DECODING PHARMA

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 Handling of Out of Specification Results of ……..

3.0 RESPONSIBILITY:

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

QA (Manager): Review, Training and effective implementation of this SOP to all concerned Departments.
Review of OOS Investigation through Root cause Analysis, Impact Assessment/Risk Assessment, and CAPA.

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

QC (Manager) : Out of Specification Investigation through Root cause Analysis, Impact Assessment/Risk Assessment and CAPA Implementation in time.

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 Specification Investigation Report. Assignment of Subject Matter Expert from Production, Warehouse, Engineering.

Head QC : Training and Effective Implementation of this SOP to concerned Department. Root Cause Analysis, Impact Assessment/Risk Assessment, and CAPA Implementation in timely manner.

5.0 DEFINITION:

5.1 Out of Specification (OOS) Test Result: Test result that does not comply with the pre-determined acceptance criteria (i.e. for example, filed applications, drug master files, approved marketing submissions, or official compendia or internal acceptance criteria).

Test results that fall outside of established acceptance criteria which have been established in official compendia and/or by company documentation (i.e., Raw Material Specifications, In-Process/Final Product Testing, Stability testing etc.).

The term OOS results includes all test results that fall outside the specifications or acceptance criteria established in drug applications, drug master files (DMFs), official compendia, or by the manufacturer. The term also applies to all in-process laboratory tests that are outside of established specifications

5.2 Aberrant/Anomalous Results: Result that are still within specification but are unexpected Questionable, irregular, deviant or abnormal. Example would be chromatograms that show unexpected peaks, unexpected results for stability test point, etc.

5.3 Assignable Cause: Documented and scientifically justified determination that the result can be traced to laboratory error. For example analyst error, instrument error, etc.

5.4 No Assignable Cause: When no reason could be identified.

5.5 Analyst Error: An error attributable to the person performing the test such as sample or standard preparation error, calculation error, use of expired standards or reagents, incorrect settings of instrument parameters etc.

5.6 Laboratory Error: An error associated with the performance of a test procedure or due to laboratory instrument failure.

5.7 Hypothesis/Investigative Testing: Testing is performed to help confirm or discount a possible root cause i.e. what might have happened that can be tested: - for example it may include further testing regarding sample filtration, sonication /extraction; and potential equipment failures etc. Multiple hypotheses can be explored.

5.8 Re-Testing: Analysis performed using the sample from same homogeneous material that was originally collected from the lot, tested, and yielded the OOS results. For a liquid product, it may be from the original unit liquid product or composite of the liquid product. For a solid dosage form, it may be an additional weighing from the same sample composite prepared for the original test. In test

procedures which ask for testing of whole unit, additional units may be tested from the original sample taken.

Performing the test over again using material from the original sample composite, if it has not been compromised and/or is still available. If not, a new sample will be used.

5.9 Re-Sampling: Re-sampling refers to specimen from any additional units collected as part of the original sampling procedure or from a new (fresh) sample collected from the batch when investigation reveals that the initial (original) sample may not be representative of batch.

A new sample from the original container where possible, required in the event of insufficient material remaining from original sample composite or proven issue with original sample integrity.

5.10 Most Probable Cause: Scientifically justified determination that the result appears to be laboratory error.

5.11 Invalidated Test: A test is considered invalid when the investigation has determined the assignable cause.

5.12 Reportable Result: Is the final analytical result. This result is appropriately defined in the written approved test method and derived from one full execution of that method, starting from the original sample.

5.13 Calculation Error: Analyst and Manager to review both initial (sign) and date correction.

5.14 Power Outage: Analyst and Manager document the event, annotate “power failure; analysis to be repeated” on all associated analytical documentation.

5.15 Equipment Failure: Analyst and Manager document the event, annotate “equipment failure; analysis to be Repeated” cross reference the maintenance record.

5.16 Obvious Errors: For example, spilling of the sample solution, incomplete transfer of a sample; the analyst must document immediately.

5.17 Incorrect Instrument Parameters: For example setting the detector at the wrong wavelength, analyst and Manager document the event, annotate “incorrect instrument parameter”; analysis to be repeated” on all associated analytical documentation.

5.18 Specification: A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests

described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture shall conform to be considered acceptable for its intended use. "Conformance to specification" means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

5.19 Regulatory Approved Specification: Specifications for release testing. If no release specifications have been established then the internal specification becomes the release specification.

5.20 Acceptance Criteria: Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures which the drug substance or drug product or materials at other stages of their manufacture shall meet.

5.21 Internal Specification: Internal Specification are also action limits within regulatory specifications.

5.22 Invalidated Test: A test is considered invalid when the investigation has determined the assignable cause.

5.23 Reportable Result: Is the final analytical result. This result is appropriately defined in the written approved test method and derived from one full execution of that method, starting from the original sample.

6.0 PROCEDURE:

6.1 OOS PROCEDURE IS APPLICABLE/NOT APPLICABLE FOR:

6.1.1 **OOS Procedure Applicable for :**

6.1.1.1 Tests performed (Pharmacopoeial and In-house) in the laboratories on Raw Materials (RM),In-process Samples, Semi – Finished Goods (SFG), Finished Products, Stability Samples.

6.1.1.2 In case of Raw material OOS investigation shall be limited to laboratory phase only.

6.1.1.3 Exhibit Batches / Registration Batches.

6.1.1.4 Batches for clinical trials.

Note: In case a special expertise required for investigation of highly complex process or method, Head QA shall assign the Subject Matter Expert from R&D or any other department.

6.1.2 **OOS Procedure Not Applicable For:**

Note: This SOP is not applicable for Microbiological OOS including Biological Assay.

6.1.2.1 Method Validation, Verification (Repeatability and intermediate precision) and method transfer studies.

6.1.2.2 Test performed for Market Complaint Evaluation.

6.1.2.3 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).

Non-routine studies such as (Not limited to):

6.1.2.3.1 Technical market sample study.

6.1.2.3.2 Innovators (Reference listed drug) analysis done for evaluation purpose.

6.1.2.3.3 Analyst validation done on specimen samples not for product evaluation.

6.1.2.3.4 Evaluation of samples (purchase sample) from vendors for vendor approval purpose not intended for use in the manufacturing of batches for market.

6.1.2.3.5 Pharmacopoeia monograph change evaluation.

6.1.2.3.6 Working standard shelf life evaluation study.

6.1.2.3.7 Hold time study sample.

6.1.2.3.8 Rinse and swab water sample.

6.1.2.3.9 Stability study conducted on additional time points intervals beyond shelf life to evaluate drug product and to generate data as well as for stability interval testing for which investigation at previous interval of same condition for OOS test result is already performed, concluded and study is further continued to generate data for information.

6.2 GENERAL PROCEDURE FOR OUT OF SPECIFICATION INVESTIGATIONS:

6.2.1 Whenever any OOS test result is observed, investigation must be conducted to determine the root cause of the OOS result and shall be recorded along with conclusion and corrective and preventive action.

6.2.2 The source of the OOS result shall be identified either as an aberration of the measurement (analysis) process or an aberration of the manufacturing process.

6.2.3 The investigation shall be thorough, timely, unbiased, well-documented, and scientifically sound.

6.2.4 At any stage of investigation, if OOS results are confirmed and root cause is identified successfully, the OOS investigation may be terminated. If OOS results for a test is confirmed as material or product defect, remaining tests as per specification need not be carried out.

6.2.5 If there is an unexpected stability trend then the result must be confirmed by the investigation. If at any stage of the investigation a previous history of OOS / A typical result for the product batch is indicated or if previous problem have been experienced with the methodology, then Head QA shall decide whether continue or not to continue with the investigation.

6.2.6 In case of OOS reported at contract analytical laboratory, investigation shall be carried out by the contract laboratory. Need based participation in the OOS investigation shall be under taken.

