PHARMA DEVILS

MICROBIOLOGY DEPARTMENT

STANDARD OPERATING PROCEDURE	
Department: Microbiology	**SOP No.:**
Title: Handling of Out of Specification results during Microbiological Testing	**Effective Date:**
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1.0 PURPOSE:

To lay down the procedure for Handling of Out of Specification (OOS) Result during Microbiological Testing.

2.0 SCOPE:

This Standard Operating Procedure is applicable at Microbiology Department.

3.0 REFERENCES:

3.1 SOP for Good Documentation Practices

3.2 SOP for Deviations/Incidents

3.3 SOP for Handling of Corrective and Preventative Actions.

4.0 RESPONSIBILITY:

4.1 Officer or Executive of Microbiology Department shall be responsible for preparation of new or revision of existing SOP.

4.2 Head of the department/designee of respective areas & QA shall be responsible for reviewing the SOP's.

4.3 Site Quality Head and Head QA shall be responsible for approval of SOP.

5.0 ABBREVIATIONS:

5.1 BMR : Batch Manufacturing Record.

5.2 BPR : Batch packing record.

5.3 CAPA : Corrective and Preventive Action

5.4 CCR : Change Control Record

5.5 CMO : Contract Manufacturing Organization

5.6 CQ : Corporate Quality

5.7 DMF : Drug Master File

5.8 GDP : Good Documentation Practices

5.9 GPs : General procedure

5.10 GPT : Growth Promotion Test

5.11 GQS : Global Quality System

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5.12 HOD : Head of Department

5.13 HQC : Head Quality Control

5.14 HVAC: Heating Ventilation and Air Conditioning.

5.15 LAF : Laminar Air Flow

5.16 MLT : Microbial Limit Test

5.17 NA : Not Applicable

5.18 OOS : Out of Specification

5.19 PDA : Parenteral Drug Association

5.20 QA : Quality Assurance

5.21 QC : Quality Control

5.22 QP : Qualified person

5.23 RA : Regulatory Affair

5.24 RCA : Root Cause Analysis

5.25 SME : Subject Matter Expert

5.26 SOP : Standard Operating Procedure

5.27 STP : Standard Operating Procedure

6.0 DEFINITION:

6.1 **SOP:** A written authorized procedure, which gives instructions for performing operations

6.2 **Critical Area:** An area designed to maintain sterility of sterile materials, sterilized product, containers, closures and equipments.

6.3 Microbiological Identification: Biochemical characterization of isolated colonies to determine the isolate genus and where feasible and appropriate the species.

6.4 **CAPA:** Corrective and Preventive action, a systematic approach that includes actions needed to correct (correction), prevent recurrence ("corrective action"), and eliminate the cause of potential non-conforming product and other quality problems (preventive action).

6.5 **Out of Specification (OOS) Results:** All test results that fall outside the specifications or acceptance criteria established in drug applications, drug master files (DMF's), official compendia or by the manufacturer.

6.6 **Investigation:** A step-by step investigation to determine if the root or assignable cause of the 'OOS' result was due to some form of laboratory error or is attributable to the material being tested. All findings of the investigation must be documented, reviewed for adequacy/ completeness by the Quality control/Quality Assurance designee.

6.7 **Re-Analysis:** For the specific purpose of microbiological testing (since the final working solution is not even remotely viable for the entire incubation period), re-analysis is considered to be a new sample preparation of the material that was originally collected from the lot, tested and yielded the OOS results. This is performed during the preliminary laboratory investigation in order to determine if the assignable cause is laboratory error. The re-analysis sample represents the same sample volume of the original sample. Any and all re-analysis activities must be proposed with adequate justification be documented and reviewed by the Functional supervisor/Head-QC prior to its execution.

6.8 **Re-Test:** Any additional test preparation of the material that was originally collected from the lot, tested and yielded the OOS results (e.g for a liquid, it may be from the original unit liquid product or composite of the liquid product for a solid, it may be an additional weighing from the same sample composite prepared for the original test) Re-testing must be justified in writing based on the results of the preliminary Laboratory investigation and / or full scale investigation.

6.9 **Preliminary Laboratory Investigation:** The fully documented, step-by-step investigation approach used by the Microbiology Functional Supervisor (may also include Head Quality Control, whenever necessary) and the microbiologist to determine whether any laboratory error is the assignable cause of an out-of-specification result.

6.10 **Re-Sample:** A new sample or a new specimen taken from the original container(s) that contained the originally submitted laboratory sample. Re-sampling is only to be done if the evidence indicates that the original sample was not representative, was improperly taken, or was not stored appropriately. In all cases any re-sampling must be decided by Site Head-Quality.

Note: An OOS result does not necessarily mean the materials under investigation fails and shall be rejected. The OOS results shall be investigated and the findings of the investigation, including re-test results if justified, shall be interpreted to evaluate the materials and reach a decision regarding the release or rejection of the same.

7.0 PROCEDURE*:*

7.1 **Discovery of OOS result during microbiological testing:**

7.1.1 After obtaining an OOS result, the Microbiologist /Analyst/Initiator who performed the initial test shall immediately inform the Functional Supervisor that an OOS result occurred.

7.1.2 The Functional Supervisor and the Microbiologist /Analyst/Initiator shall immediately check whether the OOS result is due to an "Obvious Error" that will negate the requirement for further investigations. Some examples of "Obvious Errors" are as follows:

- **Calculation/Transcription Error:** The Microbiologist /Analyst and Functional Supervisor shall review for calculation/transcription errors. If an error is found, corrections shall be made as per the current version SOP “Good Documentation Practices (GDP)”.
- **Power Outage:** The Microbiologist /Analyst and Supervisor shall document the event, annotate as "power failure, analysis to be repeated", where applicable on all associated analytical documentation.

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- **Equipment Failure:** The Microbiologist /Analyst and Supervisor shall document the event, annotate as "Equipment failure; analysis to be repeated". The maintenance record shall be cross-referenced with this record. The equipment shall be tagged as being “out of service” until it be returned to a validated state.
- **Incorrect Instrument Parameters:** For example, incorrect setting of the dry bath temperature. In such a case, the Microbiologist/Analyst and Functional Supervisor shall document the event, annotate as "incorrect instrument parameter, analysis to be repeated" on all associated analytical documentation and it shall be logged as Unplanned Deviation/Incident (refer to the current version of SOP – Deviations/Incidents).

7.1.3 If the cause of the OOS is determined to be an "obvious error", the concerned Microbiologist/Analyst/Initiator shall take necessary steps, as specified above, and also make corrections in the Analytical Raw Data Sheet/Notebook by following the current version of SOP – Good Documentation Practices (GDP). All such corrections shall be countersigned by the Functional Supervisor.

7.1.4 If the root cause is determined to be an "obvious error", no further OOS investigation is necessary, since the "OOS" result in such a case can be considered as "Invalid". However, it shall be logged as an "Unplanned Deviation/Incident" and processes as per the Unplanned Deviation /Incident workflow (refer to the current version of SOP –Deviations/Incident).

7.2 **Initiation Of OOS Record:**

7.2.1 If "obvious error" is not the root cause of the OOS, as verified based on the parameters specified in the earlier section, the Microbiologist /Analyst/Initiator shall initiate an "OOS Intimation Form" (Refer to Annexure-1).

