DECODING PHARMA

QUALITY ASSURANCE DEPARTMENT

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

1.0 OBJECTIVE:

The purpose of this SOP to lay down the procedure for dealing with out of specification (OOS) results.

2.0 SCOPE

This standard operating procedure is applicable to situations arising in the event of a product failing to meet the laid down specification. Scope of implementation of the standard operating procedure is limited to validated products, methods, processes and sample received from plant, tested accordance with existing Pharmacopoeia or In-house methods and having laid down specifications.

3.0 RESPONSIBILITY:

3.1 Executive-Quality Assurance - Prepare the SOP and follow-up the SOP accordingly.

3.2 Asst. Manager-Quality Assurance/Production/Quality Control-Provide the support to the implementation of SOP and maintained the records.

3.3 Head–QA shall be responsible for insure the compliance of the procedure and implementation of this SOP.

5.0 DISTRIBUTION

5.1 Quality Assurance

5.2 Quality Control

5.3 Production

5.4 Ware house

5.5 Engineering

6.0 DEFINITION & ABBREVIATION(S)

6.1 Definitions

6.1.1 Test results that fall outside the established specifications or acceptance criteria of in-process samples, process validation samples, finished products and stability samples shall be investigated. OOS Test Result is caused by either laboratory error or operator’s error or manufacturing process errors.

6.2 Abbreviations

6.2.1	SOP	:	Standard Operating Procedure
6.2.2	QA	:	Quality Assurance
6.2.3	OOS	:	Out of Specification
6.2.4	cGMP	:	Current good Manufacturing Practices
6.2.5	HR	:	Human resource
6.2.6	QC	:	Quality Control
6.2.7	CAPA	:	Corrective action and Preventive action
6.2.8	USFDA	:	united States food and drug administration
6.2.9	CDER	:	Center for drug evaluation and research

7.0 **PROCEDURE**

7.1 QC Investigations of "Out of Specification (OOS)" shall be done in cases of:

7.1.1 Batch release testing and testing of starting materials.

7.1.2 In- Process Control testing.

7.1.3 Stability studies on marketed batches of finished products and or active pharmaceutical ingredients, ongoing / follow up stability (no stress tests).

7.1.4 Previous released batch used as reference sample in an OOS investigation showing OOS or suspect results.

Note: The OOS process is not applicable for In-process testing while trying to achieve a manufacturing process end-point i.e. adjustment of the manufacturing process. (e.g. pH, viscosity), and for studies conducted at variable parameters to check the impact of drift (e.g. process validation at variable parameters).

7.2 Chemist finding out of specification result shall immediately stop the analysis and inform to Head QC immediately. The Analyst should retain all the sample/standard solutions.

7.3 Head QC shall carryout the primary investigation (Phase I). The investigation shall include the following but not limited to.

7.3.1 **Phase – I:** Initial Assessment

7.3.1.1 System Failure (Phase –I a Investigation)

7.3.1.1.1 Power failure

7.3.1.1.2 Calibration check failure

7.3.1.1.3 Standard/ sample spoiled by spillage/ contamination

7.3.1.1.4 Unsuitable instrument used

7.3.1.1.5 Instrument parameters incorrectly set

7.3.1.2 Analyst Failure(Phase –I b Investigation)

7.3.1.2.1 Errors in calculation

7.3.1.2.2 Errors in dilution

7.3.1.2.3 Confirm appropriate and valid standard used

7.3.1.2.4 Methods are not followed correctly

7.3.1.2.5 Inappropriate balance used

7.3.1.2.6 Inappropriate storage of samples

7.3.1.2.7 Sampling Procedure not followed

7.3.1.2.8 Hypothesis and investigation testing

7.3.1.2.9 Microbiology testing failure

7.3.1.2.10 Trend excursion

7.3.1.2.11 Assignable cause

7.3.1.2.12 Non Assignable

Note: For Microbiological analysis where possible once a suspect result has been identified ensure all item related to the test failure are retained such as other environmental plate ,dilutions, temperature data, auto- pipettes reagents-growth media. No implicated test environmental plates should be destroyed until the investigation has been completed

7.4 **Phase –I a Investigation**: If investigation proves that OOS results were because of system failure, the same analyst shall repeat the analysis on same sample preparation duplicate

7.4.1 If both the results are within specifications, the batch shall be considered for release.

7.4.2 If one or both the results are outside the specifications, Phase- I b procedure shall be followed.

7.5 **Phase –I b Investigation**:

7.5.1 All the retained solutions, test units and glass wares used in the original measurements and preparations shall be re-examined to as certain the reliability of every individual values.

