ASEPTIC PROCESS SIMULATION OR MEDIA FILL VALIDATION PROTOCOL

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ASEPTIC PROCESS SIMULATION OR MEDIA FILL VALIDATION PROTOCOL

1.0 APPROVAL PAGE:

Prepared By:

Functional Area	Name	Signature	Date
Production			
Engineering			
Validation			
Quality Assurance			

Approved By:

Functional Area	Name	Signature	Date
Head – Production			
Head – Engineering			
Head – Validation			
Head – Operations			
Head - Quality Assurance			

Authorized By:

Functional Area	Name	Signature	Date
Head - Technical Operations			

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2.0 OBJECTIVE:

- To demonstrate the capability of the aseptic process to produce sterile drug products.
- To identify the potential weakness in an aseptic processing operation which might contribute to the microbiological contamination of the product.
- To evaluate the processing steps used to manufacture a sterile product.
- Qualify or certify aseptic processing personnel
- Comply with current Good Manufacturing Practice requirements.

3.0 TYPE OF VALIDATION:

- Re-qualification.

4.0 REFERENCES:

- Process Simulation testing for aseptically filled products: Technical report No.: 22 PDA
- Annexure 1 to EU GMP
- Aseptic processing of health care products-Part 1General requirements ISO13408-1
- Validation of Aseptic Process by PIC guideline.

5.0 DEFINITIONS:

Media Fill (Process simulation):

Method of evaluating an aseptic process using a microbial growth medium.

Aseptic Filling:

Operation where by the product is sterilizes separately, then filled and packaged using sterilized containers and closures in critical processing zones.

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

Growth Promotion Test:

Test performed to demonstrate that media would support microbial growth.

Sampling Frequency:

Established period for collecting samples

Sterilization:

Validated process used to render a product free of viable organisms. In a sterilization process, the nature of microbiological death of reduction is described by an exponential function. There fore, the number of microorganisms that 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.

Shift:

Scheduled periods of work or production, usually less than 12 hours in length, staffed by alternating groups of workers.

6.0 REFERENCE DOCUMENTS:

- Documentation shall be approved, signed and dated by appropriate and authorized persons prior to commencement of the Media fill processing.
- Verify the following Documents and record in the Validation Report.

1. Media fill Record.
2. Packaging Material Specifications.

7.0 TYPE OF CONTAINERS AND CLOSURES:

Verify the type of containers and closure used in process simulation test and record in the validation report.

S. No	Material Name	Manufacturer's name	Use
1.	Clear glass vials (USP Type-III)	…….	Primary Packaging Material
2.	20 mm Grey/bromo butyl rubber plugs	…….	Primary Packaging Material
3.	20 mm flip off aluminum seals	…….	Primary Packaging Material

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8.0 DESCRIPTION OF EQUIPMENT, FACILITY AND UTILITIES INVOLVED IN PROCESS SIMULATION TEST:

- All the major equipments used for process, facility and utility as listed below shall be verified for Installation, Operational and Performance Qualification and recorded in the validation Report.
- Integrity testing of HEPA filters to be verified and should be recorded in the validation report.
- Standard operating Procedure for Filter Cleaning, Maintenance, Integrity testing of HEPA filters and sanitization of water system shall be included and verified in the Validation Report.

<table>
<tr><th colspan="2">EQUIPMENT</th><th colspan="2">FACILITY (HVAC SYSTEM)</th><th colspan="2">UTILITY</th></tr>
<tr><th>System Description</th><th>ID No.</th><th>AREA</th><th>ID No.</th><th>System Description</th><th>ID No.</th></tr>
<tr><td>Linear Vial Washing M/C</td><td></td><td>Vial Sterilization</td><td></td><td>Compressed Air</td><td></td></tr>
<tr><td>Depyrogenating Tunnel</td><td></td><td>Sterile Change Rooms 1-4</td><td></td><td>Purified Water Generation Purified Water & water for Injection Distribution System</td><td></td></tr>
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<tr><td rowspan="2">Optical Inspection M/C</td><td rowspan="2"></td><td>Incubation Room-1 (For 20-25°C)</td><td></td></tr>
<tr><td>Incubation Room-2 (For 30-35°C)</td><td></td></tr>
</table>

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9.0 CRITICAL INSTRUMENTS INVOLVED IN PROCESS VALIDATION:

- All instruments calibrated as per calibration plan ……..
- Calibration details of all the critical instruments used in the manufacturing process as listed below shall be verified for calibration before the Media Fill Validation

1) Linear Vial washing Machine
2) Depyrogenating Tunnel
3) Rubber Bung Washing Machine
4) Moist Heat sterilizer
5) Filling & Bunging Machine
6) Sealing Machine
7) Optical Inspection Machine

10.0 STANDARD OPERATING PROCEDURE:

- Standard operating procedure for the following operation shall be verified and recorded in the validation Report.