6.2.7 Based on the reported OOS by contract analytical laboratory, QA shall log the OOS and review the investigation report along with supporting documents submitted or provided by the contract laboratory as per contract agreement for further course of action.

6.2.8 If OOS is identified in the starting material, which is used in the products or which is manufactured under the contract with an outside company (i.e. trade owner / third party, contract partner) and / or for export market, information shall be sent to the MAH through Regulatory affairs through mail or fax as soon as OOS is observed during Phase-I laboratory investigation. (As per party agreement).

6.2.9 **Responsibility of Analyst:**

6.2.9.1 The first responsibility for achieving accurate laboratory testing results lies with the analyst who is performing the test. The analyst shall be aware of potential problems that could occur during the testing process and shall lookout for the problems that could create inaccurate results.

6.2.9.2 The analyst shall ensure that only those instruments meeting established performance specification are used and that all instruments are within the acceptance criteria of calibration.

6.2.9.3 The analysts shall ensure the system suitability requirement of analytical method.

6.2.9.4 Analysts shall check the data for compliance with test specifications before discarding test preparations or standard preparations. When unexpected results are obtained and no obvious explanation exists, test preparations shall be retained, if stable, and the analyst shall inform to Manager QC. An assessment of the accuracy of the results shall be started immediately.

6.2.9.5 If errors are obvious, such as the spilling of a sample solution or the incomplete transfer of a sample, the analyst shall immediately document what happened.

6.2.10 **Responsibility of Manager:**

6.2.10.1 Once an OOS result has been identified, the Manager assessment shall be objective and timely. There shall be no preconceived assumptions as to the cause of the OOS result. The raw data shall be assessed promptly to ascertain if the results might be attributed to laboratory error or whether the results could indicate problems in the manufacturing process.

6.2.10.2 The following step shall be taken as part of the Manager QC Assessment:

6.2.10.2.1 Discuss the test method with analyst; confirm analyst knowledge and performance of the correct procedure.

6.2.10.2.2 Examine the raw data obtained in the analysis, including chromatograms, weight prints, logbooks and spectra, and identify anomalous or suspect information.

6.2.10.2.3 Verify that the calculations used to convert raw data values into final

test results are correct; also determine if unauthorized or invalidated changes have been made to calculation method.

6.2.10.2.4 Confirm the performance of the instruments.

6.2.10.2.5 Determine that appropriate reference standards, solvents, reagents, Filter and other solutions were used and that meet quality control specification.

6.2.10.2.6 Evaluate the performance of the test method to ensure that it is performing accordingly to the standard expected based on method validation data.

6.2.10.2.7 Fully document and maintain the records of this laboratory assessment.

6.2.11 **Notification to Customer:**

6.2.11.1 Concerned Customer/Regulatory Agency shall be notified if any OOS is observed, which may have impact on the product quality to seek their acceptance. It is necessary to first get comments from the Concerned Customer or Regulatory Agency through scan copy / hard copy of Out of Specification Investigation Report (Annexure-II). Signed scan copy shall be attached with Original Form then only OOS shall be proceeding for Approval by Head QA.

6.3 IDENTIFYING OOS TEST RESULTS:

6.3.1 When OOS result is identified during the analysis in the Quality Control laboratory analyst shall be inform the OOS result to Manager QC immediately.

6.3.2 Analyst shall preserve all the samples, standards, glassware and instrument with status label till the completion of **Phase–I Laboratory Investigation.**

6.3.3 Instruments / Equipments shall have a status label with details of OOS.

6.3.4 Manager shall intimate to Head QA about the OOS finding immediately.

6.3.5 Initiating department shall raise the request to QA for issuance of Out of Specification Investigation Report in the Format **"Request Form for Issuance of SOP/Formats"** as per Format No. **F04** of SOP, Titled **"SOP on SOP"**.

6.3.6 QA shall assign an Out of Specification No. in the format as shown in **Annexure-I**, Titled **"Out of Specification Log"** for Raw Material, In-process, Semi finished, Finished product, Stability, Other and same number shall be assigned in **Annexure–II**, Titled **"Out of Specification Investigation Report (Phase I Investigation)"**.

6.3.7 Assignment of Out of Specification No. shall be followed as under for Raw Material, In-process, Semi Finished, Finished Product, Stability and other.

"OOS/YY/NNN"

Where,

OOS : stands for Out of Specification

YY : stands for of current calendar year

NNN : stands for serial no. starts from 001…..

Example: OOS/18/001: Denotes first Out of Specification of raised in year 2018.

6.3.8 QA shall issue a format along with check list and decide a tentative target completion date for closure and shall provide to Manager QC.

6.3.9 Manager QC shall conduct a laboratory investigation as per checklist provided in **Annexure–II**.

6.3.10 In case, additional space is required beyond the space in the controlled document of Out of Specification Report, an attachment of Format No. **F06-00** Titled **"Additional Attachment"** of SOP, Titled **"Documentation and Data Control"** shall be enclosed with reference of mother document.

6.4 INVESTIGATION OF OOS TEST RESULT:

6.4.1 Investigation shall be carried out in following stages:

- Phase-I Investigation (Laboratory Investigation)
- Phase-II Investigation (Full Scale Investigation)

6.4.2 Laboratory investigation (Phase I Investigation) shall be Initiated within 3 working days, if time exceed proper justification shall be provided as per format shown in **Annexure–IV**, Titled **"Extension Form for Out of Specification Investigation"**.

6.4.3 **Phase I Investigation (Laboratory Investigation):**

6.4.4 **Preliminary Laboratory Investigation:**

6.4.4.1.1 Preliminary Laboratory Investigation shall be carried out to determine whether there has been a clear obvious error due to external circumstances such as power failure or those that the analyst has detected prior to generating data such as spillage sample that will negate the requirement of a further Investigation.

6.4.4.1.2 Preliminary Laboratory Investigation yield Correctable Error. Examples of some correctable error are following;

- Calculation error
- Power outage
- Equipment failure
- Obvious errors
- Incorrect Instrument Parameters

6.4.4.1.3 If during the investigation any correctable error is found, the same shall be corrected and result shall be reported in new worksheet (If required).

6.4.4.1.4 Original test results shall be "**INVALIDATED**" by Manager QC as per shown below.

INVALIDATED **Sign & Date:**

6.4.4.1.5 If errors are obvious, such as the spilling of a sample solution or the incomplete transfer of a sample from composite, the analyst shall immediately document what happened. Analysts shall not knowingly continue an analysis they expect to invalidate at a later time for an assignable cause (i.e., analysis shall not be completed for the sole purpose of seeing what results can be obtained when obvious errors are known).

6.4.4.1.6 If during Preliminary Laboratory Investigation, found no error, detailed Phase-I Laboratories Investigation shall be carried out.

6.4.5 **Phase–I (Laboratories Investigation):**

6.4.5.1.1 Phase-I Laboratories Investigation conducted by the Analyst and Manager QC as per checklist provided in **Annexure–II**.

6.4.5.1.2 If required, Phase-I Laboratories Investigation shall be conducted by the Analyst and Manager QC through **"Root Cause Analysis"** as per SOP**.**

6.4.5.1.3 The Analyst and Manager investigation shall be restricted to Data / Instrument / Equipment /Analysis review only.

6.4.5.1.4 Upon completion of the Analyst and Manager QC investigation re-measurement shall be started once the hypothesis plan has been documented only to support the investigation testing if obvious error found.

6.4.5.1.5 This Initial hypothesis testing can include the original working stock solutions but shall not be include another preparation from the original sample.

6.4.5.1.6 Justification shall be thorough, timely, unbiased, well documented and scientifically justified.

6.4.5.1.7 Laboratory testing result shall be invalidated by Manager QC when a clear evidence of laboratory error identified.

