PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

PERFORMANCE QUALIFICATION

PROTOCOL

FOR

HOLDING VESSEL

EQUIPMENT ID. No.	
LOCATION	**FILTERATION AREA**
DATE OF QUALIFICATION	
SUPERSEDE PROTOCOL No.	**NIL**

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PROTOCOL CONTENTS

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

1.0 PROTOCOL APPROVAL:

PREPARED BY:

DESIGNATION	NAME	SIGNATURE	DATE
OFFICER/EXECUTIVE (QUALITY ASSURANCE)			

REVIEWED BY:

DESIGNATION	NAME	SIGNATURE	DATE
OPERATING MANAGER (QUALITY ASSURANCE)			
HEAD (ENGINEERING)			
HEAD (PRODUCTION)			

APPROVED BY:

DESIGNATION	NAME	SIGNATURE	DATE
HEAD (QUALITY ASSURANCE)			

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

2.0 OBJECTIVE:

- To carry out the Performance Qualification of Holding vessel 4000 Liter used for Holding of liquid eye drop preparation.
- To Provide Documented Verification that the Equipment as connected with ancillary system is suitable for indented purpose and produced product as per pre-defined acceptance Criteria

3.0 SCOPE:

- The scope of this qualification protocol is limited to qualification of Holding vessel (Make: Pharmatech Process Equipment) Installed in FilterationArea.

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

4.0 RESPONSIBILITY:

The Validation Group, comprising of a representative from each of the following departments shall be responsible for the overall compliance of this Protocol:

DEPARTMENTS	RESPONSIBILITIES
Quality Assurance	• Preparation, Review, Approval and Compilation of Performance Qualification Protocol. • Co-ordination with Production and Engineering to carryout Performance Qualification Activity.
Production	• Approval of Performance Qualification Protocol. • To Co-ordinate and support for execution of Operational Qualification study as per Protocol.
Quality Control	• Analytical Support (Microbiological Testing / Chemical Analysis)
Engineering	• Review of Performance Qualification Protocol. • To co-ordinate and support Performance Qualification Activity.

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

5.0 EQUIPMENT DETAILS:

Equipment Name	SS Jacketed Holding vessel
ID.Number	
Capacity	4000 Ltr.
Gross Capacity	4805 Ltr.
Manufacturer's Name	Pharmatech Process Equipment
Sr.No	
Model	cGMP Model.
Supplier's Name	Pharmatech Process Equipment
Location of Installation	Filtration Area

6.0 SYSTEM DESCRIPTION:

Application: Jacketed (Limpeted) Holding Vessel is used for Holding of Pharmaceuticals product (LVP).

System Components

Jacketed (Limpeted) Holding Vessel comprises of following parts.

• Shell

SS 316 L, Cylindrical, Vertical Shell, Top 10% Torispherical dish end & Bottom

10% Torispherical dish end welded to shell

Inside Surface Finish: Ra H 0.5 µm. Electro polish

• Limpet

SS 304, 4" NB x 3 mm Thick (Partial Limpet) @ 150 pitch Limpet coil.

• Insulation

38 mm Thick Armaflex insulation with 2 mm cladding on shell & 3 mm cladding on bottom cone. External surface finish: Ra H 0.9 µm. Mechanical polish

• Stirrer

Kweng make bottom entry magnetic stirrer

• Supports

3 Nos. of SS-304 Leg Support on load cell

• Facility Devices

For vessel top

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

Spray ball

Sterile Safety valve

Compound gauge

Rupture disc

Pneumatic operated (on/off) Diaphragm (PTFE with EPDM back up) valve for vent filter

Plain vent filter

Pneumatic operated (on/off) Diaphragm (PTFE with EPDM back up) valve for vent filter condensate

Temperature sensor with transmitter

Sterile steam trap

Piping & fittings

Halogen lamp

N2 Sparger tube

Manual operated Diaphragm (PTFE with EPDM back up) valve for sparger

Manual operated Diaphragm (PTFE with EPDM back up) valve for CA/N_2 transfer

Manual operated Diaphragm (PTFE with EPDM back up) valve for WFI inlet

Manual operated Diaphragm (PTFE with EPDM back up) valve for CIP inlet at spray ball

