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	5/2/2022-5/10/2022*
	FEI NUMBER 3007373532

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mettu Madan Mohan Reddy, Director

FIRM NAME	STREET ADDRESS
Aurobindo Pharma Limited	Unit Vii, Formulation Plant, Plot S-1, Survey 411, 425, 434-435, 458, Tsiic, Green Ind. Park
CITY, STATE, ZIP CODE, COUNTRY Polepally, Mahaboob Nagar, Telangana, 509302 India	TYPE ESTABLISHMENT INSPECTED 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

Investigations of an unexplained discrepancy and a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.

1. Investigations of out of specification (OOS) assay and dissolution results that led to the rejections of tablet batches identified a lack of control over compression machine settings including (b) (4) and compaction force as a root cause. These investigations were not extended to all tablet products to ensure appropriate limits were set and that similar variations in machine settings had not resulted in the acceptance of tablets that did not meet specifications. For example:

   a. Investigation APL Unit 07/INV/007/21 was opened March 17, 2021, when batch (b) (4) of (b) (4) Tablets USP (b) (4) mg did not meet the specification for assay of (b) (4) - (b) (4) % with a result of (b) (4) %. The batch was rejected. The investigation identified the root cause as the increase of the (b) (4) during compression to (b) (4), causing segregation of (b) (4) powder. The batch record did not have established limits for (b) (4).

   A hypothesis study showed that increasing (b) (4) during compression to (b) (4) or higher could generate tablets meeting all in-process specifications. However, the portions of batches manufactured during the trial with (b) (4) that were increased to (b) (4) or

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Justin A Boyd, Investigator Darren S Brown, Investigator	X Darren S Brown Investigator Signed By: 2001647750 Date Signed: 05-10-2022 18:13:50	DATE ISSUED 5/10/2022

higher produced tablets that did not meet assay requirements. The investigation included no retrospective review of compression PLC data to determine if (b) (4) during manufacturing for all (b) (4) batches within expiry may have caused the same variable assay results within a batch.

As part of the corrective and preventive actions, (b) (4) limits of NMT (b) (4) were established for all strengths of (b) (4) Tablets USP. The investigation did not evaluate previous batches within expiry, which used a higher (b) (4), including November 2020 batches (b) (4) that used a (b) (4).

The preventive action to implement the (b) (4) limit was not extended to other tablet products manufactured for the US market, which did not have established (b) (4) limits. Additionally, there was no review extended to PLC compression data for any other tablet product to determine if similar excessive (b) (4) may have caused variable assay values within a batch for other low dose tablets, (b) (4) compression tablets, or any other tablet produced for the US market.

b. Investigation APL Unit 07/INV/014/20 was opened June 27, 2020, when batch (b) (4) of (b) (4) and (b) (4) Tablets (b) mg/(b) (4) mg did not meet the specification of (b) (4) - (b) (4) % for (b) (4) with a result of (b) (4) %. The batch was rejected. The investigation identified the root cause to be the use of a high (b) (4) on the compression machine that caused segregation of (b) (4) material.

As a corrective action, (b) (4) limits were proposed for (b) (4) and (b) (4) (b) (4) Tablets. The investigation included no retrospective review of compression machine

PLC data to determine if high (b) (4) impacted other batches of (b) (4) and (b) (4) Tablets or any other tablet product that was within expiry.

c. Investigation APL Unit 07/INV/15/20 was opened August 8, 2020, when batch (b) (4) of (b) (4) to be used in (b) (4) Capsules (b) mg was out of specification for content uniformity during in-process testing of the (b) (4). The batch was rejected. The investigation identified that variation of the compression machine (b) (4) caused segregation within the (b) (4), causing the OOS result for content uniformity.

The investigation was not able to identify the (b) (4) used during the manufacturing. No further investigation was conducted to determine what (b) (4) would cause segregation within the (b) (4).

This investigation was not extended to review of all other tablet products that had no established (b) (4) to determine if similar variations in (b) (4) had caused portions of the batch to be out of specification.

d. Investigation APL Unit 07/INV/014/21 was opened June 2, 2021, when batch (b) (4) of (b) (4) Tablets USP (b) (4) mg was out of specification for dissolution. The batch was rejected along with batch (b) (4), which was considered borderline, but meeting dissolution specification at the L3 stage. The investigation identified the root cause to be low hardness due to low compaction force causing faster release of the drug. Limits for (b) (4) compaction force had not been established.