6.4.5.1.8 If clear evidence of laboratory error exists and the cause of OOS, shall be assigned as a laboratory error (like sample preparation, analytical method followed equipment, Instrument malfunctions etc.) In this case the original OOS result may be invalidated and repeat test shall be carried out after rectification of error.

6.4.5.1.9 Verification of initial preparation may or may not be required based on the type of assignable cause identified. If evidence is not available and experimentation is derived (based on observations), verification of initial preparation is necessary to confirm the OOS results.

6.4.5.1.10 In case of verification from original aliquot sample, Manager QC shall discuss with Head QC and derive a recommended action to confirm the repeat analysis. Based on recommended action, analyst shall initiate the proposed action (verification) in presence of Manager QC. The observation shall be reported in **Annexure–II**.

6.4.5.1.11 Repeat Analysis shall be performed after rectification of identified error by original

analysts with same aliquot sample or stock solution of same sample present in the laboratory in duplicate.

6.4.5.1.12 Based on the investigation, if the repeated OOS noticed which is similar in nature, Root Cause Analysis and Impact assessment shall be performed.

6.4.5.1.13 Preparation of fresh sample is only allowed in certain circumstances, such as insufficient amount of aliquot left to carryout repeat analysis or if aliquot cannot be held for longer time due to stability issues.

6.4.5.1.14 Retesting shall be performed using two different analysts in duplicate, one of these would be the original analyst who has reported the OOS and another analyst shall be at least as experience and qualified in the method as the original analyst.

6.4.5.1.15 If any one result found out of specification then further confirm by Third Analyst in duplicate (If required).

6.4.5.1.16 For invalidating an OOS all retesting results shall be within the specification and % RSD between different results obtained by different analysts shall meet the following acceptance criteria, where applicable;

- % RSD Not more than 3.0% for the assay of Finished products, In-process, Semi-Finished Goods and Stability.
- % RSD Not more than 2.0% for the assay of Raw Material (API/Excipients etc.)
- Other established acceptance criteria for tests other than assay e.g. Impurities (Related Substances), Residual Solvent and Assay by GC, pH testing, Loss on drying / water determination etc. as per specification.
- Use the above acceptance criteria, unless other criteria can be justified (based on experience and trend data).

6.4.5.1.17 If all replicates from the resample meet the specification, then the average of the replicates shall be reported as results of records and OOS result shall be INVALIDATED.

6.4.5.1.18 Based on the results of the repeat analysis either the batch may be released as decision or further investigation may be taken.

6.4.5.1.19 All recorded data shall be submitted to Head QA for review and necessary corrective and preventive action. (Original test result must be retained along with the explanation record).

6.4.5.1.20 During an investigation of analytical results, if the OOS result is proven to be due to a laboratory error (that is directly attributable to the Analysts), then it will be necessary to subject the analyst to an appropriate level of retraining before retesting of sample.

6.4.6 **Phase-II Investigation (Full Scale Investigation):**

6.4.6.1 Phase II Investigation (Full Scale Investigation) shall be carried out as per format shown in **Annexure-V**, Titled **"Out of Specification Investigation Report (Phase II Investigation)"**.

6.4.6.2 Phase II Investigation shall be drive by written and approved instruction against hypothesis also includes manufacturing full scale investigation to determine any possible manufacturing root cause(s).

6.4.6.3 In case the initial assessment does not determine that laboratory error caused the OOS results and results appear to be accurate, a full scale OOS investigation shall be conducted and shall consists of production process review.

6.4.6.4 For manufacturing investigation Head QA shall prepared a program of further investigation. The investigation shall incorporate all relevant departments (i.e. Production, Quality Control, Warehouse, Engineering etc.), in order to ascertain any possible manufacturing root cause(s) for OOS.

6.4.6.5 The concerned Personnel / Department Head along with the Head QA shall arrange to investigate the Out of Specification Result as per SOP, Titled **"Root Cause Analysis"** and Risk Assessment shall be performed as per SOP, Titled **"Quality Risk Management"** (if applicable).

6.4.6.6 Investigation shall be carried out by Head Production, Head Engineering along with Head QA to assess the failure during processing or any stage of manufacturing as per format shown in **Annexure-V**.

6.4.6.7 Such an investigation shall consist of;

- Manufacturing investigation shall be performed through Root cause Analysis tools i.e. Fishbone Diagram (6 M's), 5– Why's Analysis etc.
- Review / Evaluation into potential manufacturing cause(s) 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.
- Review of equipments logbook, Temperature and Relative Humidity record, MFR, BMR & BPR, Process time, parameter, cleaning logbook etc need to be verified.

6.4.6.8 The Nature and Extent of investigation may vary on a case – to – case basis.

6.4.6.9 If the investigation determines Analyst error, all analysts using the same technique performed by the concerned analyst shall be reviewed.

6.4.6.10 **Hypothesis / Investigation Testing:**

6.4.6.10.1 When considering performed additional testing that is performed using a predefined retesting plan to include retest performed by an analyst other than one who performed the original test. A second analyst performing a retest shall be at least experienced and qualified.

6.4.6.10.2 Description of the testing shall be written, and approved by QA/Contract Giver to initiating investigational testing. The description must fully document.

- The Hypothesis being tested
- The exact execution of the testing, including the specific sample solution that may have been held.
- Standard, diluent blank and system suitability sample to be tested.
- Evaluation of data.

6.4.6.10.3 Hypothesis testing may include re-measurement of the original preparation to confirm/invalidate the original OOS result.

6.4.6.10.4 The initial hypothesis testing can include the original working stock solutions but shall not include another preparation from the original sample.

6.4.6.10.5 Investigation testing shall not be used to replace an original suspect analytical result. It shall only be used to confirm or discount a probable cause.

6.4.6.10.6 If no assignable cause that could explain the results can be identified during the manufacturing investigation or the failure investigation retesting shall be considered. Part of the investigation may involve retesting a portion of the original sample.

6.4.6.10.7 **Retesting:**

6.4.6.10.7.1 Retesting shall be performed on the original sample not a different sample.

6.4.6.10.7.2 Retesting can be performed using 2nd aliquot from the same sample that was the source of the original failure.

6.4.6.10.7.3 If insufficient quantity of the original sample remains to perform all further testing then the procedure for obtaining a resample must be discussed and agreed by QA/Contract Giver. The process of obtaining the resample shall be recorded within the laboratory investigation.

6.4.6.10.7.4 The decision to retest shall be based on sound scientific judgment. The test plan Must be approved before re testing occurs.

6.4.6.10.7.5 The minimum number of retests shall be documented within the procedure and be based upon scientifically sound principles. Any statistical review with regards to %RSD and repeatability shall relate to the values obtained during method

validation (i.e. Accuracy, Precision, and Intermediate Precision)

6.4.6.10.8 **Averaging:**

6.4.6.10.8.1 The validity of averaging depends upon the sample and its purpose. Using averages can provide more accurate results. For example, HPLC consecutive replicate injections from the same preparation (the determination is considered one test and one result), however, unexpected variation in replicate determinations shall trigger investigation and documentation requirements.

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

6.4.6.10.8.3 Dependence on averaging has the disadvantage of hiding variability among individual test results. For this reason, all individual test results shall normally be reported as separate values. Where averaging of separate tests is appropriately specified by the test method, a single averaged result can be reported as the final test result. In some cases, a statistical treatment of the variability of results is reported. For example, in a test for dosage form content uniformity, the standard deviation (or relative standard deviation) is reported with the individual unit dose test results.

6.4.6.10.8.4 In the context of additional testing performed during an OOS investigation, averaging the result (s) of the original test that prompted the investigation and additional retest or resample results obtained during the OOS investigation shall not be performed unless and otherwise specific by the test method.

6.4.6.10.8.5 Laboratory shall provide all individual results for evaluation and consideration to QA. All test results must conform to specification.