Pneumatic operated (on/off) Diaphragm (PTFE with EPDM back up) valve for SIP at spray ball

Pressure sensor with transmitter

Dip Stick

For vessel bottom

Manual operated flush bottom Diaphragm (PTFE) valve with manual operated sampling valve

For shell side

Resterilizable Diaphragm (Platinum cured silicon) Sample valve

Pneumatic operated (on/off) Diaphragm (PTFE with EPDM back up) valve for SIP of sample valve

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

Manual operated Diaphragm (PTFE with EPDM back up) valve for sampling

Temperature sensor with transmitter

Sterile steam trap

Piping & fittings

Temperature sensor with transmitter for vessel

For vessel limpet side

Pneumatic operated (on/off) Ball valve for steam inlet

Pneumatic operated (on/off) Ball valve for cooling water supply and return

Pneumatic operated (on/off) Ball valve for compressed air inlet

Safety valve for limpet

Pressure gauge for limpet

Pneumatic operated (on/off) Ball valve for limpet air vent

Auto steam trap unit

SS Braided hose pipe for utility

Other accessories

Load cell with IND 570 weight indicator

Variable Frequency drive

Pneumatic operated (on/off) Diaphragm (PTFE with EPDM back up) valve for

SIP at drain

Manual operated diaphragm (PTFE with EPDM back up) valve for CIP drain

Temperature sensor with transmitter

Sterile steam trap

Piping & fittings

Conductivity Sensor with Analyzer

Flexible hose for common drain header

Flexible hose, 1000 mm long (loose supply)

SS 304 fixed skid

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

7.0 REASON FOR QUALIFICATION:

- New equipment installed in Filtration Area.

8.0 SITE OF STUDY:

Filtration Area.

9.0 FREQUENCY OF QUALIFICATION:

- Yearly as per Validation Master Plan.
- After any major breakdown or after major modification.
- Change in Location.

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

10.0 PRE – QUALIFICATION REQUIREMENTS:

Verification for availability, completeness and approval status of all the required relevant documents shall be done and observations shall be recorded in the performance qualification report.

10.1 Training Record of Validation Team:

- All the persons involved in the execution of qualification activity must be trained in all aspects of the qualification activity including the test methodology, acceptance criteria and safety precautions to be followed during working.
- Verify the training records and record the details in table mentioned in performance qualification report.

10.2 Calibration of Test Instruments:

- Calibration of all the instruments used for qualification should be mentioned along with Calibration Certificates.

10.3 Biological Indicator Detail Should be mentioned in Performance Qualification Report.

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

11.0 TESTS & CHECKS:

11.1 Equipment Volumetric Capacity (In Liters) Test:

11.1.1 Objective:

- The purpose of this test is to demonstrate that Vessel Capacity provided is as agreed with the Equipment supplier and meeting User Requirement (4850 Liters total volume and 4000 Liters Working Volume).

11.1.2 Equipment /Instrument Used:

- Process Water: Calibrated Vessel/ QC equipment to measure required quantity for charging Water for Injection.

11.1.3 Method Applied:

- Charge 4000 litres of Process Water using calibrated cylinder/ vessel. Witness the quantity of Water received by the vessel without overflowing. Operate the equipment at process parameters as per SOP on operation & cleaning of manufacturing vessel
- Three consecutive trials must be tested as described before, in order to demonstrate Consistent performance.

11.1.4 Acceptance Criteria:

- Quantity of water charged shall not be less than quantity mentioned on Equipment Tag i.e. 4000 Liter +/- 0.3% (3999.7 to 4000.3)
- Equipment runs trouble free without any problems after charging material up to working volume i.e. 4000 Liters.

11.1.5 Result Recording:

- Measure the Equipment Volumetric Capacity (in liters) & calculate the result and record the results in Performance Qualification Report.

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

11.2 Equipment Volumetric Capacity (In Liters) Test By Chemical assay Method :

11.2.1 Objective:

- The purpose of this test is to demonstrate that Vessel Capacity provided is as agreed with the Equipment supplier and meeting User Requirement

11.2.2 Equipment / Instrument Used:

- Process Water: Calibrated Vessel/ QC equipment to measure required quantity for charging Water for Injection, Sodium chloride. (0.9%) packs.

