PHARMA DEVILS

MICROBIOLOGY DEPARTMENT

STANDARD OPERATING PROCEDURE	
Department: Microbiology	**SOP No.:**
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1.0 OBJECTIVE : To lay down a procedure for Media Fill operation in the sterile dry powder Filling facility.

2.0 RESPONSIBILITY : Operator concerned/Production officer/QA Officer

3.0 ACCOUNTABILITY : Production Manager/QC Manager.

4.0 PROCEDURE :

4.1 PRE-START UP:

4.2 Ensure that all the equipments, HVAC system, water system and other utility services of the facility are validated.

4.3 Ensure that the Gamma irradiation certification report of the lactose + SCDM (Soyabean Casein Digest) mixture (3:1) from BARC and sterility test report (done in-house) is available.

Ensure that solubility test report and growth promotion/inhibition test report of sterile lactose + SCDM mixture is available. [Solubility should be NLT 1gm/10 ml of WFI].

4.4 Ensure that freshly distilled WFI to be used for filling, is autoclaved and the sample given for sterility test.

4.5 Ensure that all the contact parts of Dry Powder Filling machine are duly cleaned and sterilized or sanitized.

Ensure that the last Environmental Control Reports of the area are conforming to the acceptance standard.

4.6 Ensure that the Liquid Filling machine is done inside the sterile filling area on the previous day after autoclaving /sanitization.

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4.9 Ensure that the cleaning, sanitization and fumigation of the area is done on the previous day as per SOP.

Ensure by manometer readings, that the pressure balancing of the Sterile area is as per requirement

5.0 **START UP**

5.1 Enter the sterile area as per SOP using gowns sterilized 4 days back.

5.2 Check the cleanliness of the Sterile area.

5.3 Check the cleanliness of the Powder Filling machine.

5.4 Check and confirm the temperature and RH of powder filling room is as per the requirement.

5.5 Assemble the Powder Filling machine. Ensure that that filling of powder and liquid can be done simultaneously.

5.6 Measure the nonviable particulate count of filling cabinet and filling room

6.0 **OPERATION:**

6.1 Bring the autoclaved WFI container near the liquid filling assembly.

6.2 Transfer sterile lactose + SCDM powder mixture from the container in to powder hopper.

6.3 Transfer sterile dried rubber stoppers (sterilized 4 days back) in to the hopper of stoppering unit. Send sample for sterility testing simultaneously.

6.4 Put the inlet suction tube of Liquid Filling Assembly into the WFI container.

6.5 Set the Powder Filling machine for the respective dose.

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8.3 Remove the Liquid Filling Assembly and all the contact parts. Disinfect it, clean it and get it sterilized/sanitised.

8.4 Ensure that all the left over rubber stoppers are given outside the sterile area for destruction.

8.5 Shut down the vial powder filling machine as per SOP.

8.6 **CLEANING:**

8.6.1 Ensure that all the tools and accessories containers etc. used during media fill are given for cleaning/sanitization/sterilisation.

8.6.2 Follow the cleaning and sanitization SOP for cleaning of sterile area.

8.6.3 Do the extra cleaning and sanitization of the floor/walls/machine after media fill run with 10% Bacillocide and Lysol solution.

9.0 **ACCEPTANCE CRITERIA:**

9.1 **Initial validation:** During initial validation, it should qualify all three consecutive media fill run i.e. during each run there should not be growth in more than two vials.

9.2 **Revalidation:** Only one media fill run in which there should not be any growth in more than two vials.

10.0 **ELIGIBILITY CRITERIA FOR PERSONNEL PERFORMING MEDIA FILL RUN:**

10.1 Persons involved in media fill should be medically examined and declared fit within last one year.

10.2 Persons should be trained on general hygiene and current gowning procedure, and the present health condition should be O.K.

10.3 The personnel should be microbiologically monitored during run.

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11.0 NOTES

11.1.0 In case of any positive growth in any vial during the incubation period.

11.1.1 It should be isolated and identified to the genus level.

11.1.2 If the isolated organism is other than the house flora, thorough investigation shall be carried out by Quality Assurance and Production.

11.1.3 The source of the contamination must be established.

11.2 In case of any failure in media fill run:

11.2.1 When there is no assignable cause, media fill shall be repeated three times and production should commence only after all the three runs meet the acceptance criteria.

11.2.2 When there is assignable cause, after rectification of the cause, repeat the media fill run once.

11.3 Before and during media fill run no special cleaning shall be carried out.

11.4 Normal production can resume only after minimum one day of environmental monitoring compliance report.

11.5 Batches filled before the final result of the media fill run shall not be released to the market till the media fill run passes in case of initial validation.

11.6 The routine environmental monitoring plates shall be kept for 14 days (in case of any growth) to help in investigation of any positive growth in the media filled vials. If for any reason the media fill run is considered invalid vials shall not be incubated.

11.7 Media fill runs can be aborted for the same reason that a product lot would be aborted. All media filled units filled before an incident that would cause an aborted fill must be incubated.

11.8 During media fill all the Operators, Officers & Maintenance staff who are authorised to do the sterile filling, supervision and maintenance must be involved in media fill trial.

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11.9 The volume of liquid filled must be sufficient to wet all surfaces including the closure and to facilitate inspection.

11.10 The line must be run at a slower speed than normal production run to give greater exposure time.

11.11 Total duration of the routine media fill must be the same or more as the longest process conducted on that line.

11.12 The incubation temperature of the filled containers must be sufficient to promote microbial growth at 30-35°C. for 168 hrs. (stored upright) followed by 20-25°C. for 168 hrs. (stored upside down).

11.13 Personnel that conduct the inspection of incubated media fills must have training on basic microbiological concepts, concepts of media fill and examples of contaminated container showing various stages of growth.

12.0 POST MEDIA FILL RUN:

12.1 Filled incubated vials should be optically checked by microbiologist and certified.

12.2 Incubate the vial samples with no growth approximate 5 vials for 14 days with normal house flora and 5 vials with organisms used for the sterility test growth promotion for 14 days.

12.3 Temp. range for incubation 1st week 30 to 35° C. (vials stored upright). 2nd week 20 to 25° C.(vials stored upside down). These vials should show promotion of growth.

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ANNEXURE - I
COMBINATION OF VIAL AND RUBBER STOPPER.

S.No.	VIAL		RUBBER STOPPER	
	VIAL SIZE	TYPE	GREY BUTYL	HALO BUTYL
1.	5 ML	III	_/	--
2.	7.5 ML	III	_/	--
3.	10 ML	III	_/	--
4.	15 ML	III	_/	--
5.	20 ML	III	_/	--

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ANNEXURE - II
ACCEPTANCE CRITERIA FOR MEDIA FILL SIMULATION

MAXIMUM NO.OF REJECTED VIALS ACCEPTABLE AT 95% CONFIDENCE LEVEL	PERCENTAGE OF FAILURE	BATCH SIZES					
		5000	10000	20000	50000	100000	INFINITY
0	0.1%	2469	2668	2808	2912	2951	2995
1	0.1%	3676	4047	4339	4575	4670	4747
2*	0.1%	4684	5207	5670	6044	6207	6294
0	0.01%				24698	26686	29944
1	0.01%				46093	47047	47047
2	0.01%					62911	62911

* Normal media fill run size