PHARMA DEVILS

MICROBIOLOGY DEPARTMENT

STANDARD OPERATING PROCEDURE	
Department: Microbiology	**SOP No.:**
Title: Handling of Out of Specification (OOS) Result during Microbiological Testing	**Effective Date:**
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1. **Purpose:** To lay down the procedure for Handling of Out of Specification (OOS) Result during Microbiological Testing.

2. **Scope:** This Standard Operating Procedure is applicable at microbiology section of Quality Control department.

3. **References & Annexures:**

3.1 **References:**

3.1.1 USP

3.1.2 PDA: Technical report : Point to be consider when investigating microbiological data deviation.

3.2 **Annexures:**

3.2.1 Annexure- 1 : OOS Intimation Form.

3.2.2 Annexure- 2 : OOS Log for Microbiology.

3.2.3 Annexure- 3 : Preliminary Checklist for Laboratory Assessment.

3.2.4 Annexure- 4 : Shop Floor OOS Investigation Report.

3.2.5 Annexure- 5 : Sampling Error Investigation

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

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

3.2.8 Annexure- 8 : Request For Extension of OOS Investigation.

4. **Responsibilities:**

4.1 **Executive/ Officer - Microbiology**

4.1.1 The Microbiologist is responsible to report to immediate microbiology Head when an out of specification result is obtained.

4.1.2 Responsible for initiate OOS investigation.

4.1.3 Responsible to retain all the preparations, portions of test samples, regents and glassware used in the analysis wherever applicable.

4.2 **Section Head-QC (Microbiology)**

4.2.1 Responsible to ensure that OOS investigation is initiated.

4.2.2 Responsible to conduct the preliminary investigation with the Microbiologist.

4.2.3 To inform the 'OOS' result to the Quality Control/Quality Assurance Designee to initiate the full scale investigation for assignable cause that may be related to the manufacturing process.

4.3 **Head- Quality Control (Head-QC)**

4.3.1 Responsible for assessing the data to ascertain if the results could be attributed to laboratory error or whether the result indicates the problems in the manufacturing area.

4.3.2 The Head, Quality Control is responsible for review of investigation of preliminary investigation.

4.3.3 The Head, Quality control is responcible to follow the approved protocol where ever applicable, incase of QC related action points.

4.4 **Section Head-QA (Analytical Review)**

4.4.1 To review the OOS intimation.

4.4.2 To review and participate in Preliminary and laboratory investigation.

4.5 **Executive/Officer-QA**

4.5.1 Responsible for issuance and generation excursion number.

4.5.2 Responsible for investigation of production process.

4.6 **Head Quality Assurance (Head-QA)**

4.6.1 Responsible for of reviewing and evaluating the adequacy of OOS investigation, Root Cause investigation and for appropriate CAPA.

4.6.2 Responsible for active participation and Co-ordination inter departmental investigation(s) i.e. full scale investigation that may be initiated as a result of an inconclusive preliminary laboratory investigation.

4.6.3 Responsible for review of any re-sampling/re-testing plan.

4.6.4 Initiates appropriate controls, e.g. quarantine, operations suspension, as may be warranted, until an investigation is complete, root cause(s) is/are determined and OOS is closed.

4.7 **Head Production:**

4.7.1 Responsible for performing and active participation in full scale investigation including shop floor investigation.

4.7.2 Responsible to participate in the root cause investigation.

4.7.3 Responsible to ensure the closure of appropriate CAPA.

4.8 **Head Engineering:**

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4.8.1 Responsible for performing full scale investigation including shop floor investigation, wherever required.

4.9 **Site Head- Quality**

4.9.1 Responsible to approve of the retesting / re-sampling protocol.

4.9.2 Responsible to ensure adequate investigation including in the strategy development for inter and interdepartmental investigation and approval of the investigation report.