11.2.3 Method Applied:

- Charge qty of water to 4000 Liter Manufacturing Tank of Process Water using calibrated cylinder/ vessel or through load cell. Witness the quantity of Water received by the vessel.
- Add NaCl (0.9%) to charged vessel.

Qty of Water	RPM of stirrer	Mixing Time
1000 Ltr	200 RPM	10 Min
1500 Ltr	200 RPM	10 Min
2000 Ltr	250 RPM	10 Min
2500 Ltr	250 RPM	10 Min
3000 Ltr	300 RPM	10 Min
3500 Ltr	350 RPM	10 Min
4000 Ltr	400 RPM	10 min

- Operate the equipment at process parameters as per SOP on operation of manufacturing vessel.
- After the completion of cycle take 100 ml of rinse sample & send to QC lab for assay.
- Repeat above process by adding water as per table ,each interval up to manufacturing capacity.
- During Volumetric Capacity (In Liters) Testing Read the Reading of Dip Stick & Record in Performance Qualification report.

11.2.4 Acceptance Criteria:

- Assay of NaCl should be between 0.882% W/V – 0.912%W/V
- Equipment runs trouble free without any problems after charging material up to working volume i.e. 4000 Litres.

11.2.5 Result Recording:

- Measure the Equipment Volumetric Capacity (in liters) and calculate the result and record the results in Performance Qualification Report.

11.3 Verification Of Uniformity Of Solution:

11.3.1 Objective:

- The purpose of this test is to ensure that Equipment Operates trouble free to prepare solution and solution prepared is homogeneous (without Lumps & clear solution) as seen visually and active contents are uniform.

11.3.2 Equipment / Instruments Used:

- Sodium Chloride & Water for Injection in sufficient quantity to make 4000 Ltr. Solution of 0.9 % NaCl.
- Sample collection using calibrated sampling rod.
- Sample containers or sample bags.

11.3.3 Method Applied:

- Charge 0.9% NaCl (Sodium chloride) in the Holding vessel along with Solvent. Agitate the mixture for defined duration & defined RPM.
- Temperature of WFI should be between 30-35 ° C
- Take the Samples at the after 5, 10 & 30 minute time interval of mixing of cycle. Sample to be taken at two locations at identified potential areas of poor mixing. Sample to be taken at top and bottom.
- Three consecutive trials must be taken at minimum, & Maximum RPM.

11.3.4 Acceptance Criteria:

- At the 05 minutes, take the sample & observe visually. The sample shall be free of lumps as seen visually
- At the 10 & 30 minutes interval of cycle take the100 ml sample from manufacturing tank & send the QC Lab for assay (98% to102%) & PH (5-7)
- The Equipment should operate trouble free throughout the operation cycle.

11.3.5 Result Recording:

- Record the results of in Performance Qualification Report record .

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

11.4 CIP (CLEAN IN PLACE):

11.4.1 HOLDING VESSEL WITH PRODUCT LINE:

A) OBJECTIVE:

To demonstrate that the system is to ensure that, the washing cycles are sufficient to remove residual impurities of previously manufactured product from inner surface of the Holding Vessel.

B) PROCEDURE:

- Collect 1000 Liter water for injection in Manufacturing Vessel..
- Add 40 Liters 5 % NaOH solution in the Vessel and start stirring for 10 min.
- After completion of 5% Sodium Hydroxide Mixing then recirculate, and Finally drain the solution from Manufacturing Vessel throw Product Line with the Help of Pump.
- Start CIP cycle as per SOP.
- Take print out from the CIP system for each cycle.
- Take Pre Rinse & Final Rinse Until Conductivity Not Achieved
- Performed CIP at 5 %, 10 % ,15% NaOH Concentration.
- After completion of CIP cycle, immediately collect Sample from Product Line drain and send to QC For pH & Conductivity Analysis.