Procedure Title	Procedure No.
PLANS	
Monitoring plans for Non-Viable Particle Count	
Monitoring plans for Viable Count	
Calibration Plan	
PRODUCTION	
Receipt of raw material	
Operation, Verification and Cleaning Of Weighing Balances	
Personal Hygiene & Behavior In Sterile Area	
Entry & Exit procedure to sterile area	
Cleaning & Sanitization of the washing area	
Operation and cleaning of Linear vial washing m/c	
Operation and cleaning of Depyrogenating Tunnel	
Operation and cleaning of Bung washing m/c	
Operation and cleaning of Autoclave	
Operation and cleaning of Dry powder filling and Plugging m/c	
Operation and cleaning of vial sealing m/c	
Washing and sterilization of machine parts	
Washing and sterilization of garments	
Handling of Hopper left over of raw material & Packaging material	
Operation and cleaning of LAF	
Operation and cleaning of Dynamic Pass Box	
Entry & Exit Procedure to Washing Area	
Transfer of sterile raw material from interim RM store to sterile area	
Fumigation & Defumigation of Sterile area	
Procedure for sterilization of rubber bung	
Procedure for cleaning & sterilization of Aluminium seals	
Standard Operating Procedure for cleaning of storage vessel and pressure vessel	
Procedure for filtration of sanitization solution and WFI	
Procedure for environmental monitoring of sterile area	
Standard Operating Procedure for Particle Counter	

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Procedure Title	Procedure No.
Procedure for environmental monitoring of washing area	
Washing and sterilization of hand gloves	
Cleaning Sterilization & Operating Procedure of Cone Blender	
Operation & Cleaning of filled Vial Inspection	
QUALITY ASSURANCE	
Standard Operating Procedure for Media Fill	
Standard Operating Procedure for Sterility Testing	
Area and equipment clearance	
Environmental monitoring by air sampling	
Environmental monitoring by settle plate	
Environmental monitoring by swab sampling	
Personnel monitoring in aseptic area	

11.0 METHODOLOGY:

11.1 Process Definition:

The process is defined as all steps from the washing and sterilization of the container and closure, to the point the drug is sealed. All equipment remains same as for the routine process. All the parameters related to different equipment and environment should be maintained the way it is maintained during normal production run. No extra cleaning and sanitization will be done prior to and during filling operation. The maximum time frames for storage of the sterile drug container and Closures prior to aseptic assembly will be factored into the simulation. The process simulation test represents a worst case situation and includes all manipulations and interventions likely to be represented during a shift.

11.2 Methods selected for the process simulation tests:

Online liquid fill followed by on-line powder fill. In this approach, a liquid filling machine is added to the filling line prior to the powder filler. A specific volume of WFI is added to the container, followed by a fill of a sterile medium powder. The method was selected considering the space on the filling line. Advantage of this method is that all process is performed on-line no additional handling of containers is required. However sterile inert gases are used during normal production, process simulation tests will substitute filtered compressed air. The containers and closures are cleaned and sterilized using standard operating procedures (SOPs) as are equipment and filling parts. The filling machine is operated at the pre-determined fill rate for the container size being utilized. The containers are sealed and the medium and the medium-filled units are collected in sequentially numbered trays or boxes. The time of collection must be noted. The filled units should be briefly inverted and swirled after filling to assure closure contact with the medium.

11.3 Elements Of Process Simulation Test:

The following parameters should be considered during media fill validation;

11.3.1 Filling Line set-up:

Since the filling line set-up usually entails manual assembly of the equipment and requires more manipulation of critical surfaces than subsequent filling operations. The set-up activities have been included in the medial fill operation to detect the potential contamination from machine set-up activities.

11.3.2 Number and Type of Interventions and stoppages to be included:

The Media fill operation should include all the normal activities, which occur during an aseptic filling operation (i.e. weight adjustments, container closure re-supply etc.) in order to substantiate the acceptability of those practices in routine operation. It is possible that non-planned interventions may be necessary to correct for container breakage, fluid leakage, closure jams etc, which may occur during process simulation. To the extent that these types of problems occur on their own, and are rectified during a successful process simulation test, they can be defended as

correctable during an ordinary fill. Details of planned permitted intervention carried out during media filling are given below.

11.3.3 List Of Permitted Interventions:

Sr. No.	Planned permitted Interventions	Minimum No of Times	Frequency	
			For 30 ml	For 7.5 ml
1.	Adjustment of weight in the dosing wheel	3	After every 800 vials	After every 1600 vials
2.	Adjustment of stopper holding spring	4	After every 700 vials	After every 1400 vials
3.	Transfer of powder from container to hopper	2	After every 1400 vials	After every 2800 vials
4.	Transfer of stoppers from bag to hopper	3	After every 900 vials	After every 2000 vials
5.	Picking un-stoppered vials from the out feed to dust bin	15	After every 200 vials	After every 400 vials
6.	Adjustment of separator	2	After every 1100 vials	After every 2000 vials
7.	Picking up of fallen vials from turn table	20	After every 150 vials	After every 300 vials
8.	Cleaning of spilled powder with lint-free mop	4	After every 700 vials	After every 900 vials
9.	Adjustment of stoppering channel height	2	After every 1000 vials	After every 2000 vials
10.	Adjustment of stoppering pressure rollers	4	After every 500 vials	After every 500 vials
11.	Replacing of a piston from the wheel	2	After every 1200 vials	After every 1200 vials
12.	Adjustment of turn table over load sensor	2	After every 900 vials	After every 900 vials
13.	Crossing of a acrylic barrier by the technician	4	After every 600 vials	After every 600 vials
14.	Checking the weight in balance	6	After every 500 vials	After every 500 vials
15.	Adjustment of dosing air	2	After every 1000 vials	After every 1000 vials
16.	Pushing stopper in the channel by forcep.	10	After every 300 vials	After every 300 vials
17.	Power interruption (sample should be marked)	1	At least 200 vials to be filled after completion of targeted filled vials	At least 200 vials to be filled after completion of targeted filled vials
18.	Entry of maintenance person for repairing	1	After every 2000 vials	After every 2000 vials

