PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

STANDARD OPERATING PROCEDURE

Department: Quality Assurance	**SOP No.:**
Title: Handling of Out of Trend Results	**Effective Date:**
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1.0 OBJECTIVE:

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

2.0 SCOPE:

This SOP is applicable for Handling of Out of Trend Results in Raw materials, In-process bulk, Finished Product and Stability Sample at ……..

3.0 RESPONSIBILITY:

QA (Officer/ Executive) : Preparation, Distribution, Revision, Retrieval and Destruction of this SOP. Issuance and maintain the Out of Trend Investigation Log.

QA (Manager) : Review, Training and effective implementation of this SOP to all concerned Departments. Review of OOT Investigation.

QC (Officer/Executive) : Initiation of Out of Trend Investigation.

QC (Manager) : Review and Investigation of Out of Trend.

Production/Warehouse/Engineering: Initiation of Manufacturing Investigation (Phase II).
(Officer/Executive)

Production/Warehouse/Engineering: Review of Manufacturing Investigation (Phase II)
(Manager) Review, Training and Effective Implementation of this SOP to all concerned department.

4.0 ACCOUNTABILITY

Head QA : Approval, Authorization, ensure Training and Implementation of this SOP

Review, Approval of the Out of Trend Investigation Report. Assignment of Subject Matter Expert from Production, Warehouse, Engineering, etc.

Head QC : Training and Effective Implementation of this SOP to concerned Department.

5.0 DEFINITIONS

5.1 Out of Trend Results: An out-of-trend (OOT) result that does not follow the expected trend, either in comparison with previous results collected from past history.

5.2 Test results which are within the specifications but are significantly different from the routine result of analysis e.g. values at the extremes of the specification.

5.3 **Obvious Error:** These errors are observed during execution of analysis and associated with laboratory error like calculation error, power failure, instrument or equipment malfunctioning, testing error, incorrect instrument parameter error.

5.4 **Reanalysis:** In case of assignable laboratory error, analysis to be carried out on the same test solution or on freshly prepared sample composite from the original sample.

5.5 **Retest**: In case of non-assignable laboratory error, analysis to be carried out on the freshly prepared sample composite from the original sample or re-sample.

5.6 **Resample:** A second or additional composite sample collected from a lot or a batch of drug substance or drug product by following a standard sampling procedure.

5.7 **Assignable Cause:** A scientifically justified explanation of the reason for an out of trend test result documented during the laboratory/manufacturing investigation

6.0 PROCEDURE

6.1 IDENTIFICATION OF OOT RESULTS:

6.1.1 To judge whether a particular result is OOT, one must first decide what is expected and in particular what data comparisons are appropriate.

6.1.2 OOT results shall be considered only for finished products, Stability products and Raw materials.

6.1.3 OOT results shall be considered only for critical test parameter like Assay, Related Substance & residual solvent.

6.1.4 There is a need for efficient and practical statistical approach to identify OOT results to detect when a batch is not behaving as expected. So the 3 sigma approach uses to identify OOT.

6.1.5 A minimum of 10 batches data shall be compiled for fixing the Trend range. 10 batches shall be selected as availability of records.

6.1.6 If 10 batches data not available or not manufactured, then OOT limit shall not be determine for that particular product.

6.1.7 Results that obtained from the 10 batches tabulated and then average value & standard deviation values shall be noted.

6.1.8 Standard deviation shall be multiplied by 3 to get the 3 sigma (3S) value.

6.1.9 Maximum limit of OOT results shall be arrived by subtracting the 3S value from the Average value of 10 batches. Minimum value may come in negative also at times.

6.1.10 Same shall be calculated and recorded in format as per "Evaluation sheet for Out of Trend Limit" (**Annexure-VI**) by QC personnel.

6.1.11 A list shall be prepared and maintained to check the OOT limit as per "Index of OOT Acceptance Criteria" (**Annexure-VII**) by QC personnel.

6.1.12 If during review results will suspected, Manager QC shall evaluate the OOT as Annexure- VI.

6.1.13 Any value that shall be out of this range will be considered as Out of Trend (OOT) value or Outlier value.

6.1.14 Wherever specification has only Not more than, than only Maximum limit for trend can be considered. Minimum limit should be excluded.

