PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

STANDARD OPERATING PROCEDURE	
Department: Quality Assurance	**SOP No.:**
Title: Aseptic Process Simulation (Media Fill Run)	**Effective Date:**
Supersedes: Nil	**Review Date:**
Issue Date:	**Page No.:**

1.0 OBJECTIVE:

To lay down a Procedure for Aseptic Process Simulation (Media Fill Run).

2.0 SCOPE:

This SOP is applicable for all Aseptic.

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.
Preparation of Media Fill Protocol
Training of all the personnel participating in the media fill Activity.
Planning of Media Fill activity as per schedule.
Evaluation of the Media Fill Activity and all other related data.
Preparation and review of the Media Fill Activity report.

Plant QA (Operating Manager) : Distribution (To concern Departments), Training and effective implementation of this SOP in all the applicable areas.

Head Production : Responsible for availability of all the Facilities / Equipment, execution of the media fill run.

Quality Control : Responsible for monitoring the Environment, conducting the related Microbiological analysis and providing support for other related parameters pertaining to the media fill run.

Production and Quality Control Department: Responsible for compiling the data related to their functional activity and providing the same in appropriate formats to the Quality Assurance Department.

Head Engineering : Simulate the maintenance jobs during media fill run.

4.0 ACCOUNTABILITY:

STANDARD OPERATING PROCEDURE	
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Head CQA : Approval, Authorization, ensure Training and Implementation of this SOP.

Head QA : To ensure Training and effective implementation of this SOP at plant.

Head Production : Effective implementation of this SOP at plant.

5.0 ABBREVIATIONS :

BET	Bacterial Endotoxin Test
CFU	Colony Forming Unit
CQA	Corporate Quality Assurance
GPT	Growth Promotion Test
HEPA	High Efficiency Particulate Matter
Ltd.	Limited
MGSM	Microbiological Growth Support Medium
min.	Minutes
MLT	Microbial Limit Test
NMT	Not More Than
No.	Number
QA	Quality Assurance
QC	Quality Control
S. No.	Serial Number
SCDM	Soya Bean Casein Digest Medium
SOP	Standard Operating Procedure
USFDA	United State Food & Drug Administration
WFI	Water for Injection

6.0 PROCEDURE:

6.1 Definition(s):

6.1.1 **Media Fills:** Method of evaluating an aseptic process using a Microbial Growth Medium. (Media fills are understood to be synonymous to Simulated Product Fills, Broth Trials, Broth Fills etc.).

6.1.2 **Shift:** Scheduled periods of work or Production, usually less than 12 hours in Length, staffed by alternating groups of workers.

6.1.3 **Sterile:** Free of any viable organisms. (In practice, no such absolute statement regarding the absence of Microorganisms can be proven, see Sterilization.)

6.1.4 **Sterilization:** Validated Process used to render a product free of Viable Organisms.

Note: In a Sterilization Process, the nature of Microbiological Death of Reduction is described by an Exponential Function. Therefore, the number of Microorganisms

which survive a Sterilization Process can be expressed in terms of Probability. While the Probability may be reduced to a very low number, it can never be reduced to zero.

6.1.5 **Bioburden:** Total number of Viable Microorganisms on or in Pharmaceutical Product prior to Sterilization.

6.1.6 **Environmental Monitoring Programme:** Defined documented Programme which describes the routine particulate and Microbiological Monitoring of Processing and Manufacturing Areas, and includes a Corrective Action Plan when action levels are exceeded.

6.1.7 **Growth Promotion Test:** Test performed to demonstrate that Media will support Microbial Growth.

6.1.8 **Integral Container:** Any container that mechanically prohibits the transfer of environmental contaminants are called Integral container. For example all good vials which are properly sealed and free from sealing defect & cracks, shall be considered as Integral Vial.

6.1.9 **Non-Integral Container:** Any defects in the container that compromise the container closure is called non-integral.for example Damaged vials / leaked vials, major sealing defects vials which are considered physically fail in integrity during visual inspection activity are called as Non-Integral Vials.

6.2 Instructions & Precautions:

6.2.1 This SOP is applicable to the existing Sterile Product Filling Lines as well as newly installed / Re-commissioned Filling Lines at all respective Manufacturing Locations.

6.2.2 All the personnel involved in the Aseptic Process Simulation (Media Fill Run) shall be appropriately trained both in their job related activities and on the Aseptic Process Simulation (Media Fill Run) Protocol.

6.2.3 All Major Equipments used for Process, Facility and Utility shall be verified for their Performance Qualification and Calibration.

6.2.4 Throughout the media fill run Good Manufacturing Practices and aseptic techniques shall be followed.

6.2.5 No special precautions / care shall be taken while execution of the media fill exercise (All the steps / stages are to be performed as followed during normal Production Batches).

6.2.6 Precaution must be taken with respect to handling of media.

6.2.7 At any stage none of the filled unit shall be removed unless verified and authorised by QA.

6.2.8 The destruction of the left over media (Bulk) and of the filled units after inspection shall be done as per the respective SOP.

6.2.9 The media fill shall emulate the regular product fill situation in terms of equipment, processes, personnel involved and time taken for filling as well as for holding.

6.2.10 Where filling takes place over extended periods, i.e. longer than 24 hours (Worst Case Study), the process simulation test shall be extend over the whole of the standard filling period.

6.2.11 For process simulations, sterile filtered air shall be used instead of inert gases, Nitrogen Flushing / Purging shall not be done at any stage (irrespective of the normal product requirement) as the Inert Gas will prevent the growth of aerobic micro organisms also for breaking a vacuum.

6.2.12 Where anaerobes are detected in the Environmental Monitoring or Sterility Testing, the use of an Inert Gas shall be considered for a Process Simulation, as Inert Gas is supporting the growth of Anaerobes.

6.2.13 Where a Liquid Nutrient Medium is used it shall be prepared in a similar manner to the product. The medium shall be dissolved in Water for Injection in a standard manufacturing vessel. If heat is required to dissolve it then only minimal heat shall be used.

6.2.14 The pH of the medium shall be measured and, if necessary, adjusted to bring it into the required range. The medium shall be aseptically filtered into an aseptic holding vessel using the normal production filter and processing procedure. In justified cases it may be also acceptable to sterilize the media.

6.2.15 All Aseptic Holding Vessels shall be covered by a Process Simulation Test on a regular basis unless a Validated, Pressure Hold or Vacuum Hold Test is routinely performed.

6.3 Process Simulation Test Procedure:

6.3.1 Flow chart for Process Simulation Study (Media Fill Activity) of various Dosages Forms is provided in the Following Annexure:

- Media Fill Process Flow for Large Volume Parenteral **(Annexure-I).**
- Media Fill Process Flow for Eye / Ear Drops **(Annexure-II).**
- Media Fill Process Flow for Dry Powder Injection **(Annexure-III).**
- Media Fill Process Flow for Ampoule Line **(Annexure-IV).**
- Media Fill Process Flow for Vial Line **(Annexure-V).**
- Media Fill Process Flow for Three Piece Line **(Annexure-VI).**

- ❖ Media Fill Process Flow for Pre-Filled Syringe **(Annexure-VII).**
- ❖ Media Fill Process Flow for Lyophilizer Vial Line **(Annexure-VIII).**

6.4 Process Simulation Test Conditions:

6.4.1 Test Performance:

6.4.1.1 The Process Simulation Test shall be followed as closely as possible the routine aseptic Manufacturing Process and include all critical subsequent Manufacturing Steps.

6.4.1.2 Any person entering in aseptic area shall be "Personal Qualified".

6.4.1.3 All Equipment shall remain the same wherever practicable as for the routine process. Appropriate combinations of container size and opening as well as speed of the processing line shall be used (preferably at the extremes).

6.4.1.4 The Process Simulation Test shall represent a **"Worst Case"** situation and include all manipulations and interventions likely to be represented during a shift.

6.4.1.5 Worst case conditions are often thought to be the largest container with the widest mouth as it is exposed longer to the environment. However, there are exceptions to this and one of them is small ampoules run at the highest speed as the ampoules may be unstable and cause frequent jams thus necessitating frequent operator intervention.

