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	09/12/2024-09/20/2024 FEI NUMBER 3006418686

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Subhash Patil, Unit Head

FIRM NAME	STREET ADDRESS
Aarti Drugs Limited	Plot No. E22, M.I.D.C. Tarapur
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Tarapur, Palghar, Maharashtra 401506 India	API 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

Written procedures is not established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation is not extended to other batches that may have been associated with the specific failure or deviation.

Specifically,

<u>Market complaint</u>

A. On 8/12/2022, you received a market complaint CPL/22005 for (b) (4) for presence of foreign particle during the analysis of Appearance of solution test. The market complaint was for (b) (4) batches (**Table 1**).

You confirmed the presence of (b) (4) foreign particles by inspecting the retain samples of at least (b) (4) batch (b) (4) Through the investigation, you concluded that the root cause is the (b) (4) of the (b) (4) of (b) (4) 22101. The (b) (4) nature of (b) (4) and (b) (4) nature (of the API) caused the (b) (4) of the API at the surface of (b) (4) This (b) (4) material looks like (b) (4) or foreign particle in

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Rajiv R. Srivastava -S Digitally signed by Rajiv R. Srivastava -S Date: 2024.09.20 15:35:34 +05'30'	Rajiv R Srivastava, CSO	09/20/2024
	Suzanne N. Vallez -S Digitally signed by Suzanne N. Vallez -S Date: 2024.09.20 15:55:42 +05'30'	Suzanne Vallez, CSO	

the [redacted] (b) (4) API.

Table 1. Batches of [redacted] (b) (4) implicated with [redacted] (b) (4) foreign [redacted] (b) (4)

You implemented CAPA No. CAPA/23006 on 2/8/2023 and reworked (Corrective action) the batches and applied [redacted] (b) (4) (Preventive action) on the [redacted] (b) (4) surface of the [redacted] (b) (4)

Your investigation is deficient for multiple reasons including but not limited to:

- Your sampling procedure for analyzing the [redacted] (b) (4) impurity has no assurance that the [redacted] (b) (4) particles were part of the sample. The experiment suggests that you tested the API

for the (b) (4) impurity and not necessarily the (b) (4) foreign particle.

- You did not extend the investigation to other batches of APIs that were manufactured in the same equipment, (b) (4) 22101 during the time period that covers the manufacturing dates of the implicated batches. The implicated batches were manufactured between (b) (4) and (b) (4) (**Table 1**, Entries (b) (4) You manufactured at least (b) (4) additional batches amounting to (b) (4) of (b) (4) API between (b) (4) and (b) (4) that were not part of your investigation.

- You reworked (not reprocessed) the above implicated batches and at least (b) (4) reworked batches (b) (4) failed USP specifications for (b) (4) unknown impurity (Specification NMT (b) (4) %). You retested these batches under (b) (4) specification and shipped to the local market and at least one of the batches (Batch No. (b) (4) was shipped to Export market (Morocco). Your procedure Reprocessing and Rework of Intermediate and Finished Product SOP No. 1049 Rev 7 (Effective date 1/29/2023) does not allow shipping of reworked batch to Export market.

<u>OOS results</u>

B. On 1/26/2022 you recorded OOS result OOS (b) (4) 22/02 for (b) (4) API for Appearance of solution test. This OOS result was recorded for Batch No. (b) (4) Your investigation concluded that the probable root cause was due to improper (b) (4) (b) (4) during the (b) (4) operation. You implemented CAPA No. CAPA/22007 and reprocessed the batch and included a foot note in the batch record, "*** (b) (4) (b) (4) ***". Your QC Head (b) (6) could not explain how the operator will determine that (b) (4) Review of the batch manufacturing record suggested that you (b) (4) the failed batch (b) (4) to (b) (4)

(b) (4) the API, which is not part of the original manufacturing process. This confirmed that it was a Rework and NOT Reprocess. The failed batch was reworked to manufacture Batch No. (b) (4) You wrongly designated this batch as a reprocess bath by including "RP" in the batch number.