7.3 The same OOS shall be informed with a written communication to the Quality Assurance Department including Site Head Quality as well as the Production Department regarding the occurrence of out of specification result in “OOS intimation form” as per Annexure-1 by providing the following details;

- Short description of the OOS.
- Name of the reporting Microbiologist/ Analyst.
- Due date for OOS closure (30-calendar days from the discovery date of OOS.).
- Standard Test Procedure (STP) Number.
- Specification Number
- Stage
- Test
- Details of affected samples (batch numbers, test specification, status of the batch, sample type, stability station, reference raw data sheet, and market)

- Date of analysis.
- Discovery date of OOS.

7.4 On the basis of above notification QA Designee shall issue the "OOS investigation Report" as per Annexure-3 by allocating the OOS number and log the details in OOS log for Microbiology as per Annexure 2.

7.5 Once the OOS intimation form is acknowledge by Head Production and Site Head Quality, same shall be kept with OOS investigation report.

7.6 Each OOS Number shall be assigned a unique identification number:

Numbered as OOS/XX-M/YY-nnn

Where:- 'OOS' indicating out of specification.

'XX' indicating the facility code.

'M' indicating the Microbiology Department.

'YY' indicating the Year.

'nnn' are numerical in sequential order starting from 001 for every year.

7.7 If an OOS result is obtained for a stability sample/control sample of a batch(s) distributed in the market, a written/electronic notification shall be sent to Corporate Quality Compliance (CQ), Regulatory Affairs (RA), Manufacturing Group, Site QA Group, and Head-QA/QC. This notification shall occur within 24 hours of the discovery of the initial OOS result even if the Phase I Preliminary Laboratory Investigation for laboratory error has not been completed.

7.8 After creation of an "OOS Record" a sequential detailed Phase I Investigation process shall be conducted to determine the root cause.

7.8.1 Each step of the investigation process shall be clearly defined, including the number of replicates and the outcome of each investigational step shall be evaluated to determine whether the root cause has been identified and the investigation can be concluded or if additional investigation is necessary, and the appropriate course of action to be taken in the next investigational step.

7.8.2 If the investigation cannot be concluded after the completion of an investigational step, the next sequential step shall be performed in order to determine the root cause.

7.8.3 As part of the continuance to the next investigational step, the outcome of the previous step shall be summarized and, if applicable, a detailed analysis plan inclusive of the purpose of action shall be chosen based on the outcome of the previous investigative step.

7.8.4 Management oversight during every step of the investigation process is essential to ensure that the purpose of each investigational step is scientifically substantiated and approved prior to its execution in order for a timely, thorough root cause investigation to be performed.

7.9 **PHASE I - Preliminary Laboratory Investigation:**

7.9.1 Phase I Laboratory Investigation shall be conducted by the Functional Supervisor with the concerned Microbiologist / Analyst/Initiator on a paper form or validated electronic versions thereof

(refer to Annexure-3, Phase I "Preliminary Checklist For Laboratory Assessment"). The purpose of this investigation is to determine whether the OOS result is caused by a laboratory error.

7.9.2 The Phase I Investigation shall be completed within three business days from the date of discovery of OOS result. In case there is a need to extend the investigation, the Functional Supervisor shall prepare an interim report with reason and justification for extension. This shall be approved by the Quality Head (Refer to Annexure-8).

7.9.3 During the Phase I Laboratory Investigation, the following shall be evaluated, but not limited to:

7.9.3.1 Discussion of the test method with the Microbiologist /Analyst to confirm the Microbiologist / Analyst's knowledge/competency.

7.9.3.2 Evaluate Microbiologist/ Analyst training/qualification.

7.9.3.3 Evaluate use of specified effective STP(s), General procedures (GPs), SOP(s), Pharmacopoeial monograph procedure, and Protocol(s) referred for the analysis.

7.9.3.4 Examination of raw data obtained in the analysis, printouts, temperature charts, etc., to identify anomalous or suspect information.

7.9.3.5 Confirm the performance of any instrument(s) used in the test.

7.9.3.6 Determine that appropriate working/reference standards, media, reagents, and other solutions were used and that they meet relevant acceptance criteria.

7.9.3.7 Compare the test method performed against approved procedures.

7.9.3.8 Evaluate system suitability data, where applicable.

7.9.3.9 Evaluate measurements, calculations, conversion factors, and formulas associated with testing and reagent/media preparation.

7.9.3.10 Examine glassware used in the preparation of samples and reagents/media.

7.9.3.11 Evaluation of other tests performed on the batch in question.

7.9.3.12 Identification and evaluation of any unusual events, malfunctions, or unexpected circumstances associated with the test environment.

7.9.3.13 Evaluation of test results obtained from the same sample type and from the same instrument run.

7.9.3.14 Inspection of the work area to determine if any environmental or facility conditions could have adversely impacted the testing.

7.9.4 Additionally, during a Phase I Microbiology Investigation, the following test-specific requirements shall also be evaluated:

7.9.4.1 **Bio-Assay (if Applicable):**

- Check for any error in preparation, handling, and storage of samples.
- Confirm if the Zone Reader/Vernier Caliper was calibrated.

- Confirm if culture identity, performance, and passage number meet the requirements.

7.9.4.2 **Microbiological Examination of Non-Sterile Products:**

- Evaluate if the differential pressure of the dynamic pass box was within the acceptance criteria.
- Evaluate if the differential pressure/manometer reading of the LAF was within acceptance criteria.
- Determine if the microbial environment monitoring of LAF count and Laboratory area count observation was as per acceptance criteria.
- Confirm if the media was sterilized, as per validated sterilization cycle.
- Confirm if the samples were incubated at correct temperature, as stated in the procedure.
- Confirm if the culture media pH observation was as per acceptance criteria.
- Confirm if culture identity, performance, and passage number meet the Pharmacopoeial requirements.
- Comparison with previous trend, whether any excursions beyond limits were received in the recent past.
- Result of Growth Promotion Tests (GPT) on Media used, evaluation of positive and negative control, incubation conditions, etc.
- Confirm if sampling tools used for sampling were sterilized.

7.9.5 After completing the Phase I Laboratory Investigation, the Functional Supervisor shall determine if a laboratory error occurred or not, and subsequently forward the OOS Record to the Head Microbiology /Head Quality Control (HQC) for review. If the root cause of the OOS remains undetermined, the Functional Supervisor shall document in the OOS Record, i.e., that the cause of OOS result is "unknown at this stage".

7.9.6 The HQC/ Head Microbiology shall review the OOS Records and, if needed, request additional details from the Functional Supervisor.

7.9.7 The HQC/ Head Microbiology shall review the reason for OOS as documented by the Functional Supervisor, and edit/update/comment, if needed. The HQC/ Head Microbiology may also attach additional documents, if needed. If the root cause for OOS was not clearly identified previously by the Functional Supervisor, i.e., whether it is due to a laboratory error or not, the HQC/Head Microbiology shall make a final judgment on the same and document the decision in the record.

7.9.8 Post review, the HQC/Head Microbiology shall forward the OOS Record to the QA Designee for review.

7.9.9 The QA Designee shall examine all the related records of Preliminary Laboratory Investigation along with conclusions/recommendation made by the Functional Supervisor/HQC/Head

Microbiology. If needed, the QA Designee may request further details from HQC/Head Microbiology.

7.9.10 Based on the Phase I Laboratory Investigation records, the QA Designee shall make the final determination whether the root cause of OOS was caused by a Laboratory Error.

7.9.11 If the result of Phase I Laboratory Investigation of the OOS is: "No Laboratory Error Found"/"No Assignable Root Cause Found", then the investigation shall continue to a Full Scale Investigation, as in section 7.11.

