

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Springs, MD 20993 (301) 796-3334 Fax: (301) 847-8738	DATE(S) OF INSPECTION 4/20/2017-4/28/2017*
	FEI NUMBER 3008461619

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Madan Mohan Reddy , Director of Operations

FIRM NAME Aurobindo Pharma Limited - Unit IV	STREET ADDRESS Unit IV, Plot No. 4, 34-48 EPIP, APIIC, IDA-Pashamylaram, Pantancheru Mandal
CITY, STATE, ZIP CODE, COUNTRY Medak District, Hyderabad, Telangana, 502307 India	TYPE ESTABLISHMENT INSPECTED Sterile Human Drug Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.


DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Buildings used in the manufacturing of a drug product are not maintained in a good state of repair.

Specifically, your manufacturing equipment is not always maintained to achieve its intended purpose.

- A. On 20 April 2017, we observed Line ^{(b) (4)} Grade C area floor with cuts in the ^{(b) (4)} material that were visibly dirty and constitute a difficult to clean surface. Manufacturing of ^{(b) (4)} (batch ^{(b) (4)} and ^{(b) (4)} (batch # ^{(b) (4)} sterile injectables were respectively on-going at the time of observation.
- B. On 20 April 2017, we observed dried and cracked ^{(b) (4)} repairs to floor and drain connections as well as ^{(b) (4)} sealant particles on the floor and stuck in a return air vent in the Compounding Room ^{(b) (4)} where bulk product for ^{(b) (4)} njection (batch # ^{(b) (4)} was formulated. These surfaces create hard to clean surfaces and risk of particulate in the Grade C environment.
- C. On 20 April 2017, we observed the Line ^{(b) (4)} gowning room ^{(b) (4)} system not working, thus allowing multiple ^{(b) (4)} to be open at the same time which reduces the effectiveness of differential pressures for Grade C compounding Areas.
- D. On 21 April 2017, we observed a ^{(b) (4)} repair on the diffuser of a HEPA filter in the Grade A barrier area directly over product conveyors in the new ^{(b) (4)} block facility. During operation, ^{(b) (4)} sterile product vials would be moving directly under this ^{(b) (4)} repair which creates a risk of environmental particulates.

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- E. Vial washing and (b) (4) equipment/facilities are not adequately maintained:
- a. On 25 April 2017, I observed a (b) (4) colored fluid inside of the (b) (4) on Line (b) (4) used as a glassware (b) (4). The fluid appeared to emanate from the (b) (4) that (b) (4) the (b) (4) of air flow over glass vials entering the aseptic filling equipment. Maintenance SOP #FU4-PR-MF-OPI-002 v6 doesn't include (b) (4) (b) (4) visual checks or cleaning. This equipment creates airflow over (b) (4) glass vials to (b) (4) before entering the filling equipment.
 - b. On 21 April 2017, I also observed the accumulation of (b) (4) particulate residue in the (b) (4) system serving the vial (b) (4) equipment in Line (b) (4). Maintenance SOP# FU4-EN-MNP-028 doesn't include (b) (4) heck or cleaning of the (b) (4) unit that hold glass vials in place during the (b) (4) process on Line (b) (4).
- F. On 26 April 2017, I observed Line (b) (4) barrier facilities/equipment door and mobile LAF in dis-repair. The side access door of the mobile LAF cabinet remained open by about a 1 inch gap. This equipment is intended to provide laminar air flow storage of components until the components are loaded into the Grade A barrier around the filling machine for sterile (b) (4) products manufactured on Line (b) (4).

OBSERVATION 2

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

Specifically;

- A. There is no assurance that primary USP reference standard and/or in-house secondary standards, that are used to determine strength, purity and quality of the drug products, are performing as intended. QC Head stated that Standard-2 or Check Standard is not injected in assay testing in

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most of the drug products to ensure that peak area responses from Standard-1 or Standard are within the suitable range. The QC Head further stated that approximately (b) (4) sterile injectable drug products are tested at the site and the lab is injecting Check Standard or Standard-2 during the testing of thirteen (13) products only.