11.3.4 Container Size:

Process simulation trials will entail the filling of the largest and smallest containers on a given filling line i.e. 7.5 ml and 30 ml. The rationale for selecting the smallest and largest vial is,

- The same filling line is used for different products having vial size range from 7.5 ml to 30 ml.
- Single fill for smallest container and double fill for largest container.

11.3.5 Filling Speed/line speed:

The fill speed to be used for any container should be set at the low end of the Filling speed. For 30 ml vials (double dosing used in routine production), the speed of NLT 20 vials where as the usual speed is 110 –120 vials and for 7.5 ml vials the speed of NLT 30 vials where as the usual speed is 200 - 220 vials will be used. However higher speed results in the potential for greater interventions, which cannot be used because of liquid dosing device.

11.3.6 Volume of medium to be filled into the containers:

Regardless of actual volume, the process simulation test will include a fill Weight adjustment-using methods identical to those employed during Production. While the exact amount of medium utilized in a partial fill is not critical, there were two general criteria to decide on fill volume.

- First, there must be enough medium in the container to contact all the container-closure seal surfaces when the container is inverted and swirled.
- Second, there must be enough medium in the container to contact all the container to allow for the detection of microbial growth

The chosen volume is:

- For 30 ml vials 450 mg of medium / 15 ml of SWFI
- For 7.5 ml vials 120 mg of medium / 4 ml of SWFI

11.3.7 Duration of fill:

Process simulation test will be of sufficient duration to allow enough containers to be filled to properly determine the contamination rate. Normal aseptic manipulations such as initial set-up activities, adjusting fill weights or volumes, changing equipment and manual maintenance operations will be included in process simulation tests. Process simulation tests also will be of sufficient duration to include a representative number of typical interventions, which might occur during an actual production filling operation. Where they are part of normal operations, gown changes, breaks and shift changes will be simulated.

The minimum time starting from machine set-up till filling completion will be

- For 30 ml vials-NLT 08 hours
- For 7.5ml vials-NLT 08 hours

11.3.8 Number of units to be filled and number of runs:

The number of units filled in a media fill run should allow process variables and interventions routinely encountered during production. For single dosing NLT 6000 vials and for double dosing NLT 4000 units were selected .The total number of runs selected each vial size (7.5 & 30 ml) will be three for initial qualification and one for requalification.

11.3.9 Selection of Media:

The selected medium for Process Simulation test will be Soya been casein Digest Medium, since it is capable of supporting a wide range of microorganisms and is clear to allow for ease in observing turbidity. The medium is prepared according to the manufactures recommendations.

11.3.10 Incubation Conditions-Incubation time and temperature for the filled units:

Process simulation tests will be incubated at 20 - 25°C for 7 days immediately followed by 7 days incubation at 30 – 35°C for a total incubation time of 14 days. The temperature chosen is based upon its ability to recover microorganisms normally found environmentally or in the product bioburden. During transfer of the vials from 20 – 25° to 30 – 35°C, the vials will be inverted to allow the contact of medium with the closure.

12.0 RATIONALE FOR THE " WORST CASE" PARAMETER CHOSEN

- Using sterilized materials, Components and closures, which have remained in the aseptic processing area for extended periods.
- Increasing the size of the fill crew to more than the number necessary to fill the batch.
- Using a growth-promoting medium in the process simulation test rather than an inhibitory and preserved formulation.

13.0 IDENTIFICATION OF PROCESS TO BE SIMULATED:

I. Decartoning of vials.
II. Inspection of Vials.
III. Washing and De-pyrogenation of vials.
IV. Washing, Siliconization, Sterilization and drying of rubber plugs.
V. Autoclaving of seals.
VI. Washing and Sterilization of Machine Parts.

VII. Blending process

VIII. Filling and Sealing.

13.1 Additional Steps For Media Fill

a. Optical Inspection.

b. Incubation

c. Inspection of incubated vials.

d. Growth promotion test.

14.0 PROCESS DETAILS:

14.1 Step I: Decartoning Of Vials:

De-dust the cartons. Decartonate and remove the vials. Arrange in the S.S. trays and stack for feeding to the vial washing machine.

14.2 Step II: Inspection of Vials:

Inspect the vials visually for absence of black particles, broken glasses, fibers and other damages. Segregate the rejected vials, and destroy. Account for the rejection.

