PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

STANDARD OPERATING PROCEDURE	
Department: Quality Assurance	**SOP No.:**
Title: Handling of Out of Specification Results	**Effective Date:**
Supersedes: Nil	**Review Date:**
Issue Date:	**Page No.:**

1.0 OBJECTIVE:

To lay down a Procedure for Handling of Out of Specification Results.

2.0 SCOPE:

This SOP is Applicable to Raw Materials (RM), In-process Samples, Finished Products, Stability Samples and stoppage of analysis due to any malfunctioning of the Equipment, Analytical Error or Analyst Error at all Manufacturing Locations & Central Stability Study Facility.

The Procedure shall also be applicable for Stability Samples, which are **"Within Specification but out of Trend"**. The Procedure defines the Investigation Methodology to be followed if OOS Results are confirmed for Intermediate Samples, Finished Products and Stability Samples.

3.0 RESPONSIBILITY:

Manager-QC

4.0 ACCOUNTABILITY:

Head-QA

5.0 PROCEDURE:

5.1 PRECAUTIONS:

5.1.1 Unless it can be reasonably believed that the suspect test result or OOS is by oversight or accidental error in measurement, calculation, data transfer / transcription, etc. all samples, records, materials and such other data required for further investigation shall be preserved till the investigation is completed and concluded by Manager QC.

5.1.2 None of the result, including initial aberrant result shall be omitted from the report.

5.1.3 Investigation should be done timely, unbiased and well documented

5.2 LABORATORY INVESTIGATIONS:

5.2.1 Following are considered for investigation by QC Manager.

5.2.1.1 Results found beyond set limits.

5.2.1.2 Test / results do not comply with pharmacopoeia specification.

5.2.1.3 Analysis discontinued due to malfunctioning of equipment.

5.2.1.4 Analysis discontinued due to an error observed by analyst.

5.2.1.5 Analysis discontinued due to an error by analyst.

5.2.1.6 Any other analysis & analytical data that do not comply with laid down specification due to any unforeseen reason and leading to discontinuation of analysis.

5.2.1.7 Any discrepancy observed during data review.

5.2.2 Test like, Dissolution and Uniformity of Content are evaluated with respect to pharmacopoeia criteria. However, an investigation is carried out for Dissolution results if those are out of trend or significant variation is observed during stability studies.

5.2.3 For Raw Materials, since no detailed / back-up information is available, investigation is limited to laboratory results only.

5.2.4 As soon as any aberrant result, disruption of analysis is observed, analyst shall inform to immediate Officer/Executive and preserve all glass apparatus, sample, dilutions, printouts etc. relate to the analysis by designated Analyst I.

5.2.4.1 And at the same time inform to QA for its record & to allocate OOS Investigation no. to start Investigation findings.

5.2.4.2 QA shall allocate a unique alphanumerical system for Investigation Report follow as **……**.

Where,

QA	**:**	stands for Quality Assurance Department
OOS	**:**	stands for Out of Specification
24	**:**	stands for last 2 digits of current calendar year i.e. 2024
001	**:**	stands for serial no. starts from 001…..

5.2.5 The QC Officer/Executive carries out the investigation reports as shown in **Annexure-I**.

5.2.6 To find out the cause to be Assignable or Non-assignable. Lab Investigation shall be carried out in two Phases :

5.2.7 **Part 1: Immediate Assessment**

5.2.7.1 This shall cover initial assessment of laboratory data and to evaluate whether failure is due to laboratory error.

- Test Method review with the Analyst for correct procedure & knowledge.
- Storage and Handling of Original Sample

- Calculation and / or Transcription Errors
- Glassware used in original measurement and preparation
- Error in dilution of samples, dilution medium, mobile phase etc.
- Standardization of Volumetric Solutions used for Analysis
- Quality of Solvents, Reagents and Analytical Solution
- Correctness of Working Standards
- Calibration status & Performance of Instruments used for analysis
- The Raw Data
- After satisfactory review of the above, if cause is not found out, order, reanalysis of same aliquot (if available) by the Analyst 'I'.
- If immediate assessment does not indicate error, the Officer/Executive informs to Manager QC about the laboratory investigation.

5.2.8 Part 2: Laboratory Investigation

5.2.8.1 This facilitates to identify the probable cause of analytical failure.

5.2.8.2 Manager QC evaluates about:

- Part-1, Investigation Report
- Reanalysis of same Aliquot / sample by different Analyst
- Trend Data

5.2.8.3 **Time Frame:** All laboratory investigations are a priority matter and shall be completed within 3 working days. Depending on the nature of the investigation, time requirement may increase. It shall be justified and documented.

5.2.8.4 If required, as per flow diagram, order re-analysis by **Analyst 'II'** (more experienced & qualified than Analyst I) in duplicate by considering the same preserved samples by Analyst I, in his/her presence. If results are complying with ≤ 3.0 % RSD then OOS is invalid.