7.9.12 If the result of Phase I Laboratory Investigation of the OOS Result is: "Laboratory Error Found"/"Assignable Root Cause Found", then follow the steps as explained in section 7.10.

7.10 **Cause of OOS – "Laboratory Error" / "Assignable Root Cause" Found:**

7.10.1 If "Laboratory Error" or "Assignable Root Cause" is established during the Phase I Laboratory Investigation, the QA Designee shall perform a Root-Cause Analysis in order to identify the root cause so that CAPA may be initiated accordingly.

7.10.2 Additionally, a Retest shall be conducted to confirm the investigation findings, where applicable.

7.10.3 **CAPA Plan for Phase I:**

7.10.3.1 In order to address the identified root cause(s), CAPA Record(s) shall be initiated and implemented in accordance with the current version of SOP – Handling of Corrective and Preventative Actions. CAPA initiation is mandatory except under the following conditions:

- A CAPA of similar nature is already in place – in such a case, a cross-reference to the existing CAPA shall be given.
- CAPA is not needed based on justifiable parameters – in such a case, a "No CAPA Required" justification shall be provided.

7.10.4 **Re-Test Plan and Reporting of Results:** Re-test shall be initiated by QA and the Re-test plan shall be communicated by the QA designee to the Responsible Person selected to perform the Re-test to confirm the "Laboratory Error". Supporting evidence in combination with other evidences that may be used to invalidate original results may include, but not limited to:

7.10.4.1 Re-test results that do not confirm with the original result such as, when inadequate extraction/dilution of the sample is observed.

7.10.4.2 Product history and results of other tests from the same sample that do not confirm the original result.

7.10.4.3 Determination that the sample is not representative of the product or material. A specimen template for Re-Test Report is given in Annexure-6. The test specific Re-test requirements are described below:

7.10.4.4 **Microbiological Examination of Non-Sterile Products:**

- Re-testing shall be performed by two Microbiologists/Analysts, each in duplicate on fresh aliquot of products/material (typically prepared and analyzed in the same manner that generated the original OOS result). The Microbiologist/ Analyst who had performed the original testing shall be

preferably selected as one of the Microbiologist/Analysts. If the results of Re-Test meet the specification limit (individually), then the average of the Re-test result shall be reported as final value for the material release. The original OOS shall be invalidated.

- In case of sample constraint for Re-Test, special instructions shall be part of the task record, created by QA.

7.10.4.5 **Bio-Assay:**

- Re-testing shall be performed by two Microbiologists/ Analysts, each in duplicate, on a fresh aliquot of products/material (typically prepared and analyzed in the same manner that generated the original OOS result). The Microbiologist/Analyst who had performed the original testing shall be preferably selected as one of the Microbiologist / Analysts.
- If the results of Re-Test meet the specification limits (individually), then the re-test results shall be averaged and reported as a final value for the material release. The original OOS shall be invalidated.

7.10.5 **Conclusion and Batch Disposition:**

7.10.5.1 Based on investigation, if it is evident that the root cause of "OOS" result from original testing is due to "Laboratory Error", and if the Re-Test results by the Microbiologist /Analyst(s), both individual and average, meet the specifications the original OOS results shall be substituted with the average of the Re-test results as explained in each test as per steps 7.10.4.4 and 7.10.4.5 all data, individuals and average must be reported in the testing record.

7.10.5.2 Additionally, a notation shall be included in the Certificate of Analysis (COA) documenting that an OOS result occurred for the specific test referencing the unique investigation number. The average value may be assigned to the batch on the COA, but the individual values shall be listed as part of the OOS note.

7.10.5.3 Dispositioning the batch for release shall be considered only if the retest results, individual and average, meet the specification limits.

7.10.5.4 The final batch disposition decision shall be made by the QA Designee within 30-calendar days from the discovery date of OOS result, unless there are justified extensions granted by QA. The following details related to the batch disposition shall be documented:

- Investigation conclusion
- Root cause summary
- Justification for identification of impacted batches
- Decision for batch disposition(s) for all impacted testing

7.10.5.5 If the Re-Test results do not meet the specification limit, a Phase II Full-Scale Investigation to reassess the root cause of the OOS shall be initiated.

7.10.5.6 Wherever required, the QP/Customer, etc., shall be informed before batch disposition decision of finished products under the scope of the OOS result.

7.11 **Cause of OOS– "No Laboratory Error/ No Assignable Root Cause Found":**

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7.11.1 When the Phase I Laboratory Investigation concludes "No Laboratory Error/No Assignable Root Cause Found" and the original test results appear to be accurate, then a Phase II - Full-Scale OOS investigation shall be performed.

7.11.2 **Phase II - Full-Scale OOS Investigation:**

7.11.2.1 A Cross-Functional Team (QA, QC, Microbiology, Production, Process Development, Engineering, SME, etc. as appropriate) shall conduct a Full Scale OOS Investigation. The objective of Full scale OOS Investigation is to identify the root cause of the OOS result and implement appropriate CAPA.

7.11.2.2 Full scale OOS Investigation shall include the following components at a minimum:

- Shop Floor Investigation (Review of Production Process and Procedures). For raw materials, this investigation would be replaced with an investigation performed by the supplier.
- Sampling Error Investigation (Check for possible error in Sampling/Handling/ Storage of sample.)
- QA Assessment (Review of product documents and validation data, Trends, Product History, Product Deviations, etc.).

7.11.2.3 **Shop Floor Investigation:**

- The Designee - QA/QC/Production/Process Development/ Engineering/SME, etc. as applicable, shall conduct a Shop Floor Investigation, which includes a review of production processes and procedures.
- During the Shop Floor Investigation, if a "Process Error" is found to be the "Assignable Root Cause", then the investigation may be concluded. However, the investigation shall remain open if there is supporting evidence that implicates other batches of the same product or similar products that may be associated with the specific failure with the need to assess potential product impact.
- If an "Assignable Root Cause" for the OOS is not determined during the Shop Floor Investigation, then an extended/additional investigation is required, as described below, and should be initiated by the QA Designee.
- When extended/additional investigation is required, then additional "Investigation Record" may be initiated by the QA Designee.

7.11.2.4 **Sampling Error Investigation:**

- A Sampling Error Investigation may be performed to determine the root cause of the OOS result as a part of the Full-Scale Investigation.
- An example template of a Sampling Error Investigation Report is provided as Annexure-5.
- Based on the investigation results, the QA Designee shall be responsible for determining whether Sampling Error can be confirmed or not.
- If sampling error is established, a Re-Sampling Plan shall be prepared.

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- Re-Sampling and subsequent retesting of the fresh sample shall only be considered if it is established through the investigation that the original sample:

➢ Is not a representative sample of the batch?

➢ Was improperly taken / prepared.

➢ Was not stored appropriately.

➢ Was damaged, contaminated, or may have been adversely affected by exposure to humidity, light, or heat.

- Re-Sampling shall not be considered as an automatic next step of the investigational process when the "Assignable Root Cause" is not found for the OOS as part of the Phase I Preliminary Laboratory Investigation.

- Re-Sampling should be performed by the same qualified, personnel and methods used to take the initial sample. However, if the investigation determines that the initial sampling method was inherently inadequate, a new sampling method must be developed, documented, reviewed, and approved by the QA designee. In such a case, the re-sampling shall be done with the revised and approved sampling method.

7.11.2.5 **QA Assessment:**

- QA Assessment shall be performed by the QA Designee to determine the root cause. It shall include a purpose, an action plan with results documented in the OOS Record.

- During QA Assessment, the QA Designee shall investigate the following at a minimum:

➢ Production/process documents.

