TITLE: HANDLING OF OUT OF SPECIFICATION (OOS)

1.0 PURPOSE:

To lay down the Procedure for Handling of Out of Specification results obtained during analysis at Quality Control Department.

2.0 SCOPE:

The procedure is applicable to Raw materials, Intermediates, Finished Products, Holding time Samples and re-tests material analysis. This procedure is not applicable for In-Process test parameters being performed for reaction monitoring and/ or adjusting the process.

3.0 RESPONSIBILITY:

3.1 Analyst-QC is responsible to intimate Head-QC/ Designee during OOS result and to take OOS Investigation form from the QA department.

3.2 Analyst-QC is responsible to retain all the standards and test preparations till the complete of investigation.

3.3 Head-QC/ Designee are responsible for coordination of investigation with timely manner to the find out root cause of the OOS.

3.4 Head-QC/ designee must ensure the checking of OOS results by senior personnel from QC and He/ she shall verify the reports and inform to Head-QA/ Designee.

3.5 QA Personnel shall be responsible to assign OOS number and issue the form for reporting and investigation of OOS results based on the requisition from QC. QA Personnel shall enter the details of OOS results in the log register.

3.6 Head-QA/ Designee is responsible for approval and to inform Head-QC/ designee for re-sampling depending on the outcome of investigation.

3.7 Head-QA/ Head- QC or Head-Production shall be responsible in involving the investigation and implementation of CAPA and completion of documentation related OOS results.

4.0 DEFINITIONS:

4.1 **Out Of Specification (OOS):** All results that fall outside the specification or acceptance criteria established in house specification.

4.2 **Invalid data:** Initial analysis data which is proved and concluded to be not valid through investigation.

4.3 **Hypothesis testing:** Testing performed to confirm or support the probable root cause(s) from the assumptions made i.e., what might have happened (such as during sample holding/processing/Packing etc) that can be tested?

4.4 **Re-Check:** This analysis shall be performed by considering the aliquot preparation from the original sample preparation.

4.5 **Repeat analysis:** This analysis shall be performed by considering the new portion of the original sample.

4.6 **Re-Sample:** Additional sample shall be collected from the same batch for second time during the analysis (Phase-II investigation)

4.7 **Assignable cause:** An identified reason for obtaining an OOS result.

4.8 **No Assignable cause:** When no reason could be identified.

4.9 **Phase-I (Laboratory investigation):** It is a clear obvious error e.g.: calculation error and transcription error.

4.10 **Phase-II (Manufacturing investigation):** It is a cross functional investigation.

4.11 **Correction:** Immediate action taken to correct a situation.

4.12 **Corrective Action:** Action taken to eliminate the cause of existing non-conformity or other undesirable situation.

4.13 **Preventive Action:** Action taken to prevent the cause of potentiometry non-conformity or other undesirable situation.

4.14 **Extraneous peak:** Any peak a part from below depicted scenarios shall be constitute as "Extraneous Peak".

- Analyte peak.
- Peaks observed in blank, diluent & placebo.
- Peaks specified in test method and/or specimen chromatogram.
- Peaks due to salt
- Drift, hump, spike or gradient curve.

5.0 PROCEDURE:

5.1 Analyst shall report the OOS results within 24 hours to Head-QC/ designee.

5.2 All the standards and test preparations shall be kept till the analysis results are reviewed by the senior personnel from QC. If the review found OOS result, then the retention of Standard and test preparations to be extended till the complete of investigation.

5.3 Analyst- QC shall send a request for getting OOS Investigation Form QA011-FM033 from QA.

5.4 Designated personnel from QA shall assign The OOS number as given below: OOS-XXX-YY-NNN

whereas,

OOS : Represents Out of Specification

XXX : Represents three digits of the product

YY : Represents the year code

XXX : Represents serial number of the OOS, which starts from 001

E.g. OOS-NIM-18-001

5.5 The OOS number shall be allotted batch wise and batch number shall have unique OOS number.

5.6 If an OOS results are found for multiple tests in a particular batch number then the OOS number allotted to the first test shall be referred in the OOS forms issued for all other subsequent tests having OOS results.