7.5.2 The initial analyst (A) and another analyst (B) shall repeat the analysis on same sample in duplicate. If the results of both analysts are within specifications the batch shall be considered for release.

7.5.3 If however, one or both the duplicate results are outside the specifications, Phase II procedures shall be followed.

7.5.4 After repeat analysis when the batch is considered for release, original OOS result shall be invalidated but shall be retained as a record.

7.5.6 If initial investigation is not conclusive, a formal report shall be prepared by Head QC within two working days and shall immediately inform Head QA to initiate phase II investigation.

7.6 **Phase- II investigation**

When the phase I investigation did not reveal as assignable laboratory error Phase II investigation are driven by written and approved instructions against hypothesis/investigative

testing. Prior to further testing a manufacturing investigation should be started to determine whether there was a possible manufacturing root cause.

7.6.1 When a laboratory error is not identified, or duplicate analysis results is found out of limit then investigation shall be extended to process/manufacturing area for identifying any operator or process related error

7.6.2 The Phase-II investigation shall be carried out by Head-QA/designee in presence of Head-Production & Store Head (if necessary) as per 'Phase -II investigation report'

7.6.3 Carry out the complete evaluation of Batch Manufacturing Record (BMR) related to the subject batch

7.6.4 Trend analysis of the batch studied to see if there is any evidence to indicate failure to indicate prior to observation of OOS result and also to assess the impact of failure on previous lots

7.6.5 If in a full scale production error found then QA head take decision for further process.

7.6.6 If any assignable cause found Disposition Batch should be carried out and take CAPA as per SOP.

7.6.7 In full scale production investigation does not reveal any conclusive reason for the initial OOS result then re-sampling and re-testing and hypothesis testing shall be done (No Assignable root cause).

7.6.8 **Resample, Retesting and Hypothesis/investigative testing** :

7.6.8.1 Re sampling for retesting shall be performed if Investigation of lab error Phase-I and Production Investigation Phase-II does not reveal any conclusive reason for the initial OOS result

7.6.8.2 Re-sampling perform after the approval from Head-QA

7.6.8.3 Retesting analysis shall be done in triplicate by two analyst

7.6.8.4 The batch shall be approved and average of six values (averaging) shall be reported on certificate of analysis all six individual results are within specifications limits .in any one the case further Phase III investigation started and appropriate action shall be taken by the quality head.

7.6.8.5 **Hypothesis/Investigative Testing**: Is testing performed to help confirm or discount a possible root cause i.e. what might have happened that can be tested , for example it may be include further testing regarding sample preparation, sonication/extraction, and potential equipment failures etc Multiple hypothesis can be explored. Hypothesis should be started at phase I a and continue to Phase II if no assignable cause found

7.6.8.6 **Re Test:** Performed the test over again using material from original sample composite, If it has been compromised and or still available .If not a new sample will be used. The second analyst should be at least as experienced and qualified in the method as the original analysis.

7.6.9 **Re sampling:**

7.6.9.1 Re-sampling is done only in the following cases

7.6.9.2 If investigation shows that the original sample was prepared improperly and was therefore not representative of the batch.

7.6.9.3 If investigation shows that the sample is in process and causes such as

7.6.9.3.1 Mixing Time

7.6.9.3.2 Incorrectness of components added.

7.6.9.3.3 Manufacturing equipment malfunctioning.

7.6.10 **OOS related to Microbial Investigation:** For Out of specification related to Microbiological Testing the following points shall be reviewed.

7.6.10.1 Discuss the test method with microbiologist, confirm microbiologist's knowledge, adherence to standard operating procedure, standard test procedures relevant training.

