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TITLE: OUT OF SPECIFICATION TEST RESULTS

1.0 PURPOSE:

1.1 To lay down the procedure for investigation of Out of Specification (OOS) test result(s) of finished products, In-Process samples, Stability samples, Packaging materials and Raw materials.

2.0 SCOPE:

2.1 This procedure is applicable when analysis results of any test of a sample is not within the limit of pre-defined approved specification in Quality Control laboratory (Not applicable for Microbial Analysis) at manufacturing facility of Olive Healthcare, Unit II, daman and at customer / Marketing Authorization Holder (MAH's) Quality control laboratory.

2.2 This SOP is not applicable for Cleaning validation samples and pre-shipment samples of RM/PM.

2.3 This SOP 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).

3.0 RESPONSIBILITY:

3.1 **Analyst shall be responsible for:**

3.1.1 Reporting of OOS to the immediate supervisor / Head-QC.

3.1.2 To retain all original samples, dilutions, glassware, aliquot of samples and all initial preparations.

3.1.3 To involve in investigation and analysis as required during OOS investigation.

3.2 **Head/Designee Quality Control shall be responsible for:**

3.2.1 Report the OOS to QA department.

3.2.2 Investigating the laboratory investigations (Phase I, Phase II and Phase III investigations).

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3.2.3 Responsible for taking approval of Quality Assurance.

3.3 **Head/Designee Warehouse and Production shall be responsible for:**

3.3.1 Assist in investigation during Phase II investigation or as applicable.

3.4 **Quality Assurance Executive/Designee shall be responsible for:**

3.4.1 Issuance of Phase-I Laboratory investigation report, Phase-II investigation report & Phase-III investigation report.

3.4.2 Assist in investigation and coordinate with QC, Production, warehouse, Engineering as applicable.

3.4.3 Trending of OOS on semiannually basis

3.5 **Head/Designee Quality Assurance shall be responsible for:**

3.5.1 Investigation of OOS in co-ordination with QC.

3.5.2 Review of OOS investigation and reported results.

3.5.3 Initiation of "Failure Investigations" at Manufacturing if applicable.

3.5.4 Approval of action plan and evaluation of OOS test results.

4.0 ACCOUNTABILITY:

4.1 Head-Quality Assurance shall be accountable for ensuring the adherence of the SOP.

5.0 DEFINTIONS:

5.1 **Out of specification (OOS) Result:** Test result that does not comply with the pre-determined specification / acceptance criteria.

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

5.3 **Non-Assignable cause:** When no reason could be identified during investigation.

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5.4 **Hypothesis / Investigative testing:** Is testing performed to help confirm a possible root cause i.e. what might have happened that can be tested.

5.5 **Retesting:** Repeated testing of a portion of the original sample. The sample is taken from the same homogeneous material used for the original test.

5.6 **Re-sampling** Collection and testing of a new sample from the batch. Resampling is conducted i) if the investigation concludes that the original sample was prepared improperly and was therefore not representative for the batch ii) if quantity of original sample is not sufficient to perform further analysis.

5.7 **PROCEDURE:**

5.7.1 Follow this procedure ; in case any result found outside the specification in the test of Uniformity of content, Dissolution, disintegration test, evaluate the results against different stages mentioned in current edition of concerned pharmacopeia or as per specification and standard test procedure. If the product is within the criteria of different stages, then follow SOP for Handling of Out of Trend Results, SOP No. OHC/II/SOP/QC/121

5.7.2 In the above case, perform investigation to find out any Laboratory error. If no laboratory error is identified, then proceed for analysis as per current edition of concerned pharmacopeia or as per specification and standard test procedure. If product meets the next stage criteria, then impact assessment on product self-life shall be done.

5.7.3 If the initial results does not conform with the final stage of the test for Uniformity of content, Dissolution, disintegration test, then raise OOS and perform the investigation as detailed in this SOP.

5.7.4 In case of confirmed OOS / OOT in stability study, the samples shall not be discarded till analysis of next stations is completed. This is to support investigation activity.

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5.7.5 In case of GC (for Headspace analysis), take the sample in duplicate for investigation purpose.

5.7.6 An out of specification test result can be due to:

5.7.6.1 Assignable cause

5.7.6.2 Non-Assignable cause

5.8 Assignable cause for the OOS result can be due to the following but not limited to:

5.8.1 Laboratory error

5.8.2 Error in sampling, handling or storage of sample

5.8.3 Non-process related or operator error

5.8.4 Process related or manufacturing process error

5.9 Laboratory error may occur due to the following but not limited to:

5.9.1 Usage of Incorrect method / specification

5.9.2 Incorrect sample used for analysis

5.9.3 Usage of wrong standards

5.9.4 Calculation error

5.9.5 Usage of non-validated spreadsheet for calculation

5.9.6 Instrument not in calibrated state

5.9.7 Wrong dilutions of sample/standard solutions

5.9.8 Analyst not certified for particular test

5.9.9 System suitability condition not met

5.9.10 Usage of wrong glassware viz. flask, pipette etc.

5.9.11 Usage of wrong chemicals and usage of wrong grade of chemicals

5.9.12 Usage of expired chemicals

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5.9.13 Environmental conditions not proper

5.9.14 Specific instruction not followed as per the methodology

5.9.15 Any other error related to instrument / human

5.10 When an analyst is performing a test and observes an incident that might result in an OOS test result, the analyst shall stop the analysis and discuss the situation with immediate Section Head before proceeding further and document what happened. The analyst should not knowingly continue the analysis, which they expect to invalidate at later time for an assignable cause.

5.11 In the event, a test fails to comply with the specification or predefined acceptance criteria and an OOS result is obtained, the Analyst shall immediately inform to immediate supervisor/ Head- QC.

5.12 ***Note: In case where multiple sample preparation is done, the individual result must comply with the acceptance criteria. Though the mean result complies with the specification, it shall not be considered satisfactory.***

5.13 The original samples, dilutions, glassware, aliquot of samples shall be preserved immediately once the OOS result (i.e. questionable results or test results that fall outside the established specification or acceptance criteria) is observed & shall be retained till the investigation for OOS is not completed.

5.14 The Head-QC / Section Head shall check the following but not limited to:

5.14.1 Discuss the method with the analysis

5.14.2 Examine raw data

5.14.3 Verify calculations

5.14.4 Confirm performance of instruments

5.14.5 Confirm reference/working standards, reagents

5.14.6 Evaluate performance of method

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5.15 If OOS test result is due to calculation error, correct the error and report the corrected results.

5.16 OOS investigation is divided into 3 parts

5.16.1 Phase I: Laboratory investigation

5.16.1.1 This part involves the investigation to find out any probable assignable laboratory error through thorough review of the system, documents, preparations etc as mentioned in section 5.8.

5.16.1.2 Hypothesis study shall be conducted (if required) for root cause identification.

5.16.1.3 If no assignable cause is identified then proceed further for Phase-2 / Phase-3 Investigation, as applicable.

5.16.2 Phase II: Full-Scale Investigation

5.16.2.1 This part consists of production process review, Sampling error identification and extended laboratory investigation, if required.

5.16.2.2 Phase II investigation should be given highest priority, as the evaluation of the impact of OOS result on already distributed batches has to be done.

5.16.3 Phase III investigation:

5.16.3.1 This part involves retesting of the sample when no assignable cause is identified during Phase-I and Phase-II investigation.

5.17 **OOS log:**

5.17.1 QA shall allocate OOS number in the OOS Register and shall issue report number for Phase-I: Laboratory investigation. The OOS Register (Refer Annexure-IV) shall be controlled by QA.

5.17.2 The OOS Report Number for Finished Product/In process/Stability sample shall have prefixed 'OOS' and shall be assigned as per following example:

Example: OOS/XX/YY/ZZZ, Where,

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OOS : Out of Specification report

XX : FP (Finished Product), IP (In-process sample), SS (Stability sample), RM (Raw material), PM (Packing material)

YY : Current calendar Year

ZZZ : Sequential number

5.17.3 Formats of Phase-II and Phase-III investigation shall be logged by QA based on the outcome of Phase-I investigation, as applicable.

5.17.4 OOS investigation shall be closed within 30 working days of OOS reporting. Any delay in investigation or closure of OOS must be justified.

5.18 **Phase-I: Laboratory investigation**

5.18.1 The analyst and the immediate supervisor/Head-QC shall carry out the laboratory investigation (Phase I) as per Annexure-II in case of Raw Material, Packing Material, In-Process Sample, Finished Product and Stability samples.