6.1.15 Any maximum value or minimum value getting out of specification then consider the value up to up limit level.

6.1.16 Example 10 batches observed 98.5, 99.2, 97.9, 96.9, 97.7, 98.5, 99.5, 98.3, 96.8, 97.6, Having standard deviation 0.88 and average value 98.09.

$3S = 3 \times 0.88$

$= \pm 2.64$

Then,

Minimum value: 98.09 - 2.64 = 95.45

Maximum value: 98.09 + 2.64 = 100.73

6.1.17 **Note-** If sufficient data not available, to judge whether a particular result is OOT, one must first decide what is expected and in particular what data comparisons are appropriate.

6.1.18 Any OOT test result obtained shall be immediately reported by QC analyst to the Manager QC for investigation.

6.2 EXECUTION OF OOT RESULTS INVESTIGATION AT QC:

6.2.1 If any OOT test result detected during review, then also a investigation shall be performed by Manager QC.

6.2.2 The analyst shall retain all test preparation, glassware's used, portion of the sample solution, standard solution, chromatograms, worksheet, any records, etc. for investigation.

6.2.3 Manager QC shall inform to QA. Responsible officer/Executive of QA issue "OOT investigation Form" (**Annexure-II)**. QA shall enter the details in the "Log for OOT Test Results" **(Annexure-I)** and assign a unique OOT investigation report number as: **OOT/YY/NNN.**

For example, First OOT of year 2021 shall be numbered as: **OOT/21/001**.

Where,

OOT : Indicates Out of trend

/ : Indicates separator

18 : Indicates last two digits of year 2021

/ : Indicates separator

001 : Indicates serial number of OOT.

6.2.4 The Manager QC along with the QC analyst shall investigate the OOT test result as per "OOT Investigation Form" (**Annexure-II).**

6.2.5 Manager QC shall review work bench, glassware, portion of the sample solution, standard solution instrument parameters, HPLC/GC vial, all analytical documents concerning to OOT test result, which includes worksheet, glassware calibration record. Respective equipment usage logs. Instrument calibration, Solution preparation logs, RS/WS usage log, chromatograms, calculations, qualification of analyst, trend data etc. (Note- the list is not exhaustive and may be extended to other relevant documents).

6.2.6 During review, if any assignable cause is identified as an obvious error or laboratory error, it shall be corrected as per the method of correction recommended in **Annexure-III**. The section head shall arrange for the reanalysis if solutions are within solution stability, if applicable, of the sample solution or second aliquot of the stock sample solution/filtrate or aliquot prepared from the same portion of the original sample preferable by the original or other competent analyst in duplicate test preparation.

6.2.7 If results obtained with in trend, re analysis results shall be reported for further release and closed the investigation along with appropriate CAPA and same shall be approved by Head QA.

6.2.8 During review, if assignable cause is identified by hypothetically, same shall be proven. Based on hypothetically analysis shall be repeated with eliminating error.

6.2.9 During review, if assignable cause or hypothetically it is identified as an improper handling/storage of sample, re-sample shall be done using standard sampling procedure after correcting error. Re-sampling/reanalysis shall be authorized by QA. The section head shall arrange for retesting on fresh sample in duplicate by original & other second competent analyst in duplicate.

6.2.10 If the results of reanalysis or testing done on resample are individually within the normal trend of results, average it and report, **In such case, the initial OOT Test result shall be treated as invalidated**. The proper comment shall be made on worksheet page on initial test result. Record the investigations along with an explanation for the initial OOT Test result and retain the initial test result.

6.2.11 If the reanalysis or testing on re-sample are similar to the initial analysis test results. **In such case the initial OOT test result shall be treated as valid** and investigation shall be further processed.

6.2.12 In case of tests which measure uniformity within the batch such as uniformity of dosage unit, dissolution, blend uniformity etc. if the assignable cause for OOT is not associated with laboratory error, it shall be deal as per the procedure described in the respective pharmacopoeia or validation protocols. Sample shall to be tested to the next level of acceptance criteria of respective test. If assignable cause is identified the test shall be repeated by correcting the error.

6.2.13 In case, no assignable cause to the OOT test result is established, the Head QC shall refer the matter to the Head QA and Head Production for investigation of manufacturing process within 2 working days from the reported, in case of Finished and Stability samples.