5.7 Designated QA personnel shall record the details S. No., Date, OOS No., Name of the material, Batch No., Category, Brief Description of the OOS, Sign & Date in the Out of Specification Log (QA011-FM031) and issue the OOS Investigation Form to QC.

5.8 QC Personnel shall receive the form and record the details of OOS results in consultation with the analyst and submit to Head-QC/Designee.

5.9 Head-QC/ designee in consultation with Head-QA/ Designee shall initiate the investigation.

5.10 **Phase-I Investigation (Laboratory Investigation):**

5.10.1 In case of suspected out of specification result, the Analyst conducts a thorough check on his own work to ensure that there are no general lab analytical errors made.

5.10.2 During this process, analyst re-checks the sample for its integrity. Checks the reagents, test solutions and reference standards that are used. The analyst also checks the equipment used for its fitness / suitability, Instruments used for their state of calibration, glass ware used for their cleanliness, raw data collected, calculations made and results obtained.

5.10.3 In case there is no evidence that the general laboratory analytical errors are the cause for deviation, Head-QC/ Designee shall initiate the Phase-I investigation as per format In OOS Investigation Form (QA011-FM033). Investigating the OOS shall discuss the test method with the Analyst as per the checklist.

5.10.4 Perform laboratory investigation by interviewing the analyst, reviewing the documentation and used materials glassware for possible laboratory and/or instrument error.

5.10.5 The supervisor/in-charge shall assess the date to ascertain, if the result might be attributed to laboratory error, following steps can be followed for the initial investigation.

- Section head/ In-charge shall verify for any transcription or calculation error and shall discuss test procedure with analyst to ascertain the knowledge/ competency to perform test as per the standard test procedure.
- Instrumental errors (functioning/ calibration /noisy baseline/ poor injection reproducibility etc.)
- Methods/ procedures errors (adequate method/ poor resolution, etc.).
- Analysis errors (calculation error/ incomplete transfer of sample/ improper weighing of standards, samples, reagents etc.).
- Standards/ Samples errors (incorrect preparations of Standards, Samples, Mobile Phase/ Labeling and storage of standards/ Samples)
- Reagent errors (Improper standardizations/ Glassware contamination etc,)
- Similar history/ errors in the past and other appropriate.

5.10.6 The Laboratory investigation Phase-I initial assessment and verification shall be initiated within 48 hrs.

5.10.7 **Hypothesis testing/ Investigation testing:**

5.10.7.1 Hypothesis testing/ investigation testing is performed to confirm or discount a possible root cause. Hypothesis testing can be conducted in the laboratory during phase-I and phase-II laboratory investigation.

5.10.7.2 All hypotheses to be completed before initiating Re-testing in phase-II.

5.10.7.3 Hypothesis can be such as suspecting the sample preparation or analytical technique.

5.10.8 **Re-dilution**

5.10.8.1 If an error in contamination of the original laboratory working sample/ standard solution or pipetting of the original stock sample/ standard solutions is suspected. The analyst shall re-dilution the original laboratory stock sample / standard solutions.

5.10.8.2 Re-dilution of the original sample solution shall be done concurrently if only a portion of the analysis is being investigated.

5.10.8.3 If re-dilution is not possible prepare and inject from original sample which lead OOS.

5.10.8.4 If the re dilution/ re-analysis doesn't confirm the OOS result then the OOS results shall be rendered invalid and a repeat test may be performed on the same sample portion.

5.10.8.5 The results of this exercise must clearly support, the assignable cause analysis and be substantiated with good scientific rationale and documenting of observations. Performance of this operation shall be documented.

5.10.9 **Study on standard solutions**

5.10.9.1 If an error in standard preparation is suspected, the analyst will initiate evaluation study.

5.10.9.2 A check may be performed using multiple standard preparation/ dilution/ injections of freshly prepared standards and the original standard solution.

5.10.9.3 If the original standard solution value is not confirmed, a repeat test may be performed using freshly prepared standard and samples.

5.10.9.4 The results of this exercise must clearly support the assignable cause theory and be substantiated with good scientific rationale and observations. Performed of this operation shall be documented.