5.18.2 Throughout this step, the Analyst and immediate supervisor/Head-QC shall look for sound evidence that a laboratory error is the assignable cause of the OOS observation.

5.18.3 If the above laboratory investigation indicates that laboratory errors were made and an assignable cause related to laboratory error as mentioned under section 5.8 is found then original result shall be invalidated.

5.18.4 If the OOS test results are due to an identified human error or transient malfunctioning of instrument, Head-QC / designee shall document the assignable cause and suggest suitable corrective action including but not limited to training of analyst and re-calibration of instrument (i.e. correction of error) and re-analysis of the preserved test preparations or original sample shall be carried out in Single analysis by the same analyst omitting the error. The second analyst may be used for re-analysis due to absence of the original analyst.

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5.18.5 Analysis shall be done on a second aliquot from the same portion of the sample that was source of the first aliquot or analysis shall be done on the portion of the same larger sample.

5.18.6 Repeat analysis shall be performed after taking suitable corrective action like training to the original analyst etc. The material shall be approved, if result is within the specification and the original result shall be invalidated.

5.18.7 The initial laboratory investigation shall be completed within 3 working days.

5.18.8 If all criteria for re-analysis meet, review other batches analyzed simultaneously and release the batch. If the criteria for re-analysis do not meet with the specification, attempt should be done to identify the probable cause by conducting hypothesis or investigational testing.

5.18.9 If the results for the repeat analysis do not meet the specification criteria then investigation shall proceed for the hypothesis study.

5.18.10 The description of the hypothesis / investigational testing should be written and then approved by QA prior to initiating investigational testing. The hypothesis study plan must include

5.18.10.1 The hypothesis study details to identify the root cause.

5.18.10.2 What samples will be tested.

5.18.10.3 The exact execution of the testing.

5.18.10.4 How the data will be evaluated?

5.18.11 This Hypothesis testing may continue from the re-measurement of the original preparations.

5.18.12 The Hypothesis study involves following study as applicable:

5.18.13 Re-injection from same vial: This study shall be done to check any possible instrument malfunction. Check the solution stability of the standard / sample solutions. If found stable, then inject from the same vial to check any instrument

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malfunctioning. If the solution stability is not sufficient to perform reinjection from same vial, then this step may be omitted.

5.18.14 Re-dilution from stock solution: This study shall be done to check any possible dilution error. Check the solution stability of the standard / sample solutions. If the solutions are stable, then redilute from the original stock solution and inject the solution in new vial.

5.18.15 Further sonication / shaking of sample solution: This study shall be done to check for complete extraction of the active into the solution. Sonicate / shake the solution as per the standard testing procedure, redilute from stock solution (if applicable) and re-inject the solution in new vial.

5.18.16 Hypothesis / Investigational testing shall not be used to replace an original suspect analytical results. It shall only be used to confirm or discount a probable cause.

5.18.17 Re-sampling from the sampling container(s) for repeat analysis shall be performed only if the sample quantity is insufficient and it should be justified.

5.18.18 If the Assignable cause is identified in the hypothesis study the repeat analysis shall be considered by the same analyst in single preparation after taking suitable CAPA as applicable.

5.18.19 If the assignable cause is not identified in the hypothesis study, proceed for Phase II investigation.

5.19 **Phase-II: Full-Scale Investigation [Sampling, Manufacturing process and Extended laboratory investigation]**

5.19.1 If no assignable cause is identified from the hypothesis study then investigate to find out any sampling error / manufacturing process review.

5.19.2 Manufacturing process review shall be applicable only for Finished products/Stability study and not applicable for RM/PM.

5.19.3 If required, extended laboratory investigation shall be performed jointly by QC/QA.

5.19.4 If sampling error is identified, Head-QA/designee shall authorize for re-sampling.

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5.19.5 If sampling error is identified, re-sampling shall be done after approval of Head-QA/designee and the analysis by same analyst shall be done in triplicate. If all criteria met from the repeat analysis results release the material and close investigation with CAPA. If the re-analysis results do not meet the acceptance criteria reject the material.

5.19.6 Head-QC/Designee shall complete all details in Annexure-II and submit to QA for further investigation.

5.19.7 Head-QA/Designee shall review any deviation/incidence documented for the batch under investigation.

5.19.8 Head-QA/Designee shall also take into account if the problem had occurred previously and effectiveness of corrective actions taken.

5.19.9 In case of In-process / Finished product / Stability study, Head-QA/Designee shall thoroughly review documentation of Batch production records including dispensing of raw materials, adherence to manufacturing steps and critical process parameters, results of in-process tests, yield, equipment or system malfunction, etc. to determine the possible cause of OOS results.

5.19.10 If the investigation reveals a manufacturing defect, OOS result shall be valid and the batch shall be rejected.

5.19.11 Corrective and Preventive action shall be initiated based on the identified manufacturing defect.

5.19.12 Head-QA/Designee shall evaluate impact of OOS on other batches or product associated with the failure.

5.19.13 Head-QA/Designee shall summarize the aspects of the manufacturing process that may have caused the problem. Head-QA/Designee shall document the actual or probable cause and suggest corrective actions including revalidation of the manufacturing process.

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5.19.14 If the OOS is impacting on distributed batches and have impact on patient safety, Head-QA/Designee shall hold the batch from distribution and follow product recall SOP.

5.19.15 If Phase II investigation does not reveal a manufacturing defect or Sampling error, Head-QA/Designee shall recommend Phase III investigation and instruct Head-QC/Designee regarding the same as per Annexure-III.

5.19.16 Phase-II investigation is not applicable for Packing materials.

5.20 **Phase-III investigation:**

5.20.1 If no assignable cause is identified during Phase-I and Phase-II investigation, repeat analysis shall be planned.

5.20.2 The re-analysis shall be done in triplicate (three independent preparations) by different analyst (Analyst B) i.e. other than the original Analyst (Analyst A) and if all the results are within the acceptance criteria the analysis shall be carried out by the analyst A in presence of analyst B.

5.20.3 Reanalysis shall be performed on same sample (i.e. analysis shall be done on a portion of the same larger sample previously collected for analysis).

5.20.4 In case all the three results of triplicate (three independent preparations) analysis performed by Analyst B are within the specification, then the analysis shall be performed once again in triplicate by other Analyst (Analyst A) in presence of Analyst B.

5.20.5 If Analyst A is not available, then analysis shall be performed by analyst C in presence of analyst B.

5.20.6 The Second analyst (Analyst B / Analyst C) should be atleast as experienced and qualified in the method as the initial analyst A.

5.20.7 The material shall be approved only if the all six results of the samples comply to specification. In case the results of one or more sample preparation(s) fails to comply the specification, then the material shall be rejected.

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5.20.8 Note: Additional analysis may be planned for investigation purpose as recommended by Quality Assurance and Quality Control.

5.20.9 Head-QC/Designee shall check whether the results are within OOS acceptance criteria. Head-QC/Designee shall report the results and complete the details as per Annexure-III and submit to Head-QA/Designee.

5.20.10 Head-QA/Designee shall recommend suitable corrective action and justification shall be provided for non-identifying error during OOS investigation.

5.20.11 For Stability Samples Phase I investigation shall be performed and the finding and investigation shall be carried out with Quality Control, Product Development Department and Quality Assurance department. Phase II investigation is not applicable in case of Stability samples.

5.20.12 The investigation shall be extended to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. The investigation shall be documented and shall include the conclusions and follow-up.

5.20.13 Any unexplained discrepancy of the failure of a batch or any of its contents to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed.

5.20.14 In-Process Sample: The OOS is not applicable for in-process samples wherever subsequent processing is allowed as a part of drug manufacturing process.

5.20.15 Note: In the case of exhibit batch appropriate decision shall be taken by QA in consultation with Formulation and Development (F&D).

5.21 **Handling of OOS observed at Contract testing laboratory:**

5.21.1 The Contract testing laboratory shall follow their SOP in case any OOS is observed.

5.21.2 The Contract testing laboratory shall convey its data, findings, and supporting documentation to the QC/QA Head of Olive Healthcare.

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5.21.3 Full scale investigation shall be conducted regarding any error in sampling, integrity of packing of sample sent to contract laboratory etc.

5.21.4 After confirmation of OOS results by Contract testing laboratory, the OOS investigation report shall be shared with QC/QA department of Olive Healthcare.