C) RESULT RECORDING:

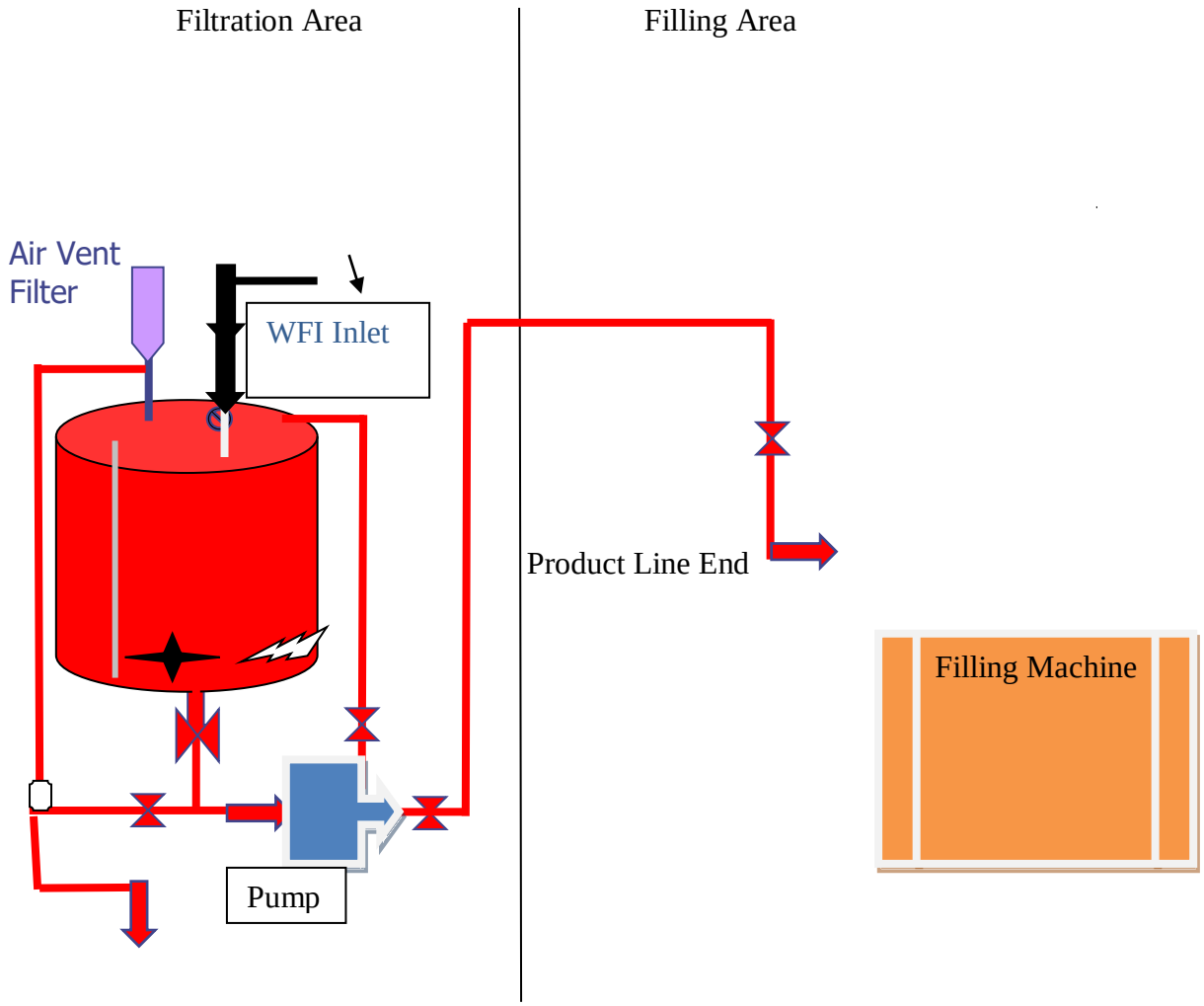
- Record the results in Performance Qualification Report

D) ACCEPTANCE CRITERIA:

- Finally rinsed WFI should meet the WFI specification
- pH (Limit 5-7)
- Conductivity (Limit: less than 1.2 µs/cm).
- Off Line Conductivity (Limit NMT 2.1 µs/cm).