5.10.9.5 The re-assessment of test preparation(s) (sample or standard solution) for investigation purpose will be performed according to the situation to be evaluated and possible cause for the OOS results under investigation.

5.10.9.6 The following guidance may be used as reference.

Foreign peaks: Perform a single injection from the original vial, a new vial and a new dilution, only from the test preparation under investigation.

Dilution error: If a dilution error occurs (i.e. the omission of internal standard in the test preparation, incorrect dilution, incorrect pipette used and confirmed), the re-injection of the original preparation solution is not required.

5.10.9.7 Proceed to re-dilution, if possible, taking in consideration the stability of the solutions and then re-dilute and re-inject the entire sample set.

5.10.9.8 The injection of the test preparation as per STP will be performed as an injection of the original vial, new vial, and re-dilution of the test preparation and working standard solution under investigation as applicable.

5.10.9.9 Adequate supporting data and evidence will be required to validate any assignable cause theory in order to justify any decision to render the OOS result as invalid.

5.10.9.10 Manufacturing, Quality Assurance and shall be involved in OOS investigation as and when required.

5.10.10 **Titrations:**

5.10.10.1 During titrimetric analysis if required, prepare additional volumetric solution or test solutions.

5.10.10.2 If necessary, re-standardize the volumetric solution in triplicate.

5.10.10.3 Calculate the results by using the average volumetric solution factor.

5.10.10.4 Each of the individual concentrations determines for a particular solution must be within 0.5% of the average concentration.

5.10.11 **Repeat Analysis:**

S. No.	Observation	Analyst	Test plan	Complies Specification	Action to be taken	Result to reported
01	Initial	1st analyst	1 analysis (as per STP)	No	Investigation phase-I	NA
02	Repeat analysis during phase-I If Assignable cause not identified	1st analyst / 2nd analyst	2 preparations	No	Investigation phase-I	NA
				Yes	Batch shall be approved/ released	Average of two preparations
03	Repeat Analysis during phase-I if cause identified	1st analyst/ 2nd analyst	2 preparations	Yes	Batch shall be approved/ released.	Average of two preparations of phase-I
				No	Batch shall be rejected and proceed for phase-II investigation	Initial results to be reported.
04	Repeat analysis during phase-II	2nd analyst	3 preparations	No	Batch shall be rejected.	Initial results to be reported.
				Yes	Batch shall be approved/ released.	Average of 2 preparations of phase-II

5.10.11.1 In phase-II if assignable cause is identified, a second analyst is required to perform the retesting. Perform the analysis for 2 times.

5.10.11.2 For any tests if an acceptance criterion is not defined in analytical method validation for % RSD. It shall be defined as recommended by QA.

5.10.11.3 If the result from repeat testing are within specification, then the data obtained through the repeat analysis will stand as record, given that sufficient scientific rationale has been provided, and given that the data is consistent with other testing performed on the same sample / lot (i.e. initially result was repeat analysis and was not confirmatory)

5.10.11.4 Additional testing may be performed during phase-II of the investigation to further evaluate the assignable cause of the aberrant results.

5.10.11.5 This testing may include sample evaluation utilizing a separate technique, hypothesis testing, etc. All evaluation testing will be "for information only''.

5.10.11.6 Experimental designs are conducted in order to provide supporting data to validate an assignable cause theory when necessary.

5.10.12 QC personal shall submit the completed 'OOS investigation report'' along with raw data to Quality Assurance.

5.10.13 Completion of corrective actions such as those pertaining to the analyst technique, test execution or test methodology will be addressed, documented and approved.

5.10.14 For inconclusive investigations (i.e., cause for the OOS results (Not to be invalidated), and together will all data generated during the investigation, be given full consideration in the disposition of the sample / lot batch.

5.10.15 At any stage in the investigation that an OOS result is believed to be confirmed, the potential impact will be evaluated.

5.10.16 If it is determined that the data under investigation is associated with an intermediate or finished product intended for commercial distribution that potentially impact product quality, then an acquisition shall be given to Head-QA.

5.10.17 In the case of the acquisition of an OOS results for distributed product (for example, a Hold time study test within the product expiry/retest period), the site QA will be immediately notified to QA.