6.2.14 In case of Raw Material, manufacturing Investigation not required as the material not manufactured at site. Re sampling or Re analysis shall be perform after Head QA approval from original sample & analysis shall be perform by the original & other second competent analyst in duplicate.

6.2.15 If result found with in trend, Head QA shall decide for further material release /reject.

6.3 EXECUTION OF OOT RESULTS INVESTIGATION AT PRODUCTION:

6.3.1 QA and production shall do joint investigation of manufacturing process to identify the manufacturing error. The investigation shall include but not restricted to:

6.3.1.1 Review of batch manufacturing record to check any deviation from manufacturing procedure or equipment operation procedure or environment monitoring parameter, and yield at different stages etc.

6.3.1.2 Trend data.

6.3.1.3 Equipment maintenance record.

6.3.1.4 Change in facility/equipment/process.

6.3.1.5 Record the investigation in the form "Manufacturing Investigation Report" (**Annexure-IV).**

6.3.2 During review, if any assignable cause is identified as a manufacturing error, Head QC shall treat **OOT Test result as valid** and discontinue the further stages of investigations, the initial OOT test result shall be retained and reported.

6.3.3 Head QA shall decide the further batch disposition.

6.3.4 The Head QA shall take a decision for appropriate Corrective and Preventive Action.

6.3.5 If no manufacturing error is observed, the retesting shall be performed (after Head QA approval) by another two competent analysts from additional portion of the original sample in duplicate.

6.3.6 If the test results are individually within the normal trend of results, the % RSD of two sample result within 2.0%, average it, and report. **In such case, the initial OOT test result shall be invalidated.** The proper comment shall be made on worksheet page on initial test result. Record the investigations along with an explanation for the initial OOT Test result and retain the initial test result.

6.3.7 If result found with in trend, Head QA shall decide for further material release /reject.

6.3.8 If the test results are individually not within the normal trend of results and the % RSD of two sample results not within 2.0%, **the initial OOT test result shall be treated as valid**.

6.4 OOT RESULTS OBTAINED ON STABILITY SAMPLES:

6.4.1 Follow stages described in the steps 6.3 & 6.4

6.4.2 Stability study related OOT results shall be considered as per respective SOP of Stability study i.e. significant change etc.

6.4.3 If the results of reanalysis are not within normal trend of results, the Head QC shall report the findings to Head QA.

6.4.4 QA and QC shall jointly investigate the storage condition of sample in the stability chamber for (a) any deviation in the maintaining of temperature/humidity, (b) location of sample in the chamber, (c) any damage to pack and for any other discrepancy.

6.4.5 In the case of new products, the Head QA may refer the investigation to F&D to identify the cause related to product design.

6.4.6 Any assignable cause noticed shall be handled through proper corrective and preventive action. If no assignable cause is noticed for storage condition, the Head QA may authorize the retest on the original portions of sample by second analysts (Analyst-II & III) in duplicate test preparation.

6.4.7 If the test results are individually not within the normal trend of results, the % RSD of two sample results not within 2.0%, initial OOT test result shall be treated as valid.

6.4.8 If the test results are individually within the normal trend of results the % RSD of two sample results within 2.0%, average it, and report. **In such case, the initial OOT test result shall be invalidated.** The proper comment shall be made on worksheet page on initial test result. Record the investigations along with an explanation for the initial OOT Test result and retain the initial test result.

6.5 All steps leading to OOT investigation shall be documented and review of each investigation for OOT shall be correlated to occurrence of similar incidences in the past. A corrective and preventive action plan shall be prepared depending upon the nature of errors found which caused OOT.

6.6 Section head QC shall review analytical error for any past history in other batches of the same product or other products. Accordingly, review of analytical method, equipment calibration or re-training of analyst may be performed. A complete review of this investigation shall be documented to eliminate recurrence of such incidents in future.

