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	8/2/2021-8/12/2021* FEI NUMBER 3004021253

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Kalakada Narasimha Reddy, Vice President-Operations

FIRM NAME	STREET ADDRESS
Aurobindo Pharma Limited (Unit I)	386 388 - 396 Borpatla Village, Survey 385
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Doultabad, Telangana, 502296, India	Active Pharmaceutical Ingredient 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.

OBSERVATION 1

Systems for evaluating and qualifying critical material suppliers is inadequate.

Specifically, there is a failure to adequately qualify key starting material (KSM) suppliers for (b) (4) products.

1. You ceased manufacturing (b) (4) (b) (4) at this facility in February 2016. Manufacturing of (b) (4) (b) (4) was resumed at this facility in February 2021. You failed to provide a rational justification demonstrating that your supplier of (b) (4) critical materials, (b) (4) can supply key starting material of intended quality and purity. You failed to provide scientific data demonstrating that your supplier can provide key starting material which would not impact the quality of (b) (4) Active Pharmaceutical Ingredient (API).
2. Prior to process validation of (b) (4) initiated on December 6th, 2019, (b) (4) (b) (4) and (b) (4) was not manufactured at this facility. You failed to adequately qualify your new vendor for key starting material, (b) (4) used in (b) (4) (b) (4) You failed to ensure that your new supplier can consistently provide key starting material at intended quality, which would not impact your final API. In addition, a rational justification was not provided for failing to follow section 5.8.2 of your "Qualification &Evaluation of External Vendor for Raw Material" procedure.

OBSERVATION 2

Inadequate sampling plans for raw materials and intermediates.

Specifically, you failed to provide scientific justification demonstrating that your current sampling plans are representative. Your sampling plans are not scientifically sound and appropriate to ensure that your raw materials and intermediates conform to established standards of quality and purity.

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(b) (4) Key Starting Material

1. (b) (4) Compound is received in a (b) (4) drum. Once the number of drums to be sampled are selected, you obtain a sample from the (b) (4) drum using a (b) (4) You failed to provide scientific data demonstrating that sampling the (b) (4) drum is adequate to determine batch homogeneity.
2. (b) (4) is received in a (b) (4) bag, a (b) (4) and then sample the bags. You failed to provide scientific knowledge demonstrating that the (b) (4) used is adequate to (b) (4) bag and obtain a representative batch sample.

Sampling of (b) (4)
Your current sampling process fails to assure that a representative sample is obtained for water and residual solvent analysis. Process validation was executed under P-A1P-PV-C1022640-01-00. (b) (4) (b) (4) Your process validation fails to scientifically demonstrate that (b) (4) will adequately be (b) (4) During process validation, a composite sample is obtained from the (b) (4) shelves. (b) (4) conducted via protocol OQ (b) (4) /20-00, fails to demonstrate (b) (4) (b) (4) Additionally, fails to contain a rational justification for the placement of the (b) (4)

Furthermore, similar inadequacies were observed with in process sampling of (b) (4)

OBSERVATION 3

Components used in manufacturing are not test and released prior to use.

Specifically,

1. Your quality control unit failed to ensure that materials are appropriately tested for impurities (b) (4) prior to manufacturing of (b) (4) process validation batches dated, February 6th, 2021 to May 28th, 2021.

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Examples of materials used prior to complete testing;

Material Name	Manufacturing Start Date	(b) (4) and (b) (4) Test Date	(b) (4) and Batch
(b) (4)			

Quality failed to provide a rational justification for conducting (b) (4) impurity testing after manufacturing had already began.

2. (b) (4) manufacturing plant (b) (4) was installed and was operational at your facility on October 6th, 2020. Prior to manufacturing use, you failed to adequately test and qualify your (b) (4) line (b) (4) line (b) (4) is used in (b) (4) to (b) (4) the sampling lines of your (b) (4) during product sampling. You failed to provide a scientific justification why (b) (4) was not tested prior to use. Additionally, impact of using untested (b) (4) during (b) (4) process validation was not conducted.