7.6.10.2 Whether negative and positive controls of all the media used were satisfactory. Review the related records.

7.6.10.3 Whether sterilized containers and sampling aids were used for sampling.

7.6.10.4 Whether sampling was done as per standard operating procedure.

7.6.10.5 Whether media were prepared as per standard operating procedure, review the media preparation records.

7.6.10.6 Whether media used for analysis were within the validity period on the date of analysis.

7.6.10.7 Whether instruments used were calibrated/validated, verified and maintained as per standard operating procedure.

7.6.10.8 Whether manometer reading of Laminar Air flow Unit was within the limit.

7.6.10.9 Whether environmental monitoring results of the testing area and laminar air flow unit was within the limit and as per trend.

7.6.10.10 Whether the documented evidence available in support of analysis carried out and checked.

7.6.10.11 Whether any other sample tested on the same date, showing out of trend results.

7.6.11 **Averaging:** The validity of averaging depends upon the sample and its purpose .Using averaging can be providing more accurate results. For in the case of microbiological assays the use of averages because of the innate variability of the microbiological test system or HPLC consecutive replicate injections from the same preparation (determination is considered one test and one result)

7.6.11.1 Averaging cannot be used in cases when testing is intended to measure variability within the product, such as powder blend /mixture uniformity or dosage from content uniformity.

7.6.11.2 Averaging has the disadvantage of hiding variability among individual test results. For this reason all individual test results should be reported as the separate values, a single averaged result can be reported as the final test result .The standard deviation (or relative standard deviation) is reported with the individual unit dose test results

7.6.11.3 Averaging must be specify in the test method and RSD should be below the 1%.

7.6.11.4 If Product is pass than release the Batch. And If fail than Disposition the batch and go next stage (Phase-III).

7.7 **Phase- III (Expanded investigation)**:

7.7.1 The Phase III investigation should review the complete manufacturing investigation and combined laboratory investigation into the suspect of analytical result by Head QA and method validation for possible cause into the result obtained. Correct cause should be identified and appropriate action should be decided.

7.7.2 To conclude the investigation report should contain summary of the investigation performed and detailed conclusion

7.7.3 For microbiology investigation, where it may not be possible the actual root cause therefore robust most probable root cause may be given. If no assignable cause found, Disposition Batch should be carried out.

7.7.4 Following point shall review thoroughly during expanded investigation.

7.7.4.1 Verify the stores physical stock of all the materials used for said batch.

7.7.4.2 The manufacturing Process.

7.7.4.3 History of the Manufacturing of the material under test.

7.7.4.4 Results of in-process testing.

7.7.4.5 Results of other tests conducted on material.

7.7.4.6 Previous history of testing the material.

7.7.4.7 Information from Supplier's Certificate Of Analysis (where appropriate)

7.8 The Quality Assurance Department assigns tracking number to Out of Specification as follows

Out of Specification Number: OOS-XY-YYY

Where, XY stands for last two digit of respective year (i.e.) 15 indicates the year 2015.

YYY- serial Number e.g. 001,002…. stands for the continuous serial number of respective out of specification in the respective year.

7.9 Note: for investigation completed time.

7.9.1 OOS investigation should be completed within 15 days from the time of report of OOS results; extension of this time should be justified and documented.

7.9.2 In case of OOS related to tests of purified water, the purified water shall not release to production till investigation and corrective action completed.

8.0 REFERENCE(S) & FORMATS (S)

8.1 References

8.1.1 MHRA (Medicine and healthcare products regulatory agency)

8.2 Formats

8.2.1 Format - I : Laboratory investigation checklist of phase-IA

8.2.2 Format - II : Laboratory investigation report phase – IB

8.2.2 Format - III : Investigation report phase – II

8.2.3 Format - IV : Final review of investigation report (PHASE III)

8.2.4 Format - V : Out of specification register

8.2.5 Format - VI : Decision Tree (OOS)

9.0 REVISION HISTORY

9.1 Refer SOP for SOP Format: X (Format for Document History sheet) as attached