14.3 Step III: Washing and De-pyrogenation Of Vials.

14.3.1 Feed the good vials into the conveyor belt of Linear Vial Washing Machine.

14.3.2 Vials are washed from inside and outside with 10µ filtered recycled Water in the first cycle followed by air.

14.3.3 Vials are further washed from inside and outside in the second cycle with 5µ filtered Purified water followed by air.

14.3.4 Finally vials are washed from inside with 5µ filtered WFI (above 80°C) followed by filtered air.

14.3.5 Washed vials are passed to the conveyor of the depyrogenating tunnel.

14.3.6 Vials are depyrogenated at 315 – 355°C for at least 3 minutes in the tunnel.

14.3.7 Depyrogenated vials are cooled, stabilized and passed directly to the sterile filling area.

14.3.8 A copy of temperature log should be attached with the protocol.

14.4 Step IV: Washing, Siliconization, Sterilization And Drying Of Rubber Plugs:

14.4.1 Open the Polybag, and remove the plugs.

14.4.2 Keep the plugs in Sodium Lauryl Sulphate solution for two hours.

14.4.3 Transfer the plugs to plug washing machine.

14.4.4 Wash with Purified water for 45-50 minutes.

14.4.5 Wash with WFI for 25-30 minutes.

14.4.6 Give Siliconization treatment with silicone oil for 10 minutes. Segregate the plugs in lint free bags (eg. nylon bags), tie properly and load in to the autoclave for sterilization.

14.4.7 Autoclave the plugs at 121.1° C for 30 minutes.

14.4.8 Dry the plugs under vacuum for 90 minutes.

14.4.9 Unload the plugs from the cool zone and take the plugs directly in to the sterile filling area.

14.4.10 A copy of temperature log should be attached with the protocol.

14.5 Step V: Sterilization Of Flip-Off Aluminium Seals:

14.5.1 Sterilize the flip off Aluminium seals in Autoclave at 121.1°C for 30 minutes.

14.5.2 A copy of temperature log should be attached with the protocol.

14.6 Step VI: Sterilization Of Machine Parts:

14.6.1 Sterilize the Machine parts in Autoclave at 121.1°C for 30 minutes. Dry the parts under vacuum for 30 minutes.

14.6.2 A copy of temperature log should be attached with the protocol.

14.7 Step VII: Transfer And Simulation Of Blending Operation On Media:

14.7.1 Spray filtered IPA of 70% on outer surface of media packet and keep the media packet in the dynamic pass box of interim / blending room under UV lamp for 5 minutes.

14.7.2 Unload the media in side blending room under LAF.

14.7.3 Open the charging lid of the blender and load the media.

14.7.4 Close the charging lid.

14.7.5 Simulation the blending operation by rotating the media in the blender for 2 hours.

14.7.6 Unload the material in the sterile S.S. container.

14.8 Step VIII: Filling And Sealing:

Take up the sterile medium for filling in 7.5 ml/30 ml previously sterilized USP TYPE III vials under compressed air using vial filling and capping line adjusted to fill weight.

14.8.1 Load the sterile medium from the SS container into the hopper of the filling machine after ensuring that the hopper, fiber disc, port hole and Stoppering unit assembly is sterilized.

14.8.2 SWFI filling, numeric injector needle has to be fitted before powder filling station.

14.8.3 Adjust the required volume of SWFI and weight of the powder delivered into the sterile vials. Check vials from each porthole during filling and sealing operation for fill weight and volume at predetermined intervals.

14.8.4 Closing of vials:

14.8.5 Vials must be closed by sterile plugs and Aluminium flip off seals. Ensure that the plugs are tightly fitted and seal is crimped properly. Get the vials sealed immediately.

14.9 Step IX: Inspection of Vials.

Perform Optical inspection of all vials for fill volume, Breakage and quality of Sealing. Transfer the inspected vials to incubation room immediately after inspection.

14.10 Step X: Incubation:

14.11 Incubation Conditions-Incubation time and temperature for the filled units

14.11.1 Process simulation tests will be incubated at 20 - 25°C for 7 days immediately followed by 7 days incubation at 30 – 35 °C for a total incubation time of 14 days. The temperature chosen is based upon its ability to recover microorganisms normally found environmentally or in the product bioburden.

14.12 Incubator Identification:

14.12.1 Because of significant number of vials to be incubated two incubation rooms were prepared.

14.12.2 Room No. 19 for 20 – 25°C

14.12.3 Room No. 18 for 30 – 35°C

14.12.4 The temperature mapping will be performed prior to incubation to qualify the incubation room. The selected temperature will be controlled and monitored continuously through out the incubation period. Temperature logs will be maintained.

14.13 Step XI: Container Inspection:

14.13.1 The units will be examined visually for evidence of growth. Containers will be manipulated during the inspection process to ensure detection of Contamination on container and closure surfaces. Inspection of vials are done by visual examination and checked on 3rd, 7th, 11th and 14th day of incubation. Any

positives noted during routine inspection should be tallied and immediately removed from incubation.

14.13.2 All these checks will be performed by personnel who have had specific training in the visual inspection of media-filled units.