6.4.1.6 Simulation tests shall be performed on different days and hours during the week and not only at the beginning of a work day.

6.4.1.7 If the same process is conducted in a separate clean room, this shall also be validated.

6.4.1.8 In order to find the possible source of contamination Video Tape or Photographs of Aseptic Fill and also number the individual Vials or segregate Vials in chronological order during incubation shall be made.

6.4.1.9 All personnel who enter the aseptic processing area, including technicians and maintenance personnel, shall participate in a media fill at least once per year as part of the Operator Qualification Process.

6.5 Selection of Media:

6.5.1 The Criteria for selection of Microbiological Growth Support Medium (MGSM) include: Low Selectivity, Clarity, Medium Concentration and Filterability.

6.5.2 **Ability to support growth of a wide range of microorganisms**:

6.5.2.1 The medium should have a low selectivity i.e. be capable of supporting growth of a wide range of microorganisms such as *Bacillus Subtilis*, *Staphylococcus Aureus*, *Candida Albicans*, *Aspergillus Brasiliensis* and Environmental Isolates.

6.5.3 Growth Promotion Test (GPT) to demonstrate that the medium supports recovery and growth of low numbers of microorganisms, i.e. 10-100 CFU/ unit.

6.5.4 Growth Promotion Testing of the media used in simulation studies to be carried out on completion of the incubation period to demonstrate the ability of the media to sustain growth if contamination is present. Growth should be demonstrated within 5 days at the same incubation temperature as used during the simulation test performance.

6.5.5 **Clarity:** The medium should be clear to allow for ease in observing turbidity.

6.5.6 **Medium Concentration:** Recommendations of the supplier shall be followed unless alternative concentrations are validated to deliver equal results.

6.5.7 **Filterability:** If a filter is used in the Aseptic Manufacturing Process, the medium should be capable of being filtered through the same grade as used in production.

6.5.8 Soya Bean Casein Digest Medium is used as Microbiological Growth Support Medium (MGSM) for Process Simulation Study.

6.5.9 The concentration of Soya Bean Casein Digest Medium (SCDM) is selected 3% w/v in Water for Injection on the basis of above selection parameters and Pre GPT Studies performed.

6.6 Selection of Process Simulation Powder / Diluent:

6.6.1 A Process Simulation Powder / Diluent is the material which enhances the Growth Promotion Properties of a Microbiological Growth Support Medium.

6.6.2 Various Process Simulation Powders / Diluents are available which can be used for Process Simulation Study (Media Fill Run) of Dry Powder Injection. e.g. Polyethylene Glycol, Lactose, Mannitol etc.

6.6.3 Lactose shall be used as Diluent for Microbiological Growth Support Medium (MGSM) i.e. Soya Bean Casein Digest Medium.

6.7 Re-Qualification Criteria:

6.7.1 Any major modification to any of the existing Equipment, System or Area/Facility after the Process Simulation Study (Media Fill), that may affect the quality of the product as intended, shall be documented through a Change Control Procedure and shall be subjected for Re-Qualification.

6.7.2 **The Re-Qualification shall be performed due to any of the following reasons:**

6.7.2.1 As per Requalification schedule / Frequency.

6.7.2.2 Any Major Modification to any of the existing Equipment, System or Area/ Facility.

6.7.2.3 Disinfectant change, Cleaning and Sterilization procedure change.

6.7.2.4 Major Maintenance.

6.7.2.5 In case of changes in process.

6.7.2.6 Exceeding an microbial action level.

6.8 Test Frequency:

6.8.1 The frequency of Periodic Validation for Process Simulation Study (Media Fill) shall be Once in Six Months (±30 days*) for existing system as per Validation Master Plan or as and when required as per **Point No. 6.7.**

6.8.2 ***If the Media Fill is planned after scheduled frequency, the same shall be documented through a Planned Deviation mentioning the reason for deviation.

6.9 Number of Runs:

6.9.1 The Production Line is initially qualified by conducting Individual Media Fills for at least Three Consecutive Separate Successful Runs to ensure that the results are consistent and meaningful as for Example New processes, new Equipment or after critical changes of Processes, Equipment or Environment as for example significant personnel changes (a new shift), Modifications in Equipment directly in contact with the product or modifications in the HVAC system.

6.9.2 For routine Semi-Annual Qualification / Re-Qualification conducted for each Production line, at least One Separate Successful Runs shall be performed to evaluate the State of Control of the Aseptic Process.

6.9.3 Exceeding an action level demands a re-validation. Depending on the result of the follow-up investigation this re-validation may require the inclusion of one to three satisfactory process simulation tests.

6.10 Duration of Runs:

6.10.1 The duration of Media Fill run shall be the time it takes to incorporate Aseptic Manipulations and Interventions, as well as appropriate consideration of duration of Actual Aseptic Processing Activity / Operation.

6.11 Size of Run:

6.11.1 The simulation run sizes shall be adequate to mimic commercial production conditions and accurately assess the potential for commercial batch contamination.

6.11.2 A acceptable starting point for run size shall be in the range of 5,000 to 10,000 units.

6.11.3 For operations with production sizes under 5,000, the number of media filled units shall be at least equal the maximum batch size made on the processing line.

6.12 Line Speed:

6.12.1 The media fill program should adequately address the range of line speeds employed during production.

6.12.2 Each media fill run should evaluate a single line speed, and the speed chosen should be justified.

6.12.3 For example, use of high line speed is appropriate in the evaluation of manufacturing Processes characterized by frequent interventions or a significant degree of manual manipulation.

6.12.4 Use of slow line speed is appropriate for evaluating manufacturing processes with prolonged exposure of the sterile drug product and containers/closures in the aseptic area.

6.12.5 Each Process Simulation Study (Media Fill) run shall evaluate a Single Line Speed.

- First Process Simulation Study (Media Fill) with Slow Line Speed,
- Second Process Simulation Study (Media Fill) with Optimum Line Speed and
- Third Process Simulation Study (Media Fill) with Fast Line Speed.

6.13 Fill Volume:

6.13.1 The Fill Volume of the containers shall be sufficient to enable contact of all the container-closure seal surfaces when the container is inverted and also sufficient to allow the detection of microbial growth.

6.13.2 Regardless of the actual fill volume selected, the process simulation test shall include a fill weight adjustment using methods identical to those employed during production.

6.14 Interventions (Worse Case Study):

6.14.1 Interventions shall be recorded in Media Fill Protocol / Report specifying the Types of Interventions, Duration of Intervention providing for consistent production practices and assessment of these practices during Media Fill.

6.14.2 The Filled units after different Interventions shall be kept separately for Incubation with Proper Status Label.

6.14.3 Aseptic Manipulation / Interventions:

6.14.3.1 Routine Interventions:

Routine Interventions are activities that are inherent parts of the Aseptic Process and integral parts of every batch. Typical Routine Interventions include:

- Aseptic Assembly of the Equipment before use;
- Initial Product Connection or Introduction;

- Start-up component supply or Introduction;
- Initial Fill Weight or Volume Adjustment
- Periodic Component Replenishment;
- Periodic Fill Weight or Volume Checking and Verification;
- Fill Weight or Volume Adjustment;
- Environmental Monitoring;
- Operator Breaks and Meals;
- Operator Shift Changes;
- Operator Fatigue
- Product Sampling;
- Filter Integrity Testing;
- Product Container Replacement;
- Component Change (different sizes);
- Fill-Volume Change;
- Any other interventional activity which is an integral part of the process.

6.14.3.2 Nonroutine Interventions:

6.14.3.2.1 Nonroutine interventions are activities that are predominantly corrective and may not be a part of every batch. Nonroutine interventions may not be necessary during the aseptic process; in practice such interventions are almost always required to correct some anomaly. Some common Nonroutine interventions involve:

- Stopper Misfeeds or Clumping;
- Fallen, Broken, or Jammed Containers;
- Defective Seals on Containers;
- Product Spillage or Leakage;
- Product Filter Change;
- Sensor Adjustments or Replacement;
- Filling Needle Replacement;
- Fill-pump Replacement;

- Stopper Bowl Changes;
- Timing Adjustments;
- Conveyor or Guide Rail Adjustments;
- Any other line malfunction requiring manual correction.