6.7 The OOT investigation shall be completed, within 30 working days of initial OOT occurrence.

6.8 The overall Flow Chart of OOT Results investigation shall be given in **Annexure-V "Flow Chart for Out of Trend Results".**

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7.0 ABBREVIATIONS:

SOP	Standard Operating Procedure
OOT	Out of Trend
RS	Reference Standard
WS	Working Standard
QC	Quality Control
QA	Quality Assurance
RSD	Relative Standard Deviation
HPLC	High Performance Liquid Chromatography
GC	Gas Chromatography
VS	Volumetric Solution

8.0 ANNEXURE

ANNEXURES No.	TITLE OF ANNEXURE	FORMAT No.
Annexure-I	Log for OOT Results	
Annexure-II	OOT investigation Form	
Annexure-III	Laboratory Error and Method of Correction	
Annexure-IV	Manufacturing Investigation Report	
Annexure-V	Flow Chart for Out of Trend Results	
Annexure-VI	Evaluation Sheet For Out of Trend Limit	
Annexure-VII	Index of OOT Acceptance Criteria	

9.0 DISTRIBUTION:

- Controlled Copy No.01 Head Quality Control
- Master Copy Quality Assurance Department

10.0 REFERENCES:

- MHRA Guideline for handling of OOS and OOT

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11.0 REVISION HISTORY:

Revision No.	Change Control No.	Details of Changes	Reason of Changes	Effective Date	Done By
00	Not Applicable	Not Applicable	New SOP		

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ANNEXURE-I

Log for OOT results

S.No.	OOT issuance date	OOT Investigation Report No.	Product/Material	Batch No.	Stage	OOT Description	OOT issued by (Sign & Date)	Investigation Completed on	OOT Valid/ Invalid	Conclusion/ Remarks

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ANNEXURE-II

OOT INVESTIGATION FORM

OOT Investigation Report No.:			**Date on issuance:**
Issued By Officer/Executive QA (Sign & Date)			
OOT Reporting (to be completed by Original analyst or Initiator)			
Material Name		**QC AR No./ Reference No**	
Batch No.		**Mfg. Date**	
Stage of Testing		**Retest/Expiry Date**	
Market/Pack		**Specification No.**	
Test Name		**STP No.**	
Result		**Test Limit**	
Stage of OOT Test Results : **Finished Good** ☐ **Raw material** ☐ **Stability Study** ☐ **Any other** ☐			
Summary of OOT Test Results			
Remark (if any)			
Original Analyst or initiator QC Name (Sign & Date)		**Manager QC Name (Sign & Date)**	

1) LABORATORY INVESTIGATION

1a) PRELIMINARY LABORATORY INVESTIGATION:

Note: Preserve all samples, standards, dilution, glassware and instrument with status label till the completion of investigation.

PRELIMINARY LABORATORIES INVESTIGATION CHECK LIST		
Check points	**Observation** **Yes/No/NA**	**Remark (if Any)**
Investigation for correctable errors		
Is the calculation performed (if any) correctly?		
Any power failure observed during the analysis?		
Was equipment/instrument/ measuring device malfunctioning observed during analysis?		

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Was correct instruments parameter used for analysis e.g. Detector wavelength, oven temperature etc.		
Any obvious error noticed during analysis? e.g. Spillage of sample solution, incomplete transfer of solution etc.		
Decision taken	**Yes/No/NA**	**Remark (If Any)**
Correctable Error found		

If No	To be start the full scale laboratory investigation (i.e. 1 b)
If Yes	Rectify the error and document the result. Original test result to be invalidated.
a. If Only calculation /Typographical error ☐	**Corrected results (For Final reporting) :**
b. If Obvious error i.e. sample or standard related error ☐	Reanalysis from original sample solution or from stock by Original / other competent Analyst in duplicate

Reanalysis Results	**Results (Test-1)**	**Result (Test-2)**	**Mean Result for Final Reporting**

Manager QC **Name:** **(Sign & Date)**		**Head QC** **Name:** **(Sign & Date)**	

CONCLUSION & RECOMMENDATION:

Head QC
Name:
(Sign & Date)

Head QA
Name:
(Sign & Date)

Note: If results found within trend then CAPA shall be initiated (if required) and further OOT investigation shall not be required.