6.4.6.10.8.6 Averaging must be specified by the test method.

6.4.6.10.9 **Re-Sampling**

6.4.6.10.9.1 Re-sampling shall rarely occur.

6.4.6.10.9.2 If insufficient quantity of the original sample remains to perform all further testing then the procedure for obtaining a resample must be discussed and agreed by Head QA. The process of obtaining the resample shall be recorded within the laboratory investigation.

6.4.6.10.9.3 Re-sampling shall be performed by the same qualified methods that were used for the initial sample. However, if the investigation determines that the initial sampling method was in error, a new accurate sampling method shall be developed, qualified and documented.

6.4.6.10.9.4 It involves the collecting a new representative sample from the batch.

6.4.6.10.9.5 Re-sampling will occur when the original sample was not truly representative of the batch or there was a documented/traceable lab error in its preparation.

6.4.6.10.9.6 Sound scientific justification shall be employed if re-sampling is required.

6.4.6.10.9.7 When all data have been evaluated, an investigation might conclude that the original sample was prepared improperly and was therefore not representative of the batch quality. Improper sample preparation might be indicated, for example, by widely varied results obtained from several aliquots of an

original composite (after determining there was no error in the performance of the analysis).

6.4.7 **For Inconclusive Investigation:**

6.4.7.1 In cases where an investigation (1) does not reveal a cause for the OOS test result and (2) does not confirm the OOS result, then testing of the original sample shall be done by two different analysts in Duplicate.

6.4.7.2 For invalidating an OOS all retesting results shall be within the specification and % RSD between different results generated by different analysts shall meet the as per acceptance criteria defined in **Phase-I Laboratory Investigation**.

6.4.7.3 In case of inconclusive OOS investigation, Head QA may decide to Release/Reject the batch based on result of retesting.

6.4.8 **For Conclusive Investigation:**

6.4.8.1 The conclusive investigation shall review the manufacturing investigation into the suspect analytical result, and / or method validation for possible causes into the result obtained.

6.4.8.2 To conclude the investigation all of the result must be evaluated.

6.4.8.3 Once a batch has been rejected there is no limit to further testing to determine the cause of failure, so that corrective action can be taken.

6.4.8.4 The decision to reject cannot be reversed as a result of further testing.

6.4.8.5 The impact of OOS result on other batches, ongoing stability studies, validated processing and testing procedures etc. shall be determine by Quality Control and Quality Assurance and be documented in **Annexure–V**.

6.4.8.6 A complete investigation report shall be shared with respective Party/QP/Contract Giver.

6.4.8.7 Quality Assurance shall review executed investigation to conclude the OOS.

6.4.8.8 Initial OOS result cannot be invalidated in favour of passing result, if no laboratory errors are identified in Phase I and Phase II investigation. All test results both passing

and suspect, shall be reported (in QC documents and Certificates of Analysis) and all data shall be considered in batch release decision.

6.4.8.9 In case no assignable cause for OOS is identified for Raw after completion of Phase-I and Phase-II investigation, the OOS investigation shall be extend up to Concerned Vendor through Intimation (Refer Annexure-VIII).

6.4.8.10 An Initial OOS result does not necessarily mean the subjected batch fail and must be rejected.

6.4.8.11 Head Quality Control, Head Production and Head Quality Assurance shall evaluate the laboratory investigation, manufacturing process investigation to determine the batch quality.

6.4.8.12 Finding of the investigation, including retest result shall be interpreted to evaluate the batch and to reach a decision regarding whether batch shall be Released or Rejected.

6.4.8.13 If investigation indicates an OOS result is caused by a factor affecting product quality (OOS result not confirmed/validated), the batch does not meet the established standard or specification the batch is rejected.

6.4.8.14 Final disposition of the batch shall be Reviewed and Authorized by Head QA.

6.4.8.15 If the OOS investigation results into a batch failure, the investigation must be extended to other batches or products that may have been associated with the specific failure.

6.4.8.16 If the material is rejected through OOS, Quality Assurance shall decide whether the material shall be returned or destroyed as per respective SOP.

6.4.8.17 If the product is rejected through OOS, Quality Assurance shall decide whether the Product shall be destroyed as per respective SOP.

6.4.8.18 After the complete review of OOS investigation, further action taken and their effect on the preceding and succeeding batches.

6.4.9 Quality Assurance shall close the OOS by the final approval signature and document the same in **Annexure-I** for Raw Material, In-process, Semi Finished goods, Finished Product, Stability, other.

6.4.10 **Corrective and Preventive Action:**

6.4.10.1 After conclusion of OOS result, Head QA and user department Head shall initiate the corrective and preventive action in order to prevent the OOS reoccurrence.

6.4.10.2 Head QA, Head Production and Head QC shall discuss the OOS test results, investigation findings and remedial action or corrective action taken (if any) and identify need to log CAPA as per SOP, Titled **"Corrective Action and Preventive Action (CAPA)"**, for logging, proposing, evaluation, assignment, completion and evaluation of effectiveness implemented of CAPA.

6.4.10.3 Document reference of CAPA No. allotted in OOS investigation report. In case CAPA is not required as remedial action is sufficient to address non conformance, describe details of remedial action taken and document justification for not logging CAPA in the OOS investigation report.

6.4.10.4 If the OOS test result occurs due to an analyst error not following required instruction during execution, impart re-training to the concerned analysts and document. In case error occurred relates to system or practice, impart group training to acquaint all the relevant analysts to avoid reoccurrence. Attach the copy of the report of retraining with OOS report.

6.4.10.5 Training imparted shall be relevant and focused to the error occurred and shall not be general. In case of OOS due to glassware contamination extraneous peak or improper sonication, training to be provided to analyst to visually inspect glassware for proper cleaning/ solution for proper dissolving dispersion of sample before analysis.

6.4.11 **OOS Observed In Case of Stability Study Analysis:**

6.4.11.1 Stability OOS situations shall be escalated as soon as the suspect result is found. Follow the investigation as above for Phase I and Phase II. For OOS situations Regulatory agencies will require notification within a short time point of discovery due to recall potential.

6.4.11.2 Product Recall Procedures shall be performed as per SOP Titled **"Product Recall"**.

6.4.11.3 Review the data of previous time points to confirm the OOS results obtained. Check whether the trend shows the deviation (increase or decrease) of test value from initial value which finally resulted in OOS.

6.4.11.4 Review data of other batches. In case of formulations, check stability data of other batches of same strength, different strengths and packs to understand probable cause of OOS.

6.4.11.5 Review degradation study data and pathway and check the results of corresponding stress condition to understand the degradation pattern.

6.4.11.6 In case of stability OOS, chamber management investigation shall be performed and specific SOP shall be referred if there is a need.

6.4.11.7 Check the characteristics of molecule and its susceptibility e.g. hygroscopic, light sensitive, thermo labile etc.

6.4.11.8 Check the container closure system and correlate the same with degradation pathway to understand the probable cause e.g. if a product is packed in a container having more head space and oxidation study data reveals significant degradation, product may show increase in impurity contents at accelerated condition.

6.4.11.9 Check the compatibility of material/product with the primary packaging component and check the possible extractable / leachable.

6.4.11.10 If unknown impurity content is found exceeding the specification, characterize and isolate the same if possible. Include the impurity in specification and based on the characteristics, establish appropriate limits.

6.4.12 **Documentation and Reporting:**

6.4.12.1 Each step in the investigation of OOS test results shall be fully documented.

6.4.12.2 From the results obtained, determine variability among the individual result. e.g. % RSD, % variation etc.

6.4.12.3 Initial laboratory investigation shall be initiated within 03 working days of reporting the OOS test results.

6.4.12.4 Complete investigation shall be closed within 30 working days.

6.4.12.5 After closing, the OOS Report shall be submitted to QA and same shall be documented by QA in the Out of Specification Log book.