During manufacturing of the two rejected batches, the PLC compaction data showed the (b) (4) (b) (4) force was (b) (4) kN for portions of the manufacturing. The PLC data was only

reviewed for batches in the same campaign, however batch (b) (4) and (b) (4) also had portions of the batch with a (b) (4) kN (b) (4) force result. The investigation does not thoroughly evaluate whether the portions of these other batches without (b) (4) would have met all dissolution specifications. Batches (b) (4) and (b) (4) were released and shipped to the US market.

An activity qualification FU7-MISC-ACTR-0094 was conducted to evaluate hardness limits. It identified the hardness range for the product should be (b) (4) - (b) (4) kp. During (b) (4), 29.3% of the (b) (4) in-process checks had hardness values below (b) (4) kp. During (b) (4), 38.5% of the (b) (4) in-process checks had hardness values below (b) (4) kp. Additionally, other released batches had in-process hardness results below (b) (4) kp for at least 40% of the in-process checks including: (b) (4) (41.4%), (b) (4) (40.3%), (b) (4) (43.7%), (b) (4) (46.8%), and (b) (4) (43.7%).

There was no review of PLC data for all (b) (4) Tablets USP batches within expiry or for other tablet products to determine if portions of other batches may have been impacted by low (b) (4) compaction forces, causing lower hardness and variation in the dissolution rate within a portion of the batch.

e. Investigation APL Unit 07/INV/003/20 was opened January 28, 2020, when batch (b) (4) of (b) (4) and (b) (4) Tablets (b) (4)/(b) (4) mg did not meet the dissolution specification. The batch was rejected. The investigation identified the root cause as low compaction force during compression resulting in tablets that were meeting in-process specifications, but had lower hardness and lower weight than the target. The less compacted (b) (4) in these tablets released the drug faster, resulting in the dissolution failure. This root cause implicated a portion of the batch, tablets produced from (b) (4) to (b) (4) on December

22, 2019, when the (b) (4) compression force was lower and in-process checks showed the tablets met specifications, but had lower hardness and weight results than the rest of the batch.

There was no established limit for setting the (b) (4) compaction force on the compression machine. The preventive action was to establish limits for the (b) (4) compaction force for this product, but this was not extended to all other tablet products, which still do not have established compaction force limits.

A hypothesis study during the investigation confirmed low compaction force tablets led to tablets with a faster drug release and tablets with high compaction force led to tablets with slower drug release. The investigation did not include a review of PLC data for all batches of (b) (4) and (b) (4) Tablets within expiry or any other products to determine if operator changes to compaction force set points during a batch could have caused the acceptance of tablets that would not meet dissolution specifications for a subset of the batch.

f. Investigation APL Unit 07/INV/004/20 was opened February 6, 2020, when batches (b) (4) Tablets USP (b) (4) mg and (b) (4) Tablets USP (b) (4) mg failed dissolution. The batches were rejected. The investigation identified the root cause as a cumulative effect of more (b) (4) in the (b) (4) along with less compaction force applied during compression.

The investigation was not extended to evaluate PLC compaction force data for all (b) (4) Tablet batches within expiry or any other tablet product to determine if similar low compaction forces impacted dissolution rates in a portion of the batch.

2. Investigation APL Unit 07/INV/020/20-02 was opened December 22, 2020, when batches

(b) (4) of (b) (4) Tablets (b) mg failed dissolution. The investigation identified a coarser particle size in supplier batch (b) (4) of (b) (4), which is used as a (b) (4). The investigation identified this coarser particle size caused uneven distribution in the (b) (4) stage and less (b) (4) to the API and other (b) (4) materials during (b) (4), which led to fast drug release and variability in dissolution.

