PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

STANDARD OPERATING PROCEDURE	
Department: Quality Assurance	**SOP No.:**
Title: Handling of Out of Specification in Microbiology Results	**Effective Date:**
Supersedes: Nil	**Review Date:**
Issue Date:	**Page No.:**

1.0 OBJECTIVE:

To lay down the Procedure for Handling of Out of Specification in Microbiology Results.

2.0 SCOPE:

This SOP is applicable to all Plants and Facilities.

3.0 RESPONSIBILITY:

CQA (Operating Person)	**:**	Preparation, Distribution (To Plant-QA), Revision, Retrieval and Destruction of this SOP.
CQA (Operating Manager)	**:**	Review, Training (To Plant-QA) and effective implementation of this SOP
Plant QA (Operating Person)	**:**	Preparation of Plant SOP in accordance with this SOP and retrieval of this SOP. Issuance and maintain the Out of Specification Investigation Log for Microbiology.
Plant QA (Operating Manager)	**:**	Training and Effective Implementation of this SOP to all concerned department. Review of Microbiological OOS Investigation through Root cause Analysis / Impact Assessment / Risk Assessment and CAPA Implementation in time. Review of Field Alert Report timely.
QC Microbiology (Operating Person)	**:**	Initiation of Microbiological Out of Specification Investigation.
QC Microbiology (Operating Manager)	**:**	Investigations through Root cause Analysis, Impact Assessment / Risk Assessment and CAPA Implementation in time. Intimation of Field Alert Report timely.
DRA (Operating Person)	:	Review OOS Report. and Field Alert Report for US Market.

4.0 ACCOUNTABILITY:

Head CQA	**:**	Approval, Authorization, ensure Training and Implementation of this SOP.
Head QA	**:**	To ensure Training and effective implementation of this SOP at plant. Review and Approval of Out of Specification Investigation Report.

		Assignment of Subject Matter Expert from Production, Warehouse, Engineering, R&D etc. Approval of Field Alert Report timely. Intimation of FAR to Head CQA.
Head QC	**:**	Training and Effective Implementation of this SOP to concerned department. Evaluation of Microbiological Out of Specification. Root Cause Analysis, Impact Assessment / Risk Assessment and CAPA Implementation in timely manner.
Head DRA	**:**	Review & Submission of Field Alert Report for US Market. Information of confirm OOS providing to QP/MAH/ Regulatory Agencies. Intimation to Customer as per time line defined in technical agreement.
Head Production / R&D / Engineering / SME	**:**	Performing the Full-Scale Phase II Investigation, wherever required.

5.0 ABBREVIATIONS:

CAPA	Corrective Action and Preventive Action
DRA	Drug Regulatory Affairs
FAR	Field alert report
LAF	Laminar Air Flow
LAL	Limulus Amoebocyte Lysate
Ltd.	Limited
MHRA	Medicines and Healthcare Products Regulatory Agency
No.	Number
OOS	Out of Specification
PM	Packing Material
Pvt.	Private
QA	Quality Assurance
QC	Quality Control
R&D	Research and development
RA	Regulatory affairs
RM	Raw Material
SOP	Standard Operating Procedure
US	United States of America

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6.0 PROCEDURE:

Note: ***This Procedure is not applicable for Environment Monitoring and Water system. The Discrepancies like GPT, Cell Suspension or Culture standardization failure shall be closed by lab incident as per respective plant SOP.***

6.1 Definition:

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

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

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

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

6.1.3 **No Assignable Cause:** When no reason could be identified.

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

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

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

6.1.7 **Re-testing:** Analysis performed using the sample from same homogeneous material that was originally collected from the lot, tested, and yielded the OOS results.

For a liquid product, it may be from the original unit liquid product or composite of the liquid product. For a solid dosage form, it may be an additional weighing from the same sample composite prepared for the original test.

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

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

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

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

6.1.9 **Most Probable Cause:** Scientifically justified determination that the result appears to be error.

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

6.2 Detection of OOS result during Microbiological Testing:

6.2.1 Microbiologist who has observed the result shall inform immediately to the Operating manager micro that an OOS result has occurred.

6.2.2 The Operating manager and Microbiologist shall check immediately whether OOS occurred result is due to an "Obvious Error" that will negate the requirement for further investigations.

6.2.2.1 **Calculation / Transcription Error:** Microbiologist and Operating Manager shall review for calculation/transcription errors. If any error is found, corrections shall be made as per the current version of **CQA SOP "Good Documentation Practices"**.

6.2.2.2 **Power Outage:** Microbiologist and Operating Manager shall document the event, annotate as "power failure, analysis to be repeated", where applicable on all associated analytical documentation.

6.2.2.3 **Equipment Failure:** Microbiologist and Operating Manager 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.

6.2.2.4 **Incorrect Instrument Parameters:** For example, incorrect setting of the water bath temperature. In such a case, the Microbiologist and Operating Manager 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 (refer to the current version of **CQA SOP "Handling of Deviations"** and for Incident refer to current version of **CQA SOP "Handling of Incidents".**

6.2.3 If the cause of the OOS is determined to be an "obvious error", the concerned Microbiologist shall take necessary steps, as specified above, and make corrections in the Analytical Raw Data Sheet / Notebook by following the good documentation procedure.

6.2.4 If the root cause is determined as an "obvious error", no further OOS investigation is necessary, since the "OOS" result in such case can be considered as **"Invalid".**

6.2.5 **"Root Cause Analysis"** shall be performed through **CQA SOP "Root Cause Analysis"** and Risk Assessment shall be performed as per **CQA SOP "Quality Risk Management"** (if applicable).

6.2.6 In case of Raw material and Packaging material, the OOS investigation shall be limited to laboratory phase only.

6.3 Initiation of Out of Specification:

6.3.1 Microbiologist shall initiate the intimation as per format shown in **Annexure-I "OOS Intimation Form"**.

6.3.2 QA shall assign the OOS No. as per **Annexure-II "OOS Investigation Log for Microbiology**" and same number shall be assigned in **Annexure-III "Checklist for Laboratory Assessment**" **(Phase I Investigation).**

6.3.3 Assignment of Out of Specification No. shall be followed in microbiology laboratory,

"**OOS/M/X/YY/NNN**"

Where,

OOS	: Stands for Out of Specification
M	: Stands for Microbiology
X	: Stands for Plant Code
/	: Stands for Separator
YY	: Stands for current calendar year i.e. 21.
NNN	: Stands for serial no. starts from 001….

Example:

OOS/M/A/24/001: Denotes first Out of Specification for Microbiology of Plant-I raised in year 2024.

Note: For Plant code Refer CQA SOP "SOP on SOP".

6.3.4 In case, additional space is required beyond the space in the controlled document of Out of Specification Report, an attachment of Format **"Additional Attachment"** of **CQA SOP "Documentation and Data Control**" shall be enclosed with reference of mother document.