1 b) Full scale Laboratory Investigation

Laboratory Investigation Checklist
(to be completed by Section Head QC with concern analyst)

1.0	Check Parameters (General)	Yes/No/NA	Comments
1.1	Whether analyst was trained & Qualified to perform the test?		
1.2	Is the sample correctly collected and labeled.		
1.3	Sample storage was done appropriately		
1.4	Correct sample was used for analysis.		
1.5	Discussion of the method with the analyst.		
1.6	Correct testing procedure and analytical method was used.		
1.7	Whether glassware were properly cleaned?		
1.8	Correct glassware used for dilutions.		
1.9	Media or Reagent prepared to accordingly to procedure.		

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1.10	Instrument used within calibration validity period.			
1.10.1	**Instrument used (Name & ID)**	**Calibration Due**	**Comments:**	
1.11	Instrument/Equipment setup & operation as per SOP.			
1.12	Appropriate grade of chemical and reagents used within the validity period.			
1.13	Correct normality/morality of volumetric solution used.			
1.13.1	**VS used**	**Valid up to date**	**Strength**	**Comments:**
2.0	**Sample/Standards Preparation**		**Yes/No/NA**	**Comments**
2.1	Sample & Standard Preparations Procedure followed as per test method.			
2.2	Is there any weighing error identified?			
2.3	Correct Potency of standard used in calculation std. is within validity period.			
2.3.1	**Std (s) used**	**Valid up to date**	**Potency**	**Comments:**
2.4	Is the sample properly shaken, sonicated or heated/warmed, extracted as per method of analysis?			
2.5	Are the sample / standard dilutions correctly performed as per method of analysis?			
2.6	Are sample filtered /centrifuged/membrane filtered properly before introduction into instrument or analysis by Classical method?			
2.7	Are samples/standards preparations stored under correct environment/time before analysis?			
2.8	Injection/granules are ground properly.			
2.9	Any errors in calculation and transcription of data.			
3.0	**Check Parameters (Chromatography)**		**Yes/No/NA**	**Comments**

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3.1	Correct column used (e.g. column make, dimension, particle size, end capped/non-end capped, pore size, carbon loading)		
3.2	Any leakages observed in the fittings.		
3.3	Is the correct instrument parameters used ?(e.g. for HPLC-type of detector, flow rate, oven temp., wavelength, Injection volume, sample temp. for GC-type of detector, flow rate, oven temp, injection volume, injection temp., detector temp.)		
3.4	Mobile phase preparation is as per the method (check for composition, pH, air bubbles)		
3.5	Correct needle wash & seal wash used while analysis?		
3.6	Any usual or unexpected response observed with standard or test preparations.		
3.7	Is the baseline was stable before and while analysis?		
3.8	System suitability acceptance criteria were met during the analysis		
4.0	Previous history of product/material		
5.0	Any other observation (If any):		
6.0	**Summary & Conclusion (Assignable/ non assignable/ most Probable cause of OOT):**		

Manager QC (Sign & Date)	**Head QC** (Sign & Date)	**Executive/Manager QA** (Sign & Date)

7.0	**Action to be followed**	**Yes/No**
7.1	**Is assignable cause/Most probable cause identified**	
7.1.1	**If no:** ☐ -Initiation of manufacturing investigation as per Annexure-IV in case of FG. -Initiation of Stability investigation as step 9.0 in case of stability study -In case of Raw material (not manufectured at site) ,Reanalysis shall be perform by the original & other second competent analyst in duplicate after Head QA approval.	
7.2	**If yes:** ☐ Following action to initiated in QC lab	
7.2.1	Reanalysis by Original analyst and other competent analyst on retained sample solution (from stocks or as required) in duplicate.	
7.2.2	Reanalysis by Original analyst and other competent analyst on original retained sample in duplicate.	
7.3	Correction in document (In case of STS/STP/Work sheet/any other).	

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7.4	Any other : for example, in case of sampling error indentified (Point No. 10)	
7.5	Re analysis from original sample by Original analyst and other competent analyst ,In case of Raw material, not manufactured at site	

Manager QC **(Sign & Date)**	**Head QC** **(Sign & Date)**

Comments:

Head QA
(Sign & Date)

8.0	**Results of Reanalysis**		
Analyst-I	**1.**	**2.**	**Average =**
Analyst -II	**1.**	**2.**	**Average =**
Mean Results of Analyst –I & Analyst –II:			

Conclusion: OOT test result is valid / invalid.
Remark: In case of raw material, investigation shall be closed on the basis of above results only.

