indicated "NR5" intervention is executed.

In addition,

5) Current procedures for the assembly / set-up of the lines currently used for the aseptic filling of USA-market drug products, do not include instructions for the sanitization of the (b) (4) surface of the equipment-part (b) (4) before these parts get introduced into the filling line enclosures. Equipment parts which are primary-packaging-component contact surfaces are washed, dried, (b) (4), sterilized, and placed in mobile LAF carts (Grade-A conditions) in which they get transferred into the filling rooms. During assembly operations, the equipment parts are removed from the mobile LAF-cart, exposed to Grade-B conditions (filling room environment external to the LAF cart and the filling line enclosure), and transferred into the filling line enclosure (Grade-A area) without the sanitization of the (b) (4) surface of the equipment-part (b) (4).

In addition,

6) Current procedures for the handling of primary packaging components during aseptic filling operations do not include instructions to assure that primary packaging components used for injectable products (i.e., vial stoppers, syringe plunger-stoppers) and (b) (4) solutions (i.e., (b) (4) bottles, (b) (4), (b) (4) caps) are properly handled before these get introduced into Grade-A conditions during aseptic filling operations.

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During aseptic filling operations the primary-packaging-component bags are kept in mobile LAF carts. To load the packaging components into their respective (b) (4) or bowls, the component bags are removed from the mobile LAF-cart, exposed to Grade-B conditions (filling room environment external to the LAF cart and the filling line enclosure), and transferred into the filling line enclosure (Grade-A area) without the sanitization of the (b) (4) surface component bag.

In addition,

7) The procedures for the execution of interventions (document # FU4-PR-MF-GEN-012 – "Aseptic Process Interventions Recording and Actions", version # 14, made effective on 2/12/18) are deficiently written and/or not followed. The following conditions were observed from the review of the procedure and evaluation of operators' aseptic practices during aseptic filling operations:

a) The procedures require the sanitization of the (b) (4) surface of the filling-line enclosure (b) (4) when these are opened to intervene in the Grade-A area within the enclosure (because the (b) (4) open to Grade B conditions exposing their (b) (4) surface to these conditions). Procedure indicates that the surface must be wiped with (b) (4) from (b) (4) to ensure there are no overlaps on the cleaned area. However, during the execution of aseptic filling operations, numerous instances were observed that by not "overlapping" the operators did not apply disinfectant to the whole (b) (4) surface area of the opened (b) (4). In addition, in instances in which the (b) (4) opened had a (b) (4) the disinfectant was not applied and/or adequately applied) to the surface of the RABS (b) (4) which was also exposed to Grade B conditions when the (b) (4) was opened.

b) The procedures indicate that the set and replace of settling plates used for environmental monitoring must be done by using the (b) (4). Current practice is to open the filling-line enclosure (b) (4) to set and replace the plates. Whenever the RABS (b) (4) can be used to do the set and replace of plates, the opening of the enclosure (b) (4) instead pose additional risks to the aseptic environment within the enclosure.

c) The procedures do not include requirements for the sanitization of the (b) (4) surface of the mobile-LAF-cart (b) (4) which are opened into Grade B conditions when primary packaging component bags are removed from the cart during primary-packaging-component loading operations.

In addition,

8) There is no assurance that the procedures for the preparation of materials for sterilization (document # FU4-PR-MF-GEN-003 – "Preparation of Material for Sterilization", version # 11, made effective on 11/6/18) are always followed when filling-line equipment parts are cleaned, dried, and prepared for sterilization. The procedures indicate that the (b) (4) surface of (b) (4) stoppering items (including (b) (4) and bowls) must be (b) (4) to sterilization. Current practice is to (b) (4) the stopper (b) (4) and stopper (b) (4) when they are big in size. Note: during assembly operations, equipment parts such as (b) (4) and bowls are removed from the mobile LAF-cart, exposed to Grade-B conditions (filling room environment external to the LAF cart and the filling line enclosure), and transferred into the filling line enclosure (Grade-A area) without the sanitization of the (b) (4) surface of the equipment-part (b) (4) and/or the (b) (4) equipment-part (b) (4) surface.

OBSERVATION 2

Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically,

There is no assurance that operators always follows the requirements established in the written procedures for the gowning of operators working in aseptic production areas (document # FU4-PR-MF-GEN-001 - "Entry and Exit Procedure for Personnel in Clean Rooms (Grade B)", version # 11, made effective on 11/26/18). On 12/3/18, one of the operators working in the filling of (b) (4) Injection Ampoules, lot # (b) (4), in Line (b) (4) Block, Filling Room # (b) (4), had his goggles / head gear slightly misplaced. Part of his nose's skin was observed exposed to the environment.

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*DATES OF INSPECTION

12/03/2018(Mon), 12/04/2018(Tue), 12/05/2018(Wed), 12/06/2018(Thu), 12/07/2018(Fri), 12/10/2018(Mon), 12/11/2018(Tue), 12/12/2018(Wed), 12/13/2018(Thu), 12/14/2018(Fri)

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