6.14.3.2.2 These interventions must be included in process simulations at a realistic frequency level.

6.14.3.2.3 Nonroutine interventions shall not be optional in simulations.

6.14.3.2.4 If operators do not practice Non-routine Interventions during simulations, the operators shall be unable to perform those interventions during actual aseptic production, schedule them as if they were integral to the process, at approximately the same frequency with which they occur during normal operations.

6.14.3.2.5 The operators shall perform the Non-routine intervention following the approved procedure as closely as possible.

6.14.3.2.6 The Media Fill observer (whose presence shall be strongly recommended during every process simulation) must ensure that nonroutine interventions are executed correctly.

6.14.4 Machine Breakdown activity for 15 minutes (Minor) based on recovery study.

6.14.5 Machine Breakdown activity for 60 minutes (Major) based on recovery study.

6.14.6 AHU of Filling Area OFF for 5 minutes.

6.14.7 Power Failure according to recovery study performed.

6.14.8 No. of Persons increased in Filling and Sealing area for 15 minutes during filling.

6.14.9 Filling Machine Speed Variations:

6.14.9.1 Fill speed, used for any container, shall be set at the low end of the filling range for the size container. If a higher speed results in the potential for greater interventions, then the speed shall be considered when selecting process simulation test parameters in the Validation Protocol.

6.15 Environmental Monitoring:

6.15.1 Media Fill shall be adequately representative of the conditions under which actual Manufacturing Operations are conducted. Following Environmental Conditions shall be monitored during Process Simulation (Media Fill):

6.15.2 Temperature, RH & Differential Pressure.

6.15.3 Active Air Sampling Before, During Filling and Sealing of Media Filled Units.

6.15.4 Passive Air Sampling (Settle Plate) Before, During Filling and Sealing of Media Filled Units.

6.15.5 Non Viable Particle Count of Filling and Sealing Area in Static Condition and Dynamic Condition (During Operation) once in a shift.

6.15.6 Microbiological monitoring of Walls and Floor after Filling and Sealing of Media Filled Units.

6.15.7 Microbiological Swab of Machine surface After Filling and Sealing of Media Filled Units.

6.15.8 Personal Monitoring by RODAC Plate & Finger Dab of all persons involved in Media Fill (after Media Fill) on every exit.

6.16 Incubation and Examination of Media-Filled Units:

6.16.1 Before Incubation, the Media Filled Units with the Microbiological Growth Support Medium shall be inverted to ensure that all surfaces including the Internal Surface of Container and Closure are thoroughly wet / rinse by the Media Solution. **All above specified integral Units shall be incubated after completion of visual inspection.**

6.16.2 The Containers shall not be completely filled with medium (NMT 70% of Unit Size) in order to provide sufficient oxygen for growth of obligate aerobes.

6.16.3 Media filled units shall be incubated under conditions adequate to detect microorganisms that might otherwise be difficult to culture.

6.16.4 Damaged Media filled units shall not be kept for incubation and shall be destroyed as per SOP for Destruction of Media

6.16.5 Incubation Temperature, Conditions and Observation:

6.16.5.1 Incubation Temperature for **Ist 7 days** suitable for **Fungal Growth: At 22.5 ^{0}C ± 2.5 ^{0}C**. Observation of Media filled unit shall be done on 7th day.

6.16.5.2 Incubation Temperature for **Next 7 days** suitable for **Bacterial Growth: At 32.5 ^{0}C ± 2.5^{0}C.** Observation of Media filled unit shall be done on 14th day. Record the visual inspection observation of media filled units in respective Media Fill BMR.

6.16.7 Incubated vials / ampoules shall be retained till obtaining post GPT results.

6.16.8 Destruction and incineration of Deactivated Sterilized bottles shall be done as per respective SOP.

6.16.9 Routine production shall be initiated after successful results of media fill.

6.17 Analytical Support:

6.17.1 Pre Growth Promotion Test (Pre GPT) of Microbiological Growth Support Medium (MGSM).

6.17.2 MLT Test & BET of WFI used for Media Preparation.

6.17.3 Bulk Solution Sampling for Bio burden before Filtration.

6.17.4 Bulk Solution Sampling after Aseptic Filtration for GPT, BET & Sterility Test.

6.17.5 Sterility Test & BET of Pre-Sterilized Units.

6.17.6 Leak Test.

6.17.7 GPT of Left over Media

6.18 Post Media Fill Cleaning of Area, Equipment and Containers:

6.18.1 Cleaning of Aseptic Area:

- Clean the Aseptic Area shall be performed after Media fill as per respective SOP.
- Wipe the Walls, Floor, and Machine Surfaces shall be performed after Media fill as per respective SOP.
- Take the Microbiological Swab of Walls, Floor, and Machine Surfaces.
- Perform the Environmental Monitoring (Active Air Sampling, Passive Air Sampling) for consecutive 03 days and observe the results.

6.18.2 Proceed for Commercial Production only, if no Microbiological Growth is observed.

6.19 Interpretation of Data and Acceptance Criteria:

6.19.1 After the Incubation Period of Media-Filled Containers, they shall be visually examined for Microbial Growth. Contaminated containers shall be examined for evidence of container / closure damage which might compromise the integrity of the packaging system. Damaged container shall not be included as failures (Positives) when evaluating results.

6.19.2 Each Media-Filled unit shall be examined for contamination by Qualified Microbiologist / Trained QA Person with appropriate Education, Training, and Experience in inspecting Media Filled Units for Microbiological Contamination. All suspected units identified during the examination shall be brought to the immediate attention of the Head QA.

6.19.3 The number of containers used for media fills should be sufficient to enable a valid evaluation. The target should be zero growth and the following should apply:

6.19.3.1 When filling fewer than 5000 units, no contaminated units should be detected.
One or more contaminated unit should results repeat Media fill following investigation.

6.19.3.2 When Filling 5,000 to 10,000 units:

- ❖ One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill following investigation.
- ❖ Two (2) contaminated units are considered cause for revalidation, following investigation.

When Filling more than 10,000 units:

- ❖ One (1) contaminated unit should result in an investigation;
- ❖ Two (2) contaminated units are considered cause for revalidation, following investigation.

6.19.4 For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that shall be investigated. Investigation of gross failures shall include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.

6.19.5 All contaminating microorganisms whether or not an alert or action limit has been exceeded shall be identified to at least genus and preferably species where practicable to determine the possible source of contamination.

6.19.6 If a process simulation tests fail then due account shall be taken of products filled between the last successful test and the test failure. Recording of any deviations during the simulation test is important to trace later on the exact cause and to evaluate the consequences. The investigation should identify batches that could be affected during this time period and the disposition of the affected batches shall be re-assessed.

6.20 Failure Investigation and Corrective Action:

6.20.1 A contaminated container shall be carefully examined for any breach in the integrity of the container system.

6.20.2 Damaged containers shall not be considered an evaluation (acceptance) of an aseptic processing capability of the process. However, a vial that is broken during incubation should be addressed.

6.20.3 All positives from integral containers shall be identified to at least genus and species whenever possible.

6.20.4 Identify the contaminant and compare the result to the database of the organisms most recently identified.

6.20.5 Processing records should be reviewed. Critical systems shall be reviewed and documented for changes.

6.20.6 Calibration records shall be checked.

6.20.7 All HEPA Filters in the Filling Area shall be inspected and decertified if warranted.

6.20.8 Personnel involved in the media fill shall be assessed for their trained and qualified.

6.20.9 Validation/Requalification and change control records shall be reviewed for any procedure or process changes.

6.20.10 A full risk analysis should be performed.

6.20.11 A media failure signals an underlying weakness of the system or the process.

6.20.12 The final investigation report should contain the following:

- A summary of the occurrence
- All systems investigated, not just the systems tied to the failure
- A conclusion as to the cause and supporting documentation
- Potential effect on previous batches since last media fill
- Corrective action
- Outcome of additional process simulation tests if they were performed
- Appropriate signatures

6.20.13 This investigation needs to be completed in a timely fashion. It may be necessary to issue an interim report.

6.20.14 Three consecutive successful process simulations are required to qualify a new or significantly revised change aseptic line or area. If there has been a failure on any process simulation without an assignable cause, one process simulation is required for re-qualification of an aseptic processing line.