4.9.3 Responsible for batch disposition decisions.

4.9.4 Responsible for implementation of appropriate CAPA.

4.9.5 Accountability for implementation of this SOP.

4.10 **Regulatory Affairs, Quality Head and Plant Head :**

4.10.1 To review and approve new or revised SOP's.

5. Distribution:

5.1 QC

5.2 QA

5.3 Production

5.4 Engineering

6. Abbreviations and Definition of Terms:

6.1 **Abbreviations:**

6.1.1 BMR : Batch Manufacturing Record.

6.1.2 BPR : Batch Packing record.

6.1.3 CC : Change Control

6.1.4 HOD : Head of Department

6.1.5 HVAC : Heating Ventilation and Air Conditioning.

6.1.6 MLT : Microbial Limit Test.

6.1.7 NA : Not Applicable

6.1.8 PDA : Parenteral Drug Association

6.1.9 QA : Quality Assurance

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6.1.10 QC : Quality Control

6.1.11 SOP : Standard Operating Procedure

6.2 **Definition of Terms :**

6.2.1 **Standard Operating Procedure (SOP):** A written authorized procedure, which gives instructions for performing operations.

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

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

6.2.4 **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).

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

6.2.6 **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.

6.2.7 **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.

6.2.8 **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.

6.2.9 **Preliminary Laboratory Investigation:** The fully documented, step-by-step investigation approach used by the Microbiology Functional Supervisor (may also include Head Quality

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Control, whenever necessary) and the microbiologist to determine whether any laboratory error is the assignable cause of an out-of-specification result.

6.2.10 **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.

6.2.11 **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. Procedure:

7.1 If an OOS result is observed, the microbiologist who has observed the result shall immediately inform the OOS result to the Section Head-QC (Microbiology)/or designee.

7.2 The executive/officer (Microbiology) shall quarantine the samples, test materials, glassware (Pipettes and volumetric flasks), filters and instrument used for analysis whenever applicable (Some microbiological solution preparations will not be viable for the full incubation period.)

7.3 The section Head-QC (Microbiology)/or designee along with executive/officer (Microbiology) shall immedialtly verify the OOS result.

7.4 If the cause of the OOS is determined to be an incorrect calculation or transcription error, the testing record shall appropriately be documented and corrected in the record of analysis with sign and date and no further investigation is required.

7.5 If the verification of the calculation results conferms an OOS, the executive/ officer (Microbiology) shall proceed for initiation of OOS investigation.

7.6 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” Annexure-1 by providing the following details;

- Product/Material description
- Batch No.
- Control No.
- Test

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- Date of Analysis
- Result
- Remarks

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

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

7.9 Each OOS number shall be allotted sequentially.

7.10 Numbered as OOS/XX-M/YY-nnn

Where:- 'OOS' indicating out of specification.

'XX' indicating the facility code for e.g PD for Pharma Devils

'M' indicating the microbiology department.

'YY' indicating the Year.

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

7.11 Batch showing the OOS and rest of the batches manufactured after the same shall be kept under hold till the completion of investigation.

7.12 After issuance of 'OOS investigation report' a stepwise investigation to find out the root cause/probable root cause shall be conducted.

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

7.14 If the investigation cannot be concluded after the completion of an investigational step, the next sequential step (Full scale investigation after laboratory investigation) shall be performed in order to determine root cause.

7.15 As part of the continuance to the next investigational step, the outcome of the previous step shall summarized and (if applicable) a details analysis plan inclusive of the purpose of the course of action chosen (based on the outcome of the previous investigative step), any justifications of alternate analysis material usage (if applicable) shall be made.

7.16 **Preliminary Investigation for Microbial Limit Test/Bio-burden test failure:**

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7.16.1 The executive/officer (microbiology) and Section Head-QC (Microbiology)/ or designee, together shall conduct the preliminary investigation. The purpose of the investigation is to determine whether there is any laboratory error.

7.16.2 The preliminary investigations shall be performed by verify the laboratory assessment checklist as per Annexure-3.

7.16.3 Investigation shall evaluate following are as but not limited to:

- Discussion of the test method with the analyst to confirm the analyst knowledge/competency.
- Error in preparation, handling, storage of samples.
- Evaluate analyst training/qualification.
- Compare the test method performed against approved procedures.
- Evaluation of other tests performed on the materials in question.
- Evaluation of test results obtained from the same sample type and from the same instrument.
- Culture identity, performance and passage number meeting the pharmacopeial requirments.
- Inspection of the work area, to determine if any environmental or facility conditions would have adversely impacted the testing. Complete document and preserve records of this laboratory assessment.
- Comparison with pervious trend, whether any out of limits or out of trend in the recent past.
- Result of GPT on media used evaluation of positive and negative control, incubation conditions etc.