8.1 If OOT invalid:

Comments:

Head QC
Name:
(Sign & Date)

Head QA
Name:
(Sign & Date)

Note: If results found within trend then CAPA shall be initiated (if required), and further OOT investigation shall not be required.

8.2 If OOT valid:

If OOT is valid, ☐ Initiation of manufacturing investigation as per Annexure-IV.

☐ Initiation of Stability investigation as step 9.0

☐ In case of Raw material (not manufectured at site) ,Reanalysis by shall be perform by the original & other second competent analyst in duplicate after Head QA approval (Result reported as point no 11)

Head QC **(Sign & Date)**	**Head QA** **(Sign & Date)**

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9.0 Stability Investigation Checklist
(To be completed by section Manager QA)

S.No.	Check Parameters (General)	Yes	No	Comments
9.1	Whether there was any malfunctioning or breakdown of stability chamber?			
9.2	Whether there was any failure of utilities? (Powder, Water, UPS)			
9.3	Is the deviation in temperature/humidity monitoring?			
9.4	Any Damage to pack.			
9.5	Whether there a deviation from SOP for sample pull out time?			
9.6	The samples, after pull out, were stored as per the conditions specified in the SOP.			
9.7	The samples were analyzed within the specified time period as in the SOP.			
9.8	Any other (to be specified)			
9.9	Is Assignable cause identified:			

If yes, proceed to step 12.0 and shall handled through proper corrective and preventive action
If no, proceed to steps 10.0 and 12.0

Evaluated by **Executive/Manager QA** **(Sign & Date)**	**Reviewed by** **Manager QA** **(Sign & Date)**

Conclusion & recommendation on the basis of Manufacturing /Stability study investigation:
(Manufacturing investigation i.e. Annexure-IV to be attached.**)**

Approved by:
Head QA
Sign & Date

10.	**RE-SAMPLING** (To be performed only if the investigation it is identified that the sample collected is not a representative of batch)
	Reason of Re-sampling

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	Sampling Plan:		
	Remarks or Special instructions:		
	Section Head QC **Sign & date**	**Head QC** **Sign & date**	
	Comment:_____ **Head QA (Approved by)** **Sign & Date**		
11.	**Result of Retesting :** ☐ On original sample ☐ On re-sample		
	S. No.	**Analyst-II** **Name of Analyst :**	**Analyst-III** **Name of Analyst :**
	1.		
	2.		
	Average		
	% RSD		
	Mean Result **(Analyst-II & III)**		

Conclusion: ☐ OOT test results invalid (Based on the Mean result of Analyst-II & III)

☐ OOT test result are valid – Report initial results

Comments : _____

Operation Manager QC
(Sign & Date)

Head QC
(Sign & Date)

12.0	**SUMMARY AND CONCLUSION:** (Based on report of laboratory and Manufacturing/Stability Investigations) **Head QC** **Sign & Date**
12.1	**CORRECTIVE AND PREVENTIVE ACTION (IF LAB ERROR OBSERVED):** **Put "√" Mark**

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	Required ☐ **Not Required** ☐ **If required, note Reference CAPA No.:**_____ **If not required mention justification:** **Head QC** **Head QA** **(Sign & Date)** **(Sign & Date)**
12.2	**SUMMARY AND CONCLUSION:** **Head QA** **Sign & Date)**
13.0	**LIST OF ATTACHMENTS:**
14.0	**SUBMISSION TO QA ON:** **Submitted By** **Received By QA** **(Sign & Date)** **(Sign & Date)**

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ANNEXURE-III
LABORATORY ERROR AND METHOD OF CORRECTION

(**Note –** The list is not exhaustive and may be extended to other laboratory errors)