5.10.18 In case of Raw / Packing materials OOS, site QA approve / reject the material based on the laboratory investigation and the same shall be informed to QC, Warehouse and purchase department for further actions.

5.10.19 In case of intermediate / finished product OOS, proceed for manufacturing investigation and this shall be part of Phase-II investigation.

5.10.20 During qualification of contract testing laboratory OOS investigation procedure shall be assessed for adequacy and approved.

5.11 **Phase-II Investigation (Manufacturing Investigation)**

5.11.1 Head-QA / Designee shall organize cross-functional investigation team from Production QC, QA, R&D if required Engineering Department / Warehouse to assess the possible cause for OOS.

5.11.2 The Team will proceed with full scale investigation by checking the following against the OOS Investigation Form with respect to BPR, but not limited to ;

- Any deviation to the fixed batch size
- Any deviation in the quantities of raw materials charged
- Any deviation in Critical Process Parameters
- Any deviations in In-process test results
- Any deviations w.r.t. equipments mentioned against BPR.

- Verification of Environmental conditions (such as temperature and humidity etc.,) of the manufacturing areas.
- Verification Maintenance records and Equipment log books.
- Verification of Measurements in product quality and quantity.
- Any out of calibration of measuring equipments, weighing balances (E.g. Temperature, Vacuum, Pressure gauge etc.)
- Checking the Reactors (e.g., SSR and GLR).
- Discussion with production personnel for any deviations taken place.
- Training records of persons who are involved in the process.

5.11.3 Phase-II Checklist shall be filled by one of the members from investigation team.

5.12 **Handling of Extraneous Peaks (Observation and reporting):**

5.12.1 Upon observation of an extraneous peak for the tests and technique depicted below, an initial evaluation shall be performed.

5.12.2 **Criteria for identification of the "Extraneous Peak"**

Test	Technique	Criteria for Investigation
Assay	HPLC/GC	1. Peak which is not in purview of 4.14 2. Area >2.0% of the area of analyte peak.
Residual solvents	GC	1. Peak which is not in purview of 4.14. 2. Any peak as an extraneous peak only if it is present in replicate preparations/injections with S/N ratio >10 consistently. 3. If any spike observed in standard/sample peak which increase/decrease the area counts. 4. Any peak observed before the diluent peak (high boilers) other than specified peak in the specification in the sample run shall be considered as extraneous peak.
Cleaning samples	HPLC/GC	1. All extraneous peak areas shall be added to the main analyte area and the total area shall be less than the standard area. 2. Any extraneous peak area in sample shall not be more than 50% of standard response area.

5.12.3 **Criteria for exclusion of "Extraneous Peaks":**

Test	Technique	Criteria for Investigation
Residual solvents	GC	1. Extraneous peaks in the initial elution region, which might be due to bad septum or improper glass wool or improper detector cleaning, provided they are present in blank and standard chromatograms. 2. Extraneous peaks at a specific retention time which is =1.5 times of the response of diluent. 3. Extraneous peaks which are observed after the elution of diluent (high boilers) which might be due to degradation of material/product.

5.12.4 **Reporting:**

5.12.4.1 Upon evaluation, if the observed extraneous peak(s) meet the identification criteria, an incident shall be logged and investigated as per SOP (SOP No. SOP-QC-051) "Handling of Laboratory Incidents".

5.12.4.2 All prepared solutions, samples and glassware which are related to analysis [in which extraneous peak(s) are observed] shall be retained until the completion of investigation.

5.12.5 **Laboratory investigation:**

5.12.5.1 The laboratory investigation shall include the review of following documents/data at the minimum.

- Check the trend of previously analyzed batches and/or other existing data for the presence of identical extraneous peak(s).
- Check the method validation data (excluding the specificity data) to correlate any peaks observed at the RRT of peaks under investigation in the chromatograms.

5.12.5.2 During course of investigation, if any probable cause is presumed (to rule out any analytical errors) the same shall be confirmed through an

"Experimental testing" to support the probable cause(s). All such experimental testing shall be carried out as per the approved procedures.

5.12.5.3 Probable sources of extraneous peak due to analytical errors from the laboratory and their suggested order shall be as per below table.