6.4.12.6 If the investigation could not be closed within 30 working days, Head QC and Head QA shall document the cause of delay in **Annexure–IV**.

6.4.12.7 The Extension Form for OOS shall be Approved by Head QA/ QC based on justification with proposed date of completion for Investigation.

6.4.12.8 For Out of specification Investigation flow chart refer format as shown in **Annexure-VI**, Titled **"Flow Chart for Out of Specification Investigation"**.

6.4.12.9 After closure of OOS during review if any gap is noticed in investigation, root cause analysis and CAPA then particular OOS shall be reopened on current date to meet the requirement and shall be closed through suitable CAPA and that case shall be captured in the Remarks column of OOS Log with the help of star mark.

6.4.13 **TREND CHART OF OOS TEST RESULTS:**

6.4.13.1 Prepare the Trend Chart (Bar/Pie) of OOS on Monthly basis by QA for better understanding to identify contributory factor causing OOS test results i.e. Analyst, Instrument, Product/Material, Inconclusive for review and recommendation as per format shown in **Annexure–VII**, Titled **"Trend Chart for Out of Specification Data"**.

7.0 ABBREVIATIONS:

CAPA	Corrective Action and Preventive Action
DMF	Drug Master File
FAR	Field Alert Report
Ltd.	Limited
No.	Number
OOS	Out of Specification
Pvt.	Private

QA	Quality Assurance
QC	Quality Control
QRA	Quality Risk Assessment
RCA	Root cause Analysis
RM	Raw Material
RSD	Relative Standard Deviation
SOP	Standard Operating Procedure

8.0 ANNEXURES:

ANNEXURE No.	TITLE OF ANNEXURE	FORMAT No.
Annexure-I	Out of Specification Log	
Annexure-II	Out of Specification Investigation Report (Phase I Investigation)	
Annexure-III	Extension form for Out of Specification Investigation	
Annexure-IV	Out of Specification Investigation Report (Phase II Investigation)	
Annexure-V	Flow Chart for Out of Specification Investigation	
Annexure-VI	Trend Chart for Out of Specification Data	
Annexure-VII	Intimation to Vendor for OOS Investigation	

9.0 DISTRIBUTION:

- Master Copy — Quality Assurance Department
- Controlled Copy No. 01 — Head Quality Assurance
- Controlled Copy No. 02 — Head Quality Control
- Controlled Copy No. 03 — Head Production
- Controlled Copy No. 04 — Head Warehouse
- Controlled Copy No. 05 — Head Engineering

10.0 REFERENCES:

- Guidance for Industry, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, Oct-2006.

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
OUT OF SPECIFICATION LOG

Year:

S. No	OOS No.	Product / Material Name			OOS For (RM/ In-process/ Semi Finished/ Finished/ Stability/Others)	OOS Description	OOS Reported Date	OOS Logged By QA (Sign & Date)	Cause identified (Analyst/ Instruments/Product/ Material/ Inconclusive/ Others)	Reference CAPA No. (If Applicable)	OOS Valid / In Valid	Closed By QA (Sign & Date)	Remarks
		Name	Batch No./ Lot No.	AR. No.									

ANNEXURE-II

OUT OF SPECIFICATION INVESTIGATION REPORT (PHASE I INVESTIGATION)

1.0 OOS No. **Date of Initiation:**

Issued By Officer / Executive QA:

Name: _____ Sign: _____ Date: _____

2.0 REPORTED OOS RESULT DETAILS:

Sample Details (put (√) tick whichever is applicable)			
Raw Material ☐		**Finished Product** ☐	
In-process/ Semi-Finished-Goods ☐		**Stability Study** ☐	
		Other (Specify) ☐	
Date of Test			
Product/ Material :			
For Stability Study :	**Exhibit Batch/ Registration Batch / Commercial Batch** **Condition : _____°C ±_____°C / _____% RH ± _____%, Interval_____**		
Batch No. / Lot No.		**AR No.**	
Mfg. Date		**Exp. Date**	
STP No.		**STS No.**	
Worksheet No.			

OOS Results:

S. No.	Test Parameter	OOS Result obtained	Specification Limit

Description of OOS Result			
Remark (If Any)			
Original Analyst QC Name (Sign & Date)		**Manager QC Name (Sign & Date)**	

3.0 PHASE- I INVESTIGATION (LABORATORY INVESTIGATION):

3.1 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**			**Remark (if Any)**
	Yes	**NO**	**NA**	
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?				
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				

1. If Yes	☐	Rectify the error and document the result. Original test result to be invalidated.
2. If No	☐	Proceed for Phase – I Investigation

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

3.2 PHASE–I LABORATORY INVESTIGATION:

Check Point (Not Limited To)	**Observation**			**Remark**
	Yes	**NO**	**NA**	
Instrument Verification:				
Were the equipment / instrument used for analysis in calibrated state?				
Were there of any evidence of malfunction of the allied equipments?				
Was the Preventive maintenance programme of the equipment performed as per schedule?				
Was the appropriate balance used?				
Was the SOP adequate and the equipment operated as per SOP?				
Was instrumental setting done as per specification?				
Was the sequence of samples on instrument correct?				
Was the correct column used in case of chromatographic analysis as per specification?				
Were instruments used as per written operating procedure?				
Was instrument number recorded in test data sheet?				

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Check Point (Not Limited To)	**Observation**			**Remark**
	Yes	**NO**	**NA**	
Were there any problem during analysis like improper flow or generation of bubble during HPLC analysis or was the sample extraction during analysis incomplete?				
Any abnormal observation in chromatogram like baseline drift, retention time shift, extraneous peak, peak splitting/shape distortion etc.?				
Is there any error message in instrument display / software?				
Is there any failure of System Suitability requirements?				
Is there any Automatic Injector mechanical failure?				
Any other Observation / Comments				
Method / Analysts Verification:				
Was the analyst trained and qualified in the particular test?				
Was the correct Analytical Method used for the analysis?				
Was the analytical method adequate and followed properly?				
Was it evident from the discussion that the analyst has understood Analytical Method and the Operation SOP of the equipment/ instrument?				
Was it evidence that the correct techniques were used by the analyst to performed the test?				
Was that evidence that the suitability requirements of the analytical method were all met?				
Had the analyst calculated the result using correct potency of the standard?				
Was the sample and standard prepared as specified in the test procedure? (i.e. properly shaken, sonicated or heated / warmed etc.)				
Were the samples and standard filtered/ centrifuged properly before introduction into instrument or analysis by classical method?				
For replicate preparations, were samples / standards treated similarly?				
Was there any similar occurrence with the analyst earlier?				
Is the mobile phase prepared as per specification?				
Are expired reagents or solutions used in preparation?				
Is the septa properly positioned on vial and crimped?				
Is the wash vial filled with sufficient volume of diluent?				
Are the vials properly labelled?				
Was there any similar history with the product/material?				
Was there any loss of sample and standard during preparation?				
Glassware Verification:				
Were proper glassware used for analysis?				
Were proper volumes of pipettes used for analysis?				
Was there any obvious evidence of glassware contamination? (Visual)				
Were there evidence or probability of the glassware was not washed or dried properly?				
Were the glassware used for analysis properly and legibly labeled?				
Analysis Verification:				

