PERFORMANCE QUALIFICATION PROTOCOL FOR STERILIZING & DEPYROGENATING TUNNEL

EQUIPMENT ID. No.	
LOCATION	**Vial Washing and De-Pyrogenation**
DATE OF QUALIFICATION	
SUPERSEDES PROTOCOL No.	**NIL**

PHARMA DEVILS	PERFORMANCE QUALIFICATION PROTOCOL FOR AUTOCLAVE CUM BUNG PROCESSOR	PROTOCOL No.:

PROTOCOL CONTENTS

PHARMA DEVILS	PERFORMANCE QUALIFICATION PROTOCOL FOR AUTOCLAVE CUM BUNG PROCESSOR	PROTOCOL No.:

1.0 PROTOCOL APPROVAL:

INITIATED BY:

DESIGNATION	NAME	SIGNATURE	DATE
OFFICER/EXECUTIVE (QUALITY ASSURANCE)			

REVIEWED BY:

DESIGNATION	NAME	SIGNATURE	DATE
HEAD (PRODUCTION)			
HEAD (QUALITY CONTROL)			
HEAD (ENGINEERING)			

APPROVED BY:

DESIGNATION	NAME	SIGNATURE	DATE
HEAD (QUALITY ASSURANCE)			

2.0 OBJECTIVE:

The objective of this protocol is to establish that Sterilization & Depyrogenating tunnel meets the following criteria:

- The Sterilization and Depyrogenating tunnel performs as per the pre-defined parameters and/or quality attributes.

3.0 SCOPE:

- The Protocol covers all aspects of Performance Qualification for the Sterilizing and Depyrogenating Tunnel **(Make – Fabtech Technologies Pvt. Ltd.)** installed in the Vial Washing & Depyrogenation.
- This Protocol will define the methods and documentation used to qualify the Sterilizing and Depyrogenating tunnel for PQ.

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	○ Initiation, Approval Compilation and Authorization of the Performance Qualification. ○ Co-ordination with Quality Control, Production and Engineering to carryout Performance Qualification Activity. ○ Monitoring of Performance Qualification.
Production	○ Review of Protocol. ○ To co-ordinate and support Performance Qualification Activity.
Quality Control	○ Review of Protocol. ○ Analytical Support (Microbiological Testing / Analysis)
Engineering	○ Reviewing of qualification protocol for correctness, completeness and technical excellence ○ Responsible for trouble shooting (if occurred during execution). ○ Maintenance & preventive maintenance as per schedule.

5.0 EQUIPMENT DETAILS:

Equipment Name	Sterilizing and De-pyrogenating Tunnel
Equipment ID.	…….
Manufacturer's Name	Fabtech Technologies Int. Pvt. Ltd.
Supplier's Name	cGMP Model
Model	Fabtech Technologies Int. Pvt. Ltd.
Location of Installation	Vial Washing and Depyrogenating Tunnel

6.0 SYSTEM DESCRIPTION:

The Unit:

- The **Fabtech** Sterilization & De-Pyrogenating Tunnel is used for sterilization and De-Pyrogenation of Glass Vials of various Sizes, enabling the integration of the process of Dry Powder Injection Automatic Filling under Aseptic Conditions in which all activities are performed under grade A or class100 area.
- The vials are washed and reloaded on the tunnel, with the help of wire loop conveyor, enter in to the drying zone where vials get dried up and passes to sterilizing zone where vials are heated to more than 300 Deg. C for not less than 3 minutes or equivalent time to make it depyrogenation.
- The height of receptacles must not exceed 100 mm. The useful belt width for carrying the vials is 450 mm. The air damper plate is adjusted for vials.
- The Sterile receptacles are then unloaded directly into the sterile area. This process eliminates intermediate Material Handling and the potential for product contamination during those steps no longer exist.

➢ **DRYING ZONE:**

- In the feed area, the air taken from the room is pre filtered and aspirated by a blower through HEPA filter. The Laminar flow of air is sent vertically down on to the containers.
- As the containers reach near the sterilizing zone, they are preheated up to 90 °C – 110 °C by the Hot Air Bleeding out of the Sterilizing Zone. This air along with water vapour is picked up underneath of the conveyor belt by the extract blower and ejected to outside.
- The Conveyor system is controlled by the container accumulation at in-feed and the set temperature point for "Conveyor Start".