6.20.15 Routine production activities shall be initiated after getting passing results of media fill.

6.20.16 Invalidation of a Media Fill:

6.20.16.1 A media fill can only be invalidated for reasons that would absolutely result in the discard of a Product Batch. These conditions must be filled out explicitly and the written justification for the media fill discard and the decision shall be made on the day of execution.

6.20.16.2 Under following condition Process Simulation is considered invalidated:

- Failure of Growth Promotion of media provided there are no positive units in the process simulation.
- Failure of physical conditions in the aseptic processing area (Power Outage, Pressurization Loss, HEPA Filter Failure).
- Failure of operators to follow proper procedures not permitted in normal production which would lead to the discontinuation of a batch and rejection of all vials filled to that point.

- Clear documentation of the event that caused the discontinuation shall be performed and maintained. Process simulations can be invalidated for any or all of the above reasons.

6.21 Batch Production & Control Record of Media Fill Activity shall be prepared by QA. Batch details shall be replaced by the Media Fill activity Details.

6.22 Media Fill Planner shall be prepared by Quality Assurance Department as per format shown in **Annexure-IX "Process Simulation Study (Media Fill) Planner"** and shall be checked by Operating Manager & approved By Head QA.

6.23 Execution Details shall be filled by Concerned Department Head & shall be verified by Head QA in format as shown in **Annexure-X "**Process Simulation Study (Media Fill) Execution Record"**.**

6.24 Failure investigation shall be carried out as per format shown in **Annexure-XI "Media Fill Failure Investigation Report"**.

7.0 ANNEXURES:

ANNEXURE No.	TITLE OF ANNEXURE	FORMAT No.
Annexure-I	Media Fill Process Flow for Large Volume Parenteral	
Annexure-II	Media Fill Process Flow for Eye / Ear Drops	
Annexure-III	Media Fill Process Flow for Dry Powder Injection	
Annexure-IV	Media Fill Process Flow for Ampoule Line	
Annexure-V	Media Fill Process Flow for Vial Line	
Annexure-VI	Media Fill Process Flow for Three Piece Line	
Annexure-VII	Media Fill Process Flow for Pre-Filled Syringe	
Annexure-VIII	Media Fill Process Flow for Lyophilizer Vial Line	
Annexure-IX	Process Simulation Study (Media Fill) Planner	
Annexure-X	Process Simulation Study (Media Fill) Execution Record	
Annexure-XI	Media Fill Failure Investigation Report	

8.0 DISTRIBUTION:

- Controlled Copy No. 01 Corporate Quality Assurance
- Master Copy Corporate Quality Assurance

9.0 REFERENCES:

- Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-Operation Scheme (PIC/S) PI 007-6, 1 January 2011 "**Validation of Aseptic Processes**".
- PDA Technical Monograph No.28 and 22.

- USFDA Guidelines for Sterile Drug Products Produced by Aseptic Processing Current Good Manufacturing Practices
- United State Pharmacopoeia 39
- WHO TRS 961; WHO Expert Committee on Specifications for Pharmaceutical Preparations, 2011
- National Sanitary Surveillance Agency (ANVISA-Brazil) Resolution - RDC No. 210, August 4, 2003

10.0 REVISION HISTORY:

CHANGE HISTORY LOG

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

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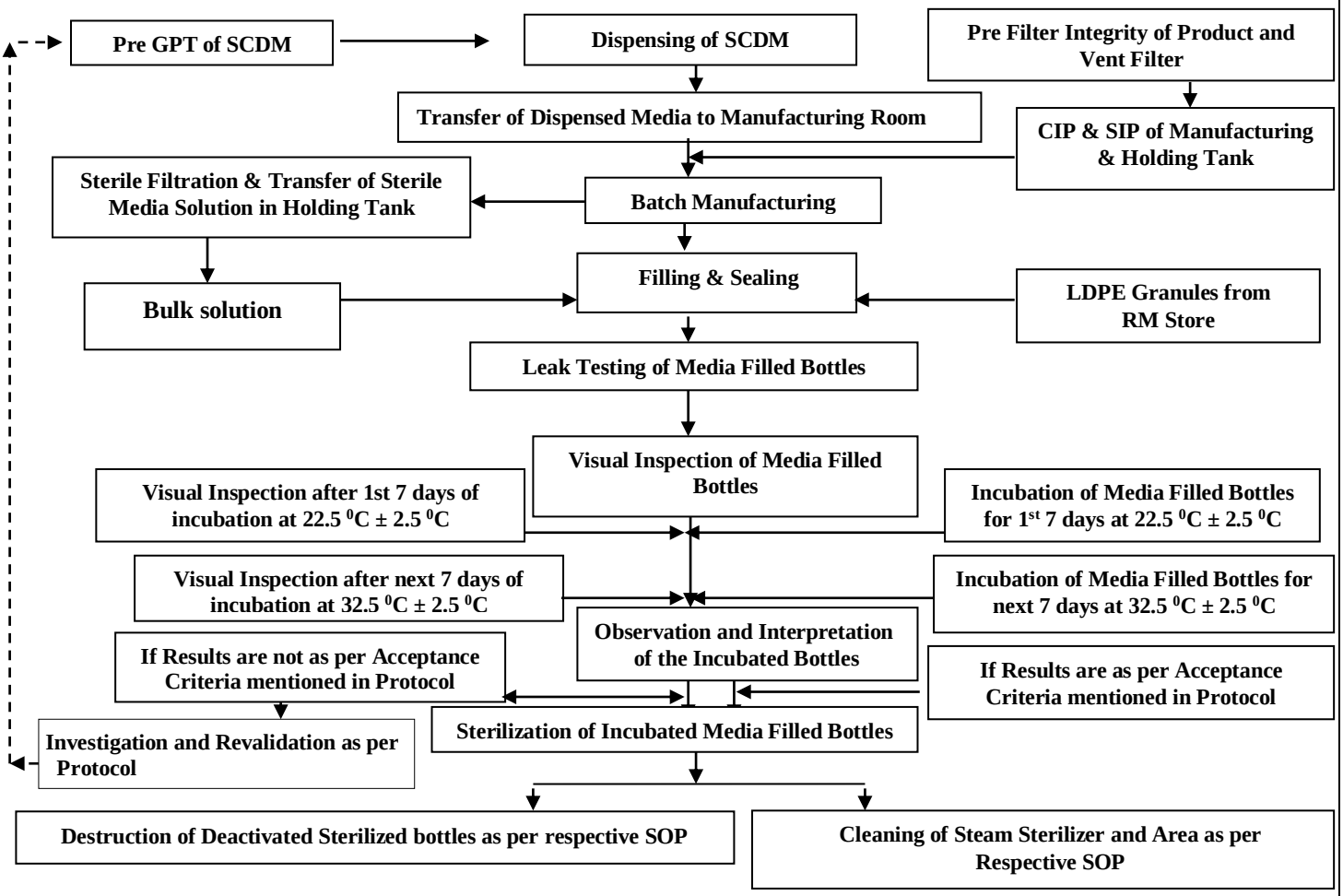
ANNEXURE-I