C. On 6/19/2022 you recorded OOS result OOS (b) (4) 22/07 for (b) (4) for Assay by HPLC method. The OOS result was reported for Batch No. (b) (4) (Mfg. date June 2022 Expiry date (b) (4) This batch was analyzed along with two other batches in the same sequence for Related Substances (RS) and Assay by HPLC method. All the three batches passed the RS test and only one batch, Batch No. (b) (4) failed for the Assay. The tested assay result for the failed batch was (b) (4) % against the Specification (b) (4) % - (b) (4) %. Phase Ia investigation did not reveal any obvious error. The hypothesis test in Phase Ib further confirmed the OOS results. Based on the passing RS test by HPLC method, you concluded that the sample preparation was the issue and made sample preparation as the Assignable root cause. You then retested a single sample and based on the passing Assay values (b) (4) % and (b) (4) %), invalidated the initial OOS result.

You did not follow your procedure for OOS results investigation, SOP No. 1094 Rev 7 (Effective date 3/19/2024) that has a provision for retesting by (b) (4) analysts in (b) (4) Your assignable root cause (Sample Preparation-Human Error) is based on your assumptions and not proven/confirmed by any experiment.

Laboratory incidence

D. On 6/15/2023, you recorded laboratory incidence AI-06-23-002 for sequence that did not start due to power failure during the analysis of (b) (4) for Related Substances (RS) and Assay by HPLC method. The root cause of power failure was due to UPS-I failure. In the Impact Evaluation, you recorded "No any impact". As per your procedure, Preventive Maintenance of UN-Interrupted Power Supply SOP No. 6437 Rev 1 (Effective date 8/28/2023), the UPS-I is

attached/connected to at least (b) (4) equipment in the Quality Control and Production area including but not limited to; Stability Chambers, Incubators, Plant (b) (4) PLC & HMI, and SCADA.

OBSERVATION 2

Test procedures is not scientifically sound and appropriate to ensure that raw materials, intermediates, and APIs, conform to established standards of quality and/or purity.

Specifically,

A. You use inhouse test method for the analysis of Related Substances of (b) (4) (b) (4) by HPLC. A review of the corresponding Analytical Method Validation Report No. MVR/RS/ (b) (4) 01 (Effective date 12/25/2012) confirmed that the method is not validated for impurities; (b) (4) You use this inhouse test method to release the (b) (4) for the manufacturing of (b) (4) API.

B. You use inhouse test method for Assay of (b) (4) by HPLC. The test method was validated at a contract laboratory (b) (4) and then transferred to your laboratory. The method validation report AMVR-009 (Effective date 7/18/2018) confirmed use of three batches of (b) (4) Batch No's. (b) (4) and (b) (4) However, your method verification/transfer Report No. AMVR/Assay (b) (4) 01 (Effective date 8/6/2018) confirmed use of two different batches of (b) (4) Batch No's. (b) (4) Your procedure, Transfer of Analytical Method SOP No. 1067 Rev 02 (Effective date 1/29/2023) requires testing of the same sample for both the sites, contract lab and the (receiving) firm.

C. You use inhouse test method for Assay of (b) (4) USP by HPLC. The test method was validated at a contract laboratory (b) (4) as per the Report No. 14113/05112016/7 (Effective date 11/5/2016). You did not perform a method transfer as per your procedure, SOP 1067 Rev 02 (Effective date 1/29/2023). You use the above method to routinely test and release the API, (b) (4) USP.

D. You use inhouse test methods for Related Substance (RS) and Assay for (b) (4) USP. These methods were validated at a contract laboratory (b) (4) and documented in Validation Report No's. 22289/280215/08, Effective date 2/28/2015 (Assay) and 10698/300315/21, Effective date 3/30/2015 (RS). On 9/19/2024, you stated that the firm has conducted the method transfer and the corresponding report was documented in Method Transfer Report and Protocol of (b) (4) According to your binder, the document was stored in Rack –(G4/5) under File No. 8/13. On 9/19/2023, you were unable to locate the document in your document repository location and were unable to share the report during the curse of inspection.

E. There is no method validation established for growth promotion test of microbiological media. There are no critical steps and parameters identified for this process such as the time limits parameter during sterilization and (b) (4) of the (b) (4) There is no assurance of the sterility of the (b) (4) without establishment and validation of the timeframes. The SOP 2004 titled "For Procure, Receipt and Maintenance Microbial Culture" also failed to provide any defined timeframes during these critical steps.

