PHARMA DEVILS

MICROBIOLOGY DEPARTMENT

STANDARD OPERATING PROCEDURE	
Department: Microbiology	**SOP No.:**
Title: Sterility Failure Investigation, Corrective and Preventive Action	**Effective Date:**
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1.0 OBJECTIVE

1.1 To lay down the Procedure for Sterility failure investigation, Corrective and Preventive Action (CAPA).

2.0 SCOPE

2.1 This procedure is applicable for Sterility failure Investigation, corrective and preventive Action (CAPA) for Microbiology department.

3.0 RESPONSIBILITY

3.1 Microbiologist shall be responsible for intimation of failures.

3.2 Investigation team comprising of members from quality control, Production & quality assurance shall investigate the failure.

4.0 ACCOUNTABILITY

4.1 Head Microbiology

5.0 EHS CONSIDERATIONS

5.1 NA.

6.0 PROCEDURE

6.1 Sterility failure shall be preliminarily investigated to find out the cause.

6.2 Whenever a sterility failure is observed, the observer shall be record the result in sterility test report and inform to In-charge/Head–Microbiology.

6.3 In charge/Head-Microbiology shall intimate the report to Head-QA through Head-QC as per Format.

6.4 Head-QA shall send a sterility failure investigation notification to Head- production as per Format.

6.5 The production activities shall be stopped till the clearance given by the Head-QA.

6.6 The copy of notification shall also be sent to Head-Plant.

6.7 Head-Microbiology shall investigate the sterility failure.

6.8 Investigation shall be carried out in two phases as per the checklist mentioned as Format.

6.9 Phase-1 includes lab investigation and phase-2 includes out of lab investigation i.e. manufacturing areas.

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6.10 **Phase-1 investigation (Lab investigation)**

6.10.1 The lab investigation shall include the review of media preparation and sterilization records, review of GPT/sterility records of the media, sterilization equipment records, environmental monitoring records, training and qualification records of the analyst, review of testing procedures and environmental monitoring procedures, equipment and or instrument qualification and validity status, testing area qualification and validity status, HVAC records etc. The investigation shall also include review of testing data for at least past six months.

6.10.2 The lab investigation report shall be evaluated by Head-QC and submitted to Head–QA.

6.10.3 Head-QA shall take the decision to retest or reject the batch based on the report.

6.10.4 Head-QA shall take the decision considering criteria mentioned below.

6.10.5 Criteria to be considered:

6.10.5.1 Sterility test failure is due to lab error (invalid test) - Repeat the test with same quantity of retention sample.

6.10.5.2 No error found in the lab conditions – Reject the batch and recommend for Phase-2 investigation.

6.10.6 Head-QA shall propose Corrective and Preventive actions to be taken by In-charge/Head-Microbiology in case of lab error.

6.10.7 In-charge/Head-Microbiology shall implement the Corrective and Preventive actions. Head-QC shall review the actions and propose further improvement if require.

6.10.8 After completion of necessary actions, Head-QA shall give the clearance to re-start the testing activities.

6.10.9 Once the actions approved, the sterility test shall be repeated with retention sample.

6.10.10 Batch shall be rejected if repeat test fails the sterility and Head-QA shall recommend for Phase-2 investigation.

6.10.11 Head-QA shall also recommend for Phase-2 investigation, if Phase-1 investigation doesn't show any lab error.

6.11 **Phase-2 investigation (Out of Lab investigation i.e. Manufacturing area)**

6.11.1 Phase-2 investigation shall also be performed by Head QA along with Head Engineering, Head Production & In charge/Head-Microbiology.

6.11.2 This phase of investigation shall include review of area maintenance records, environmental monitoring records, cleaning and sanitation records, the inherent physical or operational parameters such as changes in environmental temperature and relative humidity, the training qualification status of personnel involved in the manufacturing, Nitrogen testing report, equipment and or instrument qualification and validity status, review of utility documents like HVAC, compressed gases, water system etc., review of process simulation (media fill) data etc.