The impacted (b) (4) vendor batch (b) (4) was used to manufacture (b) (4) batches of (b) (4) Tablets (b) mg. In addition to the three OOS batches, there were (b) (4) batches that had not yet been released and all were rejected. (b) (4) batches ((b) (4) had already been released. The investigation concludes there was no impact to the released batches based on passing finished product dissolution testing results including (b) (4) batches that passed at the L3 stage, (b) (4) batches at the L2 stage, and (b) (4) batch at the L1 stage. The investigation does not justify the conclusion that this raw material found to cause faster drug release and variability in dissolution would not have impacted the released batches.

3. Investigation APL Unit 07/INV/013/20 was opened August 3, 2020, when batch (b) (4) of (b) (4) and (b) (4) Capsules USP (b) mg/(b) (4) mg failed for unspecified organic impurities and was rejected. The investigation identified the root cause as cross contamination from the previous product, (b) (4) Capsules, due to inadequate cleaning of the holes in the (b) (4) used during encapsulation. The investigation did not verify the hypothesis by determining if the previous product would cause a chromatography peak consistent with the OOS result.

The holes in the (b) (4) had not been analytically evaluated during the cleaning validation and were not reevaluated after the findings of this investigation. Additionally, there was no evaluation to

determine if the analytical methods for other products manufactured on the same shared equipment including (b) (4) Capsules, (b) (4) Capsules, (b) (4) Capsules, (b) (4) Capsules, and (b) (4) Capsules would have detected similar cross contamination if present.

Investigation APL Unit 07/INV/012/21 was opened April 26, 2021, when batch (b) (4) of (b) (4) and (b) (4) Capsules USP (b) (4) mg/(b) (4) mg failed for an unspecified organic impurity at the same retention time as (b) (4). The batch was rejected. The root cause was again attributed to (b) (4) cross contamination related to the (b) (4) used during encapsulation. The investigation did not analytically verify the peak was from (b) (4) or ensure the analytical methods for other products manufactured on the same shared equipment would have detected similar cross contamination if present.

4. Product Non-Conformance (PNC) investigations have not thoroughly investigated root causes and implemented preventive actions to prevent events that lead to disregarding of analytical chromatography data. For example, PNC trending for (b) (4) - (b) (4) shows:

a. 85 PNCs opened related to HPLC instruments including 29 instrument failures, 28 communication failures, and 7 carousel malfunctions.

b. 44 PNCs opened related to (b) (4) standard failures, resulting in the disregarding of chromatography data.

Individual PNC records did not identify corrective or preventive actions.

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	5/2/2022-5/10/2022*
	FEI NUMBER 3007373532

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Mettu Madan Mohan Reddy, Director	
FIRM NAME Aurobindo Pharma Limited	STREET ADDRESS Unit Vii, Formulation Plant, Plot S-1, Survey 411, 425, 434-435, 458, Tsiic, Green Ind. Park
CITY, STATE, ZIP CODE, COUNTRY Polepally, Mahaboob Nagar, Telangana, 509302 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

OBSERVATION 2

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Parameters including (b) (4) and (b) (4) compaction force, which can impact the variability within a batch, have not been established as part of process validation studies for any tablet product other than (b) (4) Tablets USP.

1. Values for (b) (4) and (b) (4) compaction force are documented on the "Monitoring of Critical Process Parameters During Compression" form in the batch record. This form in the batch records for the following products had no limits and the associated process validation reports did not address these compression machine parameters: (b) (4) Tablets USP (b) (4) mg; (b) (4) Tablets USP (b) (4) mg; (b) (4) Tablets (b) (4) mg; (b) (4) Tablets USP (b) (4) g; (b) (4) Tablets USP (b) (4) mg; (b) (4) Tablets (b) (4) mg; (b) (4) Tablets USP (b) (4) mg; (b) (4) Tablets USP (b) (4) mg; (b) (4) Tablets USP (b) (4) mg; (b) (4) Tablets USP (b) (4) mg; and (b) (4) Tablets (b) (4) mg.

