



# PHARMA DEVILS

PRODUCTION DEPARTMENT

## STANDARD OPERATING PROCEDURE

**Title:** Operation, Cleaning and Intervention of Ampoule Filling & Sealing Machine

<b>SOP No.:</b>		<b>Department:</b>	Production
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### 1.0 OBJECTIVE:

To lay down a Procedure for Operation, Cleaning and intervention of Ampoule Filling & Sealing Machine.

### 2.0 SCOPE:

This SOP is applicable for Operation and Cleaning of Automatic Twelve Head Ampoule Filling & Sealing Machine (Make: Truking) in Production area at Ampoule line.

### 3.0 RESPONSIBILITY:

**Operator:** Production operators are responsible to follow the SOP.

**Officer/Executive:** Production Officers and Executives are responsible to monitor and to ensure that all production personnel are following this SOP.

**IPQA:** IPQA are responsible for to ensure the compliance status of this SOP.

### 4.0 ACCOUNTABILITY:

Head – Production

### 5.0 ABBREVIATIONS:

ID No.	Identification Number
IPA	Isopropyl Alcohol
LAF	Laminar Air Flow
Ltd.	Limited
LPG	Liquid Petroleum Gas
No.	Number
PLC	Programmable logic Controller
QA	Quality Assurance
SOP	Standard Operating Procedure
WFI	Water for Injection

### 6.0 PROCEDURE:

#### 6.1 CHECKS AND PRECAUTIONS:

**6.1.1** Ensure that proper electric supply & earthing are provided to the Machine.

**6.1.2** Switch on the supply from main switch. Login Display in Screen and following levels below as:

**6.1.2.1** The ampoule filling and sealing machine equipped with PLC system and passwords.

A: Operator Level                      An individual who can only operate the system.

B: Supervisor Level                      Person who will have access to change the operational variables which are required to identify the operations.



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C: Manager: Level Person will have full access to the system.

**6.1.3** Ensure Oxygen, LPG & Nitrogen Supply is ON.

**6.1.4** Ensure that each & every ampoule rotating Bearing is working properly.

**6.1.5** Ensure that reading on Magnehelic Gauge in Laminar Flow is within limit.

**6.1.6** Ensure that Temperature of filling area NMT 25°C.

**6.1.7** Laminar Air Flow Unit continually runs 24 hours.

**6.1.8** Sanitize the hand with 70% IPA according to SOP.

### **6.2 UNLOADING OF FILLING MACHINE PARTS & FILLING ACCESSORIES :**

**6.2.1** Check whether sterilization indicator colour changed from **Violet** to **Green** ensure the sterilization of materials.

**6.2.2** Ensure that the all the filling items are available as per validated load items as mentioned in appendix-of current version of SOP.

**6.2.3** After unloading transfer the filling items using Mobile LAF to the respect filling areas or cool zone until assembling.

### **6.3 PRECAUTIONS DURING ASSEMBLING:**

**6.3.1** Transfer the filling items through mobile LAF.

**6.3.2** Switch on the online non-viable particles counters as per current version of SOP.

**6.3.3** Prior to 20 minutes of starting of assembling activity and ensure the non-viable particles counts are within the limits and carry out the plate exposure followed by filling items assembling.

**6.3.4** Care to be taken to avoid the contact of hands of opening of filling pumps, nozzles and silicone tubing during assembling.

**6.3.5** Personnel should move slowly and deliberately. Rapid movements can create the unacceptable turbulence in aseptic area processing.

**6.3.6** Non – touch techniques should be followed to prevent the contamination carry over from the gloved hand onto the filling items.

**6.3.7** Personal should disinfectant the gloved hand with sterile 70% IPA at regular intervals, whenever there is a requirement for any adjustment before and after completion.

**6.3.8** Autoclave sterilized forceps must be used instead of hand.



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**6.3.9** Do not touch the tips of the sterilized forceps even with gloved hands and tip of the forceps should be in the upright position while resting.

**6.3.10** Personnel should not lean over the wall panels and filling machine etc. during assembling in the clean room to avoid any particles, fiber falling from the personnel on to the filling machine.

**6.3.11** During assembling forceps should not be moved out of LAF area.

### **6.4 THE FOLLOWING LENGTH OF TUBES SHOULD BE USED FOR AMPOULE ASSEMBLING:**

**6.4.1** Product Tubing for Ampoule Filling.

S.No.	Tubing uses	Required length	Nos.	Silicon Tube Size
1.	Buffer tank to Solution manifold	900mm	01	15*20
2.	Solution manifold to NRV	600mm	12	06*10
3.	NRV to filling pump	100mm	12	04*06
4.	Filling pump to solution nozzle	6000mm	12	04*06
5.	Manifold outlet to pre nitrogen nozzles	600mm	12	04*06
6.	Manifold outlet to post nitrogen nozzles	600mm	12	04*06

**6.4.2** Procedure for assembling of filling items for ampoule line.

**6.4.2.1** Initially arrange the forceps stands under LAF so filling stations and place the forceps in the forceps stands and tips of the forceps should be in upward direction.