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

LOGICAL DIGRAM FOR CIP PROCESS HOLDING TANK WITH PRODUCT LINE



PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

11.5 SIP (STERILIZATION IN PLACE):

11.5.1 HEAT DISTRIBUTION STUDY FOR HOLDING TANK :

A) OBJECTIVE:

- The Objective of heat distribution study is to provide a documentary evidence for a uniform temperature distribution in Equipment Connected with Steam Line by using12 Nos. of temperature probes.

B) EQUIPMENT / INSTRUMENTS

- Duly Calibrated Data logger with calibrated sensors
- Biological Indicator 10^6 spores i.e. *Geobacillus stearothermophilus)*

C) PROCEDURE:

- Check the calibration of Digital data logger and probes.
- Insert 11 nos. of Temperature probes in following locations, as schematically shown in system drawing for Manufacturing Vessel ,
- Insert 1 Nos Temperature Probe in Product Line end
- Seal the port with clamp to ensure no steam leakage during operation.
- Connect the Pure steam Line to the manufacturing Tank. Up to Product Line
- OPEN Steam Valve and start the Process
- Set the following parameters in PLC & operate SIP Function as per SOP and also start the data logger to record actual temperatures at every 10 second.

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

D) Location of External Probe with Biological Indicator

Sr. No.	Location	No. of Probes	ID No. of Probe	No. of BI.
First Digital Data Logger (Filtration Side)				
1.	Tank Drain	1 No.	1 No.	……
3.	Vent Filter	1 No	2 No	……
4.	In Side the Nitrogen Dip Tube	1No	3 No	……
5.	In Side the CIP Inlet	1 No	4 No	……
6.	In Side Recirculation Loop	1 No	5 No	1
7.	In Side The Tank	6 No	6,7,8,9,10,11, No	6 of each
Second Digital Data Logger (Filling Side for Product Line)				
1.	In Product Line end	1 No	1No	1 Nos

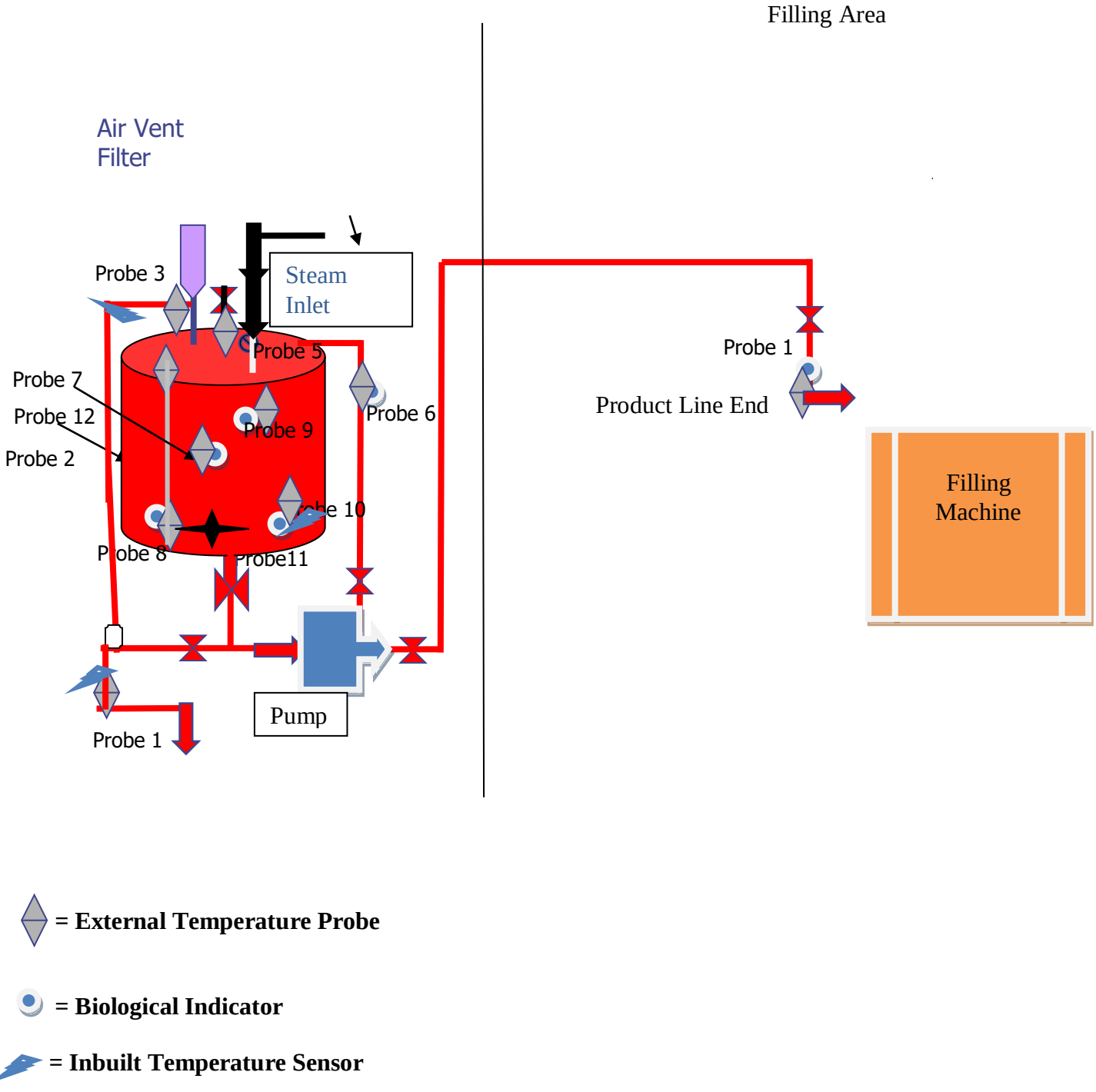
- Perform three consecutive SIP cycle for Manufacturing Tank with Product Line as per respective SOP at and 1.90 bar pressure for 30 minutes.
- Collect the BI sample from end of each Cycle and send to Micro lab for Testing

