PERFORMANCE QUALIFICATION

OF

TUNNEL STERILIZER

PERFORMANCE QUALIFICATION PROTOCOL OF TUNNEL STERILIZER (ANTICANCER LYO SECTION)

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1.0 PROTOCOL APPROVAL:

1.1 Protocol Prepared by:

AM - QA is responsible for the preparation of protocol for Performance Qualification of Tunnel Sterilizer.

NAME	DESIGNATION	SIGNATURE	DATE

1.2 Protocol Checked by:

Validation Core Committee Member responsible to review the Protocol for performance qualification of Tunnel sterilizer located in General vial section.

NAME	DESIGNATION	SIGNATURE	DATE

1.3 Protocol Approved by:

DGM - Tech is responsible to approve the performance qualification protocol.

NAME	DESIGNATION	SIGNATURE	DATE

PERFORMANCE QUALIFICATION PROTOCOL OF TUNNEL STERILIZER (ANTICANCER LYO SECTION)

2.0 OBJECTIVE:

The objective of this protocol is to establish sufficient data to assure that the Tunnel Sterilizer supplied by M/s ……. is suitable for Sterilization and Depyrogenation of Vials.

Performance Qualification Protocol shall provide the Methodology of qualification studies, Criteria of Qualification procedure and a guideline for documentation of the study. This validation protocol is intended to assure the Sterilization and Depyrogenation of the vials when the equipment is operated in accordance with standard operating procedure.

3.0 SCOPE:

3.0 These procedures are to be performed after the installation and operational qualification have been completed and approved.

3.1 These procedures are to be performed, as per the schedule given to assure that the system performance is consistent between the period, after completion of performance qualification study and before conducting a revalidation study.

3.2 These procedures are to be performed after any major modification of the equipment or relocation and for revalidation during appropriate intervals.

3.3 Any change in cycle parameters (set parameters).

3.4 To show that the Tunnel Sterilizer installed in the General vial section performs for its intended use.

4.0 RESPONSIBILITY

4.0 A plan to carry out the validation shall be prepared in the form of a protocol by the Task Force Leader.

4.1 The validation team members shall be responsible to carry out the validation.

5.0 ACCOUNTABILITY

5.1 Head – Quality Assurance.

6.0 METHOD

6.1 VALIDATION TEAM MEMBERS:

S.No.	Name	Department	
1.			
2.			
3.			
4.			
5.			
6.			

6.2 VALIDATION PLAN AND METHODOLOGY:

6.2.1 The Tunnel Sterilizer will be considered qualified for consistent and reliable performance (Validated) on successful completion of the following tests.

6.2.1.1 Calibration of Instruments.

6.2.1.2 Air Flow Direction, HEPA Filters Integrity, Air Velocity and Conveyer Speed.

6.2.1.3 Particle count testing.

6.2.1.4 Heat Distribution Study in empty static Tunnel (3 Trials)

6.2.1.5 Heat Distribution study in loaded Tunnel (3 Trials)

6.2.1.6 Spiking of Endotoxin Vials.

6.2.1.7 Heat Penetration Study with Loaded Tunnel (3 Trials for each Vial size)

6.2.1.8 Recovery of Spiked Endotoxin.

To qualify the equipment above tests should fulfill the acceptance criteria described in the individual test procedures. After completion of the qualification tests all the data generated will be compiled together to evaluate ability of the Tunnel Sterilizer to sterilize and Depyrogenate vials at the set parameters and set-loading pattern.

6.3 CALIBRATION OF INSTRUMENTS:

Instruments required for equipment qualification shall be calibrated at the start and at the end of qualification study as per the respective standard operating procedure of instrument calibration.
Instruments required for qualification

6.3.1 Data logger.

6.3.2 Flexible RTDs (Pt 100)

6.3.3 Stop Watch.

Note: Attach the copy of the calibration record.