6.11.3 This investigation shall also include review of historical data of the environmental monitoring and products manufactured at least from last process simulation date or six months whichever is greater.

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6.11.4 After investigation report shall be evaluated by Head-QC and put his comments on the investigation check list.

6.11.5 Based on the comments given by Head-QC, Head-QA shall propose Corrective and Preventive actions to be taken by Head-Production.

6.11.6 Head-Production shall implement the Corrective and Preventive actions.

6.11.7 In-charge/Head-Microbiology shall check the Corrective and Preventive actions. Head-QC shall review the actions and propose further improvement if require.

6.11.8 After completion of necessary actions, Head-QA shall give the clearance to re-start the production activities.

6.11.9 Some of the actions, which may include in the corrective and preventive actions are:

6.11.9.1 Reinforcement of training of personnel to emphasize the microbial control of the aseptic processing area / Sterility testing area.

6.11.9.2 Additional environmental monitoring at increased frequency.

6.11.9.3 Additional cleaning and sanitation.

6.11.9.4 Additional product testing.

6.11.9.5 Increased vigilance and regulation of personnel activities.

6.11.9.6 Re-qualification of the equipments / instruments / areas / Utilities.

6.11.9.7 Re-qualification of process by simulation (Media fill) etc.

6.11.10 All the batches manufactured, after the batch which fails sterility, shall be kept on hold and shall be rejected, if the investigation shows any fault which fail the product sterility.

6.11.11 All the batches manufactured, before the batch which fails sterility, shall also be kept on hold and shall be rejected if the investigation shows any reason which may fail the products manufactured in the past. If the suspected batches already dispatched in to the market, those batches shall be recalled.

6.11.12 If, the investigation concludes the release of batch, all other batches which kept on hold shall also be released based on their sterility test status.

6.11.13 Sterility failed batches shall not be re-processed and shall be disposed.

6.11.14 In the case of raw material sterility failure, the batch shall be rejected if phase-1 investigation doesn't show any fault.

7.0 DEFINITIONS AND ABBREVIATIONS

7.1 CRF No. :Change Request number

7.2 HVAC:Heating Ventilation & Air Conditioning

7.3 QC : Quality Control

7.4 QA : Quality Assurance

8.0 REFERENCE

8.1 NA.

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9.0 ANNEXURES

9.1	Annexure I-	:	Intimation of Sterility failure
9.2	Annexure II-	:	Sterility Failure Investigation Notification
9.3	Annexure II-	:	Investigation of Sterility Failure, Corrective and Preventive Action

10.0 DISTRIBUTION DETAILS

10.1 Controlled copy of this SOP shall be distributed to Quality Assurance and Microbiology.

11.0 REVISION HISTORY

Supersedes SOP No.	Change Control No.	Reason for revision	Effective date

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Annexure I
INTIMATION OF STERILITY FAILURE

Date:

To:

Head-QA

Through:

Head-QC

Dear Sir,

It is informed that the following batch of the product is failing the sterility test.

Details of the Batch:

Name of the Product			
Type	RM / FP	QC A.R. No.	
Batch No.		Microbiology Ref. No.	
Quantity Tested		Method Used	
Tested by		GTP No.	
Tested On		Growth observed On	

Yours Sincerely

(Head-Microbiology)

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Annexure II
STERILITY FAILURE INVESTIGATION NOTIFICATION

Date:

To:

Head-Production

Cc:

Head-Plant

Dear Sir,

It is informed that the following batch of the product is failing the sterility test. So, stop the further production activities till the clearance given by QA department after investigation and necessary corrective and preventive actions. However continue the routine contamination control activities.