B. Laboratory controls are deficient for USP reference standards that are used to establish identity, strength, quality and purity of the commercial drug products. During the inspection of QC Laboratory On 4/24/2017, QC Head stated that the lab does not have active controls use USP reference standard vials as for how long and how many times the standard vial can be used without compromising the potency of the reference standard. During review of USP standard usage, we noticed that:

- i. QC Lab is using more than (b) (4) USP reference standards including 37 hygroscopic USP reference standards. (b) (4) USP standard (Lot# (b) (4) In-house reference# (b) (4) was received on 6/24/12013. This standard vial was last time used on 2/21/2017. During this period, this vial opened for use for 41 times.
- ii. Other USP reference standards such as (b) (4) USP (Lot# (b) (4) In-house reference# (b) (4) and (b) (4) USP (Lot# (b) (4) In-house reference# (b) (4) were purchased in 2013 and 2014 respectively and still in use.

C. There is no assurance that laboratory equipment is performing as intended. During the inspection of your QC Chemistry and Micro Laboratories on 4/24/2017, significant vibration was noticed on the counter top where top loading balances (equipment# QC/TOPBL-002 and QC/TOPBL-003 in Chemistry and Micro Lab respectively) were placed. As per User Manual provided by the vendor of these top loading balances, vibration can have negative impact on the precision and accuracy of the instrument. QC Lab management stated that both balances are used to weigh various reagents and media that are further used to test drug products as well as sterility testing. Surface vibration on the counter top was so significant that vibrating circles in the diluent bottles,

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placed on the counter top, were noticed in chemistry lab, located on 3rd floor. When asked about the possible cause of this vibration, lab management stated they are not sure about the source.


When similar vibration was noticed on the counter top where top loading balance (equipment ID: QC/TOPBL-003) is placed in the Micro Lab located on 2nd floor. Micro Lab Head stated that vibration might be coming from (b) (4) cycles. We noticed two (b) (4) (equipment ID: QC (b) (4) -001 and QC (b) (4) -002) in that room and one of them was in operation that time. Head of the Micro Lab stated that each (b) (4) in this room runs for approximately (b) (4) cycles (b) (4) and each cycle runs for about (b) (4)

D. Laboratory equipment is not identified adequately. During the inspection of Retain Sample Room (# 82A) located on in Chemistry Lab on 3rd floor), two temperature data loggers that are used to monitor temperature data in the room, are not identified properly. Temperature data logger 1, installed near the front door is identified as "C1:SN 38229684 / 905" on the temperature summary sheets that are printed and reviewed (b) (4). Same instrument is identified as "QC/DTMRH-001" on the equipment. Data logger 2, installed in the back of the room is identified as "36609807" on (b) (4) temperature sheets. This instrument is identified as "IN/DLOGG-049" on the equipment tag.

E. Laboratory equipment is not qualified for intended use. During the inspection of Retain Sample Room (#82A), it was noticed that the room has three floor air-conditioning (equipment ID: QA/ARCLR-001, QA/ARCLR-002, and QA/ARCLR-003) units. These air-conditioning units are used to maintain the room temperature at 20-25°C. Associate Vice President QA/QC later on confirmed that these three air-conditioners are not qualified for intended use.

OBSERVATION 3

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

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Specifically changes, made to manufacturing processes, manufacturing & analytical equipment, and computer systems that are used to manufacture and test sterile drug products, are not evaluated thoroughly.


During the inspection, we noticed you made more than seven hundred changes since Sep 2016 relating to manufacturing processes, equipment, batch size, and test procedures. Approximately all of these changes were classified as "Normal Minor". Your SOP for Change Management (#CQA-CP-GEN-006, Effective date: 4/7/2017) lists six categories depending upon depending upon criticality and priority as below:

1. Emergency Major
2. Emergency Moderate
3. Emergency Minor
4. Normal Major
5. Normal Moderate
6. Normal Minor

As per your aforementioned Change Management procedure, "Normal" changes may not require immediate attention. Review of Change Control (# APL-FU4CC-16-0659) revealed that it was created when EMPOWER software was re-installed on Empower Client as hard disk of the Empower Client crashed. This particular Empower client is connected to two HPLCs. This particular change was classified as "Normal Minor". In other instances significant number of Change Controls were initiated to change the manufacturing batch size and classified as Normal Minor.