Probable Sources	**Suggested experimental testing***
Vial contamination	Refill the sample preparation in a new vial.
Flask contamination	Re-dilute the sample stock preparation into another cleaned & dried flask.
Contamination within the chromatograph	Re-inject the same vials after appropriate flushing or system/needle/septum, etc
Contamination through diluent	Re-dilute the sample stock preparation into another cleaned & dried flask with fresh diluent.
Contamination through Chemicals/reagents	Prepare solutions using the intact bottles of chemicals/reagents.
Contamination during pipetting/transferring	Re-dilute the sample stock preparation into another volumetric flask using a cleaned & dried pipette.
Contamination during sample preparation	Clean the work bench appropriately and prepare a fresh sample preparation after authorization from designated personnel of analytical quality assurance.

*Presumption the sample preparation is considerably stable.

5.12.5.4 Chromatograms with extraneous peaks and other chromatograms generated as part of experimental testing should be documented as an attachment (referencing with the incident notification number) with relevant ROA.

5.12.5.5 In case, where the source of extraneous peak is confirmed as analytical error, analysis shall be repeated (after authorization from designated personnel of quality assurance) by invalidating the initial analysis where extraneous peak is observed.

5.12.5.6 In case, where the source of extraneous peak is confirmed as laboratory error, the extraneous peaks shall be identified by using LCMS/GCMS or other hyphenated/sophisticated techniques.

5.12.5.7 If NO laboratory/analytical error has been identified then,

5.12.5.8 **In case of outsourced materials,** the information shall be shared with the concerned vendor (through appropriate channels:- SCM & VQM team) & suitable corrections and/or CAPA as appropriate shall be sought from vendor. Wherever necessitated, joint analysis (between vendor & Discovery) shall be conducted at the specific Discovery site, after the authorization from the concerned site QA head/designee.

5.12.5.9 In case of products processed at site, the investigation shall be extended to manufacturing to identify the source of contamination.

5.12.5.10 Manufacturing investigation shall be conducted as per the guidance provided in the SOP.

5.12.5.11 Manufacturing investigation shall be conducted as per the guidance provided in the SOP.

5.12.5.12 All experiments/activities as part of hypothesis and their observations/outputs should be documented and shall be attached along with relevant record as a supportive document.

5.12.5.13 Upon identification of the source of contamination, the contaminant shall be quantified followed by the identification of the root cause for contamination.

Note: If the source of contamination in UNABLE to be identified, information shall be given to AR&D to assist in identifying the contaminant peak through LCMS/GCMS or other hyphenated/sophisticated techniques.

5.12.5.14 Subsequent to identification of root cause for contamination necessary CAPA shall be initiated as per approved procedures.

5.12.5.15 An impact assessment shall be made by site QA in order to assess the risk level to the

- Batches already processed and/or
- Released to the market/customer and/or
- Other tests in the specific material/product

5.12.5.16 The impact assessment shall be made, taking into account of

- Nature of contaminant
- Safety level of contaminant
- Exposure of contaminant towards the targeted patient population.

5.12.5.17 Decision for batch disposition/release shall be made by QA, based on outcome of assessment & same should be documented.

5.13 **Re-sampling and Additional Testing**

5.13.1 Re-sampling shall be done only in experimental situations. This stage of the investigation may require the guidance of Quality Assurance together with Quality Control. Additional testing of original composite sample and / or re-sampling may be required as recommended by Quality Assurance for information only.

5.13.2 Re-sampling to collect new samples from a batch is to be done in following situations

5.13.3 If the investigation reveals that original sample may not representative and sample is found to be non-homogenous. Integrity of the sample is lost due to contamination of sample with other sample/s or spillage of other material in original sample.

5.13.4 Samples damaged during laboratory handling evident from physical appearance.

5.13.5 Sample had been exposed to adverse atmospheric conditions such as stored under inappropriate storage conditions, evident as per the material physical characteristics.

5.13.6 If the original sample is exhausted and not available for investigation. Excessive variation results from several aliquots of an original composite.

5.13.7 For re-sampling, the section Head, Head QC should derive an actual plan including the following and documents the recommended action in the re-sample request and approval form.