5.2.8.5 If ≥ 3.0% RSD, shall go as fresh start for investigation by re-sampling the same samples by QA permission and re-analysis in duplicate by **Analyst 'II' & Analyst 'III'**(More experienced & qualified).

5.2.8.6 If, difference between the average results of Analyst II & Analyst III is ≤2.0% & RSD of 6 sets of data is ≤ 3.0% then shall be consider ok, confirms the OOS Invalid. All these analysis shall be carried out from the same portion of the sample.

5.2.8.7 If, difference between the average results of Analyst II & Analyst III is ≥ 2.0% & RSD of 6 sets of data is ≥3.0% shall be consider not ok & confirms the OOS.

5.2.8.8 If needed and justified, re-analysis may be done more times. However, all results are included in investigation report.

5.2.8.9 If need & justified, previously analyzed and approved sample may be taken for analysis. The results of such analysis shall be a part of Investigation Report.

5.2.8.10 If investigations conclusively prove a laboratory error and confirms to assignable cause like:

- System suitability failure
- Calculation or transcription errors
- Correct methodology is not followed
- Correct specification & test procedure was not followed
- Dilution or contamination error

Action:

- Invalidate the aberrant result.
- Order retests using same sample (if required).
- If the results meet specification, release the subject batch.
- If the cause is repetitive in nature, institute necessary corrective measure to avoid reoccurrence
- Such results are not considered as OOS results.

5.2.9 Reporting of Data:

5.2.9.1 Average value obtained after reanalysis by **Analyst 'II'** & **'III'** (as per flow chart) be considered as the actual value for the batch.

5.2.9.2 If assignable cause is not identified and relate to product quality, safety & stability, the results are considered as **"OOS".** Report the findings along with copy of investigation report to the Head QA.

5.2.9.3 Maintain a record of all Laboratory Investigation including OOS results are maintained in the logbook shown in **Annexure-IV**.

5.3 INVESTIGATIONS BY QA:

5.3.1 QC Manager, after investigation hand over the investigation report to QA Department for reviewing and further investigation.

5.3.2 Head QA reviews the **Annexure-I (**Investigation Report).

5.3.3 If investigation does not lead to **"Assignable Cause"** or **"Laboratory Error",** evaluate **"Sampling Error"**.

5.3.4 Manager QC and Head QA shall review the data for evaluating the possibility of **"Sampling Error".**

5.3.5 Widely varying analytical data may be due to sampling related.

5.3.6 Whether there is adequate evidence to establish errors such as contamination or wrong identification etc. in the first sampling.

5.3.7 Whether it could be established unambiguously that the original OOS results were due to Faulty Sampling or Errors in sampling procedure if yes.

5.3.8 Order re-sampling of the batch.

5.3.9 Re-sampling shall be performed by the same methodology.

5.3.10 Re-sampling shall be authorized by Head QA and documented.

5.3.11 For In-process Materials and Finished Products, analysis shall be carried out from re-sample, in duplicate, by First Analyst & Second Analyst.

5.3.12 If initial OOS result shall be assessed unambiguously as due to sampling error, the results are evaluated by Manager QC and Head QA.

5.3.13 Average value obtained after re-sample testing be considered as the actual value for the batch, Averaging not allowed if individual results not comply with acceptance criteria.

5.3.14 If the investigation determines that the initial OOS result was due to sampling error, an investigation is carried out and documented.

5.3.15 Initial OOS result shall be **INVALIDATED** and the batch may be released.

5.3.16 If results shall be not in compliance with specification, **OOS** result is **CONFIRMED**.

5.3.17 Head QA shall be responsible to hold the In-process Material/Finished Product into quarantine till investigation is concluded.

5.3.18 **Phase II Investigation (Production)** :

5.3.19 When the initial assessment does not determine that laboratory error caused the OOS results & results appear to be accurate, a full scale OOS investigation should be conducted & shall consists of production review or any additional laboratory work.

5.3.20 Investigation shall be carried out by Head Production along with Head QA to assess the failure during processing or any stage of manufacturing as per **Annexure-II.**

5.3.21 If needed, **Annexure-II**, Investigation shall be carried out by a Group consisting of (or any other person as needed).

- Head QA
- Head Production
- Manager QC

5.3.22 Such an investigation shall consist of

- Review / Evaluation into potential manufacturing cause leading to OOS results.
- Evaluation of Batch Manufacturing Records related to the subject batch.
- Trend analysis of previous batches if there is any evidence to indicate failure prior to observation of OOS result and also to assess the impact of failure on previous batches.