2. Process validations initiated after September of 2020 have included proposed (b) (4), and (b) (4) compaction force, but have only proposed "tentative limits" until historical data can be gathered. Other than (b) (4), no limits have been finalized for any tablet product. The process validations studies do not include specific sampling and analytical data to demonstrate uniform tablets are produced at the proposed ranges for these compression machine settings. Until being finalized, the ranges are only "tentative limits" and the operators can operate the compression machines outside of these limits without initiating any type of investigation. For example:

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Justin A Boyd, Investigator Darren S Brown, Investigator	X Darren S Brown Investigator Signed By: 2001647750 Date Signed: 05-10-2022 18:13:50	DATE ISSUED 5/10/2022

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	5/2/2022-5/10/2022*
	FEI NUMBER 3007373532

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Mettu Madan Mohan Reddy, Director	
FIRM NAME Aurobindo Pharma Limited	STREET ADDRESS Unit Vii, Formulation Plant, Plot S-1, Survey 411, 425, 434-435, 458, Tsiic, Green Ind. Park
CITY, STATE, ZIP CODE, COUNTRY Polepally, Mahaboob Nagar, Telangana, 509302 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

a. (b) (4) Tablets USP (b) (4) mg, batch (b) (4). At the 3:48 in-process check on April 15, 2022, the (b) (4) was (b) (4) and (b) (4) compared to a limit of (b) (4); the (b) (4) was (b) (4) compared to a limit of (b) (4); and the (b) (4) compression force was (b) (4) kN (b) (4) compared to a limit of (b) (4) - (b) (4) kN.

b. (b) (4) Tablets (b) (4) mg, batch (b) (4). At the 3:20 in-process check on March 26, 2022, the (b) (4) was (b) (4) and (b) (4) compared to a limit of (b) (4) and the (b) (4) compression force was (b) (4) kN (b) (4) and (b) (4) kN (b) (4) compared to a limit of (b) (4) - (b) (4) kN.

c. (b) (4) Tablets USP (b) (4) mg, batch (b) (4). At the (b) (4) in-process check on April 4, 2022, the (b) (4) was (b) (4) and (b) (4) compared to a limit of (b) (4); the (b) (4) was (b) (4) and (b) (4) compared to a limit of (b) (4); and the (b) (4) compression force was (b) (4) kN (b) (4) and (b) (4) kN (b) (4) compared to a limit of (b) (4) - (b) (4) kN.

3. The establishment of limits for (b) (4), and (b) (4) compaction force were proposed to be added to existing commercialized batch records without requiring additional validation studies according to protocol FU7-UNITVII-ACQP-0281, effective November 6, 2020. The protocol proposed using historical data from (b) (4) batches to set limits, though no limits have been established as a result of the protocol as of May 9, 2022.

   The protocol does not require additional sampling or analytical data to show the historical ranges would produce tablets meeting all finished product specifications at the higher and lower end of the proposed ranges.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Justin A Boyd, Investigator Darren S Brown, Investigator	DATE ISSUED 5/10/2022

X Darren S Brown Investigator Signed By: 2001647750 Date Signed: 05-10-2022 18:13:50

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	5/2/2022-5/10/2022*
	FEI NUMBER 3007373532

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Mettu Madan Mohan Reddy, Director	
FIRM NAME Aurobindo Pharma Limited	STREET ADDRESS Unit Vii, Formulation Plant, Plot S-1, Survey 411, 425, 434-435, 458, Tsiic, Green Ind. Park
CITY, STATE, ZIP CODE, COUNTRY Polepally, Mahaboob Nagar, Telangana, 509302 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

4. (b) (4) limits were established for (b) (4) Tablets of (b) (4) based on historical data, but no validation studies to show these ranges are appropriate were conducted.

OBSERVATION 3

Batch production and control records do not include complete information relating to the production and control of each batch.

During tablet compression, the machines are set to reject tablets above or below a set percentage of the (b) (4) compression force setting. If the percentage limits are not properly set, the compression machine could accept tablets that may not meet all specifications. The limits are set by production supervisors during machine set-up and can be changed by the supervisor at any time during manufacturing.

The batch records and written procedures do not include any instructions for setting these rejection limits. For all tablet products distributed to the US, the rejection percentages are captured in the machine PLC data, but there is no documentation in the batch records of how the limits were set, who set them, whether they were changed during processing, or review by quality personnel to determine if the limits were established correctly in order to reject tablets with low or high compaction forces that would not meet all specifications.