**6.4.2.2** Wrapping are to be removed from sterilized materials opening under LAF just before the assembling.

**6.4.2.3** Open the filling machine door on one side and assemble the filling pumps by fixing the filling pumps to the chuck nut.

**6.4.2.4** Place the nozzles and connect the one end of silicone tube to the nozzles and other end connect to the outlet of the filling pumps.



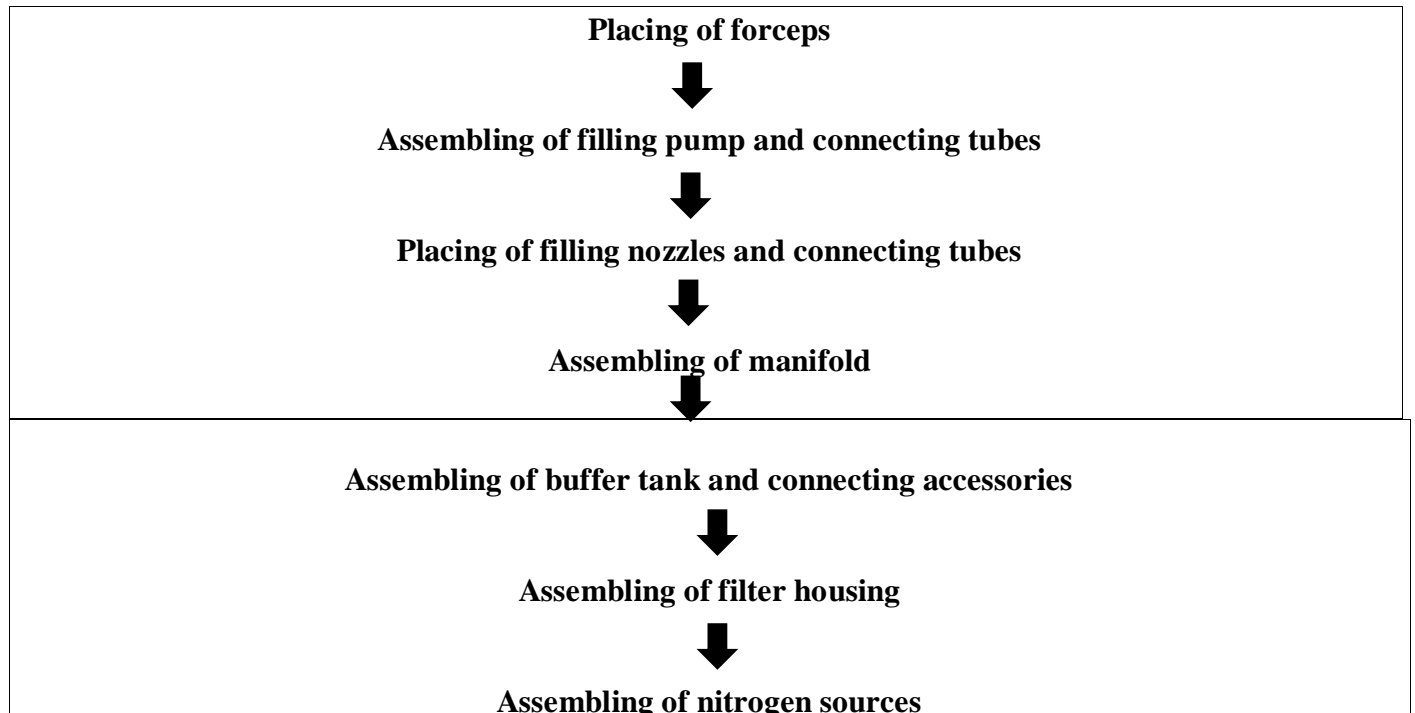
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- 6.4.2.5 Fix the manifold to the filling machine stand and connect the one end outlet of the manifold other end connect to the inlet of the filling pumps.
- 6.4.2.6 Manifold inlet of the silicone tube connected to outlet of the buffer tank.
- 6.4.2.7 Connects the one end of the silicone tube to the inlet of the buffer tank other end connects to the 0.2 micron filter housing outlet.
- 6.4.2.8 Connects the one end of the silicone tubes to the inlet of the 0.2 micron filter housing other end connect to the outlet of the product pipe line.
- 6.4.2.9 Open the other sides of the door adjust the nozzles and close the filling machine door.
- 6.4.2.10 Place the nitrogen manifold on filling machine and connects the one end to the inlet of the nitrogen nozzles other end connected to the outlet of the manifold.
- 6.4.2.11 Connect the one end of the silicone tubing to the manifold of the nitrogen nozzles other end to the nitrogen pipe line.
- 6.4.2.12 We follow sequential assembling of machine parts according to aseptic technique.