6.3.5 After creation of an **"OOS Intimation Form",** a sequential detailed Phase I Investigation shall be conducted to determine the root cause.

6.3.6 Each step of investigation shall be clearly defined, including the number of replicates and the outcome of each investigational step shall be evaluated.

6.4 Investigation of OOS test result:

6.4.1 Investigation shall be carried out as follows;

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

6.5 Phase-I Investigation (Laboratory Investigation):

6.5.1 Phase-I Laboratory Investigation shall be conducted by the Operating Manager microbiology with the concerned Microbiologist as per format shown in **Annexure-III** "**Checklist for Laboratory Assessment" (Phase-I Investigation)** to determine whether the OOS result occurred due to laboratory error.

6.5.2 Laboratory Investigation (Phase-I Investigation) shall be completed within 3 working days, if time exceeds adequate justification shall be provided as per format shown in **Annexure–IV "Extension Form for OOS Investigation"**.

6.5.3 During the Phase-I Laboratory Investigation, evaluate the followings, but not limited to:

6.5.3.1 Discussion of the test method with the Microbiologist to confirm the Microbiologist knowledge / competency.

6.5.3.2 Evaluate Microbiologist Training / Qualification.

6.5.3.3 Evaluate the use of specified effective STP(s), General Test procedures (GTPs), SOP(s), Pharmacopoeia monograph, and Protocol(s) referred for the analysis.

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

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

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

6.5.3.7 Compare the test method performed against approved procedures.

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

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

6.5.3.10 Evaluation of other tests performed on the batch/sample in question.

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

6.5.3.12 Evaluation of test results obtained from the same sample and from the same instrument.

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

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

6.5.4.1 Bacterial Endotoxin Test:

6.5.4.1.1 Evaluation of validity of reagents.

6.5.4.1.2 Depyrogenation of glassware used in the preparation of samples and reagents/media.

6.5.4.1.3 Evaluation of product positive control, product negative control, etc.

6.5.4.1.4 Calculations in case of Kinetic Turbidimetric LAL reagent (KTA) analysis.

6.5.4.1.5 Confirm whether Dry Heat Sterilizer (DHS) has been calibrated / Qualified and its temperature monitored on a routine basis.

6.5.4.1.6 Confirm whether the heating block has been calibrated and displays correct temperature.

6.5.4.1.7 Confirm whether Limulus Amoebocyte Lysate (LAL)/Control Standard Endotoxin /LAL Reagent water was stored at correct temperature.

6.5.4.1.8 Confirm whether reconstituted Lysate/Control Standard Endotoxin / LAL Reagent water within the shelf life.

6.5.4.1.9 Confirm whether test for confirmation of labeled Lysate sensitivity of the LAL reagent was within acceptance criteria.

6.5.4.2 Sterility Test:

6.5.4.2.1 Examination of sterilization of components used in the preparation of samples and reagents/media.

6.5.4.2.2 Confirm whether glassware/media/garments, etc. were sterilized, as per the validated sterilization cycle.

6.5.4.2.3 Confirm whether the manometer reading of the Laminar Air Flow hood (LAF) is within the acceptance criteria.

6.5.4.2.4 Confirm whether the sample containers were dried after sterilization.

6.5.4.2.5 Evaluation of Product Positive Controls, Negative Control etc.

6.5.4.2.6 Evaluation of test results obtained from other material of the same sample and from the same instruments.

6.5.4.2.7 Review of other samples tested on same day and also preceding and succeeding day results by the same Microbiologist.

6.5.4.2.8 Environmental monitoring of sterility testing facility (including personnel monitoring data) during the test period.

6.5.4.2.9 Confirm whether Growth Promotion Test (GPT) results of the media used in test and Negative Control were as per acceptance criteria.

6.5.4.3 Bio-Assay:

6.5.4.3.1 Check for any error in preparation, handling, and storage of samples.

6.5.4.3.2 Confirm whether the Zone Reader / Vernier Caliper were calibrated.

6.5.4.3.3 Confirm whether culture identity, performance, and passage number meet the requirements.

6.5.4.4 Microbiological Examination of Non-Sterile Products:

6.5.4.4.1 Evaluate whether differential pressure of the dynamic pass box was within the acceptance criteria.

6.5.4.4.2 Evaluate whether differential pressure/manometer reading of the LAF was within acceptance criteria.

6.5.4.4.3 Determine whether microbial environment monitoring of LAF count and Laboratory area count observation was within acceptance criteria.

6.5.4.4.4 Confirm whether media was sterilized, as per validated sterilization cycle.

6.5.4.4.5 Confirm whether samples were incubated at correct temperature, as stated in the procedure.

6.5.4.4.6 Confirm whether culture media pH observation was within acceptance criteria.

6.5.4.4.7 Confirm whether culture identity, performance, and passage number meet the Pharmacopoeial requirements.

6.5.4.4.8 Comparison with previous trend, whether any excursions beyond limits were received in the recent past.

6.5.4.4.9 Result of Growth Promotion Tests (GPT) on Media used evaluation of positive and negative control, incubation conditions, etc.

6.5.4.4.10 Confirm whether sampling tools used for sampling were sterilized.

6.5.5 Upon completion of Phase I Laboratory Investigation, Operating Manager (Micro) shall determine whether laboratory error occurred or not and subsequently forward the OOS investigation report to the Head QC for review.

6.5.6 If root cause of the OOS remains undetermined, Head QC shall document in the same OOS Investigation Report, i.e., the cause of OOS result is "unknown at this stage".

6.5.7 Head QC shall review the OOS investigation report and, if needed, request additional details from the Operating Manager Micro.

6.5.8 Head QC shall forward the OOS investigation report to QA for review.

6.5.9 QA shall examine all the related records of Laboratory Investigation along with conclusions/recommendation made by the Head QC. If needed, QA may request further details from Head QC.

6.5.10 If “No Laboratory Error” or "No Assignable Cause” found then the investigation shall extend to a Full Scale Investigation.

6.5.11 If "Laboratory Error” or “Assignable Cause" found then follow the below steps;

6.5.11.1 Based on the laboratory investigation identified root cause(s), CAPA Record(s) shall be initiated and implemented as per **CQA SOP “Corrective Action and Preventative Action (CAPA)”.**

6.5.11.2 CAPA initiation is mandatory except under the following conditions:

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

6.5.11.2.2 CAPA is not needed based on justifiable parameters – in such a case, **"No CAPA Required"** justification shall be provided.