5.21.5 In such case, the OOS number shall be generated by QA dept. of Olive Healthcare and the OOS investigation report of Contract laboratory shall be attached with the OOS format of Olive Healthcare.

5.21.6 If required, further investigation shall be done by Olive Healthcare, else material shall be rejected.

5.22 **Handling of OOS observed at Customer /Marketing Authorization Holder (MAH):**

5.22.1 The Customer shall follow their SOP in case any OOS is observed.

5.22.2 The Customer shall convey their data, findings, and supporting documentation to the QC/QA Head of Olive Healthcare.

5.22.3 Based on the data of customer, OOS shall be logged in at Olive Healthcare and further investigation shall be performed as per SOP of Out of specification of Olive Healthcare.

5.22.4 Full-scale investigation shall be conducted regarding any error in sampling, integrity of packing of sample sent to customer etc.

5.22.5 After confirmation of OOS results by Customer, the OOS investigation report shall be shared with QC/QA department of Olive Healthcare.

5.22.6 In such case, the OOS number shall be generated by QA dept. of Olive Healthcare and the OOS investigation report of Customer shall be attached with the OOS format of Olive Healthcare.

5.22.7 If required, further investigation shall be done by Olive Healthcare,

5.23 **Action to be taken in case of confirmed OOS in Raw material and Packing material:**

5.23.1 After confirmation of OOS, vendor shall be informed.

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Designation	SR.EXECUTIVE QC	HEAD QC	SR.OFFICER QA	MANAGER QA	HEAD QA
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	12/04/2024	16/04/2024

Olive HEALTHCARE	STANDARD OPERATING PROCEDURE		SOP No: OHC/II/SOP/QC/012-05
	DEPARTMENT: QUALITY CONTROL		Supersedes: OHC/II/SOP/QC/012-04
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TITLE: OUT OF SPECIFICATION TEST RESULTS

5.23.2 CAPA shall be asked from the vendor for any raw material/ packing material rejection.

5.23.3 If requested by the vendor, joint analysis with the vendor shall be performed.

5.23.4 Based on QA recommendation, appropriate actions shall be taken considering the criticality of failures and to de-list the vendor.

5.23.5 Action shall be taken in terms of immediate delisting of the vendor/supplier. Supply chain/procurement department shall be advised to hold issuing new orders for the materials to the vendor under question and to quarantine the supplies / in transit material, pending investigation and resolution.

5.23.6 A discussion with the vendor/supplier shall be arranged, if they are supplying other materials as well in addition to the material which was found failing or of poor quality.

5.23.7 Impact evaluation shall be performed by QA, on other materials supplied by the same vendor/manufacturer from the same manufacturing site and included in the approved vendor list.

5.24 **OOS acceptance criteria:**

5.24.1 All reanalysis results should individually pass. (i.e. Repeat analysis up to laboratory error and 6 analyses for Phase-III).

5.24.2 Overall RSD should be within limit as per table below:

Test	% RSD
Assay	NMT 2.0%
Residual solvent (if applicable)	NMT 25.0%
Impurity below 0.10 %	NMT 20.0%
Impurity above 0.10 %	NMT 10.0%

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Olive HEALTHCARE	STANDARD OPERATING PROCEDURE		SOP No: OHC/II/SOP/QC/012-05
	DEPARTMENT: QUALITY CONTROL		Supersedes: OHC/II/SOP/QC/012-04
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TITLE: OUT OF SPECIFICATION TEST RESULTS

5.24.3 For other tests, specific limits for % RSD shall be set by Head-QC/Designee at the time of initiation of investigation, which shall be based on variations inherent in the analytical testing.

5.24.4 In case of other tests, as applicable, the values shall individually pass.

5.24.5 In case of OOS results reported in raw materials/packaging material, review of production process is not applicable. However, transit and storage condition of material to evaluated.

5.24.6 In-case of OOS reported by approved outside testing agency, then OOS SOP as per agreement shall be followed.

5.24.7 Field alert report (FAR) to be submitted within 3 working days to the Marketing Authorization Holder if any of the failure of a distributed batch to meet any of the specification. When OOS is closed submit follow up FAR.(Reference SOP No: OHC/II/QA/066)

5.24.8 Information to the concerned contract giver (where applicable) shall be provided by Manager QA, before initiation of Phase-II/Phase-III investigation and closing of CAPA.

5.25 **Averaging of Results:**

5.25.1 Averaging of reported results shall be done on final analysis which indicate passing results and comply the criteria as mentioned in point no. 5.24.2.

5.26 **Conclusion:**

5.26.1 If no laboratory or calculation errors are identified in the Phase I and Phase II there is no scientific basis for invalidating initial OOS results in favour of passing retest results. All test results, both passing and suspect, shall be reported (in all QC documents and any certificate of analysis) and all data has to be considered in batch release decisions.

5.26.2 If the investigation determines that the initial sampling method was inherently inadequate, a new accurate sampling method must be developed, documented, and

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Olive HEALTHCARE	STANDARD OPERATING PROCEDURE		SOP No: OHC/II/SOP/QC/012-05
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reviewed and approved by the quality assurance responsible for release. Consideration shall be given to other lots sampled by the same method.

5.26.3 An initial OOS result does not necessarily mean the subject batch fails and must be rejected. The OOS result shall be investigated, and the findings of the investigation, including retest result, shall be interpreted to evaluate the batch and reach a decision regarding release or rejection which shall be fully documented.

5.26.4 In those cases, where the investigation indicates an OOS result is caused by a factor affecting the batch quality (i.e., an OOS result is confirmed), the result shall be used in evaluating the quality of the batch or lot. A confirmed OOS result indicates that the batch does not meet established standards or specifications and shall result in the batch's rejection and proper disposition. Other lots shall be reviewed to assess impact.

5.26.5 The OOS result shall be given full consideration (most probable cause determined) in the batch or lot disposition decision by the certifying Head QA and the potential for a batch specific variation also needs considering.

5.26.6 Any decision to release a batch, in spite of an initial OOS result that has not been invalidated, shall come only after a full investigation has shown that the OOS result does not reflect the quality of the batch. This must include a review of all other tests related to the batch and other batch historical data. In making such a decision, Head Quality Assurance shall always err on the side of caution.

5.27 **Trending of OOS:**

5.27.1 Trending of OOS shall be done annually by QA personnel.

5.27.2 An OOS trend report shall be prepared and shall contain necessary CAPA.

5.27.3 QA shall monitor the OOS and identify necessary CAPA to avoid repeated laboratory errors, repeated rejection of material from same supplier etc.

5.27.4 The OOS trend shall be monitored by higher management and shall take necessary action to address the problematic areas.

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Olive HEALTHCARE	STANDARD OPERATING PROCEDURE		SOP No: **OHC/II/SOP/QC/012-05**
	DEPARTMENT: QUALITY CONTROL		Supersedes: **OHC/II/SOP/QC/012-04**
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5.28 **Corrective action and Preventive action (CAPA):**

5.28.1 Laboratory errors shall not be repetitive.

5.28.2 Whenever laboratory error is identified, the root cause for the error shall be identified and shall take necessary Corrective and preventive action to prevent recurrence.

5.28.3 Previous history of the OOS shall be checked for any repetitive laboratory errors or previous history of OOS occurring in same product must be accessed.

5.28.4 The CAPA shall be scientifically biased and must be effective to prevent recurrence.

5.28.5 Training shall be imparted, as needed, and training effectiveness to be verified.

5.28.6 Raise CAPA format no. Annexure-I as per SOP No. OHC/II/SOP/QA/005.

5.28.7 Attach all respective documents with the OOS report as evidence.

5.28.8 Mention the reference OOS number in the analytical worksheet/records, as applicable.

6.0 TRAINING:

Trainer : Manager-Quality Control
Trainees : All Departmental Employee

7.0 DISTRIBUTION:

Original Copy No. : Manager-QA
Controlled Copy No. 1 : Quality Assurance
Controlled Copy No. 2 : Head-QC/Designee
Controlled Copy No. 3 : Manager-Production

	Prepared By-QC	Reviewed By-QC	Reviewed by-QA	Approved By	Authorized By
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Olive HEALTHCARE	STANDARD OPERATING PROCEDURE		SOP No: **OHC/II/SOP/QC/012-05**
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TITLE: OUT OF SPECIFICATION TEST RESULTS

8.0 ATTACHMENTS:

Annexure-I : OOS results-flow diagram (OHC/II/FM/1/04-SOP/QC/012)

Annexure-II : Phase-I Investigation report (OHC/II/FM/2/04-SOP/QC/012)

Annexure-III : Phase-III Investigation report (OHC/II/FM/3/03-SOP/QC/012)

Annexure-IV : Out of specification register (OHC/II/FM/4/02-SOP/QC/012)

Annexure-V : Phase-II Investigation report (OHC/II/FM/5/01-SOP/QC/012)

9.0 REFERENCES:

ICH Guidelines, FDA Guideline, MHRA Guideline

10.0 REFERENCE OF OTHER SOPs:

SOP OHC/II/SOP/QC/121, Title: Procedure for Handling of Out of Trend Results

SOP OHC/II/SOP/QA/005, Title.: Corrective and Preventive Action (CAPA) Management.