5.13.8 Re-sampling action plan should be approved by Head QC and authorized by QA.

5.13.9 If the investigation determines that the initial sampling method was inherently inadequate.

5.13.10 Repetitive re-sampling test plan are not permitted without scientifically justified and unique assignable cause theory.

5.13.11 In case of hold time study, buffer samples can be used for investigation based on requirements.

5.13.12 Sampling Method: Based on the abnormality of the observation, new sampling strategies may be required. For example if high variability is observed among the results, extensive sampling procedure can be employed for the withdrawal of individual sample portions from the top, middle and bottom of every container.

5.13.13 Repeat the analysis in triplicate preparations with two analysts.

5.13.14 Finally OOS investigation report shall indicate the reasons for the OOS results and recommend for Corrective actions for the OOS results. The reports shall indicate corrective and preventive action required to be implemented in order to prevent the occurrence of the failure.

5.13.15 Head QA/ Designee shall complete the OOS investigation with recommend the Corrective Action and Preventive Action.

5.13.16 The closeout shall indicate the final disposition of the material (rejection/ reprocessing of material) based on the consolidated review of investigation report.

5.14 **OOS Batch Disposition:**

5.14.1 Any decision on batch release/ rejection shall be taken only after completion of all investigations. All test results, both passing and suspect shall be reported and all data has to be retained.

5.14.2 Head-QA/ designee shall review the OOS report for completeness. If found completed, close the OOS by signing off.

5.14.3 In case of an API or intermediate, even if OOS is observed in any one parameter, complete testing of batch shall be performed for investigation / information purpose if required.

5.14.4 In case of raw materials, if OOS observed in any of the parameter, others tests need not be performed and batch can be rejected.

5.14.5 In case of rejection of raw material, Head QA / designee shall inform the supplier of the failure and request for appropriate investigation and corrective action.

5.14.6 File original OOS investigation report in QA along with the corresponding analytical report in OOS file.

5.15 **OOS closure timelines:**

5.15.1 OOS investigation shall be initiated and completed in a timely manner. All actions related to OOS shall be reviewed and acted upon promptly.

5.15.2 Investigation on OOS related to intermediates, Hold time studies shall be completed and OOS shall be close within 15 days if the investigation reveals that the OOS is due to laboratory error.

5.15.3 Investigation on OOS related to intermediates, shall be completed and OOS shall be close within 30 days from OOS occurrence if the investigation reveals that the OOS is due to manufacturing issues.

5.15.4 CAPA shall be initiated and follow- up shall be done till implementation of all corrective and preventive actions.

5.15.5 If closure of investigation is extended more than above timelines shall be recorded and justified.

5.15.6 If the investigation need extended time period as specified above, then QC head should seek further extension with a propose timeline to complete the investigation. Refer form "Delay justification form''. The justification should be reviewed and approved by QA Head.

6.0 FORMATS / ANNEXURE(S):

6.1 Out of specification log : QA011-FM031

6.2 OOS Investigation Form : QA011-FM033

6.3 Laboratory investigation checklist : QA011-FM174

6.4 OOS Phase-II Investigation checklist : QA011-FM175

6.5 Flow chart for OOS Investigation : Annexure-I

7.0 CHANGE HISTORY:

Revision No.	Effective Date	Details of Revision	Ref CCF No.
00	01.06.2007	New SOP is introduced	--
01	01.07.2009	SOP format changed and reviewed for more clarity	--
02	24.01.2011	Formats has been introduced	--
03	15.06.2014	Formats are the part of SOP. So prepared separately and more clarity.	--
04	01.07.2016	Rephrase the procedure for better clarity.	--
05	01.01.2018	1. SOP format changed make to inline with SOP-	CCF/GEN/17037

Revision No.	Effective Date	Details of Revision	Ref CCF No.
		QA-001-05.	
06	02.07.2018	1. Phase-I investigation elaborated. 2. Laboratory investigation checklist & OOS Phase-II Investigation checklist formats segregated and elaborated. 3. All together rephrase the procedure for better clarity.	CCF/GEN/18006
07		1. Observation and reporting procedure for Extraneous Peak was included under 5.12 section.	CCF/GEN/19038