6.5.11.3 Additionally, Re-test shall be conducted to confirm the investigation findings, where applicable.

6.5.12 Re-Test Plan and Reporting of Results:

6.5.12.1 Re-test shall be initiated by Microbiologist through Head QA approval to confirm the "Laboratory Error".

6.5.12.2 Supporting evidence in combination with other evidences that may be used to invalidate original results may include, but not limited to:

- Re-test results that do not confirm with the original result such as, when inadequate extraction/dilution of the samples observed.
- Material/Product Historical data of results.
- Determination that sample is not a representative sample of the product or material. A specimen template for Re-Test Report is given in **Annexure-V "Retest Summary Sheet".**

6.5.13 Microbiological Examination of Non-Sterile Products:

6.5.13.1 Re-testing shall be performed by two microbiologists, each in duplicate on fresh aliquot of products/material.

6.5.13.2 Microbiologist who had performed the original testing shall be preferably selected as one of the Microbiologist.

6.5.13.3 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 or product release.

6.5.13.4 The original test result shall be invalidated by Operating Manager (Micro) as per shown below;

INVALIDATED

Sign & date :

6.5.14 Bio-Assay:

6.5.14.1 Re-testing shall be performed by two Microbiologists, each in duplicate, on a fresh aliquot of products/material.

6.5.14.2 Microbiologist who had performed the original testing shall be preferably selected as one of the Microbiologist.

6.5.14.3 If the results of Re-Test meet the specification limits (individually), then the average re-test results shall be reported as final value for the material/product release. The original test result shall be invalidated.

6.5.15 Sterility Testing:

6.5.15.1 A Sterility test shall be repeated only when it can be demonstrated that the test was invalid for causes unrelated to the product/material being examined, restricted to one of the criteria as follows:

6.5.15.1.1 Data of the microbiological monitoring of the sterility testing facility (which includes personnel monitoring data) shows a fault.

6.5.15.1.2 Review of the testing procedure used during the test in question reveals a fault.

6.5.15.1.3 Microbial growth found in the negative controls.

6.5.15.1.4 After determination of the identity of the micro-organism isolated from the test, the growth of this species (or these species) shall be ascribed unequivocally to faults with respect to the Material/Product and/or the technique used in conducting the sterility test procedure.

Note: When conditions listed above apply, then the test shall be aborted prior to the completion of the incubation period.
If a stasis test is performed at the end of the test incubation period, failure of challenge microorganism to grow in this stasis test also invalidates the test.

6.5.15.2 If contamination is detected in the Re-test performed on the same number of test samples, the product does not comply with the test for sterility and the entire Material/Product shall be rejected.

6.5.15.3 If the results of Re-Test meet the specification limits (individually), then the initial results shall be invalidated and substituted with the average of the Re-Test results.

6.5.16 Bacterial Endotoxin Testing:

6.5.16.1 Re-testing shall be performed by two Microbiologists, each in duplicate, on a fresh aliquot of products/material

6.5.16.2 The Microbiologist performed the original testing shall be preferably selected as one of the Microbiologist.

6.5.16.3 If the results of Re-Test meet the specification limits (individually), then the initial results shall be invalidated and substituted with the average of the Re-Test results.

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

6.5.17 Conclusion and Batch Decision:

6.5.17.1 The Re-Test results of Microbiologists, both individual and average, meet the specifications the original OOS results shall be substituted with the average of the Re-test results.

6.5.17.2 The following details related to the batch decision shall be documented:

6.5.17.2.1 Investigation conclusion

6.5.17.2.2 Root cause summary

6.5.17.2.3 Justification for identification of impacted batches

6.5.17.2.4 Decision for batch disposition(s) for all impacted testing

6.5.17.3 The contract Giver/MAH/QP/Customer shall be informed through mail or fax before batch decision of material/products under the scope of the OOS result through RA shall be noticed with Phase – I Investigation report. (Wherever required).

6.5.17.4 If the Re-Test results do not meet the specification limit, a Phase II Full-Scale Investigation shall be initiated.

6.5.17.5 Sampling Error investigation and deviations occurring during transportation/storage shall be reviewed during phase II investigation.

6.5.17.6 If "Laboratory Error Not Found", OOS results shall be shared with the vendor for further investigation.

6.5.17.7 In case of confirmed raw material/packing material OOS, the material shall be rejected, and root cause/CAPA details shall be communicated/documented from the vendor's investigation report as per **CQA SOP, "Vendor Qualification".**

6.6 Phase II Investigation (Full-Scale OOS Investigation):

6.6.1 Full-scale investigation team shall be identified by Head QA from QA, QC, Microbiology, Production, R&D, Engineering, SME, etc. as appropriate.

6.6.2 The objective of Full scale OOS Investigation to identify the root cause(s) of the OOS result.

6.6.3 Full scale OOS Investigation shall include the following components at a minimum (Not limited to):

6.6.3.1 Shop Floor Investigation (Review of Production Process and Procedures).

6.6.3.2 For raw materials, this investigation shall be replaced with an investigation performed by the supplier/vendor.

6.6.3.3 Sampling Error Investigation (Check for possible error in Sampling / Handling / Storage of sample.)

6.6.3.4 QA Assessment (Review of product / material documents and validation data, Trends, Product History, Product Deviations, etc.).

6.6.3.5 Root Cause Analysis investigation shall be performed as per **CQA SOP "Root Cause Analysis"** and Risk Assessment shall be performed as per **CQA SOP "Quality Risk Management"** (if applicable).

6.6.4 Shop Floor Investigation:

6.6.4.1 The Investigation team shall conduct a Shop Floor Investigation as per format shown in **Annexure-VI "Shop Floor OOS Investigation Report" (Phase-II Full Scale Investigation)**, which includes a review of production processes and procedures.

6.6.4.2 During the Shop Floor Investigation, if "Process Error" found to be the "Assignable Cause", then impact shall be evaluated on other batches of the same products or similar products.

6.6.4.3 If an "Assignable Cause" for the OOS is not determined during the Shop Floor Investigation, then an extended/additional investigation is required and same shall be initiated by the Head QA through hypothesis study.

6.6.5 Sampling Error Investigation:

6.6.5.1 A Sampling Error Investigation shall be performed to determine the root cause of the OOS result as a part of the Full-Scale Investigation as per format shown in **Annexure–VII "Sampling Error Investigation".**

6.6.5.2 Based on the investigation Head QA shall be responsible for determining whether Sampling Error can be confirmed or not.

6.6.5.3 If sampling error established, a Re-Sampling Plan shall be prepared through Head QA approval as per **Annexure VII "Sampling Error Investigation".**

6.6.5.4 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?

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

6.6.5.6 Re-Sampling shall be performed by the same qualified personnel and methods used initially.

6.6.5.7 If the investigation determines that the initial sampling method was inherently inadequate, a new sampling method shall be developed, qualified and documented, and approved by the Head QA.

6.6.6 QA Assessment for sampling error investigation:

6.6.6.1 QA Assessment shall be performed by the Operating Manager QA to determine the root cause.

6.6.6.2 OOS Investigation report shall include a purpose, an action plan with results documented.

6.6.6.3 During QA Assessment, the Operating Manager QA shall evaluate the following (Not limited to);

- Production / Process documents.
- Review of product history.
- Review of product development and validation data.
- Review of trends.
- Review of product deviations, etc.