OBSERVATION 4
Proposed changes are not adequately evaluated.

Specifically, you failed to adequately evaluate changes to your manufacturing process that would potentially impact the quality of your product.

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1. (b) (4) specification for (b) (4) (KSM for (b) (4) was changed from NMT (b) (4) ppm to NMT (b) (4) ppm. The increase in (b) (4) has the potential of generating (b) (4) impurities, (b) (4) Your finished product (API) specifications do not specifically test for the (b) (4) impurities. In-process control tests are not conducted to demonstrate that the impurities do not potentially carry over into your finished product.
2. You failed to appropriately evaluate the impact of (b) (4) The original design length of the (b) (4) (b) (4) The current (b) (4) Prior to change implementation, you failed to assess the impact of (b) (4) (b) (4) Additionally, failed to assess the impact on product homogeneity depending on (b) (4) capacity. (b) (4) are used in production of (b) (4) Your equipment is not adequately qualified for (b) (4) production.

OBSERVATION 5

Quality control failed to ensure that investigations made into any unexplained discrepancy were scientifically sound.

Specifically, your quality control unit failed to ensure that investigations into any unexplained discrepancies were thoroughly evaluated to determine a scientifically sound root cause and initiate an adequate corrective and preventative action. For example;

1. Complaint investigations MC-CAD-002926, MC-CAD-003075, MC-CAD-003076, and MC-CAD-003077 failed to assess the impact of (b) (4) analog of (b) (4) on stability. Your customer notified you of their finished product being out of trend due an impurity in your product. You identified the impurity as analog for (b) (4) and established specification for your raw material and finished product. You failed to assess the potential increase of the impurity overtime. You have manufactured (b) (4) lots of (b) (4) since receiving the initial complaint in February 2019.

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2. You failed to evaluate potential contamination of recovered solvents arising from previous product/material used in the non-dedicated equipment. For example, deviation DE-U01-001711 and DE-U01-001714 initiated due to unknown peaks being observed from (b) (4) recovered from (b) (4) Your investigations failed to assess previous product manufactured in the non-dedicated equipment.
3. Incident A01/QI/GC120160, during method transfer for (b) (4) and (b) (4) content analysis, your initial run failed method precision. Specification, NMT (b) (4) % for (b) (4) %RSD, result obtained (b) (4) %. The original results were invalidated, and fresh samples were obtained and ran by a different analyst using a different column. You failed to provide scientific evidence supporting the identified root cause "sample preparation" or "column problem".

OBSERVATION 6
Equipment not properly maintained

Specifically, on August 2nd, 2021, during production of (b) (4) (Technical) batch (b) (4) water was observed leaking from the (b) (4) onto the production floor (b) (4) It is unknown how long the (b) (4) has been leaking. Floor staining was observed where the water droplets were falling. (b) (4) is used in manufacturing (b) (4) technical (b) (4) and (b) (4) (b) (4) You have no documentation addressing the impact on the (b) (4) mass due to leaking (b) (4)

OBSERVATION 7
Quality related activities are not documented at the time of performance.

Specifically, complete reliability of quality related documents was not assured as there is a failure to document quality related activities at the time of performance. For example,

1. On February 2nd, 2021, a Production Operator in (b) (4) ((b) (4) manufacturing block) was observed to have written batch record information for (b) (4) batch (b) (4) on his palm. Per the Operator, the information is written on the hand and then transcribed in the batch record.

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2. On December 20th, 2020, (b) (4) compound (Key Starting Material) batch (b) (4) # (b) (4) was run on GC/MS QGMQ-201 for (b) (4) impurity. The firm failed to document the batch run in the GC/MS logbook.

***DATES OF INSPECTION**
8/2/2021(Mon), 8/3/2021(Tue), 8/4/2021(Wed), 8/5/2021(12Thur), 8/6/2021(Fri), 8/9/2021(Mon), 8/10/2021(Tue), 8/11/2021(Wed), 8/12/2021(Thur)

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