PERFORMANCE QUALIFICATION PROTOCOL FOR HOLDING VESSEL (1000 Litre)

EQUIPMENT ID. No.	
LOCATION	Filtration Room of Ampoule
DATE OF QUALIFICATION	
SUPERSEDE PROTOCOL No.	NIL

PROTOCOL CONTENTS

1.0 PROTOCOL APPROVAL:

PREPARED BY:

DESIGNATION	NAME	SIGNATURE	DATE
OFFICER/EXECUTIVE (QUALITY ASSURANCE)			

REVIEWED BY:

DESIGNATION	NAME	SIGNATURE	DATE
EXECUTIVE/MANAGER (QUALITY ASSURANCE)			
HEAD (PRODUCTION)			
HEAD (ENGINEERING)			
HEAD (QUALITY CONTROL)			

APPROVED BY:

DESIGNATION	NAME	SIGNATURE	DATE
HEAD (QUALITY ASSURANCE)			

2.0 OBJECTIVE:

- To carry out the Performance Qualification of Holding vessel 1000 Liter.
- 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 Filtration Room of Ampoule.

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	• Reviewing 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.

5.0 EQUIPMENT DETAILS:

Equipment Name	1000 Ltrs. Holding Vessel
ID. Number	SMH/A1/HV/004
Manufacturer's Name	Pharmatech Process Equipment
Location of Installation	Filtration Room of Ampoule
Capacity	1000 Ltrs. Working
Gross Capacity	1225 Liter

6.0 SYSTEM DESCRIPTION:-

System Components

Holding Vessel comprises of following parts.

- **Shell**

  Cylindrical, Vertical Shell having contact parts in AISI SS316 L, with welded top & bottom dished end, having man hole on top, vessel Inside surface finish Ra < 0.5 µm Electro polish.

- **Insulation & Cladding**

- 38 mm thk Armaflex Insulation with 2 mm thick SS 304 welded cladding on Shell and 3 mm on bottom dish. Outside Surface Finish: Ra ≤ 0.9 µm Matt finish (MP).

- **Stirrer**

  Provision (only weld plate) of Kweng make bottom entry magnetic mixer.

- **Supports**

  3 Nos. of SS-304 5" NB x Sch.10 S Pipe Legs with load cells.

- **Facility Devices**
  - Rotating spray ball
  - Safety valve
  - Compound gauge
  - Plain vent cum air filter
  - Pneumatic operated (on/off) diaphragm (PTFE with EPDM back up) valve for vent cum air filter isolation
  - Pneumatic operated (on/off) diaphragm (PTFE with EPDM back up) valve for condensate and integrity testing of vent cum air filter
  - Pressure gauge for vent cum air filter
  - Sterile steam trap for vent cum air filter
  - Temperature sensor with transmitter for vent cum air filter
  - Halogen lamp
  - Pressure sensor with transmitter
  - Pneumatic operated (on/off) diaphragm (PTFE with EPDM back up) valve for spray ball isolation
  - Pneumatic operated (on/off) diaphragm (PTFE with EPDM back up) valve for CIP recirculation
  - Pneumatic operated (on/off) flush bottom diaphragm (PTFE) valve for outlet with inbuilt manual sampling valve

- Pneumatic operated (on/off) diaphragm (PTFE with EPDM back up) valve for condensate of vessel
- Pneumatic operated (on/off) diaphragm (PTFE with EPDM back up) valve for CIP drain of vessel
- Pneumatic operated (on/off) diaphragm (PTFE with EPDM back up) valve for SIP of sample valve
- Sterile steam trap for vessel
- Temperature sensor with transmitter for vessel
- Temperature sensor with transmitter for vessel bottom
- Load cell with IND 570 indicator

7.0 REASON FOR QUALIFICATION:

New Equipment Installed.

8.0 SITE OF STUDY:

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9.0 FREQUENCY OF QUALIFICATION:

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

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.

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 1000 Liters Working Volume (1225 Liters total volume and 1000 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 1000 liters 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 Holding 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. 1000 Liter +/- 0.3% (999.7 to 1000.3)
- Equipment runs trouble free without any problems after charging material up to working volume i.e. 1000 Liters.