14.14 Step XII: Media Growth Promotion:

14.14.1 Perform the growth promotion test in first run of 7.5 ml and last run of 30 ml. The samples will be tested initially upon production and after 14 days of incubation. The units used for growth promotion testing must be subjected to the same processing steps (eg. Cleaning, depyrogenation, sterilization, filling) upto the point at which they are placed into incubation. The medium's growth properties will be evaluated using Pharmacopoeial methods.

14.14.2 The strains used for media growth promotion test will be:

14.14.3 Bacillus subtilis, staphylococcus aureus, Candida albicans, Aspergillus niger, clostridium sporogenes and in house flora (isolated from monitoring plan)

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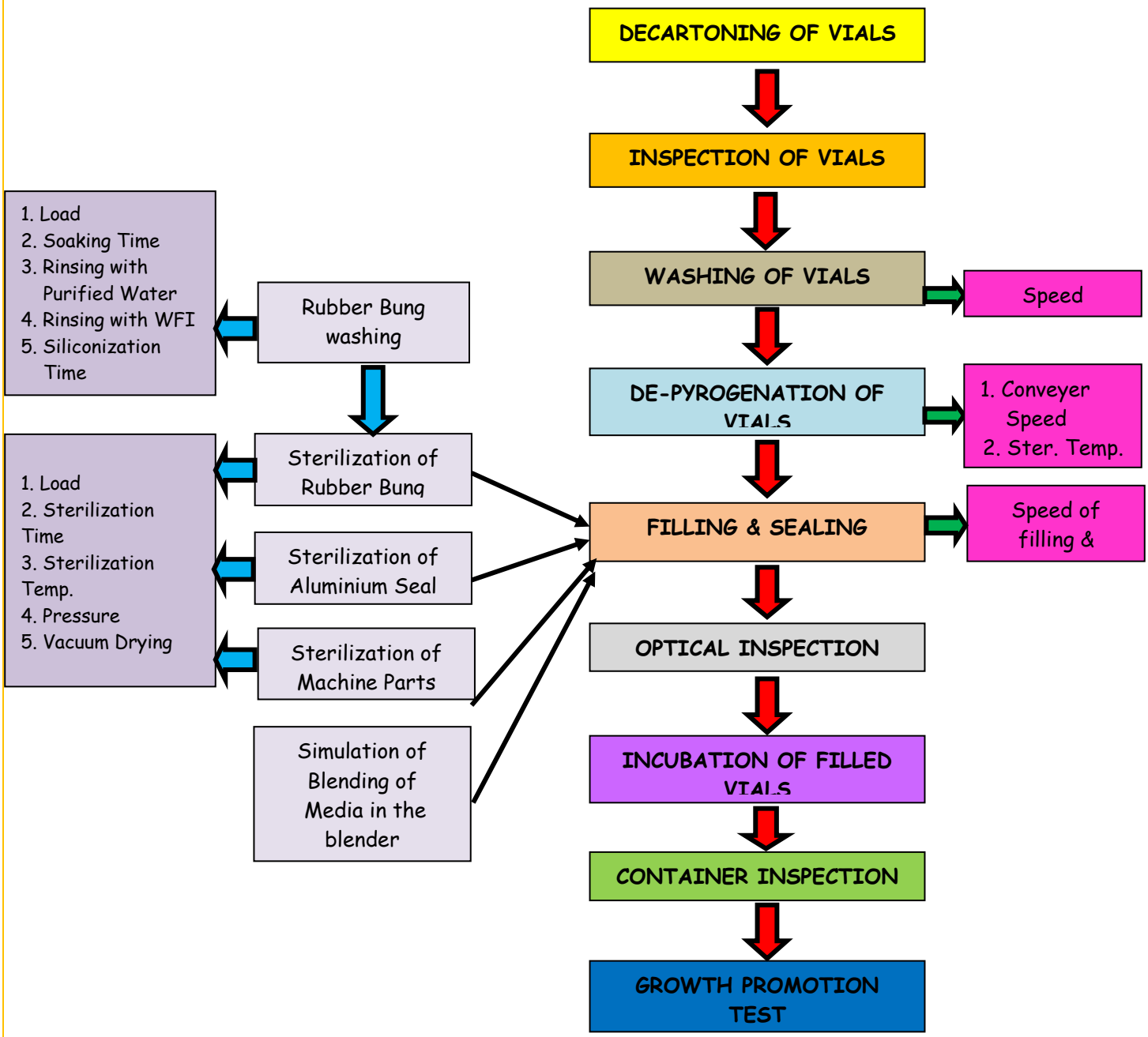
15.0 PROCESS FLOW DIAGRAM WITH VALIDATION PARAMETERS:



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16.0 MONITORING PARAMETERS:

16.1 ENVIRONMENTAL MONITORING PARAMETERS:

Sr. No.	ENVIRONMENTAL PARAMETERS	FREQUENCY	ACCEPTANCE CRITERIA
1. BUNG WASHING			
1.	Temperature	Initial and every 2 hours	Between 22-24°C
2.	Pressure gradient	Initial and every 2 hours	3.0 to 4.0 mm of WC.
2. BUNG STERILISATION			
1.	Temperature	Initial and every 2 hours	Between 22-24°C
2.	Pressure gradient	Initial and every 2 hours	5.0 to 6.0 mm of WC.
3. STERILISATION OF ALUMINIUM SEAL			
1.	Temperature	Initial and every 2 hours	Between 22-24°C
3.	Pressure gradient	Initial and every 2 hours	5.0 to 6.0mm of WC..
4. STERILISATION OF MACHINE PARTS			
1.	Temperature	Initial and every 2 hours	Between 22-24°C
2.	Pressure gradient	Initial and every 2 hours	5.0 to 6.0 mm of WC.
5. VIAL WASHING			
1.	Temperature	Initial and every 2 hours	Between 22-24°C
2.	Pressure gradient	Initial and every 2 hours	5.0 to 6.0 mm of WC.
6. STERILISATION OF VIALS			
1.	Temperature	Initial and every 2 hours	Between 22-24°C
2.	Pressure gradient	Initial and every 2 hours	5.0 to 6.0 mm of WC.
7. BLENDING OF MEDIA			
1.	Temperature	Initial and every 2 hours	Between 22-24°C
2.	Pressure gradient	Initial and every 2 hours	7.0 to 8.0 mm of WC.
3.	Relative Humidity	Initial and every 2 hours	NMT 45%
4.	Non-Viable Particle Count before Blending (Preparatory Phase)	As per Monitoring Plan	Should comply as per Monitoring Plan
5.	Non-Viable Particle Count After Blending		
6.	Viable Particle Count: Active air sampling (Preparatory Phase)		
7.	Swab Testing (Before and after Blending)		
8.	Personnel Monitoring (Before and after Blending)		
7. FILLING AND SEALING			
1.	Temperature	Initial and every 2 hours	Between 22-24°C
2.	Pressure gradient	Initial and every 2 hours	9.0 to 10.0 mm of WC.
2.	Relative Humidity	Initial and every 2 hours	NMT 45%
Non-viable Particle Count			
3.	Before filling	As per Monitoring Plan	Should comply as per Monitoring Plan
4.	During filling		
5.	After filling		
Microbial Monitoring:			
6.	Active air sampling		
7.	Settle Plate Exposure (Passive Air Sampling)		
8.	Personnel Monitoring		
9.	Swab Testing		
10.	Compressed air testing		

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Sr. No.	ENVIRONMENTAL PARAMETERS	FREQUENCY	ACCEPTANCE CRITERIA
11.	Sterile Area	Initial and every 2 hours	Pressure Gradient
	a. Air Lock-1		3.0 to 4.0 mm of WC
	b. Air Lock -2		5.0 to 6.0 mm of WC
	c. Air Lock -3		7.0 to 8.0 mm of WC
	d. Exit Air Lock		5.5 to 6.0 mm of WC
	e. Sterile Passage		5.0 to 6.5 mm of WC
	f. Sterile Passage		5.0 to 6.5 mm of WC
	g. Cool Zone		7.0 to 8.0 mm of WC
	h. Vial Filling		9.0 to 10.0 mm of WC
	i. Vial Sealing		7.0 to 8.0 mm of WC

16.2 Process Monitoring Parameters:

Sr. No.	Process Parameters	Monitoring Parameters	Frequency	Acceptance Criteria
1. Bung Washing				
1.	Soaking time: 2 Hours	NA	NA	As per BMR
2.	Rinsing with Purified Water: 45-50 mins.			
3.	Rinsing with Water for Injection 25-30 mins			
4.	Siliconization Time: 10 minutes			
2. Bung Sterilisation				
1.	Sterilization Time: 30 mins.	F_0 Value	NA	NLT 15 mins.
2.	Sterilization temp. : 121.1° C	Sterility	Once	Complies sterility Test
3.	Pressure: 1.1 Kg/cm^2			
4.	Vacuum drying: 90 mins.			
5.	Vacuum Pressure for Drying: -0.95 to - 0.6 bar			
3. Sterilisation of Aluminium Seal				
1.	Sterilization Time: 30 mins.	F_0 Value	NA	NLT 15 mins.
2.	Sterilization temp. : 121.1° C	Sterility	Once	Complies sterility Test
3.	Pressure: 1.1 Kg/cm^2			
4.	Vacuum drying: 30 mins.			
5.	Vacuum Pressure for Drying: -0.95 to -0.6 bar			
4. Sterilisation of Machine Parts				
1.	Sterilization Time: 30 mins.	F_0 Value	NA	NLT 15 mins.
2.	Sterilization temp. : 121.1° C	Sterility	Once	Complies sterility Test
3.	Pressure: 1.1 Kg/cm^2			