OBSERVATION 4

The written stability testing program is not followed.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Justin A Boyd, Investigator Darren S Brown, Investigator X Darren S Brown Investigator Signed By: 2001647750 Date Signed: 05-10-2022 16:13:50	5/10/2022

Stability samples are not tested and approved within (b) (4) of the stability withdraw date for assay and impurity methods and within (b) (4) for all other tests as required by procedure FU7-QC-GEN-032. For example, on May 6, 2022, there were 431 stability samples that had been removed from the stability chambers at least 30 working days earlier which had not yet been completed. Examples include:

1. (b) (4) Tablets USP batch (b) (4), 12-month time point with a pull date of March 3, 2022. None of the testing is approved and the dissolution testing is not yet complete. The dissolution failed the L1 stage on March 26, 2022. L2 testing was initiated on April 11, 2022, but an instrument failure caused the testing to be invalidated. Re-testing for L2 had not been initiated as of May 9, 2022.

2. (b) (4) and (b) (4) Tablets USP (b) (4) mg / (b) (4) mg, batch (b) (4), 24-month time point with a pull date of February 11, 2022. The dissolution testing was not initiated until April 21, 2022, and did not meet the L1 criteria. The L2 test had not been initiated as of May 9, 2022.

3. (b) (4) Tablets (b) (4) mg, batch (b) (4), 12-month time point with a pull date of March 6, 2022. None of the testing was approved and the dissolution testing had not yet been initiated.

4. (b) (4) Capsules, batch (b) (4), 18-month time point with a pull date of March 4, 2022. None of the testing was approved and the dissolution testing had not yet been initiated.

5. (b) (4) Suspension (b) g, batch (b) (4), 24-month time point, with a pull date of March 9, 2022. None of the testing was approved and the assay and total titratable

(b) (4) testing had not yet been initiated.

(b) (4) product non-conformance (PNC) reports have been opened to document stability samples that were not tested within established time frames. For example, the number of overdue stability samples documented in previous PNC (b) (4) reports include January 2022 (496 late samples), December 2021 (270 late samples), and November 2021 (148 late samples). No preventive actions have been implemented as part of these previous PNC reports to ensure stability samples are tested according to the established procedure.

OBSERVATION 5

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.

Analysts can delete results from the ABT software used to perform microbial identification. Additionally, the laboratory personnel did not know how to access the audit trail for the software. Form FU7-QC-FORM-0164 "Standalone Instruments Audit Trail Checklist" was completed March 25, 2022. The reviewer indicated the audit trail was enabled and there was no data deletion or modification. At that time, the reviewer did not know how to access the audit trail.

OBSERVATION 6

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

1. The PLC for (b) (4) Machine #7 displayed "0" for the (b) (4) during batch (b) (4) of (b) (4) Tablets (b) mg on May 2, 2022. For in-process checks, the operators record the

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	5/2/2022-5/10/2022*
	FEI NUMBER 3007373532

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mettu Madan Mohan Reddy, Director

FIRM NAME	STREET ADDRESS
Aurobindo Pharma Limited	Unit Vii, Formulation Plant, Plot S-1, Survey 411, 425, 434-435, 458, Tsiic, Green Ind. Park
CITY, STATE, ZIP CODE, COUNTRY Polepally, Mahaboob Nagar, Telangana, 509302 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

pre-batch reading for every time point. (b) (4) is identified as a critical process parameter for this product.

2. The (b) (4) Machine #7 PLC displays data in real time but has been configured to only record process monitoring data (b) (4). On May 2, 2022, the (b) (4), a critical process parameter, was observed outside the established limit of (b) (4), with a value of (b) (4) during the manufacturing of batch (b) (4) of (b) (4) Tablets (b) mg. This was not captured during manual operator checks, the data recorded by the PLC at (b) (4) intervals, or an alarm.

***DATES OF INSPECTION**

5/02/2022(Mon), 5/03/2022(Tue), 5/04/2022(Wed), 5/05/2022(Thu), 5/06/2022(Fri), 5/09/2022(Mon), 5/10/2022(Tue)

X Justin A Boyd
Investigator
Signed By: 2000358686
Date Signed: 05-10-2022 18:14:37

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Justin A Boyd, Investigator Darren S Brown, Investigator X Darren S Brown Investigator Signed By: 2001647750 Date Signed: 05-10-2022 18:13:50	5/10/2022