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

MEDIA FILL PROCESS FLOW FOR LARGE VOLUME PARENTERAL



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

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

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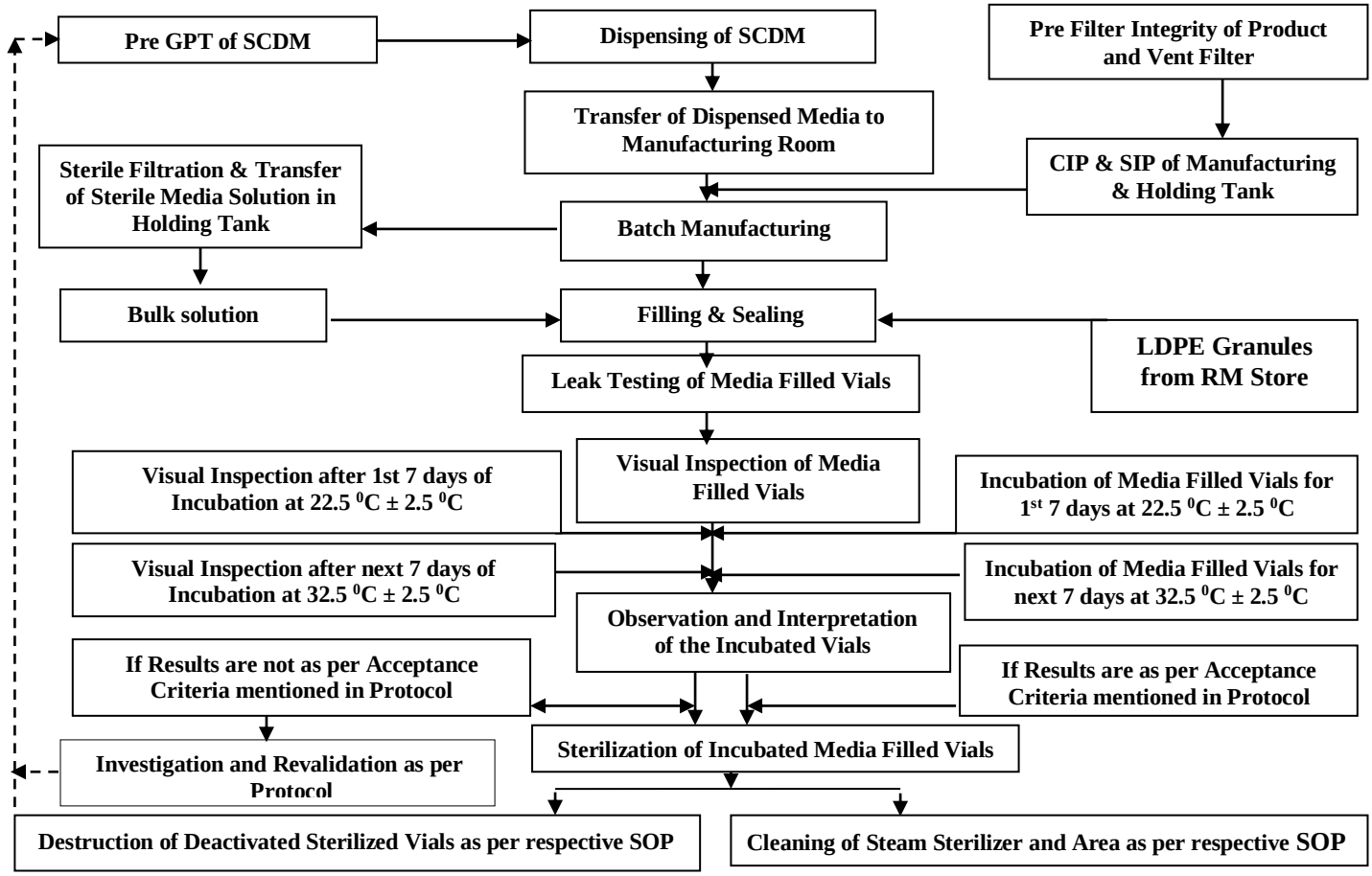
ANNEXURE-II

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

MEDIA FILL PROCESS FLOW FOR EYE /EAR DROPS



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

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

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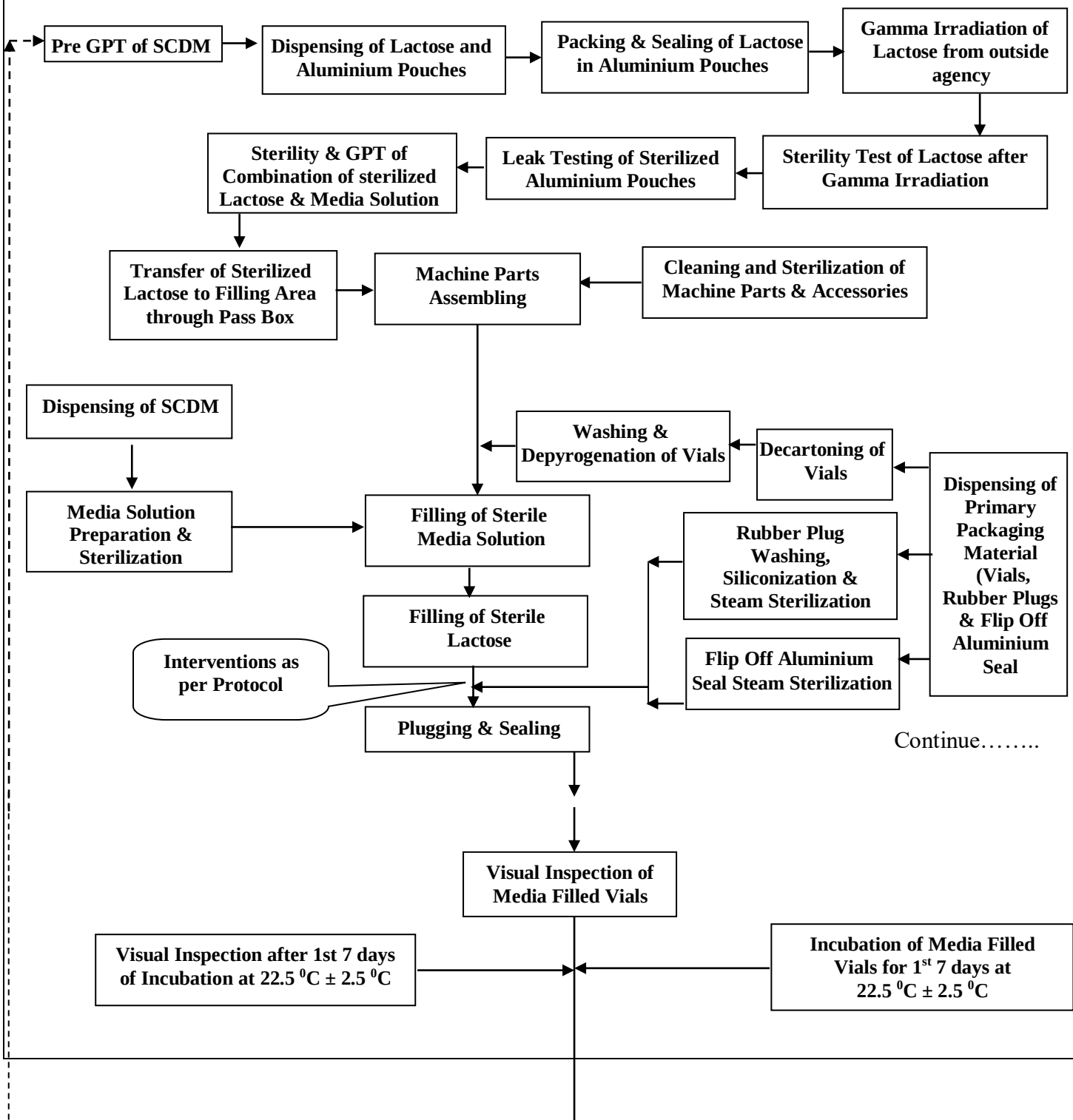
ANNEXURE-III