6.3.4 **Calibration of Magnehelic Gauges:**

6.3.4.1 **Equipment and Instrument**

Digital Manometer; Calibration frequency: Yearly

6.3.4.2 **Procedure:**

6.3.4.2.1 Remove the air pressure tube inlet that is connection to the maghenelic gauge. Ensure that the `o' reading is shown on the maghenelic gauge. If necessary adjust to the `o' reading with the help of a `Turn screw'

6.3.4.2.2 Connect one end of the `Y' tube of the calibrator to the maghenelic gauge and other end of the tube to standard digital manometer inlet.

6.3.4.2.3 Switch `on' the digital manometer.

6.3.4.2.4 Crack open the `Air control knob' of the calibrator

6.3.4.2.5 Tighten the `Pressure release valve' of the `squeeze bulb'

6.3.4.2.6 Ensure that zero reading is displayed by the maghenelic gauge and digital manometer and record the observation.

6.3.4.2.7 Slowly press the `Squeeze bulb' until the pressure shown in the maghenelic gauge is just above the maximum range of the maghenelic gauge. (i.e. 50 mm)

6.3.4.2.8 Close the `Air control knob' and adjust the air control knob in such a way that pressure in the maghenelic gauge / digital manometer begins to reduce very slowly.

6.3.4.2.9 Record the reading of the maghenelic gauge when the digital manometer reading shows 10 mm of water

6.3.4.2.10 Similarly record the reading of the maghenelic gauge when the reading on the digital manometer is 15, 25, 50 mm of water.

6.3.4.2.11 If the reading(s) of the maghenelic gauge does not comply to the above requirement, recalibrate the instrument after making suitable adjustments.

6.3.4.2.12 If the readings do not comply even after adjustment, replace the gauge with new / spare calibrated maghenelic gauge. Document the observation

6.3.4.2.13 After the calibration is complete, release the ``Air control knob' and open the `Pressure release valve' of the `Squeeze bulb.'

6.3.4.2.14 Remove the `Y tube connection to the maghenelic gauge and reconnect the room air pressure tube the maghenelic gauge.

6.3.4.3 **Acceptance Criteria:**

All the measured readings shall be within ± 5% of the standard reading

6.4 Measurement of Air velocity:

6.4.1 Purpose

To demonstrate that the air system is balanced and capable of delivering sufficient air volume to maintain a minimum cross sectional velocity under the absolute filter.

6.4.2 Equipment and Instrument

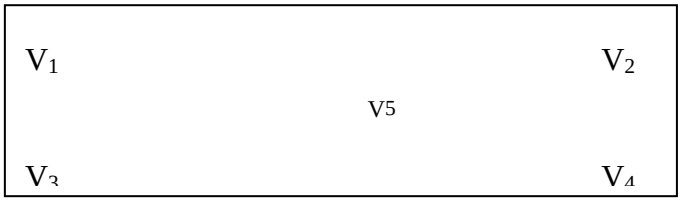
Anemometer Make: Dwyer or Lutron or Equivalent.

6.4.3 Procedure

6.4.3.1 These tests are executed on Supply diffuser.

6.4.3.2 Keep the Anemometer range as m/s mode.

6.4.3.3 Measure the Air Velocity in Feet per Minute for each filter by placing the sensor of instrument at approximately 6 inches below the grill and 6 inches away from the edge of filter grill. Take 5 readings as shown in figure and average the 5 readings.



6.4.3.4 Multiply the average velocity by the calibration factor of the instrument and record the readings.

6.4.3.5 Measurement should be taken for a minimum of 15 seconds.

6.4.4 **Acceptance Criteria**

6.4.4.1 Average Air Velocity should be 0.45 $\pm$ 20% m/s for all the laminar air flows of tunnel sterilizer.

6.5 Air Flow Direction (Smoke test):

6.5.1 **Purpose**

6.5.1.1 To demonstrate that the air – flow pattern in critical area (s) is from supply side to return side with uni – directional flow.

6.5.1.2 To demonstrate that the equipment configuration did not inhibit the air flow pattern, so that some portion remains un flushed with the filtered clean air.