6.6.7 QA Review of Phase II - Full-Scale OOS Investigations:

6.6.7.1 Operating Manager QA shall review the OOS Report after completion of the Investigations, and the findings of the Investigation shall be interpreted to evaluate the root cause and decide the next course of action.

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

6.6.7.2.1 Assignable Root Cause found:

- If Assignable Root Cause found to be "Process Error" – In such a case, the batch decision shall be determined by Head QA based on investigation results as per step 6.5.12.2.

- If Assignable Root Cause is found to be "Sampling Error", in such a case, Re-Sampling and retesting shall be conducted as explained in above step of 6.6.5 "**Sampling Error Investigation**" and a Re-Test shall be conducted to confirm the root cause analysis.

6.6.7.2.2 Assignable Root Cause not found:

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

6.6.7.3 Re-Testing:

6.6.7.3.1 Upon completion of 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 per format shown in **Annexure-V "Retest Summary Sheet".**

6.6.7.3.2 Retesting shall be performed by two Microbiologist (the Microbiologist who originally performed the testing may be selected as one of the Microbiologist), 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).

6.6.7.3.3 In case of constraints to use the original sample for Re-Test, Re-Sampling shall be carried out through Head QA approval.

6.6.7.4 CAPA for Phase-II (Full Scale OOS Investigation):

6.6.7.4.1 CAPA initiation is mandatory except under the following conditions:

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

6.6.7.4.1.2 CAPA is not needed based on justifiable parameters– in such a case, a "No CAPA Required" justification shall be provided.

6.6.8 Conclusion of Phase-II Full-Scale OOS Investigation and Batch Decision:

6.6.8.1 Head QA shall review the "OOS Investigation Report" after completion and Re-Test (if performed). Investigation findings, including Re-Test results, shall be interpreted to determine the batch Decision.

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

6.6.8.3 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.

6.6.8.4 An impact assessment shall be performed to determine if there are other potentially impacted batches.

6.6.8.5 During Phase-II Investigation in case OOS is not due to the process error that which is not affecting the batch quality (i.e., the OOS root cause is due to a laboratory or sampling error).

6.6.8.6 The batch(es) shall be taken in decision for release providing the Retest results are within the specification limits.

6.6.9 For Inconclusive Investigation:

6.6.9.1 For inconclusive Phase II Full-Scale Investigations where investigation determines a root cause for the OOS test result, the Head QA shall plan for the Decision of batch for rejection. Unless supporting scientific rationale justified that, the OOS result does not affect the quality of the batch.

6.6.9.2 For invalidating an OOS, all retesting results shall be within the specification limit.

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

6.6.10 For Conclusive Investigation:

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

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

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

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

6.6.10.5 The impact of OOS result on other batches, ongoing stability studies, validated processing and testing procedures etc. shall be determine by Quality Control and Quality Assurance.

6.6.10.6 A complete investigation report shall be shared with respective party/QP/ MAH/ Contract giver.

6.6.10.7 Head QA shall review executed investigation to conclude the OOS.

6.6.10.8 Initial OOS result cannot be invalidated in favor of passing result, if no laboratory errors are identified in Phase I and Phase II investigation. All test results both passing and suspect, shall be reported and all data shall be considered in batch release decision.

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

6.6.10.10 Head-Quality control, Head-Production and Head-Quality Assurance shall evaluate the laboratory investigation, manufacturing process investigation to determine the batch quality.

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

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

6.6.10.13 Final Decision of the batch shall be reviewed and authorized by Head QA.

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

6.6.10.15 If the material is rejected through OOS, Head QA shall decide whether the material shall be returned or destroyed as per respective Plant SOP.

6.6.10.16 If the product is rejected through OOS, Head QA shall decide whether the Product shall be destroyed as per respective Plant SOP.

6.6.11 After the complete review of OOS investigation, further action taken and their effect on the preceding and succeeding batches, Quality Assurance shall close the OOS with signature and document the same in the format as shown in **Annexure-II "Out of Specification Log for Microbiology".**

6.6.12 Corrective Action and Preventive Action

6.6.12.1 Based on conclusion of OOS investigation outcome, Head QA and User department Head shall initiate the corrective and preventive action in order to prevent the OOS reoccurrence.

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

6.6.12.3 Document reference of CAPA No. shall be allotted in OOS investigation report.

6.6.12.4 In case CAPA is not required as a remedial action is sufficient to address non-conformance, describe in details of remedial action taken and document a justification for not logging CAPA in the OOS investigation report.

6.6.13 OOS Observed in Case of Stability Study Analysis:

6.6.13.1 If an OOS result is obtained for such samples, an OOS investigation shall be initiated and Laboratory Investigation shall be performed.

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

6.6.13.3 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.

6.6.13.4 Product Recall procedures shall be performed as per **CQA SOP "Product Recall".**

6.6.13.5 If an OOS result is obtained for a stability sample of a batch(s) distributed in the market Field Alert Report (FAR) shall be reported as per **CQA SOP "Stability Study Policy.**

6.7 Reporting Test Results:

6.7.1 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.

6.7.2 An example of this would be taking the average of two or more Endotoxin analysis from the same sample vial, or averaging the result of two or more sample preparations. This can result in a more accurate result (in case of kinetic method).

6.8 Impact Assessment:

6.8.1 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.

6.9 Time Frames:

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

6.10 Decision of Product:

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

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

6.10.3 At conclusion of investigation, Head QA dispositions impacted product, i.e. release, reject, destroy etc. indicate final decision on the OOS investigation report.

6.10.4 For Out of specification investigation flow chart refer as per format shown in **Annexure-VIII "Decision Tree for Failure Investigation".**

6.11 Trending of OOS Test Results:

6.11.1 Prepare the trends of OOS on monthly basis by QA with Bar / Pie chart for better understanding to identify contributory factor causing OOS test results i.e. Microbiologist, Instrument, Product/Material, Inconclusive for review and recommendation as per format shown in **Annexure–IX "Trending of OOS Data".**

7.0 ANNEXURES:

ANNEXURE No.	TITLE OF ANNEXURE	FORMAT No.
Annexure-I	OOS Intimation Form	
Annexure-II	OOS Investigation Log for Microbiology	
Annexure-III	Checklist for Laboratory Assessment (Phase I Investigation)	
Annexure-IV	Extension form for OOS Investigation	
Annexure-V	Retest Summary Sheet	
Annexure-VI	Shop Floor OOS Investigation Report (Phase II Full Scale Investigation)	
Annexure-VII	Sampling Error Investigation	
Annexure-VIII	Decision Tree for Failure Investigation	
Annexure-IX	Trending of OOS Data	

8.0 DISTRIBUTION:

- Controlled Copy No. 01 Corporate Quality Assurance
- Controlled Copy No. 02 Quality Assurance
- Controlled Copy No. 03 Quality Assurance Department, Central Warehouse & Central Stability

9.0 REFERENCES:

- Guidance for Industry, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, Oct-2006.
- MHRA Out of Specification Investigation – 2013.
- WHO: Good Practices for National Pharmaceutical Control Laboratories.