OBSERVATION 4

There is a failure to thoroughly review whether or not the batch has been already distributed.

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Specifically, corrective and preventive actions (CAPAs), identified and initiated because of out of specifications (OOS) laboratory investigations, do not correlate to the identified root cause. In certain cases, CAPAs are not initiated at all.


QC Lab initiated OOS investigation (# SS/OOS/359/16) on 12/11/2016 when out of specification assay results were generated for ^{(b) (4)} Injection (batch# ^{(b) (4)} 3 month, 25/60, stability sample). This investigations concluded that sample solution evaporated from HPLC vial due to damaged septa, leaving higher concentration of active in the HPLC vial that yielded high assay result. In order to prevent this issue in future, you OOS investigation report states "The concerned analyst was trained on the Good laboratory practices (SOP No: FU-QC-CI-GEN-021) and on STP procedure to avoid such re-occurrence".

QC Lab initiated another OOS Investigations (# FP/OOS/024/16) on 12/13/2016 when out of specification assay results were generated for ^{(b) (4)} Injection, USP (batch# ^{(b) (4)} release testing). OOS Investigation concluded that standard solution evaporated from HPLC vial because septa was damaged leaving more concentrated standard solution in the HPLC vial that yielded low assay result. In order to prevent this issue, you OOS investigation report states "The concerned analyst was trained on the Good laboratory practices (SOP No: FU-QC-CI-GEN-021) and on STP procedure to avoid such re-occurrence".

In both aforementioned investigations, the suggested CAPAs (to train the analyst on Good Laboratory Practices SOP) are not effective, as the particular SOP does not address the root cause identified in both investigations.

OBSERVATION 5

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

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Specifically, your filling Line (b)(4) includes an obsolete (b)(4) that is located immediately above a vial conveyor that moves (b)(4) sterile drug product vials.

Your VP of Operations stated this (b)(4) was previously intended to ensure complete stoppering after the primary stoppering machine placed the stopper in the neck of the vial. However, this machine was installed in 2011 on Line (b)(4) and never effectively used to seat (b)(4) stoppers in glass vials. Additionally, this (b)(4) was not evaluated in air visualization studies dated March 2017.

On 24 April 2017, I observed Line (b)(4) being used for manufacturing sterile human drug product (b)(4) Injection (batch (b)(4) where the (b)(4) was (b)(4) less than (b)(4) above stoppered vials on the conveyor.


OBSERVATION 6

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.

Specifically, you are maintaining two parallel systems for controlling Master Record documents such as Batch Production and Packaging Records.

On 27 April 2017, I observed both the Metric Stream v6.1 software system that houses Master Batch Records and the PC located in the document storage room that is used for accessing a separate location housing Master Batch records in the "documentissue4" (K:) network drive.

While your DMS Manager stated the Metric Stream software is used for approving master records, he uses the network (K:) drive location to print records for production so that he can more easily edit the record to include batch numbers and record each print in a paper log. It should be noted that the Metric Stream software is capable of automatic print logging and full history review as a document management software.

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OBSERVATION 7

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

Specifically, glove integrity testing is not performed with a quantitative test.

Based on SOP FU4-PR-MF-GEN-020 v9.0, the (b) (4) gloves used on Lines (b) (4) and (b) (4) for aseptic processing are tested (b) (4) independent of the number of commercial batches manufactured on each line. The integrity test is performed using equipment #PN/MNGIT_001 which does not have a pressure gauge to determine either a specific applied pressure or quantitative pressure decay over time. The current method per this written procedure is to inflate the glove and visually check for any horizontal deflection of the glove after inflation to determine if there is a leak over a period of (b) (4)

Additionally, individual gloves are not identifiable with a unique number as to their history of testing or use in manufacturing.

***DATES OF INSPECTION**

4/20/2017(Thu),4/21/2017(Fri),4/24/2017(Mon),4/25/2017(Tue),4/26/2017(Wed),4/27/2017(Thu),4/28/2017(Fri)

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X Saleem A Akhtar

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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."