LOGO ***X-----**

**LOCATION

QUALITY ASSURANCE

MEDIA FILL PROCESS FLOW FOR DRY POWDER INJECTION



PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

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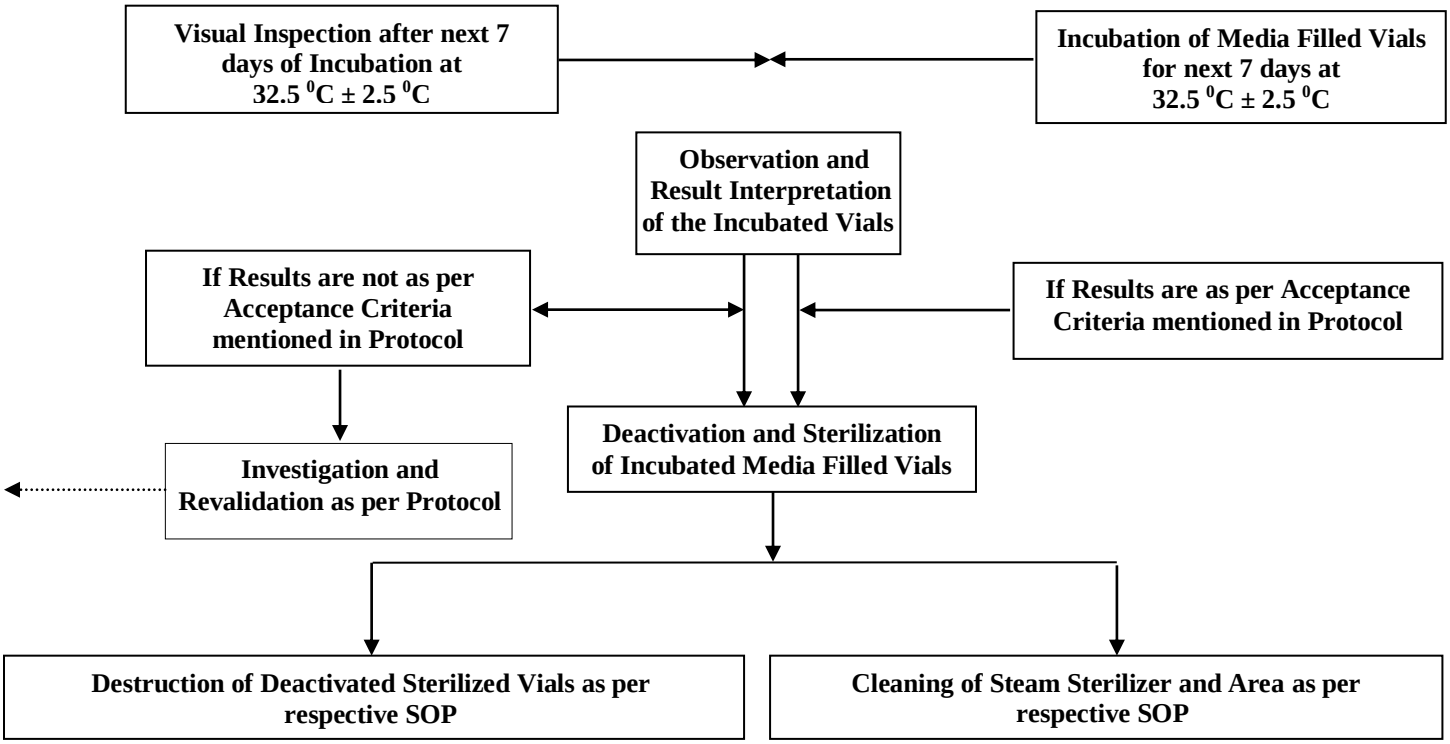

***X= Plant Name (For Plant SOP's)**

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

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STANDARD OPERATING PROCEDURE	
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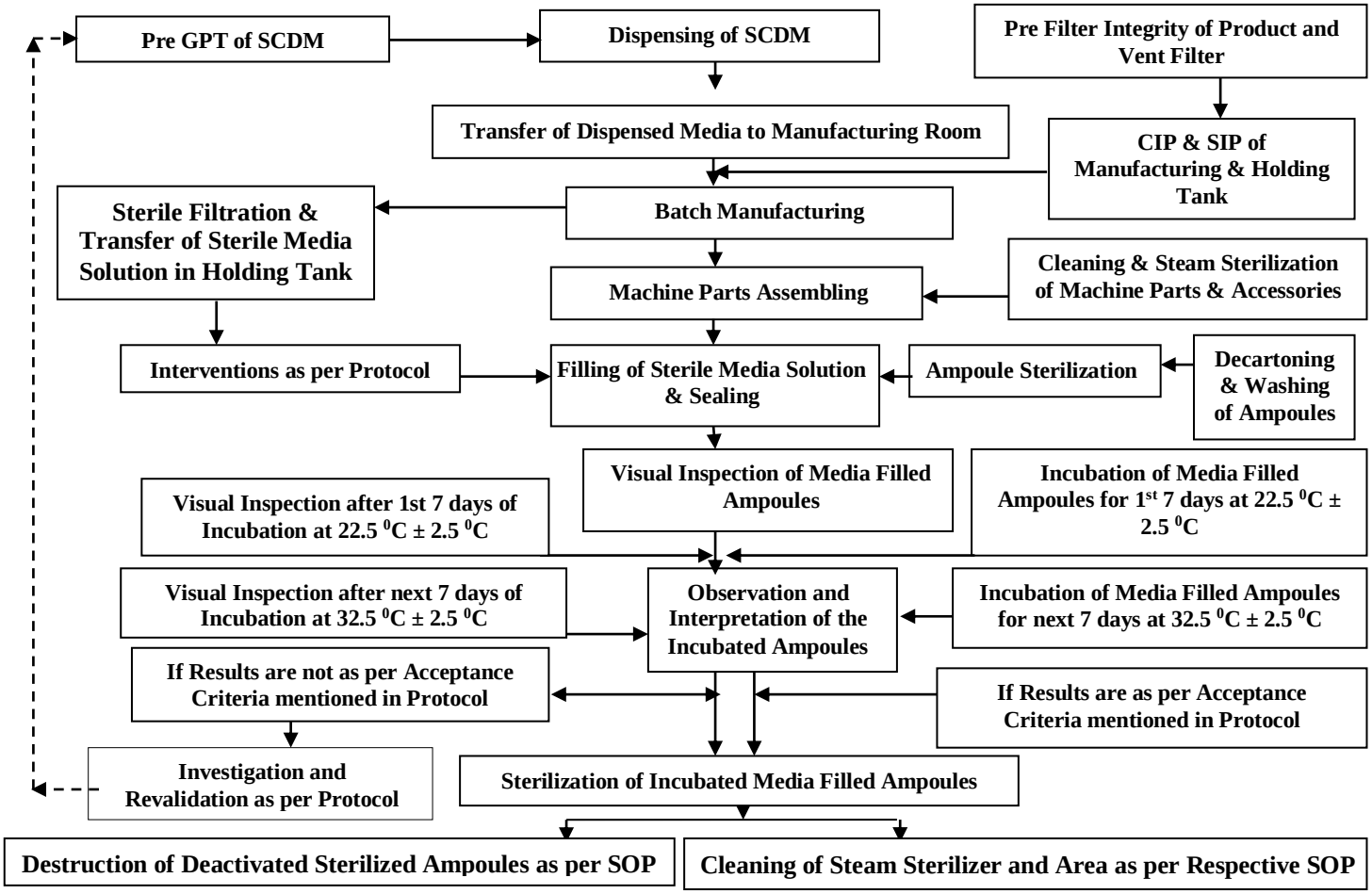
ANNEXURE-IV