➢ Review of product history.

➢ Review of product development and validation data.

➢ Review of trends.

➢ Review of product deviations, etc.

7.11.3 QA Review and Root-Cause Analysis of Phase II - Full-Scale OOS Investigations:

7.11.3.1 QA Designee shall review the OOS Record after completion of the Investigations, and the findings of the Investigations shall be interpreted to evaluate the root cause and decide the next course of action.

7.11.3.2 The following scenarios may exist after completion of Full- Scale OOS Investigation. Steps to be taken against each scenario are also listed below:

- Assignable Root Cause Found:

➢ Assignable Root Cause is found to be "Process Error" – In such a case, the batch disposition shall be determined by QA based on investigation results as per step 7.11.4.

- Assignable Root Cause is found to be "Sampling Error", in such a case, Re-Sampling and retesting shall be conducted as explained in step 7.11.2.4 and a Re-Test shall be conducted to confirm the root cause analysis.

- Assignable Root Cause Not Found:

- If an assignable cause for the OOS result is not identified during the Phase II - Full-Scale OOS Investigations, a Re-Test shall be performed to further investigate the root cause.

7.11.3.3 **Re-Testing:**

- Post Full-Scale OOS Investigation, Re-Testing shall be performed under the conditions mentioned in above steps of Assignable Root Cause for confirmation of the investigation findings/determine the root cause, as applicable. An example template – Re-Test Summary Sheet is given in Annexure-6.

- Retesting shall be performed by two Microbiologist/Analysts (the Microbiologist /Analyst who originally performed the testing may be selected as one of the Microbiologist /Analysts), each in duplicate, by utilizing the same sample that was originally tested and yielded the "OOS" result (typically prepared and analyzed in the same manner that generated the original OOS result).

- In case of constraints to using the original sample for Re-Test, Re-Sampling may be carried out, provided QA gives approval. The sampling procedure used to collect the Re- Sample and the QA approval shall be documented.

7.11.3.4 **CAPA for Phase II (Full Scale OOS Investigation):**

- In order to address the identified root cause in Phase II, CAPA Record(s) shall be initiated and implemented. CAPA initiation is mandatory except under the following conditions:

- A CAPA of similar nature is already in place – in such a case, reference to the existing CAPA shall be given.

- CAPA is not needed based on justifiable supporting rationale – in such a case, "No CAPA Justification" shall be provided mandatorily.

7.11.4 **Conclusion of Phase II - Full-Scale OOS Investigation and Batch Disposition:**

7.11.4.1 QA Designee shall review the "OOS Record" after completion of the Investigation and Re-Test (if performed). Investigation findings, including Re-Test results, shall be interpreted to determine the batch disposition.

7.11.4.2 If the Phase II Investigation determines a "Process Error" as the root cause of the OOS, the batch (es) shall be rejected.

7.11.4.3 If the Phase II Investigation determines that the OOS result was caused by a factor affecting the batch quality (i.e., an OOS result is confirmed), and the result indicates that the batch does not meet established standards or specifications, the batch (es) shall be rejected. An impact assessment must be performed to determine if there are other potentially impacted batches.

7.11.4.4 In case of OOS results obtained for a raw material/packaging material (RM/PM), a laboratory investigation shall first be performed. If the laboratory investigation determines, "Laboratory Error

Not Found", OOS results shall be shared with the vendor for further investigation. Simultaneously, a Phase II Investigation, following the OOS workflow shall be initiated; however, only a Sampling Error investigation and a review of deviations occurring during transportation/storage are required. In case of confirmed raw material/packaging OOS, the material shall be rejected, and root cause/CAPA details shall be referenced from the vendor's investigation report, as appropriate.

7.11.4.5 Should the Phase II Investigation establish the OOS is not caused by a factor affecting the batch quality (i.e., the OOS root cause is due to a laboratory or sampling error), and the subsequent Retesting results confirm conformance to established standards or specifications, the batch (es) may be dispositioned for release providing the Retest results are within the specification limits.

7.11.4.6 For inconclusive Phase II Full-Scale Investigations where investigation does determine a root cause for the OOS test result, the QA Designee shall disposition the batch for rejection, unless there is supporting rationale justified in science that the OOS result does not affect the quality of the batch. Such supporting rationale shall include, but not be limited to:

- Review of the manufacturing process and product history demonstrates that the manufacturing process is robust and that the OOS would have been detected elsewhere in the process.
- Retest results are all well within the established limits of variability for the method used, whereas the original OOS test result is outside the known limits of variability of the method used.
- If the original "OOS" result has been determined to be not representative of the material being tested based on the scientifically supported conclusion of a thorough root cause Investigation.

➢ When making such a decision, QA/QP should always err on the side of caution. The OOS result should be given full consideration (most probable cause determined) when making the disposition decision, including the potential for batch-specific variation.

➢ Use of retest results to disqualify the original OOS test result when a batch considered for release and the investigation results are inconclusive shall be justified with strong supporting rationale based in science.

- Wherever required, the QP/Customer, etc. shall be informed before batch disposition decision of finished products under the scope of the OOS.
- Reporting of Results:

➢ All test results must be reported in the batch testing records. Based on the investigation, if it is determined the OOS result is not caused by a factor affecting the batch quality, and if the Retest results by the Microbiologist / Analysts meet the specification limit, then the original OOS results shall be substituted with the average of the Re-Test results.

➢ Additionally, a note or a code (as deemed fit) shall be given in the Certificate of Analysis, indicating that an OOS result was obtained earlier for this test and the reference number of the OOS Investigation record shall be provided therewith.

➢ If the Re-Test results do not meet the specification limit and/or the OOS result is found to be caused by a factor affecting the batch quality, the original OOS results along with any retesting results shall be reported in the Certificate of Analysis.

- The Full-Scale Investigation must include an assessment extended to other batches of the same product or other products that may have been associated with the specific failure.
- The final batch disposition decision should be made by the QA Designee within 30 calendar days from the discovery date of OOS. The following details shall be documented:

➢ Investigation conclusion.

➢ Root cause summary.

➢ Batch disposition decision.

➢ Review of events during production of the batch reveals no aberrations or indication of unusual process variation.

➢ If the OOS investigation record remains open beyond the due date, a mandatory justification approved by QA is required.

- Once a batch has been rejected, there is no limit to further testing to determine the cause of failure so that corrective action(s) can be taken; however, the decision to reject shall not be reversed as a result of further testing.
- The impact of OOS result on other batches, ongoing stability studies, validated processes, and testing procedures shall be determined by QC, QA and other cross-functional team members, and be documented in the conclusion along with appropriate corrective and preventive actions.
- If needed, based on the OOS disposition conclusion and impact assessment of other batches, a regulatory notification or product recall proposal may be initiated.

7.12 **Management of OOS Results Discovered for Stability Samples while Testing at a Time Point beyond the Expiration date:**

7.12.1 If an OOS result is obtained for such samples, an OOS investigation shall be initiated and Phase I Preliminary Laboratory Investigation shall be performed.

7.12.2 If laboratory error is found, further steps as in the workflow for "Laboratory Error Found" (RCA, CAPA initiation, Re-Test, etc.) shall be performed.

7.12.3 If laboratory error is not found, further investigational steps may be skipped, with the conclusion that the "shelf-life", as established earlier, has been reconfirmed.

7.13 **Management of OOS Results Identified at Batch Release Sites, Batch Testing Sites, Contract Testing Laboratories and Contract Manufacturing Organizations (CMOS):**

7.13.1 The Batch Release Sites, Batch Testing Sites, Contract Testing Laboratories and CMO (as applicable) shall notify QA/QC Designee (of the manufacturing location) within 24 hours of discovery of an "OOS" result.