6.5.2 **Equipment and Instruments:**

6.5.2.1 White visible or yellow smoke generator ($TiCl_4$ as smoke developer).

6.5.3 **Procedure:**

6.5.3.1 Generate $TiCl_4$ smoke by dipping the stick in $TiCl_4$ solution.

6.5.3.2 Place the stick at the Drying Zone Entry, Sterilization Zone and Cooling and Stabilization Zone.

6.5.3.3 Observe the airflow pattern and record with video camera.

6.5.3.4 Ensure that the conveyor is cleaned and sanitized immediately after performing the test.

6.5.4 **Acceptance Criteria**

6.5.4.1 The airflow movement should be from Supply filter Diffuser to the Return Air Grill and most Positive area to the adjacent lower positive areas with uni directional flow.

6.6 HEPA Filters Integrity Test [DOP (Di Octyle Phthalate)]

Note: Filter test shall be performed only after operational air velocities have been verified and adjusted wherever necessary.

6.6.1 **Procedure**

6.6.1.1 Position the smoke generator and introduce DOP smoke into the air stream, ahead of the HEPA filters, at the concentration of 80 – 100 µg per liter of air at the filter's designed air flow rating and set the instrument at 100% concentration. Scan entire area of the filter by passing the probe in the down stream side of the filter. The end of the probe should be held within approximately one inch of the filter and scanned at traverse rate of not more than approximately 10 ft / min (2 inches/second).

6.6.1.2 Any leakage greater the acceptance criteria observed during scanning shall be identified and recorded.

6.6.2 **Acceptance Criteria:**

6.6.2.1 During scanning percentage of the DOP penetration shown by photometer should be less than 0.01% through the filter media and should be "zero" through mounting joints.

6.7 Non – Viable Particle Count testing:

6.7.1 **Purpose**

To demonstrate that the air supplied from the filters is free form non viable particles or within the limit to maintain a Class 100 conditions in all the zones of Tunnel sterilizer.

6.7.2 **Equipment and Instrument**

Air Borne Particle Counter; Make: PMS

6.7.3 **Procedure:**

Set the particle counter in cubic meter mode and sampling Operate the particle counter as per SOP and place the probe at different locations of the zone area and record the readings.

6.7.4 **Acceptance Criteria:**

For all the Zones

$\geq$ 0.5 micron and larger – Not more than 100

$\geq$ 5.0 micron and larger – Not more than 0

6.8 Calibration of conveyor speed:

6.8.1 **Procedure:**

Set the conveyor speed at standard speed. Put the one vial on the conveyor at the entry of drying zone and start the conveyor and stop watch at the same time. Stop the stop watch and conveyor when the vial reach out the end point of the conveyor at stabilizing zone exit. Calculate the conveyor speed by using the following formula.

Conveyor speed = Length of the conveyor/ Vial traveling time on the conveyor

6.8.2 **Acceptance Criteria:**

Conveyor speed shall be with in $\pm$ 2% of the standard speed.

6.9 Heat Distribution Study in Empty static Tunnel:

6.9.1 Through the Drying Zone of the chamber distribute all the 12 probes into the tunnel sterilizer as per the load diagram.

6.9.2 Operate the Tunnel Sterilizer as per the standard operating procedure.

6.9.3 Switch on the Data logger.

6.9.4 Monitor the entire cycle for any deviations and observe the difference in temperatures of all the probes. Run and maintain the temperature in all locations after reaching required temperature for more than six minutes.

6.9.5 After performing the cycle connect the Data logger with the computer and down load the data.

6.9.6 If the performance is as per the Acceptance criteria repeat two more cycles to check the reproducibility.

6.9.7 Attach the data for the entire three empty chambers as Attachment No. 1.

6.9.8 Take the graphical presentation of all the 12 probes data of entire cycle and attach the same as Attachment - II

6.9.9 **Acceptance Criteria:**

6.9.9.1 Temperature should not differ significantly from the set temperature.

6.9.9.2 Temperature variations from location to location in Sterilizing Zone should not exceed $\pm$ 15°C.

6.10 Heat Distribution Study in Loaded Tunnel sterilizer:

6.10.1 Through the Drying Zone of the chamber load the required size of washed vials up to cooling zone of the tunnel sterilizer with the help of washing machine and distribute all the 12 probes into the tunnel sterilizer as per the load diagram.