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

MEDIA FILL PROCESS FLOW FOR AMPOULE LINE



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

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

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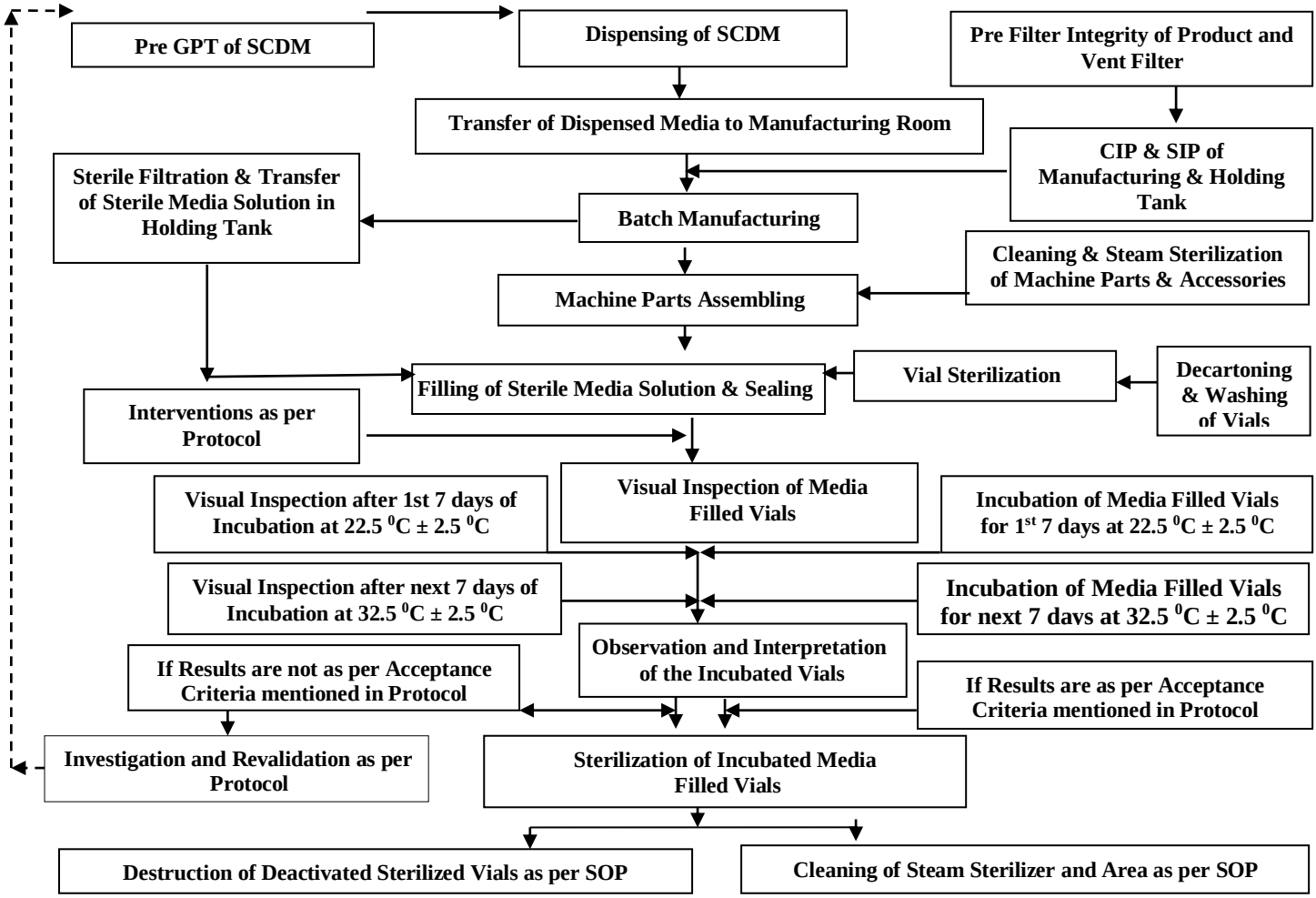
ANNEXURE-V

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

MEDIA FILL PROCESS FLOW FOR VIAL LINE



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

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

PHARMA DEVILS

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STANDARD OPERATING PROCEDURE	
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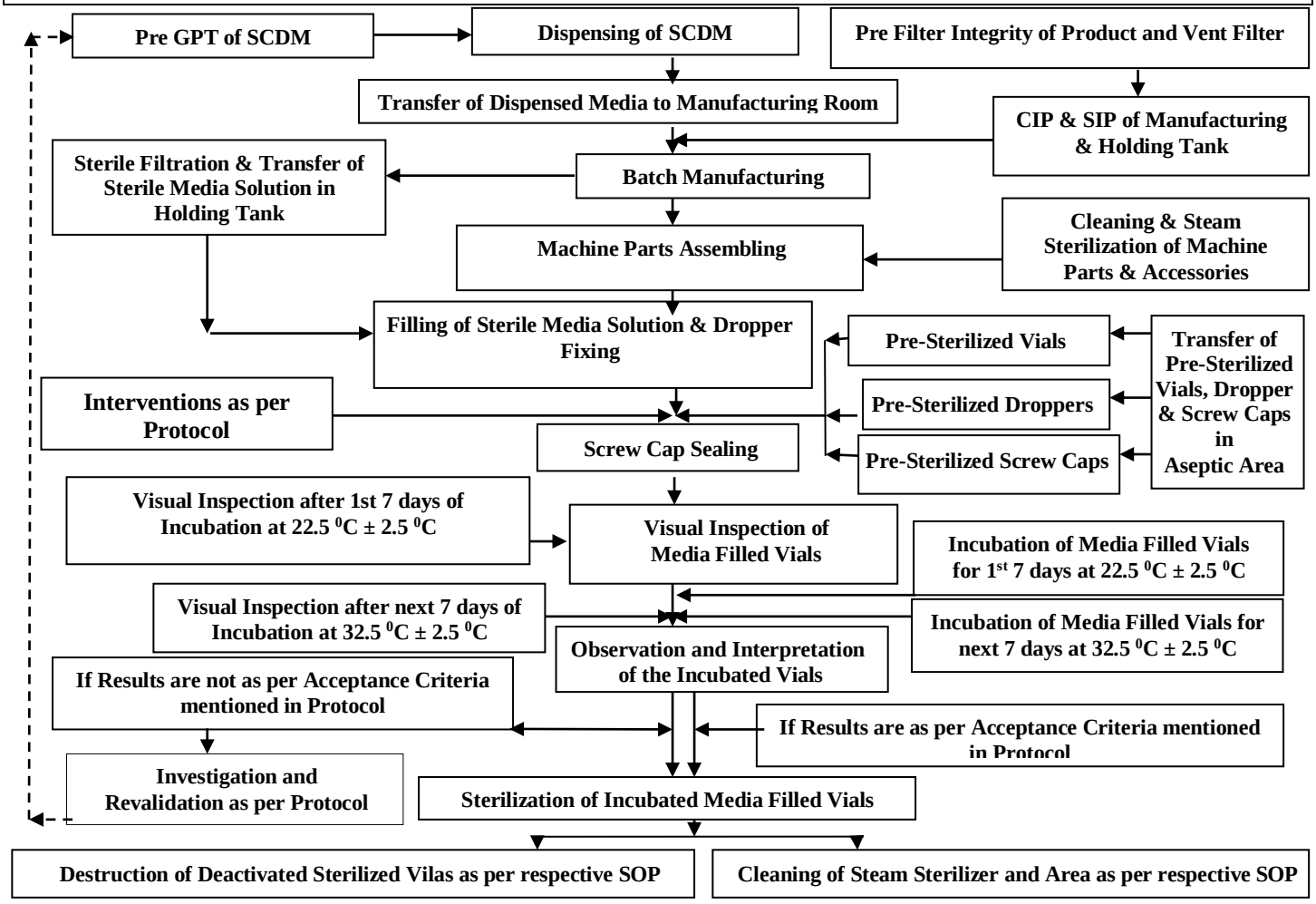
ANNEXURE-VI