7.13.1.1 **Case A:** Discovery of OOS Result at Batch Release Sites/Batch Testing Sites/Contract Testing Laboratories - where an Enterprise Quality Management System (EQMS, e.g., Track Wise) is not available.

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- On receipt of information about an "OOS" result discovery, the Batch Release Site/ Batch Testing Site/Contract Testing Laboratory (as applicable), shall log the OOS result and conduct Phase I Preliminary Laboratory Investigation activities at their site, as per their local SOP on "Handling of OOS Results".
- They shall notify the manufacturing site QA/QC Designee within 24 hours of the OOS result discovery.
- If a laboratory error is identified to be the root cause for the OOS result, further activities for the OOS result investigation process shall be performed by the Batch Release Site, Batch Testing Site, and Contract Testing Laboratory itself with the completed OOS result Investigation Report being sent to the manufacturing site within 30 days from identification of the OOS.
- If it is determined that laboratory error is not the cause for the OOS result during the Phase I Preliminary Laboratory Investigation at the Batch Release Site, Batch Testing Site, or Contract Testing Laboratory (as applicable), they shall send the Phase I Investigation Report to the manufacturing site.
- The manufacturing site shall initiate an OOS Record (electronically or manually, based on available systems) referencing the OOS document received from the Batch Release Site, Batch Testing Site, and Contract Testing Laboratory (as applicable). The OOS originator, i.e., Batch Release Site Batch Testing Site, or Contract Testing Laboratory, as applicable, shall be notified regarding initiation of the OOS Record, and completion of the Phase II Full-Scale Investigation at the manufacturing site.
- On completion of the OOS investigation, the manufacturing site shall send the OOS Investigation Report to the Batch Release Sites, Batch Testing Site, or Regional QA for closure.

7.13.1.2 **Case B:** Discovery of OOS Result at CMO - where an EQMS is not available.

- The CMO shall intimate the concerned contact point within 24 hours of the OOS discovery.
- The entire OOS investigation (i.e. Laboratory Investigation, as well as Phase II Full-Scale Investigation, if needed) shall be carried out at the CMO; once the investigation is completed, the report shall be sent to the contact point.
- QA/QC Designee shall review the "OOS" report received from the CMO and document the same as per procedures.

7.14 **Requirements**

7.14.1 All laboratory OOS investigations shall follow a two-phase approach. The Phase I investigation will focus on identifying if a laboratory error is the source (root cause) of the OOS result. If the Phase I investigation does not confirm a laboratory error caused the OOS result and testing results appear to be accurate, a Full-Scale Phase II Investigation, including a review of production and sampling procedures and possibly additional laboratory testing shall follow.

7.15 **Resampling:**

7.15.1 Resampling involves analyzing samples from additional units collected as part of the original sampling procedure, or from a new sample collected from the same batch of product. Resampling must be approved by QA. Resampling of new bulk samples shall only be performed using predetermined procedures and sampling strategies and when insufficient sample remains to perform the required analyses, or scientific evidence exists that the initial sampling method was inherently inadequate or compromised.

7.16 **Reporting Test Results:**

7.16.1 The reporting and interpretation of test results include (1) Averaging and (2) Outlier Tests. The appropriate use of Averaging involves obtaining several discrete measurements for the same sample preparation. An example of this would be taking the average of two or more endotoxin analyses from the same sample vial, or averaging the result of two or more sample preparations. This can result in a more accurate result.

7.17 **Outlier Tests:**

7.17.1 An Outlier Test is a statistical procedure for evaluating a value, which is widely different from values in a series, obtained using a validated method. Outlier Tests shall be rarely used for statistical purposes, only as part of the investigation and not used to discard OOS results.

7.18 **Impact Assessment:**

7.18.1 The requirement to perform an impact assessment based on the determined root cause on the lots analyzed concurrently with the suspect lot(s) and previously released lots shall be addressed.

7.19 **Time Frames:**

7.19.1 The required time frame for completing the Phase I Investigation shall be three (3) business days (except for sterility failures) and for Phase II Investigations thirty (30) calendar days. Extensions shall be granted by the QA Head. Investigations shall be thorough, timely, unbiased, well-documented, and scientifically sound. Retained Sample preparations shall be examined promptly to aid in the investigation.

7.20 **Corrective and Preventive Actions:**

7.20.1 OOS investigations shall include appropriate Corrective and Preventive Actions to be taken (CAPAs) as a result of the OOS investigation (refer to the current version of SOP– Handling of Corrective and Preventive Actions.

7.20.2 The CAPA guidance shall require follow up by the QC/QA Departments after a specified time period with regard to the effectiveness of the preventative action stated in the investigation.

7.21 **Disposition of Product**

7.21.1 QA maintains quarantine of impacted product until investigation is completed and conclusions are determined.

7.21.2 QA expands actions to control impacted product or other lots as warranted by the findings and conclusions of the completed investigation.

7.21.3 At conclusion of investigation, QA dispositions impacted product, i.e. release, reject and destroy

etc.

7.21.4 Indicate final disposition on the OOS investigation report.

7.21.5 Refer Annexure-7 decision tree for investigation.

8.0 DISTRIBUTION:

8.1 Quality Assurance

8.2 Quality Control

9.0 ANNEXURES:

9.1 Annexure-1: OOS Intimation Form.

9.2 Annexure-2: OOS Log for Microbiology.

9.3 Annexure-3: Preliminary Checklist for Laboratory Assessment.

9.4 Annexure-4: Shop Floor OOS Investigation Report.

9.5 Annexure-5: Sampling Error Investigation.

9.6 Annexure-6: Retest/Repeat Analysis- Summary Sheet.

9.7 Annexure-7: Decision Tree for Failure Investigation of Microbial Limit Test.

9.8 Annexure-8: Request for Extension of OOS Investigation.

10.0 REVISION HISTORY:

Version Number	Revision Details	Effective Date	Ref. CCR Number
00	New SOP		NA

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ANNEXURE 1

OOS INTIMATION FORM

Date			
Product		Batch No.	
Product Type (Mark:√)	(Intermediate/Validation/FP/Stability/RM/PM)		
Test			

1	Date of Analysis	
2	Discovery Date	
3	Due Date of OOS closure	
4	Analyst Name	
5	Standard Test Procedure/Monograph/Compendia	
6	Control Number (Analytical Raw data Sheet No.)	
7	Specification	
8	Out of Specification initial Results	
9	Brif Description of the Event:	

Microbiologist
(Sign & Date)

Head- QC/Micro
(Sign & Date)

Head-Quality Assurance
(Sign & Date)

Head-Production
(Sign & Date)

Site Head- Quality
(Sign & Date)

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ANNEXURE 2

OOS LOG FOR MICROBIOLOGY

Date	OOS No.	Sample/Material Name	Batch No.	A.R. No.	Test	OOS Completed On	Initiate By	Reviewed By	Remarks

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ANNEXURE 3
PRELIMINARY CHECKLIST FOR LABORATORY ASSESSMENT

OOS Number:.....