SOP OHC/II/SOP/QA/066, Title.: Control Sample (Reserve sample) Management.

SOP OHC/II/SOP/QA/029, Title.: Field Alert and Post Marketing Reports.

11.0 VERNACULAR LANGUAGE SOP:

Not Applicable.

12.0 REVISION HISTORY:

Revision No.	Reason for revision	Effective Date
00	New SOP	09/07/2012

	Prepared By-QC	Reviewed By-QC	Reviewed by-QA	Approved By	Authorized By
Name	PRAFULL THAKUR	SURESH KUMAR	ADARSH KASHYAP	PRATIK PANDYA	VIKASH JHA
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Olive HEALTHCARE	STANDARD OPERATING PROCEDURE		SOP No: **OHC/II/SOP/QC/012-05**
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Revision No.	Reason for revision	Effective Date
01	Change Control No.: D/13/09/002	16/10/2013
02	Reference DCR No.: DCR/QC/16/004	12/11/2016
03	Reference CCP No.: CCP-U2-QC-18-0002	16/01/2018
03	No change	13/01/2021
04	Reference CCP No.: CCP-U2-QC-22-0065	03/12/2022
05	Reference CCP No.: CCP-U2-QC-24-0013 1) Following steps are updated to rectify the mentioned references of steps number as follows: i) Step no.5.16.1 is updated as follows: "This part involves the investigation to find out any probable assignable laboratory error through thorough review of the system, preparation etc. as mentioned in section 5.8. ii) Step no. 5.25.1 updated as follows "Averaging of reported results shall be done on final analysis which indicate passing results and comply the criteria as mentioned in point no. 5.24.2" 2) Typographical error, minor editorial change updated in SOP. Reference CCP No.: CCP-U2-QA-24-0025 1) Annexure-IV is revised to capture the root cause & OOS logged by along with OOS detail. 2) Scope and procedure incorporated for OOS reported at Contract testing laboratory as well as at customer / Marketing Authorization Holder (MAH) and Annexure-I updated accordingly.	29 APR 2024

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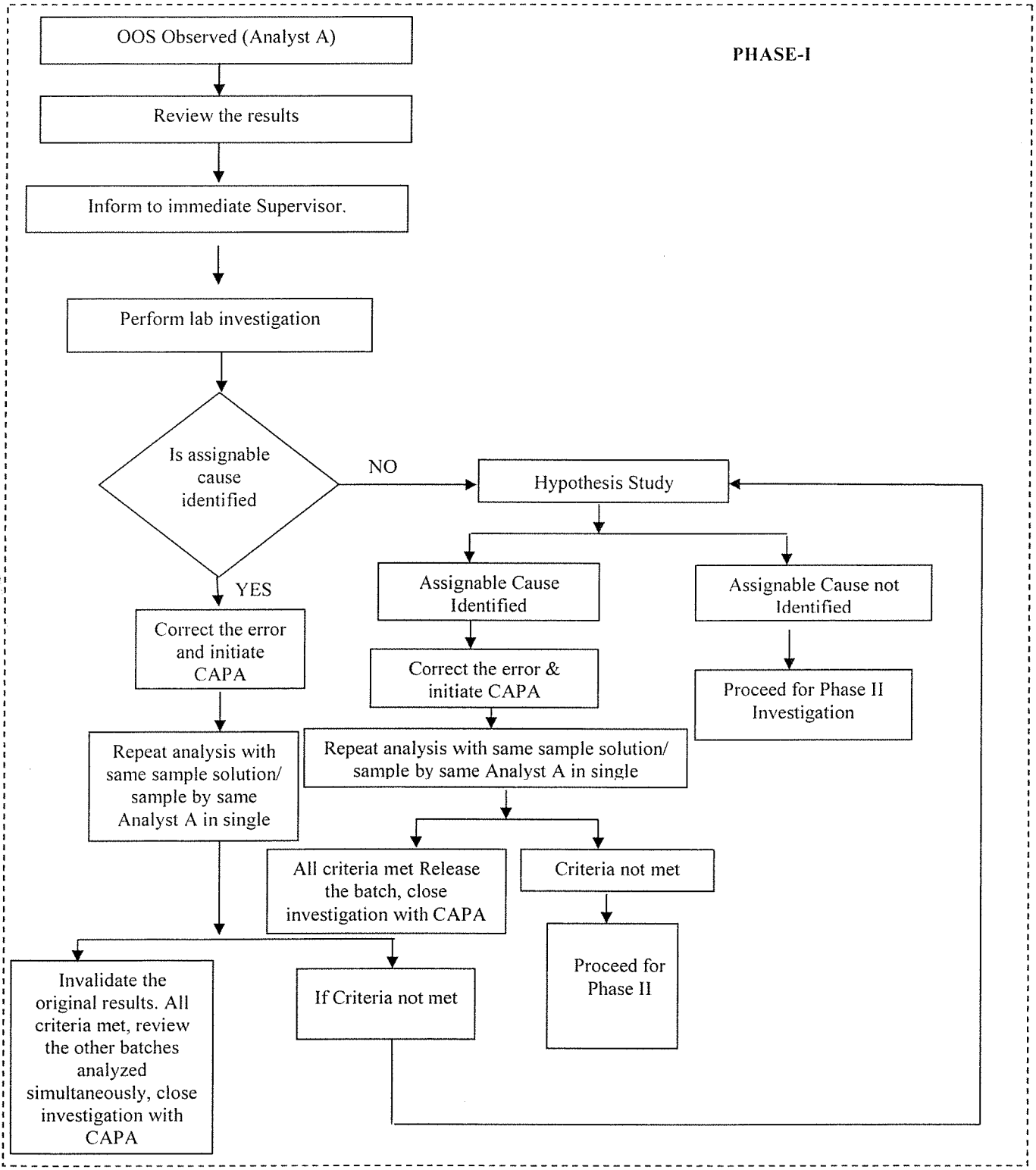
Annexure – 1