OBSERVATION 3

You assign the storage conditions and retest or expiry dates of the APIs using test procedures that are not stability indicating.

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Specifically,

A. Your protocol for forced degradation study of [redacted] (b) (4) Document No. AD/FDP/2020/005-09 Effective date 12/16/2020, stated degradation limit to be [redacted] (b) (4) % - [redacted] (b) (4) %. However, the corresponding report, Document No. AD/FDR/2020/005-00 Effective date 2/8/2021 confirmed no degradation such that the subjected API (under all the forced conditions) met the API release specifications.

B. Your protocol for forced degradation study of [redacted] (b) (4) Document No. FDSP-[redacted] (b) (4) -004/2023 Version 00 Effective date 5/10/2023 has no degradation limit stablished and the corresponding report, Document No. FDSR-[redacted] (b) (4) 004/2023 Version 00 Effective date 6/7/2023 confirmed no degradation such that the subjected API (under all the forced conditions) met the API release specifications.

C. Your protocol for forced degradation study of [redacted] (b) (4) Document No. [redacted] (b) (4) FDS/001 Effective date 10/5/2006, stated [redacted] (b) (4) must show some degradation. However, the corresponding report, Report of Forced Degradation Study of [redacted] (b) (4) Effective date 11/9/2006 confirmed no degradation such that the subjected API (under all the forced conditions) met the API release specifications. You concluded the report with a statement, "method followed for forced degradation study is stability indication".

D. Your protocol for forced degradation study of [redacted] (b) (4) USP, Document No. [redacted] (b) (4) 0302 Effective date 2/3/2015, stated degradation limit to be [redacted] (b) (4) % - [redacted] (b) (4) %. However, the corresponding report, Document No. 22290/040315/11 Effective date 3/4/2015 confirmed no degradation such that the subjected API (under all the forced conditions) met the API release specifications.

Your Quality Control department head [redacted] (b) (6) stated that the purpose of the forced degradation study is to evaluate the inherent stability of the API under the forced conditions. He further

stated that all the above forced degradation study confirmed that the corresponding APIs are stable under the forced degradation conditions.

OBSERVATION 4

Written procedures are not established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs.

Specifically,

Your firm has not established adequate cleaning validation for your equipment located in Plant (b) (4) and Plant (b) (4) used in the production of the APIs for the U.S. market. There is no sufficient documentation to support your cleaning method and choice of reagents for your API products. There is also no procedure on how to determine the location of your swabbing and justification for your hard to clean areas selected. For example, your (b) (4) ID # (b) (4) 22101 has only a single swabbing location at the (b) (4) and your (b) (4) ID# (b) (4) 22101 have only a single swabbing location at the (b) (4) but no rationale to support these decisions. In addition, there is also no dirty hold time (DHT) and clean hold time (CHT) studies established for your equipment.

OBSERVATION 5

Responsibilities and procedures for quality units are not in writing and/or followed to ensure the API and intermediates manufactured at your facility are in compliance with CGMP.

Specifically,

A. Your firm failed to provide a comprehensive assessment and remediation plan for your deviation reports DEV-24004, DEV24001 and DEV-24002 to ensure effectiveness. There was no corrective action plan established for DEV-24001 and DEV-200 and the corrective action plan

established for DEV-24004 did not adequate to address the deficiencies.

B. Your firm changed from predominantly [redacted] (b) (4) plates to now exclusively [redacted] (b) (4) plates. There is no documentation of a change control conducted to show adequate implementation and risk assessment of this change. The firm's current SOP 2025 titled "Cleaning of Glassware in Microbiology Laboratory" is the only documentation that has any reference to the use of [redacted] (b) (4) plates in the context of how to clean the plate.

C. Your firm fails to have an adequate tracking system in place to ensure sample traceability in each of the laboratory. There is an initial registration completed upon receival into QC sample storage room. However, after the initial registration there is no sample logbooks maintained by any of the laboratories to provide traceability of the samples and their quantities received or removed from the laboratories.