I. Details of OOS *(To be completed by the Analyst)*

Date				
Product		Batch No.		
Product Type (Mark:√)	(Intermediate/Validation/FP/Stability/RM/PM)			
Analyst		Test		

1	Date of Analysis	
2	Discovery Date	
3	Microbiologist Name	
4	Specification	
5	Standard Test Procedure/Monograph/Compendia	
6	Control Number (Analytical Raw data Sheet No.)	
7	Out of Specification initial Results	
8	Brief Description of the Event:	

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9	Head-QA must be notified of OOS within one business day for the following: • Stability test result from any protocol for a marketed product. • Product test result from a returned complaint sample • Product test result from a control (retain) sample or other sample retriever from the market. • Discovery of a methodology issue that impacts test results of product on the market.

OOS Number:.....

Parameters to be Investigated			Remarks
A. Written Procedure			
1.	Is the document numbers and version correct ?	□ Yes □ No □ NA	
2.	Was the procedure followed correctly?	□ Yes □ No □ NA	
3.	Are there any mistake in the document?	□ Yes □ No □ NA	
B. Analysts			
1.	Has the analysts been trained and when ?	□ Yes □ No □ NA	
2.	What is the previous error hostory?	□ Yes □ No □ NA	
3.	Has analysts been qualified in particular test and when?	□ Yes □ No □ NA	
4.	When was the last retraining done?	□ Yes □ No □ NA	
5.	How long has the analyst been performing this test?	□ Yes □ No □ NA	
6.	Physical conditions of the analyst at the time of testing (Health)	□ Yes □ No □ NA	
7.	What was the workload impact at the time of testing?	□ Yes □ No □ NA	
C. Raw Data Verification			
1.	Was the data properly recorded ?	□ Yes □ No □ NA	
2.	Was data initiated and dated as required.	□ Yes □ No □ NA	

3.	Evaluation of data performed correctly?	□ Yes □ No □ NA	
4.	Transfer of data correct ?	□ Yes □ No □ NA	
5.	Calculation were performed corretly ?	□ Yes □ No □ NA	
6.	Were other results found deviated from the acceptable limits?	□ Yes □ No □ NA	
7.	Was the isolate identified?	□ Yes □ No □ NA	

OOS Number:.....

Parameters to be Investigated		Remarks
D. Historical Data		
Product	□ Yes □ No □ NA	
Process	□ Yes □ No □ NA	
Method	□ Yes □ No □ NA	
Microorganism	□ Yes □ No □ NA	
Analysts	□ Yes □ No □ NA	
E. Concurrent Results		
1. Were similar microbes (is applicable in case of sterility test found in other results at the same time?	□ Yes □ No □ NA	
2. Were other deviations found in the same time period with similar organisms?	□ Yes □ No □ NA	
F. Equipment		
1. Is the equipment part of the calibration/maintenance program?	□ Yes □ No □ NA	
2. Is it within the current schedule of calibration?	□ Yes □ No □ NA	

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3.	Is it operating in a state of control?	□ Yes □ No □ NA	
4.	Has it been used correctly?	□ Yes □ No □ NA	
5.	Was it functioning correctly?	□ Yes □ No □ NA	
6.	Was there any recent maintanance on the system?	□ Yes □ No □ NA	
7.	Were there any recent change control activity on the equipment?	□ Yes □ No □ NA	

OOS Number:.....

Parameters to be Investigated			Remarks
Method of Analysis			
1.	Was the sample collected correctly?	□ Yes □ No □ NA	
2.	Was storage of the sample conducted at the specified conditions and time?	□ Yes □ No □ NA	
3.	Was the correct sample analysed?	□ Yes □ No □ NA	
4.	Validity of method?	□ Yes □ No □ NA	
5.	Was the correct amount used for test?	□ Yes □ No □ NA	
6.	Was preparation of the sample performed correctly?	□ Yes □ No □ NA	
7.	Were proper dilutions made?	□ Yes □ No □ NA	
8.	Was the specified diluting fluid used?	□ Yes □ No □ NA	
9.	Did the diluting fluid pass the sterility test?	□ Yes □ No □ NA	
10.	Was the correct amount of the diluting fluid used?	□ Yes □ No □ NA	
11.	Was the media successfully growth promoted?	□ Yes □ No □ NA	

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12.	Was the media successfully sterilized ?	□ Yes □ No □ NA	
13.	Was the media used within the specified expiration date?	□ Yes □ No □ NA	
14.	Was the correct media used for the test?	□ Yes □ No □ NA	
15.	Did negative controls yield the expected results?	□ Yes □ No □ NA	
16.	Were there negative control sterilized?	□ Yes □ No □ NA	
17.	Were there any unusual occurrences during processing, i.e. technique related or non-technique related?	□ Yes □ No □ NA	
18.	Was the data interpreted correctly?	□ Yes □ No □ NA	

OOS Number:.....

Parameters to be Investigated		Remarks
Method of Analysis		
19.	Were there techniques related issues in the test?	□ Yes □ No □ NA
20.	Were there techniques related issues in the test, e.g. analyst's errors?	□ Yes □ No □ NA
21.	Were calculations performed correctly?	□ Yes □ No □ NA
22.	Were the correct standards used?	□ Yes □ No □ NA
23.	Were the standards within the expiration date?	□ Yes □ No □ NA
24.	Were other human error or equipment failure noted?	□ Yes □ No □ NA
25.	Use of expired or incorrect reagents	□ Yes □ No □ NA
26.	Incubation temprature/time as per approved procedure	□ Yes □ No □ NA
27.	Preincubated/approved plates used for	□ Yes □ No □ NA

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	analysis.		
Any other observations:			

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Cleaning and disinfection record	Disinfectant used		Prepared and filtered on	
	Concentration		Cleaning Done by	
Area Fogging details	Disinfectant used		Prepared and filtered on	
	Concentration		Fogging done by	
Environmental conditions during test	Temprature		Diffrential pressure	
	Relative Humidity		Non viable monitoring count	
Analyst Qualification & training details	Analyst Name		Analyst Qualification done on	
	Analyst Qualification Due on		Training status of analyst	
	Health status of analyst			

Functional Supervisor (Sign/Date)

Head-Microbiology/QC (Sign/Date)

QA Designee (Sign/Date)

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Conclusion/Recommendations_____

_____

_____

_____

_____

Error in the laboratory analysis:

□ Yes □ New Test □ Re-Test □ Re-Sample

□ No, Proceed with full investigation

Corrective Action and Preventive action (Mentioned CAPA taken, if any, in brief also mention CAPA No.:

Functional Supervisior (Microbiology)

*NAME:*_____*SIGNATURE*_____*DATE*_____

Head-QC (Microbiology)

*NAME:*_____*SIGNATURE*_____*DATE*_____

QA Designee

*NAME:*_____*SIGNATURE*_____*DATE*_____

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Microbial Limit Test/Bio-burden test failure Investigation Report-Microbiology Lab Investigation

1.	**Sterilization Details for media used:**				
	Steam sterilizer inst. ID		Validation done on		
	Validation due on		Name of media/Diluents		
	Lot No.		Sterilization Parameters		
	Date of sterilization		Positive Control results		
	Negative control results				
2.	**Test Method Used: Membrane filteration/Plate Count Method**				
	Filtration unit	Sterilization Parameters	□ Complies □ Not Complies	Steam Sterilizer Inst. ID	
		Validation Done on		Validation Due on	
		Date of sterilization		Load No.	
3.	Petri Plate	Sterilization Parameters	□ Complies □ Not Complies	Steam Sterilizer Inst. ID	
		Pre-sterilized Petri plate lot no.		Validation Due on	
		Pre-sterilized Petri plate Expiry date		Load No.	
		Date of sterilization		Load no.	
4.	Microbial monitoring date of MLT area on the day of analysis	Media Used: SCDA/TSA Lot. No.		Settle Plate	□ Complies □ Not Complies
		Sterilization date		Air sampling	□ Complies □ Not Complies