OHC/II/FM/1/04-SOP/QC/012

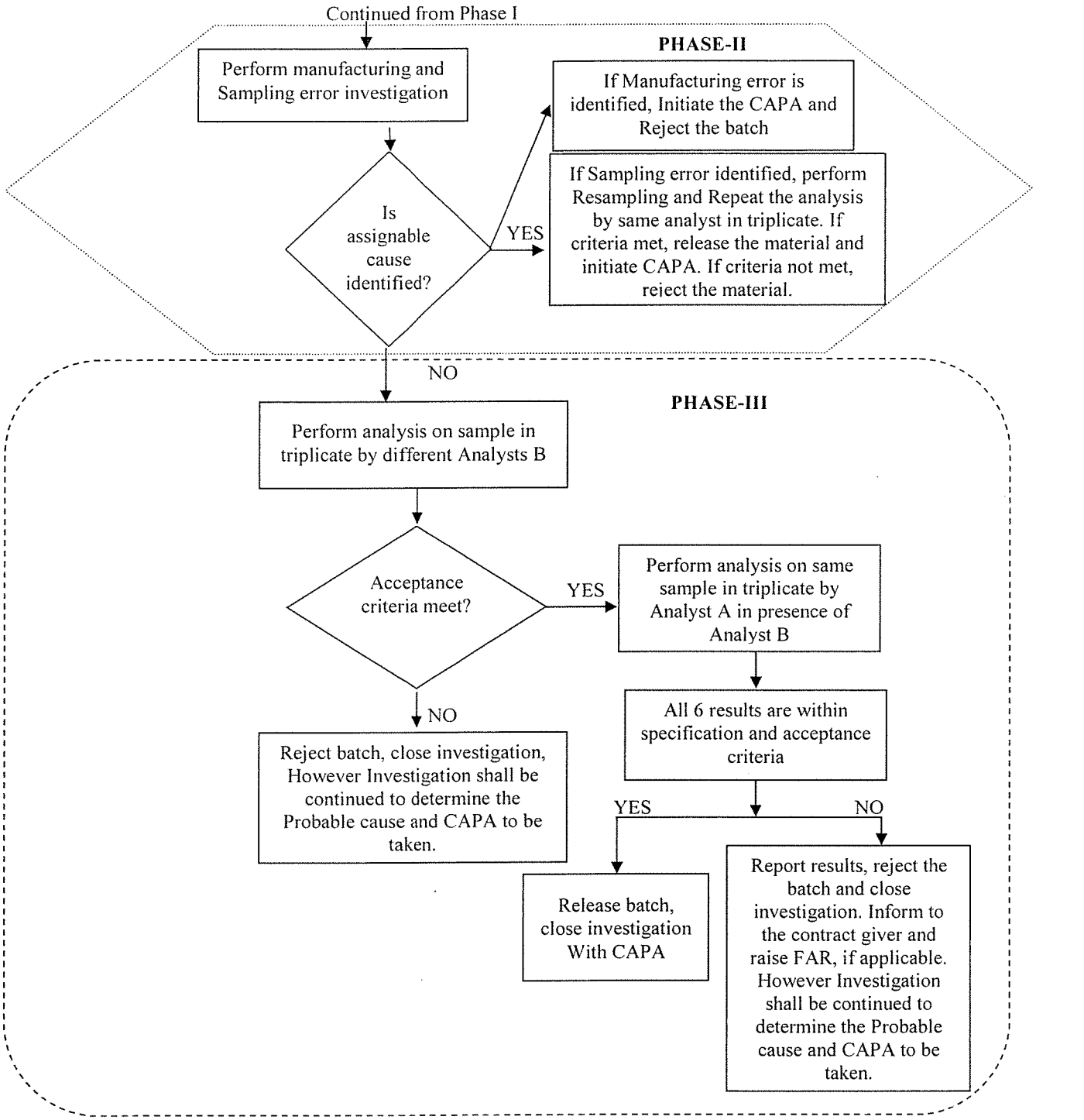
Olive HEALTHCARE	DEPARTMENT: QUALITY CONTROL	Page No. 1 of 6
	OOS RESULTS – FLOW DIAGRAM	

For Finished Product /In Process / Stability Study



	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure – I

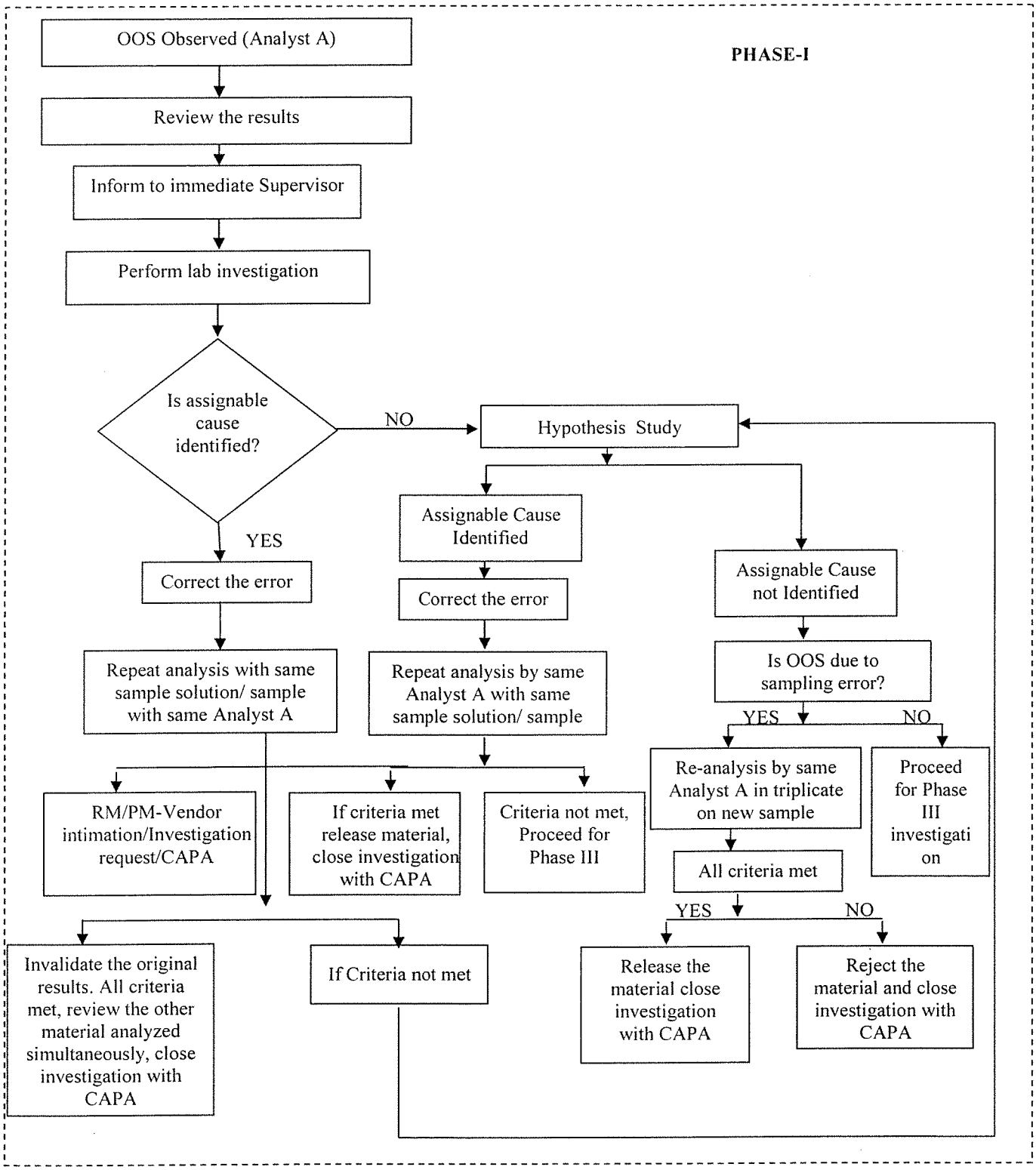


Note: *OOS intimation to be given to the Contract Giver at the initial and closing of CAPA and for approved ANDA FAR to be submitted.*

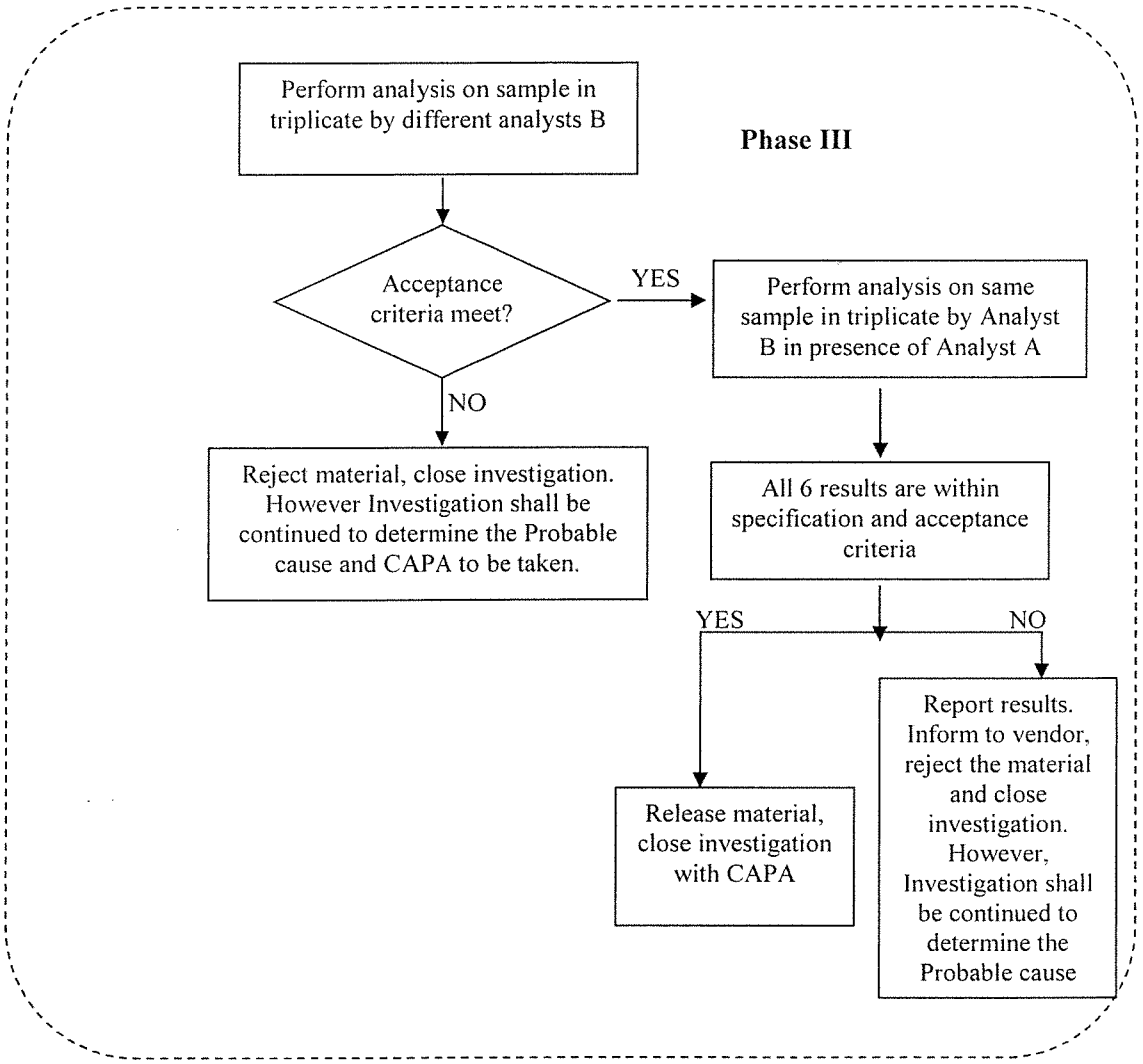
	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure – 1