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Check Point (Not Limited To)	**Observation**			**Remark**
	Yes	**NO**	**NA**	
Was there any evidence that the sample was not stored properly?				
Was correct sample analyzed?				
Is there any possibility of contamination of the sample during testing (e.g. sample left open to air or unattended)				
Were the dilutions made in sample / standard preparations as per analytical method?				
Is the sample prepared freshly (wherever applicable) and vials placed timely in the Autosampler tray?				
Were the environmental conditions (temperature, humidity, light) during analysis appropriate?				
Were any instrument related problems noticed?				
Chemical / Standard Verification:				
Were the reagents / chemicals used of recommended grade and prepared as per the analytical method?				
Molarity/Normality of Volumetric solution?				
Was the correct standard used for analysis?				
Were the standard, reagents used properly stored?				
Was there any evidence that the standards, regents were not properly labeled?				
Were standards, reagents used within their expiration dates?				
Was there evidence that the standard, reagents have degraded?				
Was there evidence that the reagents, standards or other materials used for test were contaminated?				
Were working standard standardized as per the analytical method?				
Verification of other factors:				
Were correct specification applied?				
Was there is there evidence of any anomalous or suspect peak in the chromatogram or any suspect data in the raw data?				
Any other potentially testing / activities occurring at the time of the test?				
Is there similar problem encountered with the data for other batches performed within the same analysis set?				
Is there any other OOS result obtained on the batch of material under test?				
Is the sample prepared freshly (wherever applicable) and vials placed timely in the Autosampler tray?				
Are adequate cautions exercised during the handling of material w.r.t. its characteristics like light sensitive, thermolabile etc?				
Is the syringe free from all defects (like needle is not bent, plunger is gas tight etc.)				
Are all gas pressures within recommended limit wherever applicable?				
Is instrument maintained in good condition i.e. instrument leakage, buffer deposition, wash bottle overflow, rinse bottle empty etc.				

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Check Point (Not Limited To)	**Observation**			**Remark**
	Yes	**NO**	**NA**	
Comments: (Including details on questions if any)				
Manager QC: Name _____ Sign & Date_____				

3.3 HEAD QC OR DEPUTY TO COMPLETE THE FOLLOWING DETAILS:

ROOT CAUSE ANALYSIS:

Put "√" Mark: Required ☐ Not Required ☐

If Required, RCA No.:

If Not Required, then mention Justification / Comments:

QUALITY RISK ASSESSMENT: If Applicable

Put "√" Mark: Required ☐ Not Required ☐

If Required, RCA No.:

If Not Required, then mention Justification / Comments:

Declaration	**Yes**	**NO**	**Remark**
Has this OOS result for this test on this material/product, occurred three or more times previously or is the result indicative of an analytical trend?			
Does this OOS result indicate a general trend with respect to result on recently manufactured batches?			
Have previous problem been experienced with the methodology that may explain the OOS, typical or Borderline results? (If YES, record details below)			
Details: (if any)			
Head QC: (Sign & Date)			
Conclusion of Initial Assessment to be completed by the Head QC or Deputy			
Declaration	**Yes**	**NO**	**Remark**
The OOS result shall be consider as Laboratory Error?			
If OOS result shall be subjected to Phase – II Investigation?			
Tentative / Proposed Date of Implementation:			
Head QC: (Sign & Date)			

3.4 QUALITY CONTROL DECISION

Decision	**Yes**	**No**	**NA**	**Remark**
Laboratory Error Found				

1. If **YES**, Following action required:

Original Aliquots to be used for re-testing,

RETEST RESULT WITH ORIGINAL ALIQUOTS:

Repeat test: Original Analyst in Duplicate with original aliquot, specification Limit ( )			
	Result 1	**Result 2**	**Mean**
Analyst 1			
Analyst 1 **Name:** **(Sign & Date)**			
Comments: **Head QC** **(Sign & Date)**			

2. If **YES**, Following action required:

If fresh aliquots need to be prepared and justification for the same to be provided.

(I) RETEST **(II) RESAMPLING ***

REASON FOR FRESH SAMPLE PREPARATION		
Left over sample quantity of original aliquot is in-adequate.		**Others (If Any):**
Evidence of contamination of original aliquot.		
Laboratory investigation reveals error during aliquot preparation.		
Other (Provide details in the box provided)		

(Mark √ whichever us applicable)

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

**** In case of RE-SAMPLE and RETEST, Mention the reason for re-sampling and approval from Head QA is required***

REASON FOR RE-SAMPLING		
Left over sample quantity of original aliquot is in-adequate.		**Others (if any):**
Evidence of contamination of original aliquot.		
Other (Provide details in the box provided)		
(Mark √ whichever is applicable)		
Comments: **Head QC** **(Sign & Date)**		

APPROVAL OF RE-SAMPLING BY HEAD QA
Comments: **Head QA** **Sign & Date)**

RETEST RESULT: (IF CAUSE ASSIGNED):

Repeat test: Two different analyst in duplicate, specification Limit ( )

	Result 1	**Result 2**	**Mean**	**% RSD (If Any)**
Analyst 1 (Repeat Result)				

Analyst 2				
Analyst 3 (If Required)				
Average value of Analysis:				

Analyst 1 **Name:** **(Sign & Date)**	**Analyst 2** **Name:** **(Sign & Date)**	**Analyst 3 (If Required)** **Name:** **(Sign & Date)**

Comments :

Head QC

(Sign & Date)

3.5 CORRECTIVE AND PREVENTIVE ACTION (IF LAB ERROR OBSERVED):

Put "√" Mark

Required ☐ **Not Required** ☐

If required, note Reference CAPA No.:_____

If not required mention justification:

Head QC **Head QA**

(Sign & Date) **(Sign & Date)**

Conclusion of Initial Assessment to be completed by the Head QC or Deputy:

Declaration	**Yes**	**NO**	**Remark**
The OOS result shall be consider as Laboratory Failure?			
Whether OOS is Confirmed			

Note: If OOS is Confirmed, Submit the copy of Investigation report & enclosures to QA

Comments from Concerned Customer/Regulatory Agency:

Name: **Sign & Date:**

Comments :
Head QC: **Sign & Date:**

4.0 SUMMARY AND CONCLUSION:
Head QA
(Sign & Date)

5.0 SUBMISSION TO QA ON:

Submitted By **Received By QA**
(Sign & Date) **(Sign & Date)**

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EXTENSION FORM FOR OUT OF SPECIFICATION INVESTIGATION

OOS No. :

Name of item/Product :

Batch No. / Lot No. :

Test Name :

A.R. No. :

Current Status of Investigation:

QC Officer/Executive **QA Officer/Executive**

(Sign & Date) **(Sign & Date)**

Justification for extension of Investigation:

Responsible person:

Proposed date of completion of Investigation:

Head QC **Head QA**

(Sign & Date) **(Sign & Date)**

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ANNEXURE-IV

OUT OF SPECIFICATION INVESTIGATION REPORT
(PHASE II INVESTIGATION)

1.0 DATE OF INITIATION:

Issued By Officer / Executive QA:

Name: _____ Sign: _____ Date: _____

2.0 DESCRIPTION:

Description of OOS:			
Product/ Material :			
Batch No. / Lot No.		**AR No.**	
Mfg. Date		**Exp. Date**	
STP No.		**STS No.**	
Investigation started on			

3.0 PHASE- II INVESTIGATION:

3.1 ROOT CAUSE ANALYSIS:

Put "√" Mark

Required ☐ **Not Required** ☐

Reference RCA No.:_____

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

3.2 QUALITY RISK ASSESSMENT:

Put "√" Mark

Required ☐ **Not Required** ☐

Reference QRA No.:_____

Tentative Closing Date of OOS:

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

3.3 HYPOTHESIS ANALYSIS: (To be compiled by Manager QC)

(If additional sheet required shall be attached as per Format **"Additional Attachment"** of SOP No. **QAC/196**, Titled **"Documentation and Data Control"**)

Head QC
(Sign & Date)

	Yes	**No**	**Remarks**

Sampling error observed			
Whether re-sampling required			
Re-sampling to be performed*			

*** Re-sampling to be performed only after approval of Head QA**

(I) RETEST **(II) RE-SAMPLE, then RETEST**

Record below reason for re-sampling

OOS No.:

REASON FOR RE-SAMPLING

Left over quantity of original sample is in-adequate.		Others:
Evidence of contamination of original sample.		
Other (provide detail in the box provided)		

(Mark✓ whichever is applicable else NA to be done

Head QC
(Sign & Date)

3.4 QUALITY ASSURANCE DECISION.

Review and Approval of Re-Sampling :

Head QA
(Sign & Date)

3.5 ANALYST RETRAINING REQUIRED:

Yes ☐ No ☐

Head QC (Sign & Date)

Retraining performed as result of analyst related laboratory error:

Subject Title/ topic: _____

SOP / Document Reference (s) no.: _____

Retraining Completed: Yes ☐ **No** ☐

Remark: _____

Executive QC:
(Sign & Date)

Head QC:
(Sign & Date)

OOS No.:

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3.6 RETEST RESULTS:

Repeat Test: Two different analyst in duplicate with specification limit ( )

	Result 1	**Result 2**	**Mean**	**% RSD (If Any)**
Analyst 1				
Analyst 2				

Average value of Two Different Analyst	
Analyst 1 **Name:** **(Sign & Date)**	**Analyst 2** **Name:** **(Sign & Date)**

Comments :

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

3.7 MANUFACTURING INVESTIGATION: (Not Limited to)

Investigation carried out by:

Head – Production : Name _____ (Sign & Date) _____

Head – Warehouse : Name _____ (Sign & Date) _____

Head – QC : Name _____ (Sign & Date) _____
(if part of investigation team)

Head – QA : Name _____ (Sign & Date) _____
(If necessary, attach separate sheets for detail as Annexure with Investigation Report)

A. Materials used for Manufacturing

S. No.	**Check Point**	**Recommendation**	**Observation**
1.	Input Raw Material	Input material (API and Excipients) shall be checked as per respective document (i.e. as per BOM/ BPCR)	
2.	Vendor source	API and Excipients shall be used as per approved vendor list.	
3.	Sampling/Dispensing	Sample shall be collected in clean and dry glass bottle. Hygroscopic, volatile and light sensitive material precautions Dispensing procedure, cleaning of tools, approval status and retest to be added.	
B. Manufacturing Process			
1.	Manufacturing Process	Manufacturing Process shall be executed as per approved BPCR	
2.	Cleaning and sanitization of instrument and equipment	cleaning and sanitization procedure shall be validated	
3.	Fumigation frequency	Fumigation activity shall be performed as per pre-approved scheduled for manufacturing area.	

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C. Machines/Equipments			
1.	Process Equipment	Validated equipments shall be use in the Manufacturing Process	
2.	Equipment Cleaning Procedure	Equipment cleaning procedure shall be validated	
3.	Preventive maintenance program	The preventive maintenance program shall be available for the checking process equipments (Mobile LAF & vial sealing and capping LAF)	
4.	LAF	LAF Shall be validated	
5.	AHU	AHU Shall be validated	
D. Manpower			
1.	Manufacturing area Personnel for aseptic area	Personnel shall be trained to perform their respective jobs in aseptic manufacturing area manner.	
OOS No.:			
2.	Personnel Qualification	Personnel Qualification of all the microbiologist and operators participating the cleaning, sampling and sanitization process shall be available .Only qualified Personnel are authorized to work in aseptic areas.	
3.	Personnel hygiene	There is a personnel monitoring program available for checking the hygiene level of Personnel who enters in the aseptic areas	
4.	Aseptic area gowns	Washing and sterilization of the aseptic area gowns shall be done as per approved procedure.	
E. Environment monitoring program			
1.	Temperature and RH	Temperature and RH shall be maintained during manufacturing as per predefined approved criteria.	
2.	Environmental monitoring for viable counts	All the environmental monitoring records for viable counts shall be within limits during sampling and manufacturing.	
F. Maintenance Activity			
1.	Maintenance work procedure in Aseptic area.	Area shall be cleaned and monitoring to be done as per predefined schedule in aseptic area.	
G. Breakdown			
1.	Breakdown record	Each breakdown shall be record with risk evaluation	
H. Procedure and Documentation			
1.	BPCR		
2.	SOP		
3.	Protocol / Report		
4.	STS/ STP		
4.0 CORRECTIVE AND PREVENTIVE ACTION:			

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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) _____

5.0 IMPACT ASSESSMENT:

5.1 Impact On

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

(Mark✓ whichever is applicable else NA to be done)

5.2 Detail of Impact Assessment:

Manager QA
(Sign & Date)

6.0 RECOMMENDATION:

Head QA
(Sign & Date)

7.0 PRODUCT RECALL : (If Applicable)

Put "√" Mark

Required ☐ Not Required ☐

Head QA
(Sign & Date)

8.0 DISPOSITION OF THE BATCH:

Head QA
(Sign & Date)

9.0 SUMMARY AND CONCLUSION:

Head QA
(Sign & Date)

10.0 SUBMISSION TO QA ON:

Submitted By
(Sign & Date)

Received by QA
(Sign & Date)

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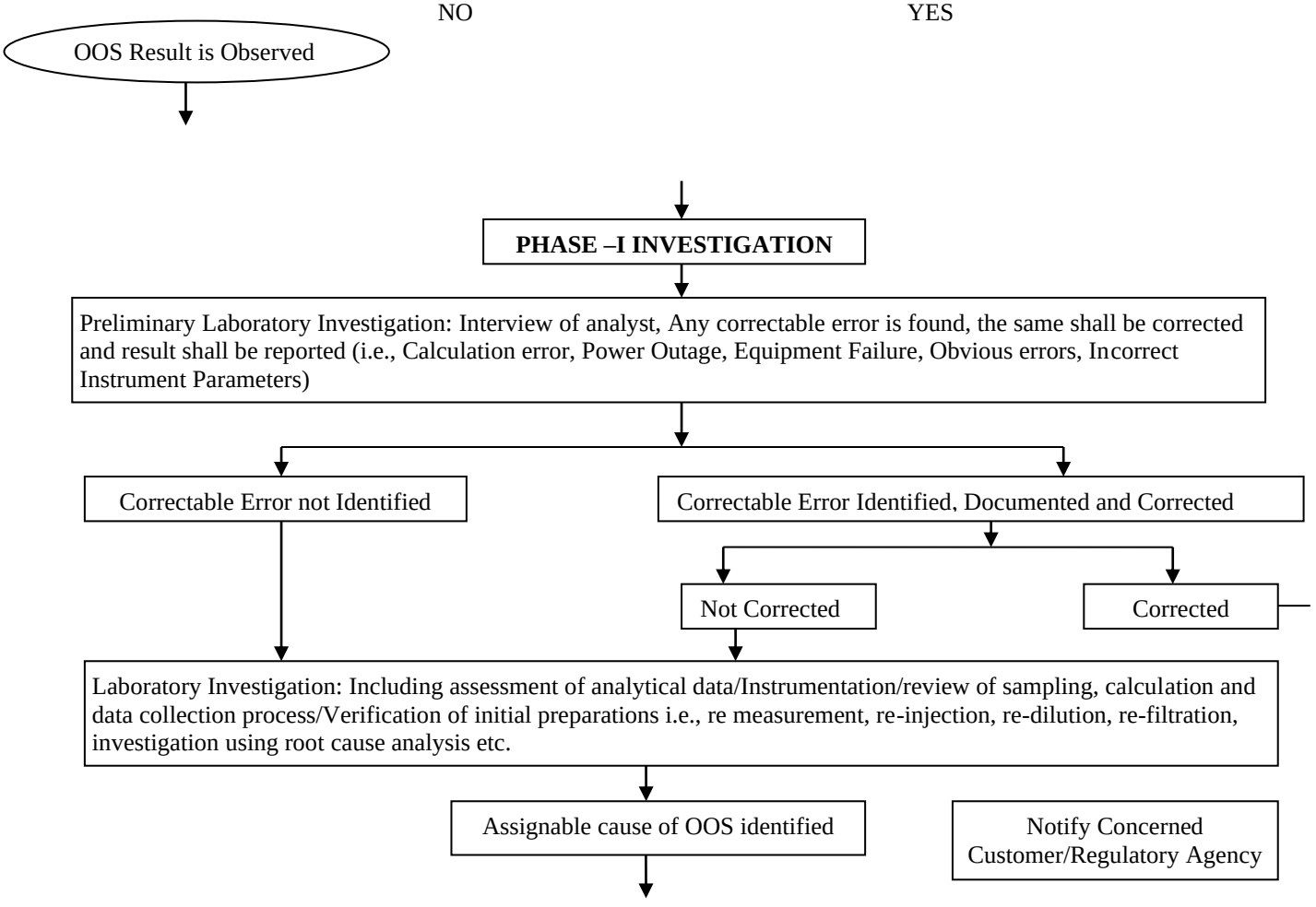
ANNEXURE-V
FLOW CHART FOR OUT OF SPECIFICATION INVESTIGATION