10.0 REVISION HISTORY:

CHANGE HISTORY LOG

Revision No.	Change Control No.	Details of Changes	Reason for Changes	Effective Date	Updated By

STANDARD OPERATING PROCEDURE	
Department: Quality Assurance	**SOP No.:**
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ANNEXURE-I

OOS INTIMATION FORM

LOGO	***X-----** **LOCATION **QUALITY ASSURANCE**	
Date:		
Name of Product / Material:		
Batch No. / A.R. No.:		
Product Type (Put √ Mark): (In-process / Validation / Semi-Finished / Finished / Stability / RM / PM)		
Test		
1.	**Date of Analysis**	
2.	**Initiation Date**	
3.	**Due Date of OOS closure**	
4.	**Analyst Name**	
5.	**Standard Test Procedure/Monograph/Compendia**	
6.	**Control No. (Worksheet Sheet No.)**	
7.	**Specification Limit**	
8.	**Out of Specification Initial Results**	
9.	**Breif Description of the Event:**	

Microbiologist (Sign & Date)	**Head QC (Sign & Date)**	**Head Production (Sign & Date)**	**Head QA (Sign & Date)**

***X= Plant Name (For Plant SOP's)**
**Location: It is the location of the plant and place.

ANNEXURE-II

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

STANDARD OPERATING PROCEDURE	
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LOGO	***X-----** **LOCATION **QUALITY ASSURANCE**

OOS INVESTIGATION LOG FOR MICROBIOLOGY

S. No	OOS No.	Product / Material Detail			OOS Description	OOS Initiated Date	OOS Logged By QA (Sign & Date)	OOS Closing Status	Reference CAPA No. (If Applicable)	OOS Valid / In Valid	Closed By QA (Sign & Date)
		Name	Batch No. / Lot No.	AR. No.							

***X: Plant Name (For Plant SOPs)**

**Location: It is the location of the plant and place.

PHARMA DEVILS

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ANNEXURE-III

LOGO	***X-----** **LOCATION **QUALITY ASSURANCE**
CHECKLIST FOR LABORATORY ASSESSMENT (PHASE I INVESTIGATION)	
OOS No.:	

I. Details of OOS :

Date			
Product / Material		Batch No.	
Product Type (Mark:√)	(In-process / Validation / Semi-Finished / Finished / Stability /RM / PM)		
Microbiologist		Test	

1.	Date of Analysis	
2.	Initiation Date	
3.	Microbiologist Name	
4.	Specification Limit	
5.	Standard Test Procedure / Monograph / Compendia	
6.	Control Number (Worksheet No.)	
7.	Out of Specification initial Results	
8.	Brief Description of the OOS:	

(To be filled by QA)
Sign & Date:

OOS No.:
Root Cause Analysis: Put "√" Mark Required ☐ Not Required ☐ Reference RCA No.:_____ Operating Manager QA (Sign & Date) Head QA (Sign & Date)

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

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Quality Risk Assessment:

Put "√" Mark

Required ☐ Not Required ☐

Reference QRA No.:_____

Operating Manager QA (Sign & Date)

Head QA (Sign & Date)

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. Microbiologist			
1.	Has the analysts been trained and when ?	□ Yes □ No □ NA	
2.	What is the previous error history?	□ 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	
OOS No.:			
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	
D. 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	
E. General Procedure			
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.	Were the equipment / instruments calibrated / qualified?	□ Yes □ No □ NA	
4.	Was the validity of method/reagents checked before use?	□ Yes □ No □ NA	
5.	Was the correct amount of sample used for test (sample volume / sample weight)?	□ Yes □ No □ NA	
6.	Was preparation of the sample performed correctly?	□ Yes □ No □ NA	
7.	Were proper dilutions made?	□ Yes □ No □ NA	
OOS No.:			
8.	Was the specified diluting fluid used?	□ Yes □ No □ NA	
9.	Was diluting fluid / media sterile and within specified hold time?	□ Yes □ No □ NA	
10.	Was correct amount of the diluting fluid used?	□ Yes □ No □ NA	
11.	Was the GPT done on the media successful?	□ Yes □ No □ NA	
12.	Was the sterility test on the media performed successfully?	□ 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 any unusual occurrences during sample processing, i.e., technique related or non technique related?	□ Yes □ No □ NA	
17.	Was the data interpreted correctly?	□ Yes □ No □ NA	
18.	Were there "technique related" issues in the test?	□ Yes □ No □ NA	
19.	Were there "non-technique" related issues in the test, e.g., Microbiologist/Analyst errors?	□ Yes □ No □ NA	

20.	Was the Incubation temperature/time as per approved procedure?	□ Yes □ No □ NA	
21.	Were the Pre-incubated/approved plates used for analysis?	□ Yes □ No □ NA	
22.	Was the volumetric pipette calibrated before use?	□ Yes □ No □ NA	
23.	Was the Laboratory temperature, Rh, and ΔP observation as per acceptance criteria?	□ Yes □ No □ NA	
24.	Were the Laboratory cleaning/sanitization and mopping procedures followed correctly?	□ Yes □ No □ NA	
25.	Did the Microbiologist/Analyst follow the correct Gowning Procedure?	□ Yes □ No □ NA	

OOS No.:

F. Test-Specific Requirements - Bacterial Endotoxin Test

1.	Was the Dry Heat Sterilizer calibrated / qualified?	□ Yes □ No □ NA	
2.	Was the Dry Heat Sterilizer temperature checked on a routine basis?	□ Yes □ No □ NA	
3.	Was the heating block calibrated and displaying correct temperature?	□ Yes □ No □ NA	
4.	Was the Reconstituted Lysate/Control Standard Endotoxin/Lal reagent water within the shelf-life?	□ Yes □ No □ NA	
5.	Was Limulus Amoebocyte Lysate/Control Standard Endotoxin/Lal Reagent water stored at correct temperature?	□ Yes □ No □ NA	
6.	Were the results of the product positive control, negative control as per the acceptance criteria?	□ Yes □ No □ NA	
7.	Was the test result for confirmation of Labeled Lysate Sensitivity within the Acceptance Criteria?	□ Yes □ No □ NA	
8.	Was the depyrogenated glassware used in the preparation of samples/reagents/media?	□ Yes □ No □ NA	
9.	Were the calculations correct in case of KTA analysis?	□ Yes □ No □ NA	

G. Test-Specific Requirements – Bio-Assay

1.	Was the Zone Reader/ Vernier Caliper calibrated?	□ Yes □ No □ NA	
2.	Was there any error in the preparation, handling, and storage of samples?	□ Yes □ No □ NA	