For Raw Material



	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024



Note: *OOS intimation to be given to the Contract Giver and Vendor at the initial and closing of CAPA.*

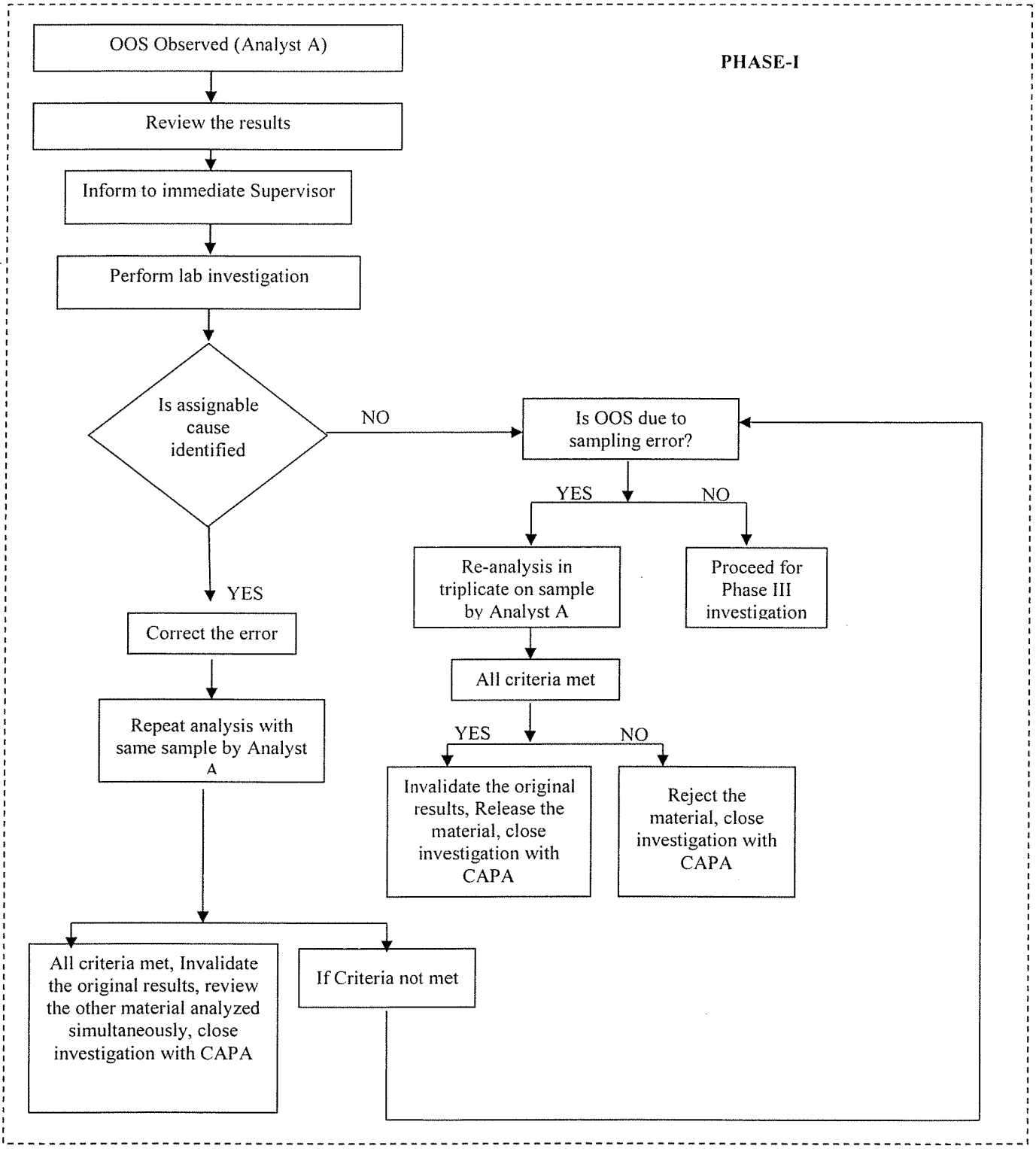
	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure – I