E) Parameter :

Parameter	Acceptance Criteria
Purging Time	002 Second
Sterilization Pressure	1.90 Bar
Pressure Dead band	00.02 Bar
Sterilization temperature	121.4 º C
Heating ON Temperature	123.5 º C
Heating OF Temperature	124.0 º C
Sterilization Hold Time	30 Minute
Sterilization Fail Temperature	119.0 º C
Overshoot Temperature	130.0 º C
Cooling Temperature	80 .0 º C

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

TEMPERATURE SENSOR & BI'S LOCATION FOR HOLDING TANK WITH PRODUCT LINE:



= **External Temperature Probe**

= **Biological Indicator**

= **Inbuilt Temperature Sensor**

11.5.2 BIO-CHALLENGE STUDY

A) OBJECTIVE:

The purpose of Bio-challenge study is to provide documentary evidence that the SIP cycle is capable to achieve microbial inactivation, to an SAL 10^{-6} by using *Geobacillus Stearothermophilus.*

B) PROCEDURE

- During the heat distribution study, place the biological indicator in a horizontal position in the following locations as specified in system drawing
- After completion of sterilization cycle remove the biological indicator with the help of safety gloves. Content of the ampoule are hot and under pressure. Allow to cool at room temperature for 10 to 15 minutes.
- Sent the exposed biological indicator to microbiology laboratory for incubation.
- After incubation observe the indicator for growth. (+ve when purple color change to yellow color, -ve when purple color remain as such).
- Place the processed units and one unprocessed unit (control) in a vertical position in an incubator at 55 -60^{0}C for 48 hours.
- Observe the incubated units after each 48 hrs and record the observation in respective format
- If exposed indicator shows positive results increase holding time and validate the cycle for this period to get minimum Sterility Assurance Level (SAL) 10^{-6}.Run three consecutive cycles.
- After 2 days incubation, all positive units should be discarded as per SOP.

A) ACCEPTANCE CRITERIA:

- If positive control unit does not show sign of growth consider the test invalid.
- A negative control unit should not show any growth during incubation.
- A failed sterilization cycle is indicated by turbidity or color change toward yellow in exposed biological indicator.
- Test unit that retains its purple color after sterilization indicates that sterilization parameters have been met.