3.	Were the culture identity, performance, and passage number meeting the requirements?	□ Yes □ No □ NA	
H. Test-Specific Requirements – Sterility Test			
1.	Was the manometer reading of the LAF within acceptance criteria?	□ Yes □ No □ NA	
OOS No.:			
2.	Was the growth promoting test results of the media used in test and negative control as per acceptance criteria?	□ Yes □ No □ NA	
3.	Were the samples containers dried after sterilization?	□ Yes □ No □ NA	
4.	Were the glassware/media/garments, etc., sterilized as per validated sterilization cycle?	□ Yes □ No □ NA	
5.	Were the components used in the preparation of samples/reagents/media sterilized?	□ Yes □ No □ NA	
6.	Was the sterility testing facility microbial monitoring data (including personnel monitoring data) during the test period adequate?	□ Yes □ No □ NA	
7.	Were the results of the product positive control, negative control as per acceptance criteria?	□ Yes □ No □ NA	
I. Test-Specific Requirements – Microbiological Examination of Non-Sterile Products			
1.	Was the media sterilized as per validated sterilization cycle?	□ Yes □ No □ NA	
2.	Were the samples incubated at correct temperature as stated in the procedure?	□ Yes □ No □ NA	
3.	Was the Differential pressure/manometer reading of the LAF within acceptance criteria?	□ Yes □ No □ NA	
4.	Was the Differential pressure of the Dynamic Pass Box within acceptance criteria?	□ Yes □ No □ NA	
5.	Was the Microbial Environmental monitoring of LAF count/Laboratory area count observation as per acceptance criteria?	□ Yes □ No □ NA	
6.	Was the used culture media pH observation as per acceptance criteria?	□ Yes □ No □ NA	
7.	Were the culture identity, performance, and passage number meeting the requirements?	□ Yes □ No □ NA	
OOS No.:			
8.	Were the previous trend compared, if any	□ Yes □ No □ NA	

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	excursions observed beyond limits level in the recent past?		
9.	Were the results of GPT on the media used, incubation conditions, etc., adequate?	□ Yes □ No □ NA	
10.	Confirm if sampling tools used for sampling were sterilized?	□ Yes □ No □ NA	
J. 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	
K. 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.	Was the correct amount used for test?	□ Yes □ No □ NA	
5.	Was preparation of the sample performed correctly?	□ Yes □ No □ NA	
6.	Were proper dilutions made?	□ Yes □ No □ NA	
7.	Was the specified diluting fluid used?	□ Yes □ No □ NA	
8.	Did the diluting fluid pass the sterility test?	□ Yes □ No □ NA	
9.	Was the correct amount of the diluting fluid used?	□ Yes □ No □ NA	
10.	Was the media successfully growth promoted?	□ Yes □ No □ NA	
11.	Was the media successfully sterilized ?	□ Yes □ No □ NA	
12.	Was the media used within the specified expiration date?	□ Yes □ No □ NA	
OOS No.:			
13.	Was the correct media used for the test?	□ Yes □ No □ NA	
14.	Did negative controls yield the expected results?	□ Yes □ No □ NA	
15.	Were there any unusual occurrences during processing, i.e. technique related or non-technique related?	□ Yes □ No □ NA	
16.	Was the data interpreted correctly?	□ Yes □ No □ NA	
17.	Were there techniques related issues in the test?	□ Yes □ No □ NA	

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

L. Any other observations:

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	Temperature		Diffrential pressure	
	Relative Humidity		Non viable monitoring count	

OOS No.:

Microbiologist training & Qualification details	Microbiologist Name		Microbiologist Qualification done on	
	Analyst Qualification Due on		Training status of Microbiologist	
	Health status of Microbiologist			

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			

Filtration unit	Sterilization Parameters	□ Complies □ Not Complies	Steam Sterilizer Inst. ID	

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	Validation Done on		Validation Due on	
	Date of sterilization		Load No.	
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.	
Review of EM trends & EM condition data in testing area for last 3 months for the following parameters	Date of sterilization Microbial Monitoring Trends	□ Complies □ Not Complies	Load No. Temperature Monitoring data	□ Complies □ Not Complies
	% relative Humidity Data	□ Complies □ Not Complies	Pressure differential data	□ Complies □ Not Complies

OOS No.:				
Intervention during testing, any abnormality or Incidence				
Any Deviation during testing				
Test History of the affected product				
Assignable cause found / Not found				
Result of repeat test incase of assignable cause found	Date of Resample		Sampled by	
	Sample Quantity		Retested by	
	Result of Reanalysis			
Conclusion / Recommendations				

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Error in the laboratory analysis:

□ Yes □ 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.:

Operating Manager (Micro)

Name :_____Sign:_____Date_____

Head-QC

Name :_____Sign:_____Date_____

Head QA

Name :_____Sign:_____Date_____

***X= Plant Name (For Plant SOP's)**

**Location: It is the location of the plant and place.

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ANNEXURE-IV

LOGO	***X-----** **LOCATION **QUALITY ASSURANCE**
EXTENSION FORM FOR OOS INVESTIGATION	
OOS No.:	
Product Name:	**Batch No.:**
Date of Analysis:	**Analysed By:**
OOS Reporting Date:	
Detail of OOS:	
Reason for Extension:	
Justification for Extension of Investigation: **Responsible person:** **Proposed date of completion of Investigation:** **Prepared By:** **Name:** **Sign:** **Date:**	
QA Evaluation with (Impact Assessment): **Name:** **Sign:** **Date:**	
Approved By: **(Head QA)** **Name:** **Sign:** **Date:**	

***X= Plant Name (For Plant SOPs)**

**Location: It is the location of the plant and place.

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ANNEXURE-V

LOGO ***X-----**
**LOCATION
QUALITY ASSURANCE

RETEST SUMMARY SHEET

OOS No. :
Product:
Batch No. :
Specification No.:
Test:
Limit:

Date	Microbiologist/ Analyst Name	Initial Results	Repeat Analysis Results	
			Microbiologist (I) Name:	Microbiologist (II) Name:
Average of Individual Microbiologist				
Average of Two Microbiologist				

Summary & Conclusion:

Operating Manager (Micro) **Head QC** **Head QA**
(Sign & Date) **(Sign & Date)** **(Sign & Date)**

***X= Plant Name (For Plant SOP's)**
**Location: It is the location of the plant and place.

PHARMA DEVILS
QUALITY ASSURANCE DEPARTMENT

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ANNEXURE-VI

LOGO	***X-----** **LOCATION **QUALITY ASSURANCE**
SHOP FLOOR OOS INVETIGATION REPORT (PHASE II FULL SCALE INVESTIGATION)	
OOS No.:	