5.3.23 The nature and extent of investigation may vary on a case – to – case basis.

5.4 DISPOSITION OF THE BATCH & CORRECTIVE ACTION:

5.4.1 Information included in the **Annexure-I & II** Investigation Report shall be reviewed by the Group consisting of:

- Head Production
- Manager QC
- Head QA

5.4.2 Group shall be responsible to establish and document the cause of failure and also to recommend corrective action.

5.4.3 Observations are recorded in investigation report as shown in **Annexure-III.**

5.4.4 The final disposition of the batch will be reviewed and authorized by Head QA.

5.4.5 To establish the reasons for failure and evolve a corrective action plan, repeated sampling and analysis of the OOS batch is permitted.

5.4.6 The cause analysis shall be carried out by the Group and necessary preventive action is identified.

5.5 DOCUMENTATION:

5.5.1 All documents related to **Annexure-II** & **Annexure-III** investigations are compiled by Quality Assurance Department and reports of all such investigations shall be maintained by Head QA.

5.5.2 All OOS shall be recorded in a logbook & to be maintained by QA.

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5.6 TIME FRAME:

5.6.1 Complete investigations shall be completed within 30 working days.

5.6.2 Based on the investigation, there may be a deviation in mentioned time frame. The same shall be recorded.

6.0 REFERENCE:

(CDER) Guidance–OOS Oct.-2006

7.0 ANNEXURES:

ANNEXURE No.	TITLE OF ANNEXURE	FORMAT No.
Annexure-I	Investigation Report	
Annexure-II	Investigation Report	
Annexure-III	Investigation Report	
Annexure-IV	Out of Specification Investigation Log Book	
Annexure-V	Flow Chart For Out Of Specification Results	

ENCLOSURES: SOP Training Record

8.0 DISTRIBUTION:

- Controlled Copy No. 01 — Head Corporate Quality Assurance
- Controlled Copy No. 02 — Head Quality Assurance Plant-I
- Controlled Copy No. 03 — Head Quality Assurance Plant-II
- Controlled Copy No. 04 — Head Quality Assurance Plant-III
- Controlled Copy No. 05 — Head Quality Assurance Plant-IV
- Controlled Copy No. 06 — Head Quality Assurance Plant-V
- Controlled Copy No. 07 — Head Central Warehouse & Stability Center
- Master Copy — Corporate Quality Assurance Department

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9.0 ABBREVIATIONS:

SOP	Standard Operating Procedure
No.	Number
QA	Quality Assurance
RSD	Relative Standard Deviation
QC	Quality Control
OOS	Out Of Specification
RM	Raw Material
PM	Packing Material

10.0 REVISION HISTORY:

CHANGE HISTORY LOG

Revision No.	Details of Changes	Reason for Change	Effective Date	Updated By

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ANNEXURE-I
INVESTIGATION REPORT
(To be compiled by Quality Control Department)

Date _____

Investigation Report No.	**: QA/OOS/…../…..**
Name of Finished Product / Raw Material / Stability sample & Additional Description (eg. Stability Conditions)	**:**
Lot / Batch No.	**:**
Specification No. & Review No.	**:**
Test Procedure No. & Review No.	**:**
Test in which OOS result is found	**:**
Result Obtained / Description of Problem	**:**
Specification / Issue in Analysis	**:**
Analyst (Referred as Analyst 'I')	**:**
Date of Analysis	**:**
Investigation Started On	**:**
Name of Supervisor	**:**

1.1 Investigation Findings:

Discussion on Test Method with the Analyst:

- Work Book Reference
- Any spillage of solution
- Dilution error

- Any other abnormal observation during analysis
- Review of critical steps followed during analysis.

1.1.1 Whether sample was labeled, stored properly or not:

1.1.2 Calculation and Transcription Errors:

1.1.3 Weighing Errors:

1.1.4 Any error in usage of incorrect / improperly cleaned glass apparatus:

1.1.5 Errors associated with dilutions, mobile phase, filters, and chromatographic conditions etc. that are required by the corresponding analytical procedure:

1.1.6 Whether properly prepared test solution(s) or volumetric solution(s) are used in the analysis:

1.1.7 Whether Reference Standard(s) / Working Standard(s) used in the analysis are correct and assay values are determined correctly:

1.1.8 Review of System Suitability Parameters obtained for the test:

1.1.9 Any malfunctioning and / or out of calibration analytical instruments is used in the analysis:

1.1.10 Any other techniques in analytical procedures which were not appropriately applied during testing:

1.1.11 Review of Raw Data:

1.1.12 Any unusual or unexpected response observed with standard or test preparations:

1.2 Was Assignable cause(s) found? Yes ☐ No ☐

If Yes, Specify the cause(s)

- If cause is calculation error, mention the recalculated result.

1.3 If cause is assignable, re-testing from same aliquot / originally drawn sample.

- Whether such observations are noticed earlier (due to analyst, method, equipment etc.)