**Flow chart for sequential steps of Filling and sealing machine assembling activity**



- 6.4.2.13 After completion of assembling activity the machine doors towards Grade-A should be wiped with 70% IPA before preceding the filling activity.



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**6.4.2.14** Before start of the filling activity check the height of all the pre and post nitrogen nozzles. Nozzles should be near and center of the ampoules neck to purge the nitrogen in to the ampoule and liquid product filling nozzles should be near and center position of the ampoule.

**6.4.2.15** Now start the machine by inching switch and adjust the volume as per Specification till it becomes ok.

**Remark:** Line clearance shall be taken after successful filling m/c setting.

**Note :** *during assembling if online particle counts reach the alert level stop the assembling activity until resume the particle count resume the below alert level.*

**If online particle counts reach the action limit stop the assembling activity close the filling machine door and away from the filling area. Once particle resume the below alert level purging area for 5 minutes and restart the assembling activity.**

**6.4.3** Procedure for disassembling of filling items for ampoule line.

**6.4.3.1** Disassemble done in reverse order of assembling.

**6.4.3.2** Disassemble the filling silicone tubing manifold, filling pumps and nozzles and place them in SS surgical drum.

**6.4.3.3** Disassemble the silicone tubes from the buffer tank, product filter and load them on trolley a send to unit preparation area through dynamic pass box.

**6.4.3.4** After transferring the filling items filling area to be cleaned as per current version of SOP.

### 6.5 FILLING OPERATION:

**6.5.1** Qualified and trained personnel are allowed to operate the ampoule filling and sealing machine.

**6.5.2** Check and make sure that ampoule filling and sealing machine and aseptic area.

**6.5.3** Make sure that line clearance is duly checked and signed by IPQA personnel as per SOP.

**6.5.4** Enter the password and login in to the HMI. Select the validated set parameters recipe.

**6.5.5** Monitor the LAF pressure and ensure the requirements of class 100.

**6.5.6** Adjust the oxygen pressure between 0.3 to 0.5 Mpa and LPG using gas pressure between 0.03 to 0.05 Mpa.

**6.5.7** Ensure the ampoules which come from Depyrogenation tunnel to start the filling activity.

**6.5.8** The ampoules are passed continuously through infeed worm, which is turn transfer, the ampoules to filling station with the help of in feed star wheel.

**6.5.9** Check the five intermittent station are listed below before the batch start up



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- 6.5.9.1 Front charging station** Pass nitrogen in to the empty ampoules.
- 6.5.9.2 Filling station** Check the pumps rotation.
- 6.5.9.3 Rear charging station** Pass nitrogen in to the empty ampoules.
- 6.5.9.4 Pre heating station** Check the empty ampoules are preheated by the nozzles of LPG and oxygen then verify spin automatically by the idler wheel.
- 6.5.9.5 Sealing station** Ampoules are softened by heat and sealed.
- 6.5.10** Check alarm display and sensor challenge.
- 6.5.11** Run the machine three strokes, check there is any blockage.
- 6.5.12** Adjust the fill volume to be filled delivered from the filling pumps by piston movement through filling tubes and nozzles finally in the ampoules as BMR specification.
- 6.5.13** After getting the required volume, check & adjust post Nitrogen flushing pressure between 0.3 to 0.5 Mpa of the Ampoule & then run the Machine.
- 6.5.14** Check the volume of ampoules from each needle respectively. Ensure volume of individual Ampoule is within permissible volume limits specified in the BMR.
- 6.5.15** Perform the in process volume checks as frequency mentioned in BMR and record the details in respective BMR.
- 6.5.16** Then filled ampoules are moved to sealing station through preheating.
- 6.5.17** In pre heating station the ampoules neck are pre heated and the pre heated necks are gripped by the draw the tongs and sealed.
- 6.5.18** Perform the in process checks of sealed ampoules as frequency mentioned in BMR. Record the details in respective BMR.
- 6.5.19** Filled and Sealed Ampoules are collected in cleaned perforated SS trays.
- 6.5.20** Record the Operation details as per “**Machine Utilization Record**”