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

1.	Product / Material Name		Mfg. Date	
	Date of Testing		Exp. Date	
	Batch No.		OOS Observation on	
	A.R. No.		Final Date of Observation	
2.	**Sampling Details (if applicable)**			
	Sample done by		Sampling done on	
	Any Abnormal observation/ Incidence/ Deviation during sampling	□ Complies □ Not Complies	Training and Qualification 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 Area in-charge	□ Complies □ Not Complies
3.	Conclusion			
4.	**Root Cause Analysis:** Put "√" Mark Required ☐ Not Required ☐ Reference RCA No.: Operating Manager QA (Sign & Date) Head QA (Sign & Date)			
OOS No.:				
5.	**Quality Risk Assessment:** Put "√" Mark Required ☐ Not Required ☐ Reference QRA No.:_____ Operating Manager QA (Sign & Date) Head QA (Sign & Date)			
6.	Manufacturing details	**Area**		**Activity**

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		Temperature		RH		
		Power failure (Number & Duration)		Unusual events / Intervention (if any)		
		Deviation (if any)				
7.	Cleaning & Sanitization records of the equipment/ Instruments used	Disinfectant used		Cleaning Done by		
		Dilution		Cleaning Checked by		
		Prepared by				

8.	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

9.	Review of EM monitoring trends & environment condition data for last 3 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
		ΔP	□ Complies □ Not Complies		
10.	Training of the persons involved	□ Complies □ Not Complies		Utility qualification details	□ Complies □ Not Complies
11.	Review of BPCR	□ Complies	□ Not Complies	Entry / Exit Procedure	□ Complies □ Not complies

OOS No.:

	Check Point	**Recommendation**	**Observation**
12.	Input Material	Input material (RM and PM) shall be checked as per prescribed process (i.e. as per bill of material)	
13.	Vendor source	RM and PM shall be used as per approved vendor list.	
14.	Packing container for sampling	Sample shall be collected in clean and dry, Sterile/ de-pyrozenation glass bottle.	
15.	Manufacturing Process	Manufacturing Process shall be executed as per approved BPCR	
16.	Cleaning and Sanitation of instrument and equipment in aseptic area	Cleaning and Sanitation procedure shall be validated	
17.	Fumigation frequency	Fumigation activity shall be performed as per pre-approved scheduled for manufacturing	

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		area.	
18.	Preventive maintenance program	The preventive maintenance program shall be available for the checking process equipments (i.e. Mobile LAF, vial sealing and capping LAF etc.)	
19.	Area and LAF	Differential pressure and velocity shall be within limit as per GMP requirements before Plate exposing.	
20.	AHU	AHU Shall be validated	
21.	DHS/Tunnel/Autoclave Sterilization Temperature and Time		
22.	Manufacturing area Personnel for aseptic area	Personnel shall be trained to perform their respective jobs in aseptic manufacturing area manner.	
23.	Personnel hygiene	There is a personnel monitoring program available for checking the hygiene level of Personnel who enters in the aseptic areas	
OOS No.:			
24.	Aseptic area gowns	Washing and sterilization of the aseptic area gowns shall be done as per approved procedure.	
25.	Breakdown record	Each breakdown shall be record with risk evaluation	
26.	Personnel Qualification	Personnel Qualification of all the Concerned personnel.	
27.	Past deviations, problems or changes can provide a clues on indication of the origin of problem		
28.	Out come of the investigation		
29.	Corrective Action and Preventive action (Mentioned CAPA taken, in brief also mention CAPA reference No.)		
30.	Conclusion		

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

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Investigation carried out by:

Head Production : Name _____ (Sign & Date)_____

Head Engineering : Name _____ (Sign & Date)_____

Operating Manager : Name _____ (Sign & Date)_____

(Micro)

Head QC : Name _____ (Sign & Date)_____

Head QA : Name _____ (Sign & Date)_____

***X= Plant Name (For Plant SOPs)**

**Location: It is the location of the plant and place.

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ANNEXURE-VII

LOGO	***X----- **LOCATION **QUALITY ASSURANCE**
SAMPLING ERROR INVESTIGATION	
OOS No.:	

OOS Details:

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

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 Materials	
7.	Natute of sample (Hygroscopic/light sensitive)	
8.	Is sample stored under prescribed condition	
9.	Any Spillage notified	
10.	Any contamination / Possibility of contamination	
11.	Silica sachet part of packaging configuration Yes/No, if Yes, condition of silica Sachet.	
12.	Is sealing condition of primary container proper.	
13.	Is sealing condition of primary container proper	

14.	Any deviation from recommended packing condition as per Protocol/Specification Yes/No, if Yes, Specify	

Summary of findings:

Prepared By:
Operating Manager (Micro):
Name: **Sign:** **Date:**

Review Comments:

Head QC
Name: **Sign:** **Date:**

Approved By:
Head QA:
Name: **Sign:** **Date:**

***X= Plant Name (For Plant SOP's)**
**Location: It is the location of the plant and place.

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

STANDARD OPERATING PROCEDURE	
Department: Quality Assurance	**SOP No.:**
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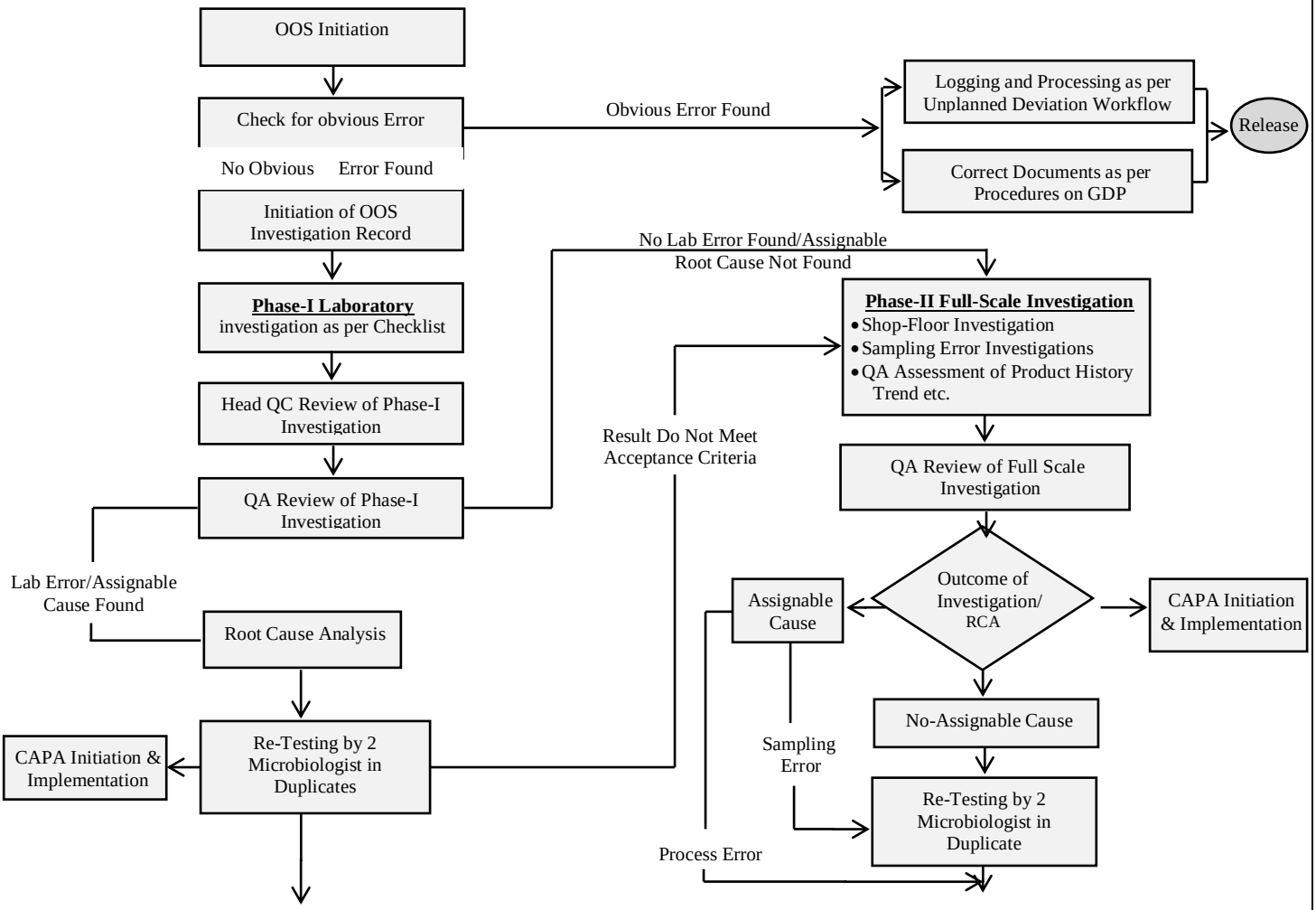
ANNEXURE-VIII