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Microbial Limit Test/Bio-burden test failure Investigation Report-Microbiology Lab Investigation

5.	Microbial monitoring data of LAF on the day of analysis.	Media Used: SCDA/TSA Lot. No		Settle Plate	□ Complies □ Not Complies
		Sterilization date		Air sampling	□ Complies □ Not Complies
6.	LAF Used for analysis (ID No..)	Validation done on		Validation Due on	
7.	Review of EM trends & EM condition data in MLT area for last 2 months for the following parameters	Microbial Monitoring Trends	□ Complies □ Not Complies	Temprature Monitoring data	□ Complies □ Not Complies
		% relative Humidity Data	□ Complies □ Not Complies	Pressure differential data	□ Complies □ Not Complies
8.	Calibration record of instrument/Equipment used in testing/ testing area				
9.	Intervention during testing, any abnormality or Incidence				
10.	Any Deviation during testing				

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Microbial Limit Test/Bio-burden test failure Investigation Report-Microbiology Lab Investigation

11.	AHU Validation	Date of Validation		Next Due date	
12.	Validation Parameters	Velocity	□ Complies □ Not Complies	Non Viable Particulate count	□ Complies □ Not Complies
		Filter integrity test	□ Complies □ Not Complies	Number of Air Changes	□ Complies □ Not Complies
13.	Identification of contaminant: Microscopic evaluation	Colony Characteristics		Gram Character	
14.	Identification of Isolated up to spcies level	Name of Organism Identified		Method Used	
15.	Results of other products/Batches tested at same time/same date	□ Complies □ Not Complies	Refer COA as Annexure_____	Sign./Date	
16.	Result of Product/Batches tested one day before	□ Complies □ Not Complies	Refer COA as Annexure_____	Sign./Date	
17.	Result of Product/Batches tested one day after	□ Complies □ Not Complies	Refer COA as Annexure_____	Sign./Date	
18.	Test History of the affected product				

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Microbial Limit Test/Bio-burden test failure Investigation Report-Microbiology Lab Investigation

19.	Interview of the analyst by Head Microbiology	□ Complies □ Not Complies	Refer COA as Annexure_____	Sign./Date		
20.	Outcome of the Investigation					
21.	Assignable cause found/Not found					
22.	Conclusion					
23.	Result of repeat test incase of assignable cause found	Date of Resample		Sampled by		
		Sample Quantity		Retested by		
		Result of Reanalysis				
24.	Corrective Action and Preventive action (Mentioned CAPA taken, in brief also mention CAPA reference No.)					
25.	Conclusion					
Functional Supervisor (Sign./Date)		Head-Microbiology (Sign./Date)	QA Designee (Sign./Date)	Site Head-Quality(Sign./Date)		

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Microbial Assay Test failure Investigation Report-Microbiology Lab Investigation

1.	**Sterilization Details for media used:**			
	Steam sterilizer inst. ID		Validation done on	
	Validation due on		Name of media/Diluents	
	Lot No.		Sterilization Parameters	
	Date of sterilization		Positive Control results	
	Negative control results			
2.	**Test Method Used: □ Cylinder test Method or Plate Assay/ □ Turbidimetric or Tube Assay**			
	Procedure Followed as per current version of SOP	□ Complies □ Not Complies	Sample prepared/Dilution prepared as per procedure mentioned in SOP	□ Complies □ Not Complies
	Glassware used for microbial assay was cleaned as per cleaning procedure	□ Complies □ Not Complies	Passage used for Microbial Assay was as per Pharmacopeial requirment	□ Complies □ Not Complies
	Recommended Media used as per current version of SOP	□ Complies □ Not Complies	Selection of microorganism done as per product requirment given in current pharmacopeia	□ Complies □ Not Complies
	Media Quantity used for plate preparation was done as per SOP	□ Complies □ Not Complies	Incubation temprature and Time	□ Complies □ Not Complies
	Validation of Incubator Done on	□ Complies □ Not Complies	Validation of Incubator due on	□ Complies □ Not Complies
	Homogeneously distribution of Microorganism in Media	□ Complies □ Not Complies	Any other contamination of microorganism whil addition of culture during handling	□ Complies □ Not Complies

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Microbial Assay Test failure Investigation Report-Microbiology Lab Investigation

	Potency of reference standard used for dilution	□ Complies □ Not Complies	Expiry of reference standard used for dilution	□ Complies □ Not Complies
	Batch no. and Expiry date of reference standard used for analysis		Media Negative contorl	□ Complies □ Not Complies
	Laboratory Environment Condition	□ Complies □ Not Complies	Sample quantity used for inoculation as per SOP	□ Complies □ Not Complies
	Standard quantity used for inoculation as per SOP	□ Complies □ Not Complies	Growth promotion test of media used for Microbial Assay	□ Complies □ Not Complies
	Incubator ID (Used for GPT)		Validation of Incubator Done on	Date
	Validation of Incubator Due on	Date	Instrument ID ZONE reader	
	Calibration status of ZONE reader.	□ Complies □ Not Complies	Instrument ID of UV, used for turbidimetric assay	
	Qualification status of UV instrument	□ Complies □ Not Complies	Calibration status of UV instrument	□ Complies □ Not Complies
	Validation done on		Validation due on	
	Micropipette id		Micropipette calibration status	□ Complies □ Not Complies
	Correct Bore size used as per SOP	□ Complies □ Not Complies	Results of other samples tested simultaneously using same condition on same day	□ Complies □ Not Complies

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Microbial Assay Test failure Investigation Report-Microbiology Lab Investigation

Calculation	□ Complies □ Not Complies	Any other Parameters		□ Complies □ Not Complies
Analyst qualification & training details	Analyst Name		Training status of analyst	
	Analyst Qualification due on		Analyst Qualification done on	
Whether incidence, mishap or deviation occurred during testing				
Outcome of the Investigation				
Assignable cause found/not found				
Result of repeat test incase of assignable cause found	□ Complies □ Not Complies	Refer COA as Annexure_____	Sign./Date	
Corrective Action and Preventive action (Mentioned CAPA taken, in brief also mention CAPA reference No.)				
Conclusion				

Functional Supervisor (Sign./Date)	**Head-Microbiology (Sign./Date)**	**QA Designee (Sign./Date)**	**Site Head-Quality (Sign./Date)**

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ANNEXURE 4
SHOP FLOOR OOS INVETIGATION REPORT

OOS Number:.....

Microbial Limit Test/Bio-burden Test failure Investigation Report-Manufacturing Investigation

1.	Product/Material Name		Mfg. Date	
	Date of Testing		OOS Observation on	
	Batch No.		Exp. Date	
	Final Date of Observation		Control No.	

2.	**Sampling Details (if applicable)**			
	Sample done by		Sampling done on	
	Any Abnormal observation/ Incidence/ Deviation during sampling	□ Complies □ Not Complies	Qualification and training of the person performed sampling	□ Complies □ Not Complies
	Health status of the person performed the sampling	□ Complies □ Not Complies	Interview of the person performed sampling with in charge	□ Complies □ Not Complies
3.	Conclusion			

Head Production Sign./Date	**QA Designee Sign./Date**	**Site Head-Quality Sign./Date**

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MICROBIOLOGY DEPARTMENT

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4.	Manufacturing details	**Area**		**Activity**	
		Temprature (Range)		RH (Range)	
		Power failure (Number & Duration)		Unusual events/ Intervention (if any)	
		Deviation (if any)			
5.	Cleaning & Sanitization records of the equipment/ Instruments used	Disinfectant used		Cleaning Done by	
		Dilution		Cleaning Checked by	
		Prepared by			

6. Review of calibration records for all the instruments and equipments used in product processing

S.No.	Instrument/Equipment Name	ID No.	Calibration Done on	Calibration Due on
1.				
2.				
3.				
4.				