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### 6.6 PROCEDURE FOR ALARM HANDLING:

S.No.	Faults	Reason for Faults	Action for Rectification
1.	Infeed belt not moving	belt stuck gear damaged reducer damaged Position for in feed worm and in feed start wheel is not correct. Retaining spring piece damaged.	Stop the PLC. Manually the checks the motor functions and eliminate the motor fault and restart the filling machine. Check the reducer and gear movement and restart the filling machine.
2.	Ampoule is broken in feed worm	Ampoule in feed plate damaged. Position for in feed worm and in feed star wheel is not correct	Adjust the plate movement. Regulate the in feed worm and star wheel position.
3.	filling needles trips	Air Leakage in Filling tube Bubbles at filling tube suction return volume is too small Air leakage at manifold.	Verify the air pockets associated silicone tubes Verify the parameters and increase the suction return volume.
4.	Solution not filled	Sensor position is not correct. Pump is broken Liquid is not moving from the manifold.	Check and verify the piston movement. Check the function of the metering pump.
5.	Heating flame nozzle uneven	Pipe stuck-up	Verify the LPG and Oxygen pressure by adjusting rotameter. Adjust the Flame. Check the flame nozzle.
6.	No rotation during sealing	nozzle burned	1. Adjust the spin roller. 2. Check and verify the tooth belt synchronization. Keep roller dry.
7.	slightly burn during heating of the ampoules	Rotatory rubber wheel wear too much wheel do not compress the ampoules Rotatory tooth belt damage liquid on ampoule roller	1. Adjust the position of flame head. 2. Check the motor speed and adjust the speed in line with volume of heating flame.



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S.No.	Faults	Reason for Faults	Action for Rectification
		surface.	

### 6.7 PROCEDURE FOR ATTENDING AND DOCUMENTING INTERVENTIONS MANUALLY DURING FILLING AND SEALING

- 6.7.1** The term intervention is used to describe any aseptic manipulation or activity requires personnel in the aseptic processing area, it is accepted that are the most significant source of contamination.
- 6.7.2** Very few operations are performed in a click of button but most of the activities involve human interventions to control some of the manual operations like adjusting the fill weights, collecting the product samples, clearing the ampoules jam and fallen, broken ampoules etc.
- 6.7.3** Before and after attending the intervention sanitize the gloved hand with 70% IPA.
- 6.7.4** Interventions should not attend the simultaneously through either side of the filling machine at a time.
- 6.7.5** Personnel movement should be slow and rhythmic during interventions.
- 6.7.6** After rectification of problem, perform the sanitization of filling machine door and then gloved hand with 70% IPA and restart the filling and sealing operation.
- 6.7.7** Intervention occurred during filling operations shall be monitored and recorded in the respective intervention record for all the batches are filled.
- 6.7.7.1 Routine intervention:** The term used routine interventions that are regularly involved in aseptic filling process. The list of routine interventions as follows;
- 6.7.7.2** Aseptic assembling of sterilized machine parts.
- 6.7.7.3** Initial product connection.
- 6.7.7.4** Initial fill volume adjustment.
- 6.7.7.5** Periodic fill volume / weight checking & verification.
- 6.7.7.6** Handling of ampoule using forceps.
- 6.7.7.7** Operator break & meals.
- 6.7.7.8** Tea break for 30 minute.
- 6.7.7.9** Environmental monitoring (Active Air sampling).
- 6.7.7.10** Environmental monitoring (Passive Air sampling).
- 6.7.7.11** Operator Shift change.





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6.7.7.12 In process product sampling.

6.7.7.13 Gloves replacement.

6.7.7.14 Ampoule jammed.

**6.7.8 Non routine intervention:** The term used non routine interventions that are not regularly involved in the aseptic filling process.

6.7.8.1 Sensor adjustment or Replacement.

6.7.8.2 Piston / filling nozzle replacement.

6.7.8.3 AHU / Power failure of filling area off for 10 minute.

6.7.8.4 Filling room door open for 2 minute.

6.7.8.5 Machine breakdown activities for 15 minute (Minor).

6.7.8.6 Machine breakdown activities for 60 minute (Major).

6.7.8.7 Increase in no. of person for 15 minutes (Not more than 7 persons).

6.7.8.8 Highest filling machine speed.

6.7.8.9 Slowest filling machine speed.

6.7.8.10 Conveyer or guide rail adjustment.

6.7.8.11 Operator fatigue.

6.7.8.12 Product spillage.

6.7.8.13 Flame setting after burner on/ off.

6.7.8.14 Oxygen and LPG pressure Low.

**6.7.9 Handling of new interventions :**

6.7.9.1 New intervention also to be filled in the respective intervention record for the all the manufacturing batches.

6.7.9.2 Follow the below instruction when attending the new interventions.

6.7.9.3 Stop the filling activity and record in filling intervention record mentioning type of intervention.

6.7.9.4 Sanitize the filling machine door the glove hand with 70% IPA before entering in to the filling zone and after the filling interventions.