OHC/II/FM/1/04-SOP/QC/012

Olive HEALTHCARE	DEPARTMENT: QUALITY CONTROL OOS RESULTS – FLOW DIAGRAM	Page No. 5 of 6

For Packing Material

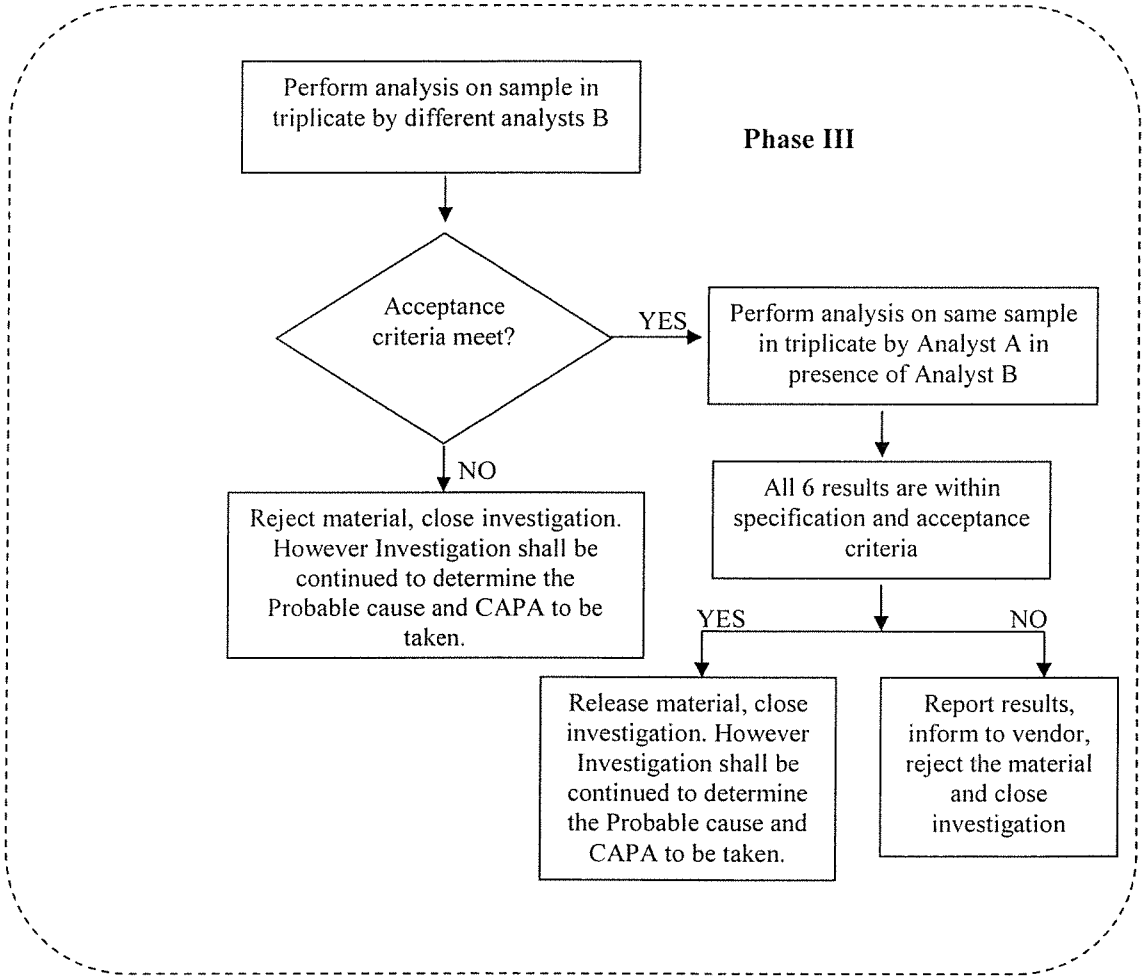


	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure – I

OHC/II/FM/1/04-SOP/QC/012

	DEPARTMENT: QUALITY CONTROL	Page No. 6 of 6
Olive HEALTHCARE	OOS RESULTS – FLOW DIAGRAM	



	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure-II

Olive HEALTHCARE	DEPARTMENT: QUALITY CONTROL PHASE-I – LABORATORY INVESTIGATION REPORT	Page No. 1 of 12

Olive Healthcare, Unit II, Daman	Initial Assessment of OOS results	Report No. : OOS/
Date of OOS Observed:	**Date of OOS Closed:**	
Sample Type: Raw Material / Packing Material / In Process / Finished Product / Stability Other (Please specify) _____		
Name of the Material/Product under testing:		
Batch No./Lot No.:	AR No.:	
Mfg. Date:	Expiry Date:	
Specification No.& Rev. No. :	STP No. & Rev. No.:	
Stability Time Point:(For stability samples only)	Stability Conditions: (If applicable)	
Test in which OOS result is found:		
Result Obtained:	Specification Limit:	
Analyst:	Date of Analysis:	
Problem / Discrepancy:		

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure-II

Olive HEALTHCARE	DEPARTMENT: QUALITY CONTROL PHASE-I – LABORATORY INVESTIGATION REPORT	Page No. 2 of 12

I.	Laboratory Investigation (RM/PM/IP/FP/Stability Sample)	YES	NO	Comments
1.	Aliquot and standard solutions preserved.			
2.	Were correct samples were used for analysis.			
3.	Were the specification and standard test procedure used were correct and current versions were followed during analysis.			Specification No.: STP No.:
4.	Whether analyst was certified to perform the test.			
5.	Appearance of the sample (Visual examination (solid and solution) reveals normal or abnormal appearance)			
6.	For Weighing errors			
6.1	Whether the correct balance used for weighing was calibrated.			Balance ID. No.: Calibration due date:
6.2	Were the weighing technique properly applied by the analyst.			
6.3	Were the sample / standard / reagent weight as per the standard testing procedure.			
6.4	Were the analytical instrument properly operated and calibrated.			Instrument ID. No.: Calibration due date:
7.	For calculation error (whether calibrated calculator / validated spreadsheet used for calculation)			
8.	Glassware			
8.1	Were Class A glassware used for analysis.			
8.2	Were the volumetric flask correctly used (check the capacity, type of glassware i.e. amber or transparent).			

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

I.	Laboratory Investigation (RM/PM/IP/FP/Stability Sample)	YES	NO	Comments
8.3	Whether the glassware integrity was proper i.e. damaged glassware was not used for analysis etc.			
8.4	Were the glassware properly labeled.			
8.5	Were the glassware properly stored as per the storage condition.			
9.	Were the Sample stored as per the respective storage condition.			
10.	Assessment of the possibility that the sample contamination (sample left open to air or unattended) has occurred during analysis.			
11.	Were the dilutions as per the Standard testing procedure.			
12.	Inspect the respective vials for any droplets present on the septa of vial, sufficient solution available in vial, any septa related error.			
13.	Were correct filter paper used during filtration of sample / standard solutions as per the Standard testing procedure.			
14.	Chromatographic conditions:			
14.1	Were the mobile phase properly prepared as per the ratio and filtered as per the procedure.			
14.2	Was the mobile phase filtered as per the requirement.			
14.3	Were the correct column used for analysis as per the standard testing procedure.			Column ID. No.: Total number of injections injected in the column:
14.4	Were the instrument method proper as per the Standard testing procedure. (For HPLC: Check Wavelength, Flow, Temperature, Gradient			

Annexure-II

I.	Laboratory Investigation (RM/PM/IP/FP/Stability Sample)	YES	NO	Comments
	programme (if applicable) For GC: Check the Detector temperature, Injector temperature, column flow, temperature programme etc.)			
14.5	Was there any leakage at column ends, tubings, etc.			
14.6	Was there any pressure fluctuations during the sequence run.			
14.7	Inspect the tubings of HPLC for presence of any air bubble.			
14.8	Was there any error in the sample set/batch/sequence with respect to Injection volume, Vial number, method name etc.			
14.9	Was the column temperature / sample temperature as per the standard testing procedure.			
14.10	Were correct integration parameters applied for processing of data.			
14.11	Whether correct rinsing solvent was used in analysis.			
15.	Were correct chemicals used for analysis (i.e. check the correctness of chemical name, grade/make/validity of chemical etc.)			
16.	Whether volumetric solution used was properly prepared & standardized.			Name of Volumetric solution: A.R. No.: Standardization due on: Use before date:
17.	Were the critical steps followed during analysis; techniques in analytical procedures were appropriately applied.			

Annexure-II

Olive HEALTHCARE	DEPARTMENT: QUALITY CONTROL PHASE-I – LABORATORY INVESTIGATION REPORT	Page No. 5 of 12

I.	Laboratory Investigation (RM/PM/IP/FP/Stability Sample)	YES	NO	Comments
18.	Whether reference standard / working standard used were correct (in terms of appearance, purity, LOD/water content & its storage and within their expiry) and assay values determined correctly.			RS/WS Used: _____ Lot No. : _____ Potency : _____ Valid upto : _____
19.	System suitability: Were the RSD, resolution factor and other parameters required for the suitability of the test system as per STP. Check if any out of limit parameters included in the chromatographic analysis, correctness of the column used previous use of the column.			
20.	Was any loss or spillage of standard solution or test solution during preparation occurred.			
21.	Was any unusual or unexpected response observed with standard or test preparations (e.g. Whether contamination of equipment by previous sample observed).			

Additional observation / Comments (Attach additional sheet if required):

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	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure-II

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Remarks: The above investigation shall be completed within 3working days from the date of recording of OOS. Otherwise delay justification to be provided.

Previous history of the product / material for any OOS reported and review of its CAPA:

OOS No. (If available): .....

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Justification for delay in investigation:

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	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure-II

Olive HEALTHCARE	DEPARTMENT: QUALITY CONTROL PHASE-I – LABORATORY INVESTIGATION REPORT	Page No. 7 of 12

FINDINGS & CONCLUSION:	
Assignable cause found	**YES / NO**
Cause of Analysis:	
If yes, then proceed for repeat analysis using same sample by the same analyst in presence of Second analyst / Section head by correcting the error.	**YES / NO**
If no, then proceed for Hypothesis study to identify the root cause.	**YES / NO**
Information to concern contract giver, provided by manager QA	**YES / NO**
Sign/date (QA manager)	

	Analyst	Investigated by	Reviewed by	Approved by
Department	**QC**	**QC**	**QC-Head/Designee**	**QA-Head/Designee**
Sign/Date				

HYPOTHESIS STUDY:

Details of the Hypothesis study planned to find out the root cause of OOS results:

- Reinjection from the same vial to check any instrument malfunctioning ☐
- Reinjection from the final solution using new vial to check any contamination ☐
- Re-dilution from the stock solution to check any subsequent dilution error ☐
- Re-dilution from the stock solution after extra drug extractions to check less drug extraction while initial sample preparations ☐
- **Any other study (to be defined in detail: attach additional sheet if required)**

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure-II

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Prepared By: **Reviewed By:** **Approved By QA:**
(Sign/Date) **(Sign/Date)** **(Sign/Date)**

- **Results of Hypothesis Study:**

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Done By: **Verified By QA:**
Sign/Date **Sign/Date**

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure-II

Olive HEALTHCARE	DEPARTMENT: QUALITY CONTROL PHASE-I – LABORATORY INVESTIGATION REPORT	Page No. 9 of 12

FINDINGS & CONCLUSION OF HYPOTHESIS STUDY:	
Assignable cause found	**YES / NO**
Cause of Analysis:	
If yes, then proceed for repeat analysis using same sample by the same analyst in presence of Second analyst / Section head by correcting the error.	**YES / NO**
If no, then proceed for Phase-II investigation.	**YES / NO**

	Analyst	Investigated by	Reviewed by	Approved by
Department	QC	QC	QC-Head/Designee	QA-Head/Designee
Sign/Date				

If Assignable cause is identified, details of the repeat analysis planned:

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	Done by	Reviewed by	Approved by
Department	QC	QC-Head/Designee	QA-Head/Designee
Sign/Date			

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure-II

Olive HEALTHCARE	DEPARTMENT: QUALITY CONTROL	Page No. 10 of 12
	PHASE-I – LABORATORY INVESTIGATION REPORT	

Results of Repeat analysis:

Sign/date:

Remarks: Is the results within / not within the specification.