Details of the Batch:

Name of the Product			
Type		QC A.R. No.	
Batch No.		Microbiology Ref. No.	
Quantity Tested		Method Used	
Tested by		GTP No.	
Tested On		Growth observed On	

Yours Sincerely

(Head-QA)

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Annexure III
INVESTIGATION OF STERILITY FAILURE, CORRECTIVE AND PREVENTIVE ACTION

Name of the Product			
Type	RM / FP	QC A.R. No.	
Batch No.		Microbiology Ref. No.	
Quantity Tested		Method Used	
Tested by		GTP No.	
Tested On		Growth observed On	

Lab Investigation (Phase-1)

S.No.	Check	Observation
01	Name of the medium, in which the growth was observed	
02	Identify the microorganism (s), from the medium in which the growth was observed (Mention the name of identified microorganism)	
03	Check the 'Blank test' result	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
04	Check the viable particle monitoring records of environment and personnel	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
05	Check the media suitability (GPT and Sterility) test record	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
06	Check the sterilization record of the media used	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
07	Check the sterilization records of the aseptic area garments	

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S.No.	Check	Observation
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
08	Check the records of temperature and RH	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
09	Check the pressure differential records	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
10	Check the LAF operation record	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
11	Check the records of other batches which were tested simultaneously with failed batch	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
12	Check calibration status of all the instruments	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
13	Check the training and qualification report of analyst for his entry and work in sterility testing area	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
14	Check the training and qualification report of analyst for sterility test	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
15	Check the disinfectant preparation records of the sterility testing area	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
16	Check the fogging records of the sterility	

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S.No.	Check	Observation
	testing area	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
17	Check the validation status of HVAC	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
18	Check validation status of all the equipments like Autoclave, LAF, pass boxes etc.	
	a) Any abnormality observed?	Yes / No
	b) If yes, explain	
19	Verify the deviation logs	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
20	Verify change control logs	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	

Comments: _____

_____

Investigated by (Head-Microbiology):

Evaluated by (Head-QC):

Conclusion:

Recommended for Retest	
Batch Rejected and Recommended for Phase-2 investigation	

Put (√) mark in appropriate column

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Concluded by (Head-QA):

Proposed Corrective and Preventive actions (In case of Lab error):

_____

_____

_____

_____

Proposed by (Head-QA):

Completion of corrective and preventive actions

_____

_____

Remarks: _____

Implemented by (Head-Microbiology)	Reviewed by (Head-QC)	Approved by (Head-QA)

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Out Lab Investigation (Phase-2)

S.No.	Check	Observation
01	Check the number of persons involved in aseptic processing of the batch	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
02	Check the training and qualification reports of the persons for aseptic processing area entry and to work	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
03	Check the viable particle monitoring records of environment and personnel	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
04	Verify the reports of raw material used	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
05	Check the records of temperature and RH	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
06	Check the pressure differential records	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
07	Check the sterilization records of aseptic area garments	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
08	Check the cleaning and sterilization records of the machine parts	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
09	Check the sterilization records of the rubber stoppers	

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S.No.	Check	Observation
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
10	Check the depyrogenation records of the vials	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
11	Check the disinfection/sterilization records of the aluminum seals	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
12	Check the records of line clearance checks of the batch	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
13	Check the records of in process checks of the batch	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
14	Check the records of disinfectant preparation and storage	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
15	Check the records of cleaning and disinfection of the processing area	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
16	Check the fogging record of the area	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
17	Check the filter integrity records of the sterilization filters of compressed gases	
	a) Any abnormality observed?	Yes / No

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S.No.	Check	Observation
	b) If yes, details	
18	Check routine records and validation status of HVAC	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
19	Check routine records and Validation status of Water system	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
20	Check routine records and Validation status of compressed gases system	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
21	Check calibration status of all the instruments	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
22	Check validation status of all the equipments	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
23	Verify the deviation logs	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
24	Verify change control logs	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	
25	Verify raw material reports	
	a) Any abnormality observed?	Yes / No
	b) If yes, details	

Comments: _____

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Investigated by (Head-Microbiology):

Evaluated by (Head-QC):

Conclusion:

Concluded by (Head-QA):

Proposed Corrective and Preventive actions (in Production):

Proposed by (Head-QA):

Completion of corrective and preventive actions

Remarks:

Implemented by (Head- Production)	Checked by (Head-Microbiology)	Reviewed by (Head-QC)	Approved by (Head-QA)