7.16.4 Laboratory preliminary investigation shall be completed within 3 business days after finding OOS. In case there is a need to extend investigation, microbiology laboratory head shall prepare interim report with reason, justification for extension in the remark column in Annexure- 8. Site Quality Head shall approve the justification.

7.16.5 After thr priliminary investigation are completed, the section Head-QC (Microbiology)/or designee shall identify whether is a laboratory error or not subsequently shall submit the priliminary investigation to Head-Quality Control.

7.16.6 Head-Quality Control shall review the investigation and if additional details are required then Head-Quality Control shall re-direct it to the Section Head-QC (Microbiology)/or designee.

7.16.7 Head-Quality Control may add additional activity to be completed as part of investigation. After the completion of all the assigned activity the Section Head-QC (Microbiology)/or designee shall forward it again for the Head- Quality Control for review.

7.16.8 After completion of all identified action plan, Head-Quality Control shall review the reason for OOS.

7.16.9 Head- Quality Control may attach additional documents, if any and OOS investigation record shall be submitted to Site Quality Head for review.

7.16.10 Head Quality shall review all the related records and if any additional data is required, he/she may ask to Head-Quality Control to submit the same.

7.16.11 If the preliminary investigation of the Out of Specification result demonstrates the result is attributable to a determinate analytical identifiable error(s) (e.g. non-adherence to monograph instructions, incorrect sample dilutuion use of unsuitable reagent/glassware accessories, incorrect non-pyrogenated sampling tools or any other assignable cause etc.) the OOS result, the same shall be recorded in the preliminary investigation report with suitable explanation.

7.16.12 On determination of analytical/Laboratory error or assignable root cause preliminary Laboratory Investigation shall be concluded and appropriate CAPA shall be taken for the identified root cause.

7.16.13 If laboratory error or assignable root cause is not found and furture investigation is deemed necessary as an outcome of preliminary Laboratory Investigation then full scale investigation shall be carried out.

7.17 **Preliminary Investigation for Microbial Assay Failure;**

7.17.1 The executive/officer (microbiology) and Section Head-QC (Microbiology)/ or designee, together shall conduct the preliminary investigation. The purpose of the investigation is to determine whether there is any laboratory error. Refer Annexure 3 for preliminary investigation.

7.17.2 The preliminary investigations shall be performed by verifing the laboratory assessment checklist and examind the raw data obtained in the analysis, including identify anomalous or suspect information.

- Determine that appropriate reagents were used and that they met quality control specifications.
- Evaluate the performance of the test method to ensure that it is performing according to the standard expected based on method validation data and historical data.
- Compare the test method performed against approved procedures.

- Evaluate positive or negative controls.
- Evaluate measurments, conversion factors and formulas assosiated with testing and reagent preparation.
- Evaluate analyst training/experiences.
- Examination of glassware used in the preparation of samples and reagents.
- Evaluation of other tests performed on the sample lot in question.
- Identification and evaluation of any unusual events, malfunctions or unexpected circumstances associated with the test environment.
- Inspection of the work area to determine if any environmental or facility conditions would have adversely impected the testing.
- Full document and preserve records of this laboratory assessment.

7.18 **Laboratory Error:** if a laboratory is determined during the preliminary investigation in the test as mentioned above; site Head- Quality shall recommend for further course of action.

7.18.1 **Microbial Limit Test/Bio-burden Test:**

- Perform the reanalysis on a written and approved protocol, after correcting the error by same executive/ officer (microbiology) on fresh aliquot of product/material along with required training to the concerned microbiologists. The protocol shall be approved by site Head-Quality.
- If the results of reanalysis meet the acceptance criteria (individually), then the results shall be reported as a final value for the materials release.
- The original OOS results shall be invalidated.
- Supporting evidence in combination with other evidence that may be used to invalidate original results can include;
- Re-analysis results that do not confirm the original result such when inadeqate extraction/dilution of the sample is observed.
- Product history and results of other tests from the same sample that do not confirm the original result.
- Determination that the sample is not representative of the product or material.