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Sr. No.	Process Parameters	Monitoring Parameters	Frequency	Acceptance Criteria
4.	Vacuum drying: 30 mins.			
5.	Vacuum Pressure for Drying: -0.95 to -0.6 bar			
5. Sterilization of WFI				
1	Sterilization Time: 30 mins.	F_0 Value	NA	NLT 15 mins.
2	Sterilization temp. : 121.1° C	Sterility	Once	Complies sterility Test
3	Pressure: 1.1 Kg/ cm^2			
4	Vacuum drying: 2 mins.			
5	Vacuum Pressure for Drying: -0.95 to -0.6 bar			
6. Vial Washing				
1.	Speed of Vial Washing Machine	Pressure recycled Water	Every hour	NLT 1.0 Kg / cm^2
	180 vials / min	Pressure Purified Water	Every hour	NLT 1.0 Kg / cm^2
		Pressure WFI	Every hour	NLT 0.5 kg / cm^2
		Process Air Pressure	Every hour	NLT 0.2 kg / cm^2
7. Sterilisation Of Vials				
1.	Conveyer Speed: a) 10.5Hz for 7.5 ml b) 9.5Hz for 30 ml	Temperature of Sterilization Zone Entry	Every hour	315 – 355° C
		Temperature of Sterilization Zone Exit	Every hour	315 – 355° C
		Manometer Reading: Drying Zone Sterilizing Zone Cool Zone	Every hour	10-15 mm of WC 18-25 mm of WC 10-15 mm of WC
2.	Sterilization Temperature: 300 – 350 ° C	Sterility	Once	Should comply the sterility test.
8. Blending Process				
1.	Speed of blending process	RPM	Once	
		Sterility	Once	Should comply the sterility test.
9. Vial Filling And Sealing				
1.	Speed of Filling and Sealing Machine	Vacuum Pressure	Every hour	550 to 610 mm of Hg
2.	a. NLT 30 vials / min for 7.5 ml vials. b. NLT 20 vials / min for 30 ml vials.	Compressed Air Pressure	Every hour	1.5 to 2.5 kg / cm^2
		Uniformity of Weight	Every 30 mins.	± 5%
		Filled volume variation	Every 30 mins.	± 1.0 ml for 30 ml ± 0.5 ml for 7.5 ml

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17.0 ACCEPTANCE CRITERIA FOR PROCESS SIMULATION TEST PARAMETERS:

Parameters	Acceptance criteria
Assembled filling line Holding Time	NLT 3 hours
Filling & sealing duration	NLT 8 Hours
Holding time for stoppers A) After Siliconization	NLT 12.0 hours
B) After sterilization: (Stoppers used as last)	NLT 30.0 Hours
Holding times for vials: After washing (Vials used as first)	NLT 2.0 Hours
Number of Different persons present in sterile area	NLT 08 Nos.
Total man hours	NLT 70.0 Hours
Maximum number of persons present in sterile area for longer than 15 minutes	NLT 6 Nos.
Duration of maximum number of persons present in sterile area	NLT 1.0 hours for at least one run
Maximum time one person was present in sterile area	NLT 4 hours
Total Number of entries	NLT 18 Nos.
Total number of Material entries	NLT 5.0 numbers
No. of failures	Nil
Filling line speed	NMT 20 Vials per min. for 30 ml NMT 30 Vials per min. for 7.5 ml
Total number of interventions	NLT 90 Nos.
Maximum time for power failure	NLT 1 minutes
No. of incubated vials	NLT 4000 Vials for 30 ml NLT 6000 Vials for 7.5 ml

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18.0 TRAINING DETAILS:

Each person who works in an aseptic suite will participate in a simulation test on a periodic basis. All selected new persons, who are considered for sterile area entry and aseptic operations should undergo training of SOPs mentioned in SOP No.:…... Logs of personnel who have participated in each fill will be maintained as part of the documentation. All personnel who enter the aseptic processing area, including technicians and operating, Micro labs. Personnel shall be covered in a media fill at least once in a year for re-authorization.

Name of Person	Department
COORDINATOR (Head – QA)	
SUPERVISORY STAFFS	
1. Head - Production	Production
2. Manager	Production
3. Executive(s)	Production
4. Officer(s)	Production
5. Manager	Q.A.
6. Executive(s)	Q.A./IPQA
7. Officer(s)	Q.A./IPQA
8. Manager	Validation
9. Executive(s)	Validation
10. Officer(s)	Validation
11. Executive(s)	Microbiology
12. Officer(s)	Microbiology
13. Manager	Engineering
14. Executive(s)	Engineering
15. Officer(s)	Engineering
OPERATORS	
1. Technician	Engineering
2. Operators	Production Operator
3. Helper (Material transfer)	Production Operator

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19.0 EXECUTION:

Execution of the protocol is performed through the batch record. The Batch record will give detailed instructions on how to perform the process simulation test. It will be written in the same format as a normal batch record and contain all the normal data and sign of elements. All information, which normally would be attached to the simulation batch record i.e. cleaning records for pieces of equipment used, release stickers for the containers and closures etc. All interventions, planned or unplanned, and stoppages must be documented

In the Batch records as to the type of intervention, time the intervention occurred, duration of the intervention or stoppage and number of the box or tray being filled. The last step is to document the following

- Number of units filled
- Number of units incubated
- Number of units positive
- Number of units rejected for cause (damaged container, defective seal)
- Growth promotion of medium (After incubation)

20.0 FAILURE INVESTIGATION AND CORRECTIVE ACTION:

A contaminated container should be examined carefully for any breach in the integrity of the container system. Damaged container should not be considered in the evaluation (Acceptance) of the aseptic processing capability of the process. All positives (from Integral Containers) should be identified to genus and to species whenever possible. A comprehensive consistent sampling and identification scheme will be part of the investigation and determination of the contaminant source. In the instance when the process simulation test does not meet the established acceptance criteria all possible sources of contamination should be investigated. A detailed history of the investigation is to be maintained.