Conclusion:

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Sign/date:

OOS: Valid / Invalid.	**Type of Error:** Method / Man / Machine / Measurement / Material / Mother nature

Corrective action:

Sign/date:

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure-II

	DEPARTMENT: QUALITY CONTROL	Page No. 11 of 12
Olive HEALTHCARE	PHASE-I – LABORATORY INVESTIGATION REPORT	

Preventive action:

Reference CAPA No.: .....

Sign/date:

Batch: Accepted / Rejected

Attach all relevant chromatograms / spectra / raw data / CAPA closure documents.

Recommendation by QA : Proceed / Not to proceed for Phase II /Phase III investigation.

Remarks (by QA Head):

Sign/Date:

Extension Justification for delay in closure (If applicable):
If OOS is not closed within 30 working days, provide justification and take approval for extension:

Extension Justification:

Sign/date: **Approved by/date:**

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure-II

OOS Closure:

1) All relevant closure documents attached with OOS: Yes/No
2) Reference of OOS mentioned in respective report/Analytical data sheet: Yes/No
3) Identified CAPA implemented: Yes/No

Any other comment:

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Sign/Date:

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authonized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure–III

OHC/II/FM/3/03-SOP/QC/012

Olive HEALTHCARE	DEPARTMENT: QUALITY CONTROL PHASE-III – INVESTIGATION REPORT	Page No. 1 of 3

Olive Healthcare, Unit II, Daman	Investigation Report	Report No. : OOS/

Name of the Material/Product under testing:			
Lot / Batch No.:		A.R No.:	
Mfg. Date:		Expiry Date:	
Specification No. & Rev. No.:		STP No. & Rev. No.:	
Test in which OOS result is found:			
Specification Limit:			
1.	Re-analysis of original material by two analysts in triplicate		
	Analyst B:	Sign :	Date :
	Analyst A/C:	Sign :	Date :
2.	Results of Re-analysis		
	Analyst B	Analyst A / C	
	Mean of the six results:		
	% RSD of the six results:		
	Remark: The results are within / not within the specification.		
	Conclusion:		
	OOS result: Valid / Invalid.	**Type of Error:** Method / Man / Machine / Measurement / Material / Mother nature	
	Head-QC/Designee: Date:		

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure–III

OHC/II/FM/3/03-SOP/QC/012

3.	**QC Investigation Report** .... Head-QC/Designee: Date:
4.	**QA Investigation Report:** .... **Batch Accepted / Rejected** Head-QA/Designee: Date:
5.	**Corrective & Preventive Actions:** .... Reference CAPA No.: ..... Head-QA/Designee: Date:

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure–III

OHC/II/FM/3/03-SOP/QC/012

Olive HEALTHCARE	DEPARTMENT: QUALITY CONTROL PHASE-III – INVESTIGATION REPORT	Page No. 3 of 3

Extension Justification for delay in closure (If applicable):
If OOS is not closed within 30 working days, provide justification and take approval for extension:

Extension Justification:

Sign/date: Approved by/date:

OOS Closure:
1) All relevant closure documents attached with OOS: Yes/No
2) Reference of OOS mentioned in respective report/Analytical data sheet: Yes/No
3) Identified CAPA implemented: Yes/No

Any other comment:

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Sign/Date:

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure–IV

OHC/II/FM/4/02-SOP/QC/012

	DEPARTMENT: QUALITY CONTROL	Page No. 1 of 1
Olive HEALTHCARE	OUT OF SPECIFICATION REGISTER	

OOS Report No.	Date	Description	OOS Logged By (Sign/date)	OOS Valid / Invalid	Root cause	Close Out Sign/date

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure–V

Olive HEALTHCARE	DEPARTMENT: QUALITY CONTROL PHASE-II – INVESTIGATION REPORT	Page No. 1 of 6

Olive Healthcare, Unit II, Daman	Investigation Report	Report No. : OOS/

Name of the Material/Product under testing:		
Lot / Batch No.:		A.R No.:
Mfg. Date:		Expiry Date:
Specification No. & Rev. No.:		STP No. & Rev. No.:
Test in which OOS result is found		
Specification Limit:		
Sampling investigation		
1	Reference Sampling procedure followed	
2	Sampled by	
3	Whether sampling person is trained	Yes / No
4	Correct sampling device was used for sampling	Yes / No
5	Environmental conditions [Temperature / Humidity] were appropriate at the time of sampling	
6	Sample was packed properly after sampling	Yes / No
7	Any specific instruction to be followed during sampling and whether it is followed	
8	Any other observation (Please specify in detail):	
Assignable cause identified: YES / NO		
Investigation done by/date:	Reviewed by/date (QA):	

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure–V

Extended Laboratory investigation
Details of Investigation:
Outcome of Investigation:
Assignable cause identified: YES / NO
Investigation done by: Reviewed by/Date:

Manufacturing Process investigation [Applicable for Finished products]:			
1.	Reference Batch No. of BMR reviewed		
2.	**Parameters**	**Reviewed [Yes / No]**	**Remarks / Observation**
2.1	Raw material dispensing		
2.2	In-process parameters		
2.2.1	Medicament preparation		
2.2.2	Gelatin manufacturing		
2.2.3	Drying		
2.2.4	Others (Please specify):		

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure–V

Olive HEALTHCARE	DEPARTMENT: QUALITY CONTROL PHASE-II – INVESTIGATION REPORT	Page No. 3 of 6

Attach additional sheets for detailed investigation.	
Assignable cause identified	YES / NO

Cause of the OOS:

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OOS result valid / Not valid.	**Type of Error:** Method / Man / Machine / Measurement / Material / Mother nature

If Assignable cause is identified, details of the repeat analysis planned:

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	Done by	Reviewed by	Approved by
Department	**QC**	**QC-Head/Designee**	**QA-Head/Designee**
Sign/Date			

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure–V

Results of Repeat analysis:

Sign/date:

Conclusion:

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Sign/date:

QC Investigation Report:

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Head-QC/Designee: Date:

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure–V

OHC/II/FM/5/01-SOP/QC/012

Olive HEALTHCARE	DEPARTMENT: QUALITY CONTROL PHASE-II – INVESTIGATION REPORT	Page No. 5 of 6

QA Investigation Report:

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Head-QA/Designee: Date:

Batch Accepted / Rejected

Recommendation by QA : Proceed / Not to proceed for Phase II /Phase III investigation.

Head-QA/Designee:

Date:

Corrective & Preventive Actions:

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Reference CAPA No.: .....

Head-QA/Designee: Date:

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024

Annexure–V

Olive HEALTHCARE	DEPARTMENT: QUALITY CONTROL PHASE-II – INVESTIGATION REPORT	Page No. 6 of 6

Extension Justification for delay in closure (If applicable):
If OOS is not closed within 30 working days, provide justification and take approval for extension:

Extension Justification:

Sign/date: **Approved by/date:**

OOS Closure:
1) All relevant closure documents attached with OOS: Yes/No
2) Reference of OOS mentioned in respective report/Analytical data sheet: Yes/No
3) Identified CAPA implemented: Yes/No

Any other comment:

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Sign/Date:

	Prepared By-QC	Reviewed by-QC	Reviewed by-QA	Approved by	Authorized By
Signature					
Date	11/04/2024	11/04/2024	11/04/2024	13/04/2024	16/04/2024