6.10.2 Operate the Tunnel Sterilizer as per the standard operating procedure.

6.10.3 Switch on the Data logger.

6.10.4 Monitor the entire cycle for any deviations and observe the difference in temperatures of all the probes. Run and maintain the temperature in all locations after reaching required temperature for more than six minutes.

6.10.5 After performing the cycle connect the Data logger with the computer and down load the data.

6.10.6 If the performance is as per the Acceptance criteria repeat two more cycles to check the reproducibility.

6.10.7 Attach the data for the entire three empty chambers as Attachment No. 1.

6.10.8 Take the graphical presentation of all the 12 probes data of entire cycle and attach the same as attachment - II

6.10.9 **Acceptance Criteria:**

6.10.9.1 Temperature should not differ significantly from the set temperature.

6.10.9.2 Temperature variations from location to location in Sterilizing Zone should not exceed ± 15°C.

6.11 Spiking of Endotoxin Vials.

6.11.1 Spike the vials with Endotoxin as per the procedure given below.

6.11.2 Reconstitute the vial containing 100,000 EU / Vial of Endotoxin with 2.0 ml of LRW.

6.11.3 Vortex the vial for 30 minutes.

6.11.4 Dispense 0.2 ml in each into 10 vials.

6.11.5 Air dries the vials by keeping it under LAF over night.

6.12 Heat Penetration Study with Loaded Tunnel:

6.12.1 Load the Chamber with vials as per the loading pattern as per the load diagram.

6.12.2 Place all the probes as per the load diagram within the vials.

6.12.3 Place 10 spiked Endotoxin vials at different locations along with probes.

6.12.4 Operate the cycle as per the standard operating procedure.

6.12.5 Switch on the Data logger.

6.12.6 Monitor the entire cycle for any deviations and observe the difference in temperatures of all the probes. Run and maintain the temperature in all locations after reaching required temperature for more than six minutes.

6.12.7 After performing the cycle connect the Data logger with the computer and down load the data.

6.12.8 If the performance is as per the Acceptance criteria repeat two more cycles to check the reproducibility.

6.12.9 Attach the data for the entire three empty chambers as Attachment No. 1.

6.12.10 Take the graphical presentation of all the 12 probes data of entire cycle and attach the same as Attachment - II

6.12.11 **Acceptance Criteria:**

6.12.11.1 Temperature should not differ significantly from the set temperature.

6.12.11.2 Temperature variations from location to location in Sterilizing Zone should not exceed $\pm$ 15°C.

6.12.11.3 Minimum peak temperature above 300^0C for above six minutes should be achieved with in all parts of load.

6.13 Recovery of Spiked Endotoxin

6.13.1 Reconstitute the Endotoxin spiked vial containing 10,000 EU/0.2 ml vial with 4 ml of LRW.

6.13.2 Vortex for a minimum of 10 min. and make further dilutions as shown below.

S.No.	Endotoxin Concentration	Total Concentration
1.	0.1 ml of 2500 EU/ml + 0.9 ml LRW	250 EU/ml
2.	0.1 ml of 250 EU/ml + 0.9 ml LRW	25 EU/ml
3.	0.1 ml of 25 EU/ml + 0.9 ml LRW	2.5 EU/ml
4.	0.1 ml of 2.5 EU/ml + 0.9 ml LRW	0.25 EU/ml
5.	0.5 ml of 0.25 EU/ml + 0.5 ml LRW	0.125 EU/ml
6.	0.5 ml of 0.125 EU/ml + 0.5 ml LRW	0.0625 EU/ml

6.13.3 Test the dilutions at Sr.No. 5 and 6 in duplicate using the LAL having confirmed labeled sensitivity equal to 0.125 EU/ml and 0.0625 EU/ml respectively.