S.No.	Laboratory Error	Corrective Action
1.	Missing critical steps during analysis, techniques in analytical procedure were not appropriately applied	Repeat analysis with fresh preparation of all solutions or prepare final dilution by diluting previous stock solution (if within solution stability).
2.	Dilution error	
3.	Use of non-appropriate and/or calibrated volumetric glassware	
4.	Glassware not properly cleaned	
5.	Use of non-appropriate grade of chemical, reagents, reference standard, glassware and filter papers.	
6.	Non standard quality of volumetric solution, RS/WS solution, resolution, impurity test mixtures etc. within the expiry period or usage of contaminated chemicals, reagent and volumetric solutions	
7.	Weighing errors (check sample weight and measurements)	
8.	Non homogeneity of sample (process related error/sampling error)	
9.	Instrument/equipment malfunction or poor performance of equipment/instrument	Repeat analysis with same solutions (if within solution stability) after resolve the error or use of another appropriate equipment / instrument / column
10.	Poor HPLC/GC column performance	
11.	Selection of wrong chromatographic parameters	
12.	Septa, glass insert, HS bottle sealing problem in GC/HPLC	
13.	Failure of system suitability	
14.	Software problem	
15.	Calculation error (check raw data)	Striking off incorrect values and inserts the correct value and recalculate. Put signature and date with proper reason
16.	Transcription error with respect to value of LOD/Water or potency of Reference standard/working standard used	
17.	Transcription error	
18.	Analyst error	Repeat test by removing analyst error and Use of correct specification
19.	Use of incorrect specification	

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ANNEXURE-IV
MANUFACTURING INVESTIGATION REPORT

OOT Investigation Report No.:			**Date if issuance:**
Issued By Officer / Executive QA (Sign & Date)			
Product Name		Mfg. date	
Batch No.		Expiry Date	
Test Name		STP No.	
Result		Test Limit	

MANUFACTURING INVESTIGATION CHECK LIST
(To be completed by Head Production & Verified by Head QA)

S.No.	CHECK PARAMETERS (General)	YES/NO/NA	COMMENTS
1.	Is correct batch manufacturing record used?		BMR No.
2.	Correct quantities of correct ingredients were used in manufacturing.		
3.	Balance used in dispensing/verification were calibrated using valid standard weights?		
4.	Equipment as specified in the batch manufacturing record were used in manufacturing.		
5.	The processing steps were followed in correct sequence as per BMR.		
6.	All the processing parameters were within the range specified in BMR.		
7.	The components, intermediates, in-process materials were stored as per the conditions specified in the BMR.		

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S.No.	CHECK PARAMETERS (General)	YES/NO/NA	COMMENTS
8.	The storage hold times for various stages were exceeded.		
9.	Environmental conditions during manufacturing were as per the limits in BMR.		
10.	Whether there was any deviation from the manufacturing process?		
11.	The yield at different stages were within the acceptable range as defined in the BMR.		
12.	All the monitoring equipments used in the processing were calibrated.		
13.	All the processing equipment were maintained as per preventive maintenance schedule.		
14.	Whether there was any malfunctioning of equipment or breakdown during processing?		
15.	Whether there were any failure of utilities (like power, water, compressed air steam etc) associated with the process?		
16.	All the in-process checks were performed as per the defined frequency and the results were within acceptance criteria.		
17.	Any other (To be specified)		
18.	Summary & Conclusion (Assignable/ non assignable/ most Probable cause of OOT):		

Manager Production (Sign & Date)	**Head Production** (Sign & Date)	**Executive/Manager QA** (Sign & Date)

S.No.	Action to be followed	Yes	No
19.	**Is assignable cause/Most probable cause identified**		
19.1	**If no.:** Head QA shall be decide for further re-sampling /re analysis		
19.1.1	**COMMENT OF HEAD QA FOR RE -SAMPLING/REANALYSIS/OTHER IF ANY.** (Continue Laboratory investigation as Annexure-II , point no 10 , 11 & 12) **Head QA**		

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	(Sign & Date)
19.2	**If Yes:** Head QA shall be decide for batch deposition.
19.2.1	**SUMMARY AND CONCLUSION OF MANUFACTURING INVESTIGATION:** **Manager QA** **(Sign & Date)**
19.2.2	**CORRECTIVE AND PREVENTIVE ACTION:** **Put "√" Mark** **Required** ☐ **Not Required** ☐ **If required, note Reference CAPA No.:**_____ **If not required mention justification:** **Head – Production :** Name (Sign & Date) _____ **Head – QC :** Name (Sign & Date) _____ **Head – QA** : Name (Sign & Date) _____
19.2.3	**IMPACT ASSESSMENT:** **Impact On** **(Mark✓ whichever is applicable else NA to be done)** **Detail of Impact Assessment:** **Manager QA** **(Sign & Date)**
19.2.4	**RECOMMENDATION:** **Head QA** **(Sign & Date)**