LOGO	*X----- **LOCATION **QUALITY ASSURANCE**

DECISION TREE FOR FAILURE INVESTIGATION



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QUALITY ASSURANCE DEPARTMENT

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Department: Quality Assurance	**SOP No.:**
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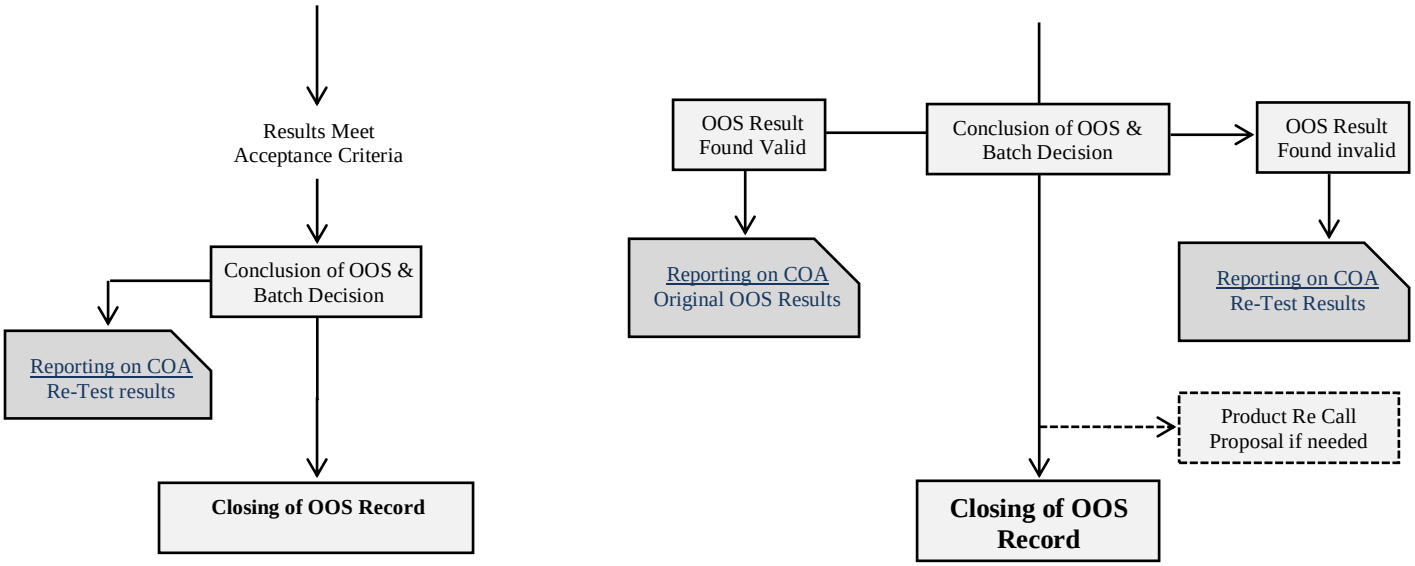

***X= Plant Name (For Plant SOP's)**

**Location: It is the location of the plant and place.

PHARMA DEVILS
QUALITY ASSURANCE DEPARTMENT

STANDARD OPERATING PROCEDURE	
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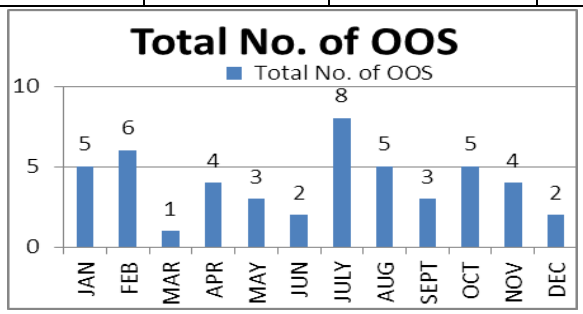
ANNEXURE-IX

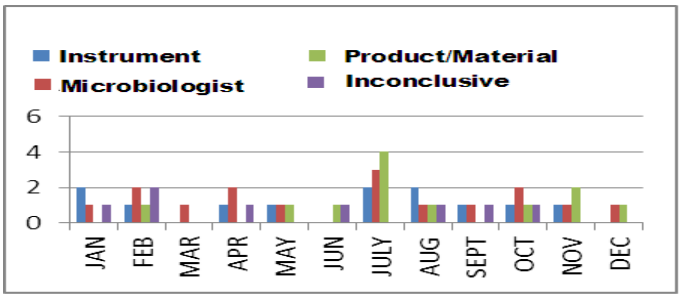
LOGO	*X----- **LOCATION QUALITY ASSURANCE DEPARTMENT
	TRENDING OF OOS DATA

Month: **Year:**

OOS Distribution

S. No.	Month	Total No. of OOS	Instrument	Microbiologist	Product/Material	Inconclusive
Total						





Review and Comments:

Operating Manager QA
(Sign & Date)

Head QA
(Sign & Date)

***X= Plant Name (For Plant SOP's)**
**Location: It is the location of the plant and place