6.13.4 Analyze the sample as per GTP for Endotoxin testing.

6.13.5 Perform the same exercise for the other two loads.

NOTE: Vortex each dilution for at least 1 min. before making further dilution.

6.13.6 **Acceptance Criteria:**

6.13.6.1 More than three log reduction should be achieved in Endotoxin level when spiked and operated as per the GTP.

6.14 Action To Be Taken In Case of Failure:

If minimum sterilization and Depyrogenation temperature of 300°C is not achieved in one or more location(s) during sterilization hold period of Empty Tunnel Heat distribution cycle and Loaded Tunnel Heat Penetration cycle following action are taken:

6.14.1 Engineering department will be informed to check the calibration of instruments like temperature indicating probe, Digital temperature indicator, Data logger, etc. However all the instruments are checked for calibration before validation hence engineering departments will be asked to send the reference instruments for re-calibration to Calibration agencies. If fault is found due to error in calibration of Tunnel, Sterilization cycles will be repeated.

6.14.2 Engineering department will check mechanical operation of Heaters, Pre-filters, and any leakage through HEPA gaskets and other joints. If fault is found due to mechanical error, cycle will be repeated putting 2 probes in the location of lower temperature.

6.14.3 Necessary corrective actions will be taken to rectify the known (or identified) defect and a revalidation of the sterilization cycle will be undertaken before commencement.

6.15 FREQUENCY OF REVALIDATION:

6.15.1 **UNSCHEDULED REVALIDATION:**

6.15.1.1 For unscheduled revalidation empty chamber and loaded chamber revalidation shall be carried out. The pattern of the study shall be based on case-to-case basis and promptly documented.

6.15.1.2 Revalidation shall be carried out in case of the following.

6.15.1.3 Major Maintenance of Major parts.

6.15.1.4 Change of cycle program.

6.15.1.5 Inclusion of new load.

6.15.2 **REVALIDATION SCHEDULE:**

Validation criteria	Frequency
Calibration of all instruments e.g., Temperature monitoring probes, Magnelhelic gauges and conveyor speed.	Every six months
Air velocity measurement, Integrity testing of HEPA filters, Air flow direction and particle count testing.	Every six months
Empty Tunnel heat distribution studies (3 cycles)	Every six months
Loaded Tunnel heat distribution studies (3 cycles)	Every six months
Loaded chamber heat penetration studies (3 cycles for each size of vial with specific loading pattern)	Every six months.

7.0 RECORDING:

7.1 After completion of each study, a report shall be prepared by the validation team members which shall include the following information.

7.1.1 Tabulated Data.

7.1.2 Trend Analysis Plots.

7.1.3 Validation Team Members and their Signatures.

7.1.4 Summary Report

7.1.5 Evolution of results

7.1.6 Conclusions.

7.1.7 Quality Assurance Department Certification.

PERFORMANCE QUALIFICATION PROTOCOL OF TUNNEL STERILIZER (ANTICANCER LYO SECTION)

8.0 ABBREVIATIONS:

8.1 RTD → Resistance Temperature Device.

8.2 NMT → Not More Than.

8.3 NLT → Not Less Than.

8.4 GTP → General Test Procedure

8.5 LRW → LAL Reagent Water

8.6 EU → Endotoxin Units

8.7 E. Coli → Escherichia Coli

9.0 REFERENCES:

9.1 GTP → General Testing Procedure for Endotoxin Testing.

10.0 REVISION OF PROTOCOL:

10.1 Protocol has been changed due to the incorporation of HEPA filter integrity testing and air flow direction.

11.0 ANNEXURES:

11.1 Annexure – I → DATA SHEET FOR CALIBRATION DETAILS

11.2 Annexure – II → DATA SHEET FOR VALIDATION DETAILS