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

11.5.3 F_0 CALCULATION

A) Numerical F_0 Value:

The actual observations obtained during the heat distribution study at different temperature sensing locations are complied in the table and the observed temperature shell be subjected for calculation of F0 values at that particular location. The lethality factor calculations are done by using the following formula and the computed (during the sterilization period) are given in the following table.

$F_0 = dt \sum 10^{(T-121)/Z}$ _____ (a)

$F_0 = dt \sum$ (Sum of lethality factors)

Where,

dt : Time interval between successive temperature measurements (in min).

T : Observed temperature at that particular time (as per the actual temperatures recorded)

Z = change in the heat resistance of Geobacillus stearothermophilus spores as temperature is changed (as mentioned in COA).

B) F_0 Value for Biological Indicators:

The biological Fo value for biological indicator strip exposed during the sterilization can be calculated as follows.

$Fo = D_{121} (\log A - \log B)$ …… (b)

Where,

D_{121}	D value of the biological indicator at 121^0C
A	Experimental Biological indicator concentration or spore population
B	Desired level of sterility (SAL- 10^{-6})

C) Desired Spore log reduction:

Calculate the desired reduction in spore population by using the formula-

$SLR_{desired} = \log A - \log SAL_{desired}$ ----------(c)

Where,

A	Experimental population of Biological Indicator
$SAL_{desired}$	Desired level of sterility (10^{-6})

D) Actual Spore log reduction:

Calculate actual reduction in spore population by using the formula-

$SLR_{Actual} = F_0 / D_{121}$---------- (d)

Where,

F_0 : Minimum calculated F_0 value

D_{121} : D value of the biological indicator at 121^0C.

E) ACCEPTANCE CRITERIA:

The calculated numerical Fo value of SIP cycle should be more than the biological indicator value, which is exposed in SIP validation.

11.0 CHECKLIST OF ALL TESTS & CHECKS

S.No.	Name of Test or Check	Execution (Yes/No.)	Remark
1.	Calibration Status of Test Instrument		
2.	Equipment Volumetric Capacity (in liters) Test		
3.	Equipment Volumetric Capacity (in liters) Test by		
4.	Verification of Uniformity of Solution		
5.	CIP		
6.	Heat Distribution Study (SIP)		

12.0 REFERENCES:

The Principle Reference is the following:

- Validation Master Plan.
- Schedule - M – "Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products."
- WHO Essential Drugs and Medicines Policy, QA of Pharmaceuticals, Vol-2.Good Manufacturing Practices and Inspection.
- SOP for "Operation & Cleaning of manufacturing Vessel".
- HTMS 2010
- PDA

13.0 DOCUMENTS TO BE ATTACHED:

- Test Report from QC lab
- Any other Relevant Documents.
- Calibration Certificate of test Instruments.

14.0 NON COMPLIANCE:

- In case of any Non compliance observed during PQ, inform to Head QA for necessary action. Document the details observed.
- The Head QA will study the impact of Non compliance. If Non compliance is acceptable and it does not have an impact on performance of the Qualification, prepare final conclusion.

15.0 DEVIATION FROM PRE-DEFINED SPECIFICATION, IF ANY

- In case of any deviation observed during PQ, inform to Head QA for necessary action.
- Document the deviation detail in observed deviation section.
- The Head QA will study the impact of deviation. If deviation is acceptable and it does not have an Impact on performance of the Qualification, prepare final conclusion & prepare final conclusion.

16.0 CHANGE CONTROL, IF ANY

- If any change control is required during PQ, inform to Head QA for necessary action.
- Document the details observed.
- The Head QA will study the impact of change. If change is acceptable and it does not have an Impact on performance of the Qualification, prepare final conclusion & prepare final conclusion.

PERFORMANCE QUALIFICATION PROTOCOL FOR SS JACKETED HOLDING VESSEL (4000 LITER)

17.0 ABBREVIATIONS:

%	:	Percentage
cGMP	:	Current Good Manufacturing Practices
ID.	:	Identification
Ltr.	:	Liter
MFT	:	Manufacturing vessel
Nacl	:	Sodium chloride
No.	:	Number
PPQ	:	Performance Qualification Protocol
QC	:	Quality Control
S.S	:	Stainless Steel
SOP	:	Standard Operating Procedure
WHO	:	World Health Organization