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

MEDIA FILL PROCESS FLOW FOR THREE PIECE LINE



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

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

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Department: Quality Assurance	**SOP No.:**
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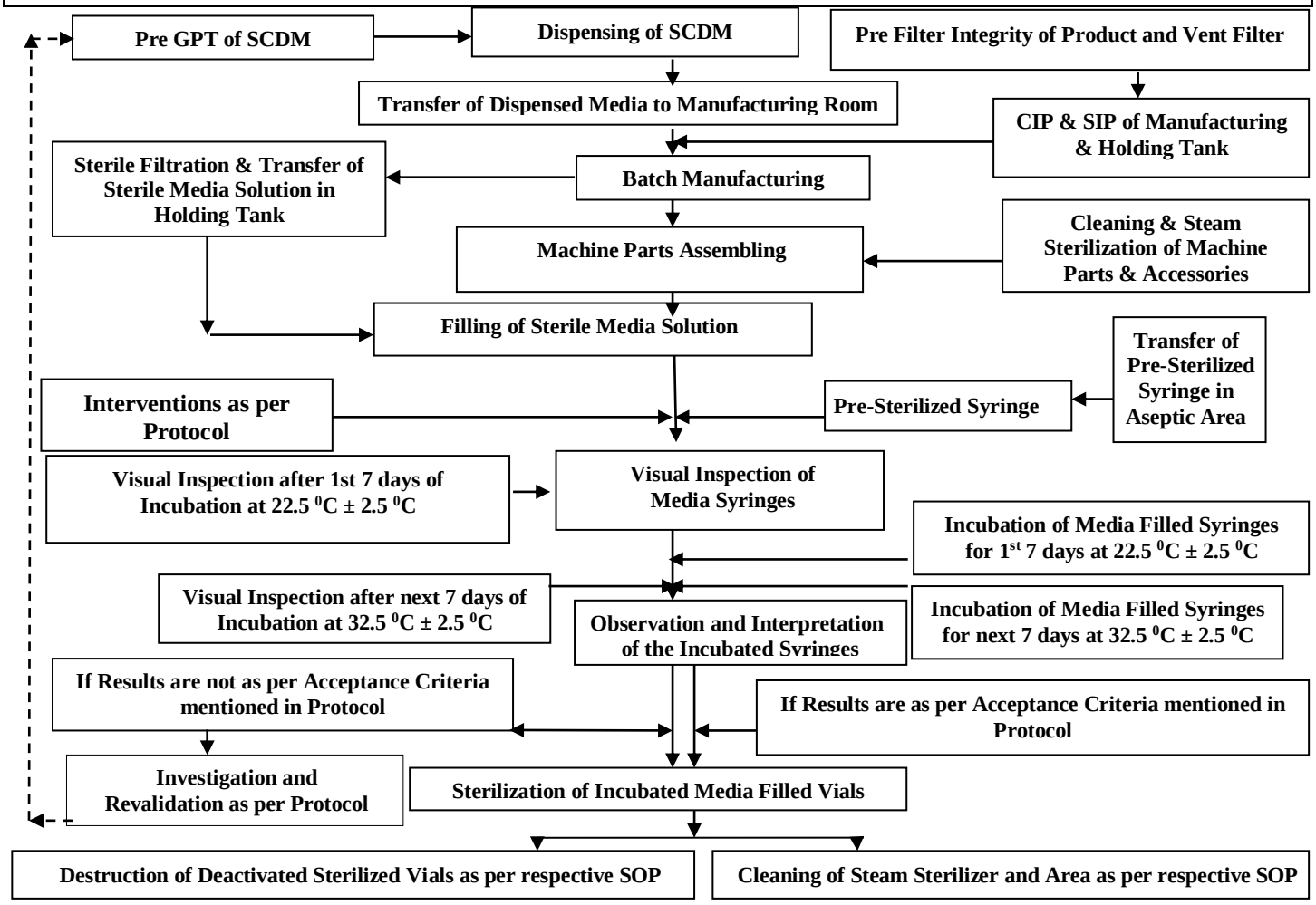
ANNEXURE-VII

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

MEDIA FILL PROCESS FLOW FOR PRE-FILLED SYRINGE



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

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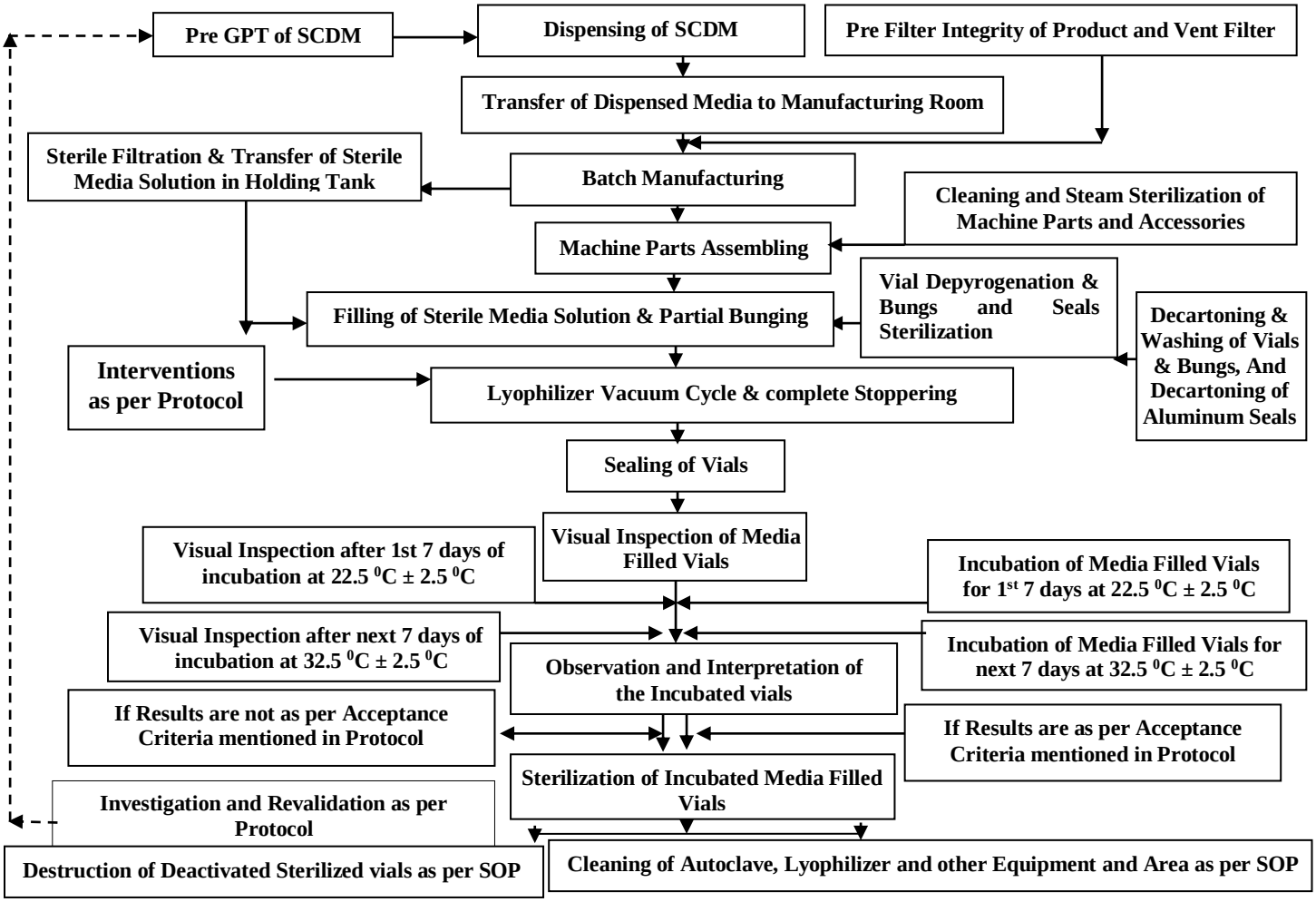
ANNEXURE-VIII

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

MEDIA FILL PROCESS FLOW FOR LYOPHILIZER VIAL LINE



***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**
PROCESS SIMULATION STUDY (MEDIA FILL) PLANNER	

Block: **Year:**

S.No.	Production Line / Area	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.

	Prepared By Operating Person QA	Checked By Operating Manager	Approved By Head QA
Sign			
Date			
Name			

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

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

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ANNEXURE-X

LOGO	***X-----** **LOCATION **QUALITY ASSURANCE**
PROCESS SIMULATION STUDY (MEDIA FILL) EXECUTION RECORD	

Block: **Year:**

S. No.	Production Line / Area	Media Fill Due On	Performed On	Result Fail / Pass	Re Validation in case of Failure		Checked By Sign & Date	Verified By QA Sign & Date	Remarks
					Media Fill Date	Performed on			

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

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ANNEXURE-XI

LOGO	***X----- **LOCATION **QUALITY ASSURANCE**
MEDIA FILL FAILIURE INVESTIGATION REPORT	

Media Fill Due On:		**Media Fill Performed on:**	
Performed on (Line):		**Block:**	
No. of Contaminated Units:		**Interventions Details:**	

Summary of Occurrence:

Investigation:

Production **Sign & Date**	**Quality Assurance** **Sign & Date**	**Quality Control** **Sign & Date**

Details of Potential Effect on Previous Batches (Since Last Media Fill):

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Corrective Action:

Outcome of Additional Process Simulation Tests (if Performed)

Conclusion:

Checked By
Head Operations
Sign & Date

Approved By
Head QA
Sign & Date

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