7.18.2 **Microbial Assay Failure:**

- If a laboratory Error is identified during the preliminary investigation, the original reportable result (OOS) may be invalidated, if and only if there has been a conclusive, scientifically justified, probable cause for the OOS result.
- Re-testing the same sample shall be done only if the sample has not been compromised by contamination, damage, degradation or modification since the original sample time. If there are any reason to suspect any of the above, re-sample should be considered, the original discarded and the decision fully document as part of the investigation.
- A re-test plan and protocol shall be written and approved by the Site Head-Quality. A maximum number of re-tests shall be defined in the re-test protocol.
- The number of re-tests should not be adjusted from the original plan based on the results obtained. Following re-testing plan (as per the retest protocol), if the results remain unsatisfactory a disposition decision shall be made by the Head-QA.
- If the laboratory error is in conclusive (reason for the error is not identified), analyst 'A' shall do re-analysis and different analyst (say'B') in triplicate carry out using the same test preparations. (Including the composite or the homogenous source of the aliquote tested).
- If the result of analysts 'A' & 'B' passes acceptance criteria- invalidate OOS results.
- If the result of analysts 'A' & 'B' fails in any acceptance criteria- OOS confermed/validated.

Note:

- In the case of microbiologoical assay, the U.S. Phamacopiea (USP) prefer the use of averages because of the innate variability of the biological test system.
- Since there is a inherent variability in Bio Assay in terms of method to established the potency of the product, investigation procedure other then mentioned can be used after approval of protocol through Site Head-Quality.

7.19 **No Laboratory Error:**

7.19.1 When the preliminary Laboratory Investigation (Including Re-analysis, if any) determines that the cause of OOS result is 'No Laboratory Error'/not assignable root cause and testing results appear to be accurate, then a full scale OOS investigation shall be performed.

7.19.2 Incase of undetermined/non assignable cause is concluded in the preliminary investigation, the same shall be informed to Site Head Quality for futther investigation i.e. full scale.

7.19.3 Site Head Quality form a cross functional team (Designee-QA/QC/ Production/Engineering etc.) shall conduct a Full Scale OOS investigation. The purpose of the investigation is to determine whether the assignable cause of the OOS result was due to the laboratory testing process or due to the manufacturing process. Even if a batch is rejected based on an OOS

result, theinvestigation is necessary to determine if the result is associated with other batches of the same drug product or other products.)

7.19.4 Full scale OOS investigation includes following investigations, but not limited to:

- Shop floor investigation (Review of Production Process and Procedures).
- Sampling Error Investigation (Error in sampling/ Handling/ Storage of sample).
- QA Assessment (Review of product documents and validation data, Trends, product history, product deviations etc.)
- Re-Testing (additional Laboratory Testing, this includes potentially retesting the original sample and/or re-sampling).

7.19.5 Shop Floor Investigation:

- The designee QA/QC/Production/Engineering etc. shall conduct shop floor investigation which includes the review of Production Process and Procedures. Refer Annexure 4.
- If the assignable or root cause is found during shop floor investigation and the investigation shall be concluded and appropriate CAPA shall be initiated and the same shall be documented implemented. Howerwe if necessary investigation is to be extended to other materials of same product or other products that may have been associated with the specific failure on investigations and shall also be documented in the investigation report.
- If the cause of OOS result is not determined during Shop Floor Investigation, then the next course of action (extended/additional investigation)shall be decided by Site Head Quality.
- When extended /additional investigation is required, then additional 'Investigation' shall be conducted on the basis of approved protocol including the reason and scope of investigation.
- Additional investigation (Such as Sampling Error Investigation, QA Assessment, Re-Testing) (only if deemed necessary by the outcome of the shop floor investigation) shall be conducted.
- Investigation plan shall be approved by site Head Quality to perform Re- Testing (inclusive of the purpose and the course of action (s) chosen) a protocol shall be written and documented on the basis of scintific rationale.
- QA designee shall document CAPA record to address the identified root cause.

7.20 **Sampling Error Investigation:**

Only if deemed necessary by the outcome(s) of the preliminary Laboratory investigation, i.e No Laboratory Error or part of Full Scale Investigation, shall be performed to determine the root cause.

7.20.1 Site Head-Quality shall take the decision for determining sampling Error (Refer Annexure-5; Sampling Error Investigation).

7.20.2 If sampling error is established (only if deemed necessary by the outcome(s) of the sampling error investigation), Re-sampling Plan shall be prepared and shall be approved by Site Head-Quality only.