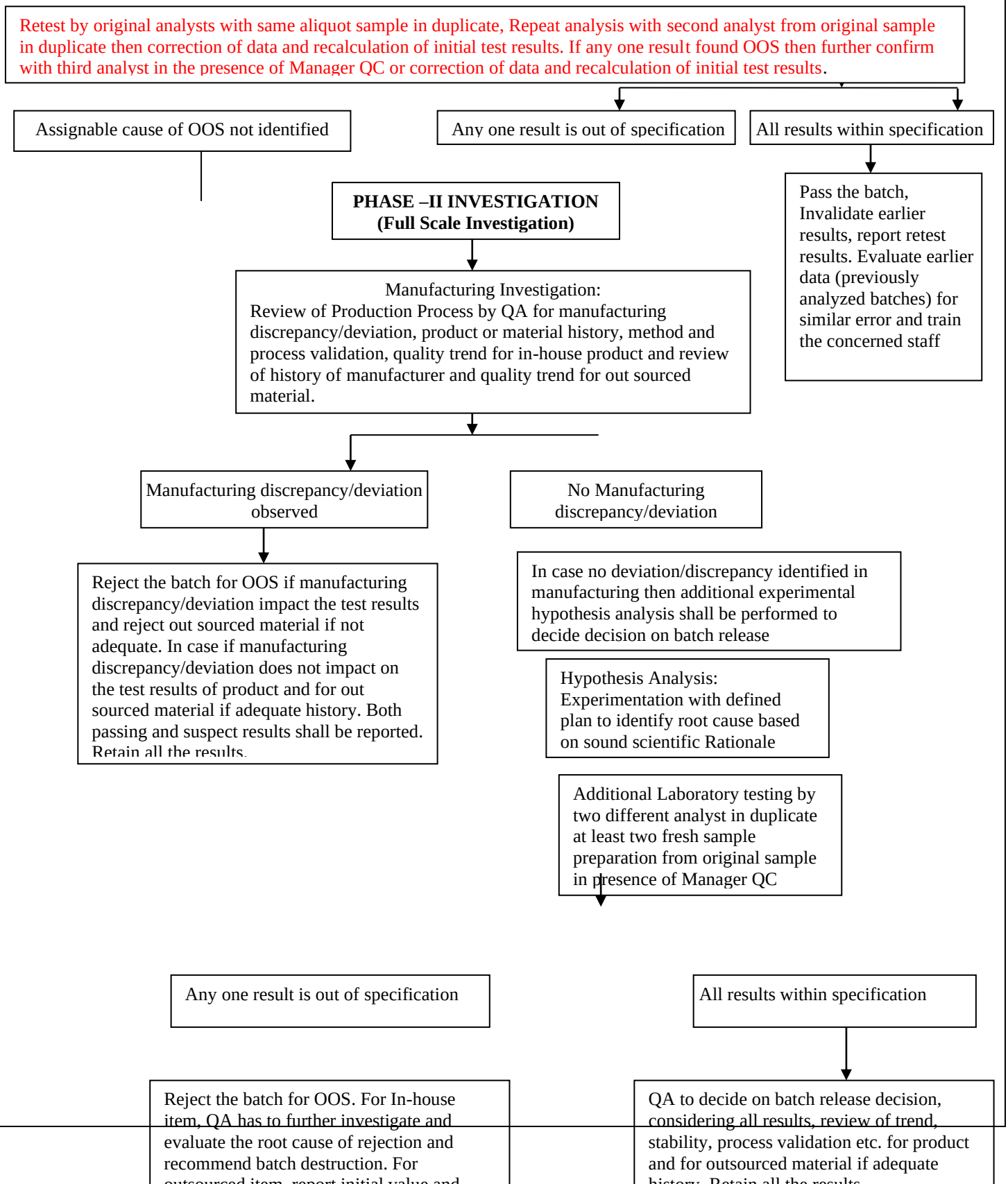


DECODING PHARMA

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.:**



STANDARD OPERATING PROCEDURE

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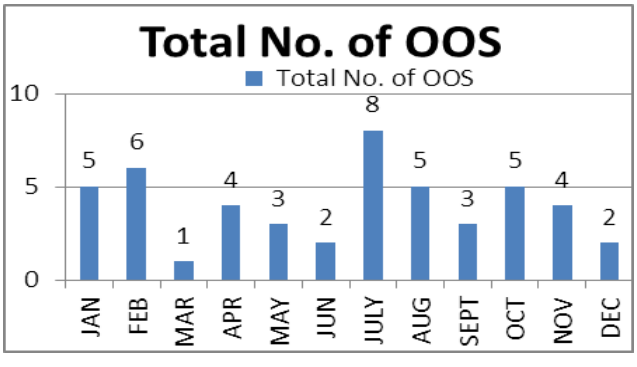
Supersedes: Nil	**Review Date:**
Issue Date:	**Page No.:**

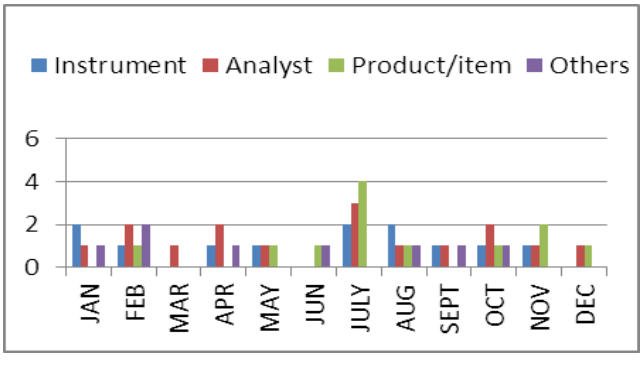
ANNEXURE-VI

TRENDING OF OUT- OF-SPECIFICATION DATA

Month/ Year:

OOS Distribution						
S.No.	**Month**	**Total No. of OOS**	**Instrument**	**Analyst**	**Product/Item**	**Inconclusive**
Total						





Review and Comments:

Executive QA
(Sign & Date)

Head QA
(Sign & Date)

STANDARD OPERATING PROCEDURE

Department: Quality Assurance	**SOP No.:**
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ANNEXURE-VII

INTIMATION TO VENDOR FOR OOS INVESTIGATION

OOS No. :
Name of Raw :
Batch No. / Lot No. :
Test Name :
A.R. No. :

Material (RM)received from party :
Quantity of material (RM) received :

Current Status of Investigation:

QC Officer/Executive
(Sign & Date)

QA Officer/Executive
(Sign & Date)

Justification for extend of Investigation up to Vendor:

Responsible person:

Proposed date for completion of Investigation:

Head QC
(Sign & Date)

Head QA
(Sign & Date)