Yes ☐ No ☐

- Re-analysis

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Permitted ☐ Not permitted ☐

Re-analysis permitted by (Immediate Officer/Executive):

Results	Analyst 'I'	Analyst 'I' (Repeat)
1		
2		
Average		
Work Book Ref. No.		

Difference between average results (NMT 2.0%):

Sign & Date: Analyst 'I' **Officer/Executive**

Evaluation of Laboratory Investigation (by Manager – QC):

- Review of Investigation Report
- Review of re-analysis data from Analyst 'I'
- Review of trend data (if required)
- Whether analysis by other analyst is required.
- If re-analysis is required, whether from same aliquot or sample.
- Summary of results after re-analysis:

Results	Analyst 'I' (Repeat Results)	Analyst 'II'	Analyst 'III' (If Required)
1			
2			
Average			
Work Book Ref. No.			

Difference between average results (NMT 2.0%):

Analyst 'I' : Date :
Analyst 'II' (if applicable): Date :

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Analyst 'III' (if applicable): **Date :**
Officer/Executive : **Date :**

Conclusion *(Include corrective action / preventive action, if required)*:

Laboratory Failure; Yes ☐ No ☐

Whether OOS is confirmed; Yes ☐ No ☐

(If OOS is confirmed, submit the copy of Investigation Report & enclosures to QA)

Manager – QC (Sign & Date): _____

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ANNEXURE-II
INVESTIGATION REPORT
(To be compiled by Quality Assurance Department)

Date _____

Investigation Report No. **: QA/OOS/…../…..**

Name of Finished Product / Raw Material / Stability Sample **:**

Lot / Batch No. **:**

Test in which OOS result is found **:**

Result **:**

Investigation Started on **:**

Evaluation of Annexure – 1 - Investigation **:**

Evaluation of Sampling Procedure

Sampling Error:

- Any sampling error suspected – Yes ☐ ☐ No
- Remark (if sampling error is suspected) :
- Re-sampling ☐ Permitted ☐ Not permitted
- Re-sampling authorized by Head – QA : _____
- Initially sampled by _____ Re-sampled by _____
  Analysis Data after re-sampling
  Details of results observed:

Results	Analyst 'I'	Analyst 'II'
1		
2		
Average		
Work Book Ref. No.		

Difference between average results (NMT 2.0%):

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Do no include original OOS results:

- **"Sampling Error" confirm -** **Yes** ☐ **No** ☐

Corrective action(s) if an Assignable cause(s) was found?

Conclusion of Investigation:

OOS result is invalidated / confirmed.

Reviewed By: _____ _____

Manager – QC Head – QA

Batch Status: **APPROVED/ REJECTED**

Perform further investigation Yes ☐ No ☐

Head – QA **Date:**

(To be compiled by Production Department)

Date _____

Investigation Report No.	**: QA/ OOS/…../…..**
Name of Finished Product / Raw Material / Stability sample	**:**
Lot / Batch No.	**:**
Test in which OOS result is found	**:**
Result	**:**
Investigation Started on	**:**
Evaluation of Manufacturing process	**:**
Evaluation of Manufacturing Records	**:**
Other Records related to Manufacturing	**:**
Any other Records (eg. Trend analysis etc.)	**:**

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Investigation carried out by:

Head – Production : _____

Head – QA : _____

Manager – QC (if part of investigation team) : _____
(If necessary, attach separate sheets)

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ANNEXURE-III
INVESTIGATION REPORT
(To be compiled by Quality Assurance Department)

Date:----------

Investigation Report No.	**: QA/OOS/…../…..**
Name of Finished Product / Raw Material / Stability sample	**:**
Lot / Batch No.	**:**
Test in which OOS result is found	**:**
Result	**:**
Investigation Started on	**:**
Investigation Completed on	**:**
Evaluation of Annexure – I, Investigation	**:**
Evaluation of Sampling Error	**:**
Evaluation of Annexure –II, Investigation	**:**
Overall Evaluation of Investigation	**:**
Root Cause	**:**
Impact Assessment	**:**
Corrective & Preventive Action	**:**
Justify Delay in Completion of Investigation (if more than 30 days) :	**:**

Reviewed By :

Head – Production

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Head – Quality Assurance

Manager – Quality Control (if part of investigation team)

Head – Manufacturing

Corrective Action Plan :

Disposition of the batch :

Investigation Report Approved By:

Head – QA **Date**

ANNEXURE-IV
OUT OF SPECIFICATION INVESTIGATION LOG BOOK

S.No.	Date of Issuance of OOS Format	Investigation Report (Attached / Not Attached)		OOS Investigation Report No.	Name of the Material / Product	Batch No.	Investigation Started On	Investigation Completed On	Conclusion	Checked By Sign & Date	Remarks
		Quality Control Investigation Report	Quality Assurance Investigation Report								

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ANNEXURE-V

FLOW CHART FOR OUT OF SPECIFICATION RESULTS