7.20.3 Re-sample shall not be considered as an automatic next step of the investigational process even when the assignable or root cause is not found as part of Laboratory Preliminary Investigation.

7.20.4 Re-sampling and Re-testing shall only be considered if it has been determined at any point of the investigation reveals that:

a) Original sample was not representative sample.

b) Original Sample was improperly sampled.

c) Original Sample was not stored appropriately.

d) Original sample may have been adversely affected by exposure to humidity, light or heat.

e) If the quantity available is insufficient then re- sampling shall be performed. (For stability sample, sample from stock shall be used.)

f) Re-sampling should be performed by the same qualified, validated methods that were used for the initial sample. However, if investigation determines that initial sampling method was inherently inadequate, a new sampling method must be developed, documented, reviewed and approved by QA Head/designee.

g) Re-sampling record shall be a part of 'Investigation Record' and shall be approved by QA Head/Designee.

h) Re-sampling plan and Re-testing shall be written, performed and approved as follows:

- The Head-QA shall develop a Re-testing and/or Re-sampling plan protocol.
- The Site Head-Quality shall approve the Re-sampling protocol, prior to Re-sampling activities; Re-testing shall be performed as described by the protocol and pursuant to above.

7.21 **QA Assessment:**

7.21.1 QA Assessment (only if deemed necessary by the outcome(s) of the Preliminary Laboratory Investigation, i.e. No laboratory Error or as a part of full scale investigation), shall be performed by QA-Head/ Designee to determine the root cause.

7.21.2 QA designee shall review following areas, but not limited to:

a) Review of product documents.

b) Review of product history.

c) Review of product development and Validation data.

d) Review of Trend.

e) Review of product deviations etc.

7.21.3 QA Assessment (inclusive of the purpose and the course of action (s) chosen) shall be a part of 'Investigation Record', created by QA Designee.

7.22 **Re-Testing**

7.22.1 Testing in case of Raw Material (only if deemed necessary by the outcome(s) of the preliminary Laboratory Investigation, i.e. No Laboratory Error), shall be performed to determine the root cause and confirm the OOS results.

7.22.2 Re-testing in case of Inprocess / Finished product (only if deemed necessary by the outcome(s) of the Shop Floor Investigation and/or Sampling Error investigation), shall be performed to determin the root cause. (Excluding the sterility samples) (Refer Annexure-6).

7.22.3 Site Head-Quality shall take the decision for determining sampling error (Refer Annexure-5; Sampling Error Investigation). If sampling error is established, re sampling shall be performed and retest by same microbiologist shall be done.

7.22.4 Re-sampling record shall be a part of 'Investigation Record' and shall be approved by Site Head Quality.

7.22.5 If there is no laboratory/sampling error established for OOS results of finished product, Head-QA/Designee shall review the investigation record.

7.22.6 The production Head/Head-QA/ Engineering Head shall conduct a full root cause shop floor investigation. The objective of the shop floor investigation is to identify the root cause of the OOS result.

7.22.7 Shop floor investigation shall be reviewed by QA. If found satisfactory and root cause identified, CAPA plan shall be proposed by QA as per the recommendation in the investigation report.

7.22.8 If shop floor investigation is not satisfactory and further investigation is required, additional investigation plan shall be proposed.

7.22.9 Head-QA/Designee shall review all OOS record after completion of the assigned investigations.

7.22.10 To conclude the full scale root cause investigation, the analysis results shall be evaluated and the Site Head Quality shall make a final disposition decision within 30 calender days from the observation of OOS. Following shall be completed in investigation report.

- Investigation conclusion.
- Root cause summary.
- Decision for Material disposition determined.
- Where the root cause investigation indicates that the OOS result is caused by a factor affecting the materials quality (i.e., an OOS result is confermed), and that the result indicates that the materials does not meet established standards or specifications, the materials (s) shall be rejected.
- The investigation must be extended to other materials or products that may have been associated with the specific failure on investigations.
- The identified root cause shall be discussed with all concerned stake holders and corrective and preventive action (CAPA) shall be identified.