6.7.9.5 Make necessary adjustments to the equipment by using sterilized /sanitized tools.

6.7.9.6 Once adjustment work is done, ensure to run the machine with fewer units for smoother operations.



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**6.7.9.7** Remove and discard all the units empty/filled during these adjustments and purge the area for NLT 10 minutes.

**6.7.9.8** Operator who attends the new intervention should change the gloves before resuming the operations.

**6.7.9.9** This new interventions considered to simulate during next media fill validation.

### **6.7.10 Handling of LAF failure during filling activity:**

**6.7.10.1** Stop the filling machine activity Inform to engineering department through breakdown slip or SAP system.

**6.7.10.2** Inform to production head and QA HEAD and initiate the incident as per SOP.

**6.7.10.3** Segregate the filled ampoules and mark as LOT-I.

**6.7.10.4** Remove the empty ampoules which are present in the filling machine mesh conveyor removed and discarded .record the details in respective log book.

**6.7.10.5** Dismantle the filling items and send to unit preparation area through dynamic pass box for sterilization.

**6.7.10.6** Perform the area fogging, area cleaning and sanitization as per sop respectively.

**6.7.10.7** Assemble the sterilized machine parts and restart the filling and sealing Operation.

**6.7.10.8** Segregate the filled ampoules after restart the filling and sealing operation and mark as Lot II.

**6.7.10.9** Send finished goods sample from Lot I and Lot II separately for sterility test, this should be continued for all subsequent breakdowns, if any.

### **6.7.11 Machine Shutdown after working:**

**6.7.11.1** Firstly turn off LPG when converted flame blue to yellow.

**6.7.11.2** Turn off oxygen supply and then exhaust.

**6.7.11.3** Stop the PLC.

**6.7.11.4** Finally close the main utility supply valve (LPG & OXYGEN).

## **6.8 CLEANING:**

**6.8.1** Switch off the electric supply of the machine.

**6.8.2** Turn off the supply of nitrogen gas, oxygen gas and LPG.

**6.8.3** Dismantle the filling parts: - Syringes. Needles, Silicone Tubes etc. & transfer it to washing area (Equipment washing area) through the Dynamic pass box for its cleaning and sterilization.



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**6.8.4** Remove all the spread solution from the outer and inner side of the machine.

**6.8.5** Wipe all the guards, machine body & conveyor belt with WFI using lint free cloth.

**6.8.6** Clean all the guards, machinery & conveyor belt using 70% IPA solution spraying all over the Machine and by lint free cloth.

**6.8.7** Sanitize the surrounding area of the machine using scheduled disinfectant solution.

### **6.9 CLEANING OF FILLING & SEALING MACHINE CHANGE PARTS (SYRINGES, NEEDLES, AND SILICONE TUBES ETC.):**

**6.9.1** Flush out the dismantled parts using plenty of Purified water.

**6.9.2** Apply 0.2 % non-ionic liquid soap (Sodium Lauryl Sulphate) on all parts and clean it by using nylon scrubber. (If required).

**6.9.3** Wash all the dismantled parts thoroughly with Purified water thrice.

**6.9.4** Wash all the dismantled parts with WFI.

**6.9.5** Finally rinse all the dismantled parts with WFI and rinse sample to be analyzed for residual clearance.

**6.9.6** After wash all the dismantled parts dry with filtered compressed air.

**6.9.7** After dry all machine parts and tubing Rap with the help of sealing machine.

**6.9.8** All machine parts and tubing storage in 24 hours laminar air follow.

**6.9.9** After QA clearance, all machine parts and tubing to be sterilized in Autoclave as per validated load pattern.

### **6.10 FREQUENCY:**

Before use or every batch / product change over.

### **7.0 ANNEXURES:**

Not Applicable

**ENCLOSURES:** SOP Training Record.

### **8.0 DISTRIBUTION:**

- Controlled Copy No.01      Quality Assurance
- Controlled Copy No.02      Production
- Master Copy                      Quality Assurance



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### 9.0 REFERENCES:

Not Applicable.

### 10.0 REVISION HISTORY:

#### CHANGE HISTORY LOG

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