The identity of the microorganism from the contaminated units should be determined. The identification of the contaminant should be compared to the database of the organisms recently identified. The biochemical (genus/species) profile of the contaminating micro-organisms can then be compared to that of micro-organisms obtained from the sterility tests. And Bio-burden and environmental monitoring programme in order to help identify the potential source of the contaminant. These isolates should be checked for possible identification matches, as should isolates for any areas, which exceed their count limits or are trending upward

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Processing records should be reviewed. Any deviations, downtimes and repairs before or during filling should be noted. Filter integrity testing results and all sterilization records associated with the product components and equipment should be examined. Cleaning and sanitisation records should be reviewed. Critical systems (HVAC, Compressed Air / Gas, Water, Steam) should be reviewed for documented changes and re-qualification or acceptance criteria for those changes.

Calibration records should be checked. All HEPA filters in the filling area should be checked and rectified if warranted. Training records for all individuals (Production, Maintenance, Cleaning) involved in the fill should be reviewed to assure proper training was provided.

Validation records can be reviewed for any procedure or process changes. All deviations from the original validation should have an associated justification for not performing a new validation.

Based upon the outcome of investigation, the cause of the failure is either assignable or not assignable. It may be clearly assignable to a single source or vaguely associated with multiple system or process, which required re-defining. If the cause is assignable corrective action needs to be taken and documented. The root cause and the corrective action will detect the no. of process simulation test required to demonstrate that the process is operating within the expected parameters. If no cause can be found the process should be validated as though it were a new process. Multiple consecutive process simulation tests should be performed to demonstrate the ability to consistently produce acceptable product.
The failure investigation report should contain

A summary of occurrence;

- All systems investigated, not just the system tied to the failure.
- A conclusion as to causes and supporting documentation.
- Potential effect on previous batches produced.
- Corrective action taken.
- Outcome of additional process simulation tests, if performed.
- Appropriate signatures. In addition to the signatures of the investigators of the individual systems the head of Production and Quality should sign the overall reports.

The investigation needs to be completed in a timely fashion. It may be necessary to issue an interim report, with anticipated time lines, if the investigation or corrective actions require excessive time.

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21.0 REVALIDATION:

There will be a routine process simulation test program for the aseptic filling line, which should be performed at least twice per year± 15 days. Performance of process simulation tests prior to the scheduled reassessment may be necessary following a process change of such scope that previous qualification studies would be initiated. In such cases, the number of process simulation tests may vary, depending upon the extent of the change. Examples of such changes include:

- Major Modifications to the equipment or immediate product containers / closures (Interchanging standard parts does not constitute a major equipment modification)
- Modification to equipment of facilities, which potentially affects the air quality of airflow in the aseptic environment.
- Major changes in the number of production personnel or initiation of second (or third) shift production when the facility has been qualified only for singles shift operations.
- Major changes to the aseptic production process and / or procedures.

It also may be necessary to re-qualify with acceptable process simulation test in response to adverse trends or failures in the on going monitoring of the facility or process, such as:

- Continued critical area environmental monitoring results above the alert / action levels.
- An increased incidence of product sterility test failures.
- Breach of asepsis in the aseptic processing area.

When such incidents occur, the process and any changes, which may have occurred since the previous qualification should be evaluated. Appropriate action can then be taken to restore the facility or process to its “qualified state” has been re-established testing may be appropriate to assure that the “qualified state” has been re-established.

22.0 METHODS FOR RECORDING AND EVALUATING RESULTS:

- The Protocol should be pre-approved prior to its execution and the protocol should have detailed sampling plan and acceptance criteria for Process Simulation test parameters.
- Wherever applicable the graph and data print outs of critical process parameters will be obtained and attached.
- Data will be recorded using pen in the report and the recorded data will be identified by date and signature of responsible person.
- Process parameters that are to be monitored during validation will be recorded directly by the validation team.
- All parameters will be recorded in relevant records (e.g. Forms, Media Fill Records green sheets etc.)

- For Environmental parameters like viable and non-viable particles Count shall be done as per the environmental monitoring plans.
- For parameters, which are recorded more frequently, Minimum and maximum values will be presented.
- For all results reference to source document will be given.

23.0 REPORT:

The final report is a summation of the data from the batch record and environmental monitoring samples. Based upon this information, a conclusion is formulated regarding the acceptability of the manufacturing process and facility.

The following documents to be attached with the validation report.

- Media fill record.
- Media sterility report/certificate (Manufacturer's certificate).
- Compressed air sterility report.
- WFI sterility report.
- Entry log to sterile area.
- Temperature logs of incubators.
- Reports of microbiological monitoring.
- Growth support testing requirements and result (pre-incubation).
- Sterility report with tray number identification.
- Report of sterility test of Soya been Casein Digest Medium.
- Solubility test report of Soya been Casein Digest Medium.
- Report of growth promotion of sterile Soya been Casein Digest Medium (Post-incubation).
- Dynamic Pass box entry log book
- Vial destruction note after incubation