7.23 **Disposition of Product**

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

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

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

7.23.4 Indicate final disposition on the OOS investigation report.

7.23.5 Refer Annexure-7 decision tree for investigation.

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OOS INTIMATION FORM

Date			
Product		Batch No.	
Product Type (Mark:√)	(Intermediate/Validation/FP/Stability/RM/PM)		
Test			
1	Date of Analysis		
2	Date of Observation		
3	Specification		
4	Standard Test Procedure/Monograph/Compendia		
5	Control Number		
6	Out of Specification initial Results		
7	Brif Description of the Event		

Officer/Executive-QC (Micro)
(Sign & Date)

Section Head- QC (Micro)
(Sign & Date)

Head-Quality Control
(Sign & Date)

Head-Production
(Sign & Date)

Site Head-Quality
(Sign & Date)

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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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	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	Specification			
4	Standard Test Procedure/Monograph/Compendia			
5	Control Number			
6	Out of Specification initial Results			
7	Brief Description of the Event			
8	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.			

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PRELIMINARY CHECKLIST FOR LABORATORY ASSESSMENT

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	

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PRELIMINARY CHECKLIST FOR LABORATORY ASSESSMENT

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	
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	

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PRELIMINARY CHECKLIST FOR LABORATORY ASSESSMENT

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	
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	

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PRELIMINARY CHECKLIST FOR LABORATORY ASSESSMENT

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 analysis.	□ Yes □ No □ NA	

Any other observations:

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	PRELIMINARY CHECKLIST FOR LABORATORY ASSESSMENT

OOS Number:.....

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			

Section Head-QC (Microbiology)
(Sign/Date)

Section Head-QA (Reviewer)
(Sign/Date)

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OOS Number:.....

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.:

Original Officer/Executive (Microbiology)

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

Section Head-QC (Microbiology)

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

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PRELIMINARY CHECKLIST FOR LABORATORY ASSESSMENT

OOS Number:.....

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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	PRELIMINARY CHECKLIST FOR LABORATORY ASSESSMENT

OOS Number:.....

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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PRELIMINARY CHECKLIST FOR LABORATORY ASSESSMENT

OOS Number:.....

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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PRELIMINARY CHECKLIST FOR LABORATORY ASSESSMENT

OOS Number:.....

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				

Section Head-QC (Microbiology) Sign./Date	Section Head-QA (Reviewer) Sign./Date	Head-Quality Control Sign./Date	Site Head-Quality Sign./Date

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DEPARTMENT: MICROBIOLOGY

PRELIMINARY CHECKLIST FOR LABORATORY ASSESSMENT

OOS Number:.....

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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PRELIMINARY CHECKLIST FOR LABORATORY ASSESSMENT

OOS Number:.....

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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PRELIMINARY CHECKLIST FOR LABORATORY ASSESSMENT

OOS Number:.....

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				
Section Head-QC (Microbiology) Sign./Date	Section Head-QA (Reviewer) Sign./Date	Head-Quality Control Sign./Date	Site Head-Quality Sign./Date	

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Annexure -4

	DEPARTMENT: MICROBIOLOGY
	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	Head Quality Assurance Sign./Date	Site Head-Quality Sign./Date

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SHOP FLOOR OOS INVETIGATION REPORT

OOS Number:.....

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

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.N.	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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	DEPARTMENT: MICROBIOLOGY
	SHOP FLOOR OOS INVETIGATION REPORT

OOS Number:.....

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

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

	DEPARTMENT: MICROBIOLOGY
	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 APIs 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	

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	SAMPLING ERROR INVESTIGATION

15.	Any deviation from recommended packing condition as per Protocol/Specification Yes/No, if Yes, Specify	
Summary of findings:		
Functional Supervisor/Designee:		
Re Sampling Approved By: Site Head Quality Sign./Date		

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	DEPARTMENT: MICROBIOLOGY
	RETEST/REPEAT ANALYSIS- SUMMARY SHEET

Product:

B. No. :

Test :

Limit :

Date	Name of Analyst	Initial Results	Repeat Analysis Results

Summary & Conclusion:

Section Head-QC (Microbiology)
Sign/Date

Section Head-QA (Reviewer)
Sign/Date

PHARMA DEVILS

MICROBIOLOGY DEPARTMENT

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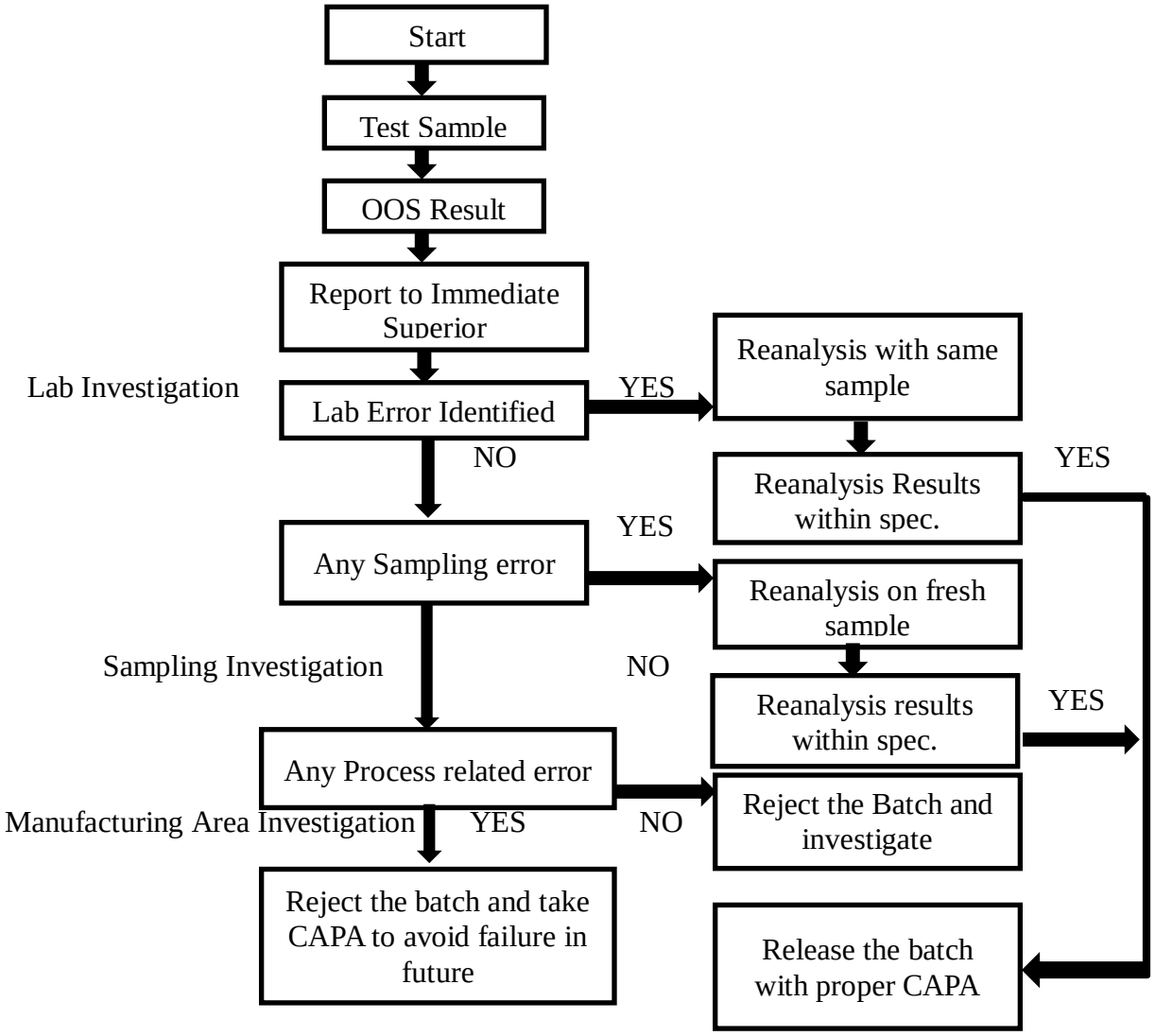
DEPARTMENT: MICROBIOLOGY

DECISION TREE FOR FAILURE INVESTIGATION OF MICROBIAL LIMIT TEST



PHARMA DEVILS

MICROBIOLOGY DEPARTMENT

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	DEPARTMENT: MICROBIOLOGY
	REQUEST FOR EXTENSION OF OOS INVESTIGATION

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

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8. History:

Revision No	Effective Date	Revision Details	CC No
00		New SOP	NA