11.1.5 Result Recording:

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

11.2 RIBOFLAVIN CHALLENGE TEST (CIP STUDY):

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:

- Prepare 5 liter solution of 1% Riboflavin solution and 3% Starch solution in one container
- Apply riboflavin solution uniformly on the vessel and Nozzle.
- Allow the Vessel to dry (Say 20- 30 Minutes)
- Close all open conn. Provided on Vessel.
- Start CIP cycle as per SOP.
- Take Rinse until Conductivity not achieved.
- After completion of CIP cycle, immediately collect Sample from Product Line drain and send to QC for pH & Conductivity Analysis.
- Carry out visual inspection from inside of vessel surface under UV light.
- Adequate precautions to protect the eyes from UV radiation should be taken.
- The areas where having significant residue of Riboflavin, It will glow prominently under the UV illumination.
- Take print out from the CIP system for each cycle.

C) RESULT RECORDING:

- Record the results in Performance Qualification Report.

D) ACCEPTANCE CRITERIA FOR THIS TEST:

- Finally rinsed WFI should meet the WFI specification
- pH (Limit 5-7)
- Conductivity (Limit: less than 1.3 µs/cm).
- Off Line Conductivity (Limit NMT 2.1 µs/cm).
- No residue of riboflavin.

11.3 SIP (STERILIZATION IN PLACE):

11.3.1 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 using 11 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 Holding Vessel ,
- Insert 11 Nos Temperature Probe as per defined location as given in below table:-

D) Location of External Probe with Biological Indicator:

S.No.	Location	No. of Probes	ID No. of Probe	B.I No	No. of BI.
First Digital Data Logger (Filtration Side)					
1.	Inside tank (upper portion)	1 No.	01 No.	01	1
2.	Inside tank (upper portion)	1 No	02 No	-	……
3.	Inside tank (lower portion)	1No	03 No	-	……
4.	Inside tank (lower portion)	1 No	04 No	-	……
5.	In Bottom to product line(Buffer tank) near TS-7	1 No	05 No	02	1
6.	In Vent filter line near TS-8	1 No	06 No	03	1
7.	After Final filter-3 near TS-9	1 No	07 No	04	1
8.	After Final filter-3 near TS-10	1 No	08 No	05	1
9.	Inside Buffer tank	1 No	09 No	06	1
10.	Inside Buffer tank	1 No	10 No	-	……
11.	After Buffer vessel steam trap-9(ST-9)	1 No	11 No	07	1

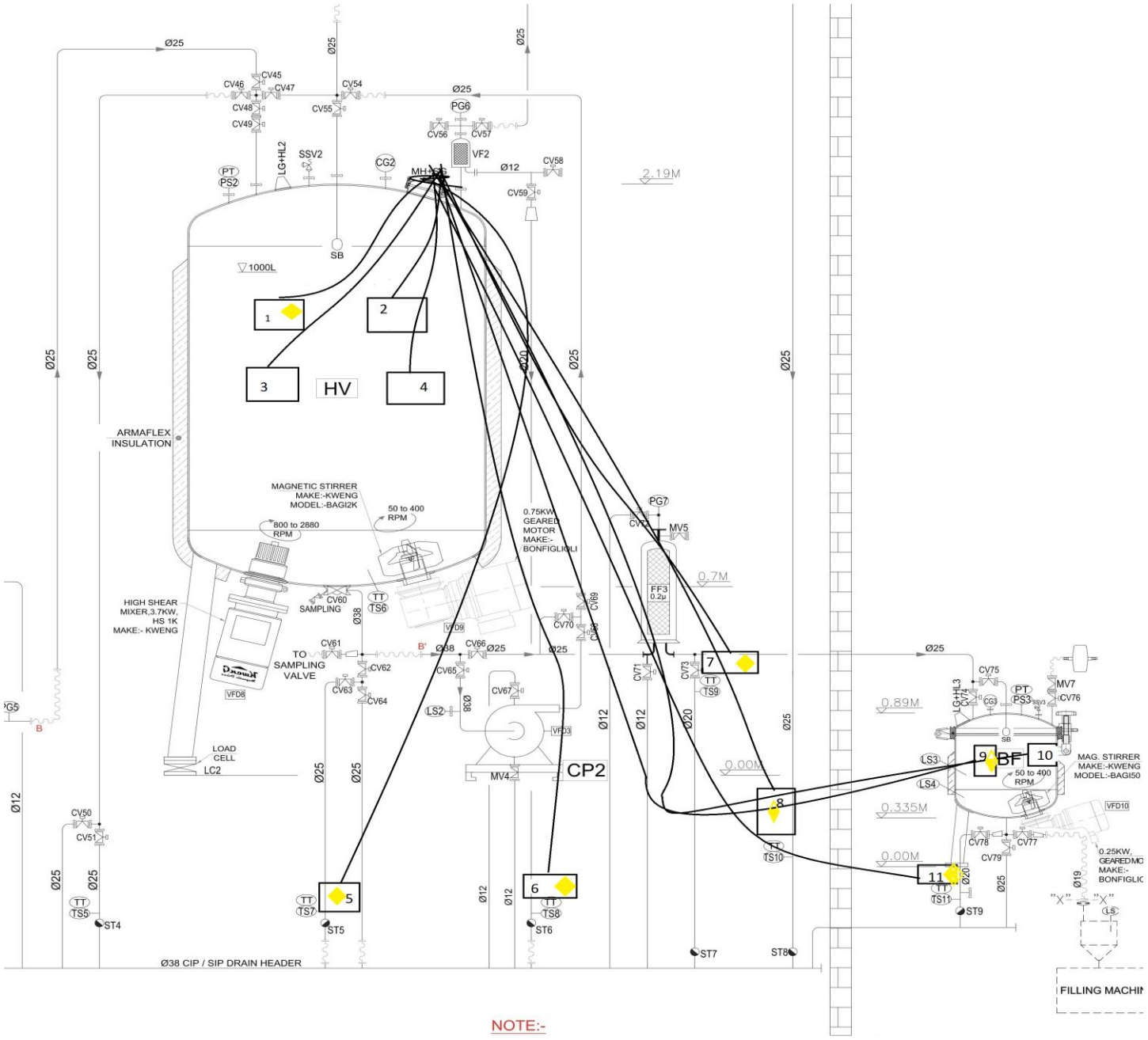
- Perform three consecutive SIP cycle for Holding Tank with Product Line as per respective SOP.
- Collect the BI sample from end of each Cycle and send to Micro lab for Testing.
- Seal the port with clamp to ensure no steam leakage during operation.
- Connect the Pure steam Line to the Holding Tank. 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 record actual temperatures at every 10 second.