D. Your firm does schedule and monitor training throughout [redacted] (b) (4) however, the training provided to your firm is insufficient. There are several incidents where activities at the facility are inadequately completed despite training given. For example, your firm has had to retrain several personnel on the same topic due to inadequate completion of an activity, even though all personnel had recently received their required training on the topic. E.g., On 7/29/2023, you recorded laboratory incidence LE-07-23-020 when your employee [redacted] (b) (6) from Intermediate Manufacturing failed to follow procedure to correctly use Electronic Laboratory Notebook (ELN). On 8/9/2023 you recorded another laboratory incidence, LE-09-23-004 for the same issue when your employee from HPLC department [redacted] (b) (6) failed to follow the procedure to correctly use ELN. This confirms that your training is not effective.

E. Your procedure, Reprocessing and Rework of Intermediate and Finished Product SOP No. 1049 Rev 7 (Effective date 1/29/2023) has provision for shipping the reworked batches only after obtaining the stability data for [redacted] (b) (4) You shipped multiple batches of reworked APIs before

completing the (b) (4) of stability data. Batches of reworked APIs that were released/shipped without (b) (4) of accelerated and/or long-term stability data including but not limited to; (b) (4) API Batch Nc (b) (4) Mfg. date December 2023, Shipped on (b) (4) Mfg. date December 2023, shipped on (b) (4) Both batches were manufactured from reworked parent batches.

F. Your procedure, Reprocessing and Rework of Intermediate and Finished Product SOP No. 1049 Rev 7 (Effective date 1/29/2023) has provision for not shipping the reworked batches to Export market. You shipped multiple batches of reworked APIs to Export market. E.g., (b) (4) (b) (4) API Batch No's (b) (4) (shipped to (b) (4) Barcelona) and (b) (4) (shipped to Morocco).

G. Your procedure, Investigation and CAPA SOP No. 1037 Rev 15 (Effective date 6/29/2022) lacks procedure for the Impact Assessment such that you failed to investigate at least (b) (4) batches, amounting to (b) (4) of (b) (4) API. These batches were manufactured along with (b) (4) other batches of (b) (4) API that were implicated with (b) (4) foreign particles as per Market Complaint, CPL/22005.

OBSERVATION 6

Your internal audit is not effective to verify compliance with the principles of CGMP for APIs.

Specifically,

A. Your firm's internal audit is not robust and are all preannounced audits based on a predefined checklist that is included in SOP 1017 titled "For Internal Quality Audit" The selected auditors do not have any defined qualification to be selected as an auditor besides the completion of a

general internal audit training course. There is no assurance that the auditor selected are adequate to conduct the assessment and that the internal audits produce effective results.

B. The Quality Unit conducts a "QA (b) (4) Vigilance Round Observation" activity of the facility (b) (4) these (b) (4) reports are reviewed and trended by the Quality Unit for internal assessment. Neither of these quality activities; the (b) (4) vigilance reports, or the (b) (4) trending, have an establish written procedures on how Quality is to properly conduct and evaluate their findings.

OBSERVATION 7

Records associated with the API distribution were not readily available for inspection. You submitted list of APIs that were manufactured and shipped during the years 2022, 2023 and 2024. During the course of inspection and document reviews, it was discovered that multiple API batches were missing from the submitted list.

Specifically,

A. On 9/15/2024 you submitted a list of Reprocess and Reworked APIs that suggested no (b) (4) batches were Reworked and/or Reprocessed in 2022 and 2023. However, your Market Complain # CPL/22005 suggested that multiple batches of (b) (4) were returned (**Table 1**). These batches were then reworked and distributed to the local as well as Export market. Your Site Head (b) (6) acknowledged the missing data from the shared API list and promised to provide updated list.

B. On 9/19/2024, during the review of OOS result OOS/ OOS (b) (4) 22/07 for (b) (4) for Assay by HPLC method, I noted that the corresponding Batch No. (b) (4) (Mfg. date

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June 2022 Expiry date (b) (4) was missing from the initial list submitted by the firm and from the updated list "Dispatched Detail of Reprocess Batches" shared by the firm on 9/16/2024. Upon review of the Logbook Issuance Register for 2022, I noted the Batch No. (b) (4) was recorded on Page 023 and the bath was shipped to Export market. I also found at least (b) (4) bathes with (b) (4) suffix were recorded in the Logbook Issuance Register. Your QA Executive (b) (6) stated that batch no. with (b) (4) suffix indicates the (b) (4) Bathes. Once again you stated that the during the list compilation, the (b) (4) batches were missed out.

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