7.	Review of EM monitoring trends & environment condition data for last 2 months for the following parameters	Microbial Monitoring Trends	□ Complies □ Not Complies	Temprature Monitoring Data	□ Complies □ Not Complies
		% Relative Humidity data	□ Complies □ Not Complies	Review of other process control record	□ Complies □ Not Complies
8.	Training of the persons involved	□ Complies □ Not Complies		Utility qualification details	□ Complies □ Not Complies

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9.	Review of Batch production Record/Batch Manufacturing Record	□ Complies □ Not Complies	Utility qualification details	□ Complies □ Not Complies
10.	Past deviations, problems or changes can provide a clues on indication of the origin of problem			
11.	Out come of the investigation			
12.	Corrective Action and Preventive action (Mentioned CAPA taken, in brief also mention CAPA reference No.)			
13.	Conclusion			

Head Production Sign./Date	Head Engineering Sign./Date	Head Quality Assurance Sign./Date	Site Head-Quality Sign./Date

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ANNEXURE 5
SAMPLING ERROR INVESTIGATION

S.No.	Check Points	Observations
1.	Sampled/Distributed by (Name of Person)	
2.	Is the person trained	
3.	Sampling Tool cleaning record	
4.	Sampling Container	
5.	Sample Labeling	
6.	Sample Description evaluation w.r.t Retention Sample/ Previous Materils (For API's only)	
7.	Natutr of sample (Hygroscopic/light sensitive)	
8.	Is sample stored under prescribed condition	
9.	Any Spillage notified	
10.	Any contamination/ Possibility of contamination	
11.	Sample Pacaging (For Stability Sample only)	
12.	Silica sachet part of packaging configuration Yes/No, if Yes, condition of silica Sachet.	
13.	Is sealing condition of primary container proper.	
14.	Is sealing condition of primary container proper	
15.	Any deviation from recommended packing condition as per Protocol/Specification Yes/No, if Yes, Specify	

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Summary of findings:	
Prepared By: **Functional Supervisor** **(Sign./Date)**	
Review By: **Head Microbiology/QC(Sign./Date)**	
Approved By: **QA Degignee** **(Sign./Date)**	

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ANNEXURE 6
RETEST/REPEAT ANALYSIS- SUMMARY SHEET

Product:

Batch No. :

Specification No.:

Test :

Limit:

Date	Microbiologist/ Analyst Name	Initial Results	Repeat Analysis Results			
			Microbiologist/ Analyst Name		Microbiologist/ Analyst Name	
Average of Individual Microbiologist / Analyst						
Average of Two Microbiologist / Analysts						
Overall RSD						

Summary & Conclusion:

Functional Supervisor Sign/Date) **Head Microbiology/QC (Sign/Date)** **QA Designee (Sign/Date)**

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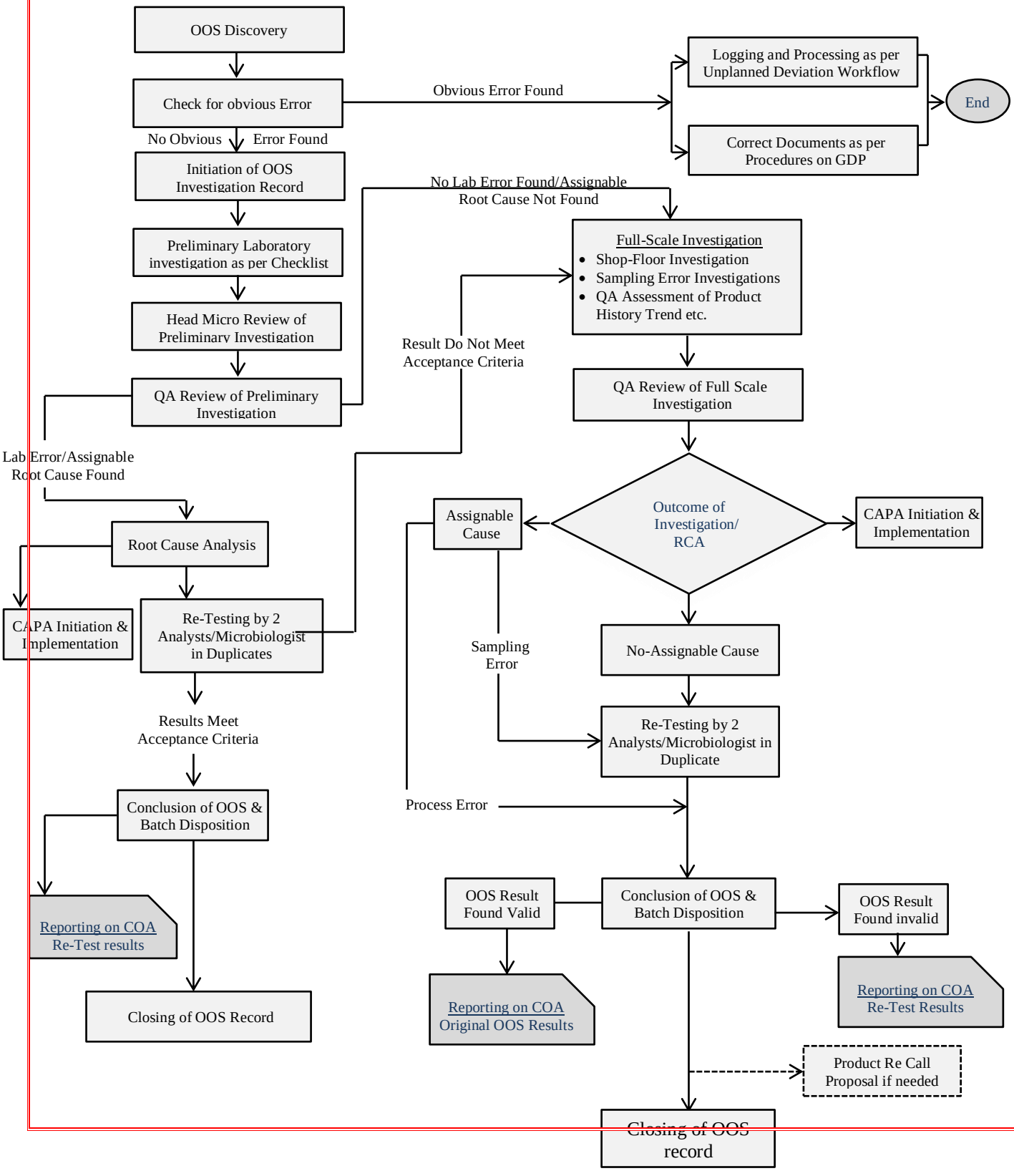
ANNEXURE 7
DECISION TREE FOR FAILURE INVESTIGATION OF MICROBIAL LIMIT TEST



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ANNEXURE 8
REQUEST FOR EXTENSION OF OOS INVESTIGATION

OOS No.			
Product Name		Batch No.	
Date of Analysis		Analysed By	
OOS Reporting Date			
Detail of OOS			
Reason for Extension:			
QA Evaluation: **Name** **Sign.** **Date**			
Request By: **Name** **Sign.** **Date**			
Approved By: **(Site Head Quality)** **Name** **Sign.** **Date**			