Complete Batch		Equipment	
Product Quality		Formulation	
Specification		Stability Studies	
STP		Validation Studies	
Training		Other	

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19.2.5	**DISPOSITION OF THE BATCH:** **Head QA** **(Sign & Date)**
19.2.6	**SUMMARY AND CONCLUSION:** **Head QA** **(Sign & Date)**
21.	**SUBMISSION TO QA ON:** **Submitted By** **Received By QA** **(Sign & Date)** **(Sign & Date)**

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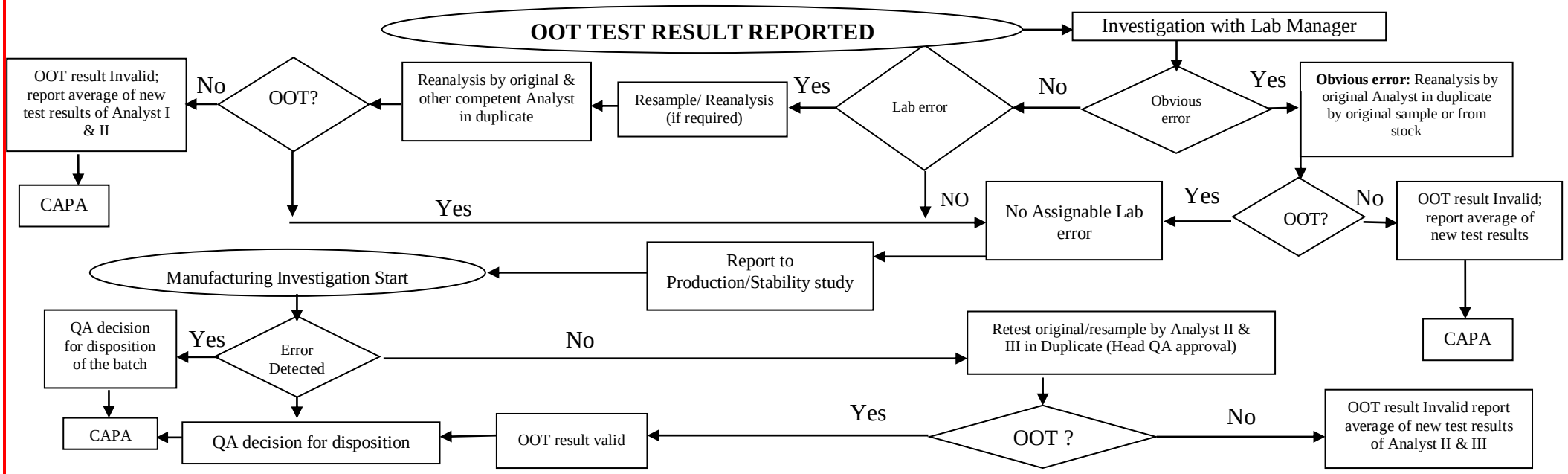
ANNEXURE-V
FLOW CHART FOR OOT RESULTS



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ANNEXURE-VI
EVALUATION SHEET FOR OUT OF TREND LIMIT

Generic Name:
Strength:
Dosage Form:
Test Name:

S.No.	Batch No.	Mfg. date	Exp. date	Observed results (Limit)
Average value				
Standard Deviation (SD)				
3 sigma value (3S) = 3 x SD				
Minimum limit = Average value - 3S value				
Maximum limit = Average value + 3S value				
Evaluation of OOT Results (Based on the above calculations)				**Minimum limit:** **Maximum limit:**

Conclusion:

Prepared By	Checked By	Approved By
Officer/Executive QC	Manager QC	Head QC
Sign &Date	Sign & Date	Sign& Date

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ANNEXURE-VII
INDEX OF OOT ACCEPTANCE CRITERIA

Effective Date: **Revision No.:**

S.No.	Generic Name	Strength	Dosage Form	Test	Minimum limit (%)	Maximum limit (%)

Remark (If any):

Prepared By
Officer/Executive QC
Sign & Date

Checked By
Manager QC
Sign & Date

Approved By
Head QC
Sign& Date