E) Parameter :

Set Parameter	Value	Unit
Set leak test Pressure (PS1)	1.50	BAR
Leak test pressure stabilize time	60	SEC
Leak Rate NMT	0.30	BAR
Pressure Hold time	5	MIN
Sterilization temperature	122.0	°C
Sterilization stabilizing time	120	SEC
Sterilization Hold Time	30	MIN
Sterilization Fail Temperature	120.9	°C
Overshoot Temperature	140.0	°C
Cooling High pressure	1.50	BAR
Cooling Low pressure	1.20	BAR
Print interval	60	SEC

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



NOTE:-

= External Temperature Probe

= Biological Indicator with sensor **TS = Inbuilt Sensors**

11.3.2 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 table.
- 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 ^{0}C -60^{0}C for 48 hours.
- Observe the incubated units after each 24 hrs and record the observation in respective format
- If exposed indicator shows positive results increase 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.

11.3.3 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-

$SLR_{desired} = \log A - \log SAL_{desired}$ ----------©

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.

12.0 CHECKLIST OF ALL TESTS & CHECKS

S.No.	Name of Test or Check	Execution (Yes/No.)	Remark
1.	Calibration Status of Test Instrument		
2.	Volumetric Capacity in liter by measurement		
3.	Riboflavin Challenge test (CIP study)		
4.	Heat Distribution Study		

Verified By
(Quality Assurance)
Sign/Date: ……

Inference:

……

……

……

……

Reviewed By
(Quality Assurance)
Sign/Date: ……

13.0 REFERENCES:

The Principle Reference is the following:

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

14.0 DOCUMENTS TO BE ATTACHED:

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

15.0 NON COMPLIANCE, IF ANY:

- 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.

16.0 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.

17.0 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.

18.0 ABBREVIATIONS:

%	:	Percentage
cGMP	:	Current Good Manufacturing Practices
ID.	:	Identification
Ltr.	:	Liter
Nacl	:	Sodium chloride
No.	:	Number
PQ	:	Performance Qualification Protocol
S.S	:	Stainless Steel
SOP	:	Standard Operating Procedure
WHO	:	World Health Organization
A-1	:	Ampoule
HV	:	Holding Vessel

19.0 REVISION HISTORY:

Revision No.	Change Control No.	Detail of Changes	Reason for Change	Effective Date	Updated By
00	NA	NA	New Protocol		Naresh Kumar