➢ **STERILIZING ZONE:**

- The dried containers are moved over to the sterilizing zone. The Sterilizing Zone mainly comprises of resistance heating elements, HEPA Filter and Temperature Sensing Devices. Hot filtered air at more than 300 °C is re-circulated in this zone which sweeps the containers from top to bottom. The equal pressure drop across the filters enables in creating an extremely even distribution of air circulation. This uniformity distributed hot air sterilizes and de-pyrogenates the containers by heating the containers at more than 300 deg. C for more than 03 minutes.
- Due to the over pressure in the sterilizing zone (normal air quantity passing into the area through heater terminals and Hot air turbine shaft) small amount of air flows to the Drying & cooling zones thus allowing adequate exchange of air.

➢ **COOLING AND STABILIZING ZONES:**

- In this area (arrangement are similar to that of Drying Zone) the containers are subjected to laminar flow of HEPA filtered air taken from the room. The air flow is profiled in such a way that the Glass Temperature as it exited the sterilizing zone would be transitioned at a nearly linear rate. This zone is long enough to significantly reduce the stress between the 300℃ – 25 ℃ range resulting in reduced breakages.
- The exhaust blower below the conveyor belt extracts heated air and ejects outside.
- Stabilizing zone is similar to the drying zone and is used as a transition area separating the critical between filling area and washing area. This is achieved by controlling the air volume exhausted by adjusting the damper provided.
- At the tunnel out feed, the glass container / Vials are bulk-feed into the in feed turn table of the downstream machine. Proximity switches provided on in feed and out feed control conveyer movement with reference to container accumulation and loading.

USE:

1. To Sterilize and De-pyrogenating Various Sized Glass vials which shall be transferred to the Aseptic Area for Aseptic Filling of the Drug Product.

7.0 REASON FOR QUALIFICATION:

- New equipment in Sterilization & Depyrogenating Tunnel.
- After completion of the Operation Qualification of the Equipments, it is imperative to perform the Performance Qualification. The study will establish that the parameters are followed, critical variables are under control and the quality of the output is, as desired.

8.0 SITE OF STUDY:

Vial Washing & Depyrogenation area.

9.0 FREQUENCY OF QUALIFICATION:

- Once in six month ± 30 Days.
- After any major breakdown or after major modification.
- After Change of Location.

10.0 PRE – QUALIFICATION REQUIREMENTS:

The below mentioned activities should be completed prior to commencing the performance qualification activity:

- Design Qualification.
- Installation Qualification.
- Operational Qualification.
- Calibration of all critical instruments which are used for verifying the performance such as Anemometer, Photometer, Particle Counter & Duly Calibrated Data Logger with temperature sensors.
- Preparation of SOP for Operation & Cleaning of Sterilizing & De-Pyrogenation Tunnel.
- Preparation of SOP for Preventive Maintenance Sterilizing & De-Pyrogenation Tunnel.

11.0 TESTS AND CHECKS:

11.1 FILTER INTEGRITY TEST FOR HEPA :

- **Objective:**

  To check the Integrity of the each HEPA Filters installed in the Sterilization & Depyrogenating tunnel.

- **Equipment / Instruments Used:**
  - Calibrated Aerosol Generator
  - Calibrated Aerosol Photometer.

- **Method Applied:**
  - Before starting the test start the Depyrogenating Tunnel before one hour.
  - Check PAO solution level aerosol photometer tank.
  - Connect the compressed air to aerosol photometer.
  - Orient the supply tube of aerosol toward the riser and orient the PU (for downstream concentration) tube on opening of supply aerosol tube – than check the upstream concentration 100 % above the HEPA through port.
  - Keep the aerosol supply tube near the riser grill.
  - Scan the supply grill (HEPA grill) for checking filter integrity test, Adjust the concentration of aerosol above HEPA 100 %.

- **Acceptance Criteria:**

  During Scanning, leakage penetration should not be more than 0.03%.

- **Result Recording:**

  Record the results in the Performance Qualification Report and record the details of the instruments used including its Calibration Status.

- **Evaluation of Result:**

  Results, complying with the Acceptance Criteria, shall establish the Integrity of each HEPA Filters suitable for clean area. If any leakage is observed from the mounting, it has to be rectified through adjustment and application of Food Grade Silicon Sealant.

11.2 AIR VELOCITY MEASUREMENT:

- **Objective:**

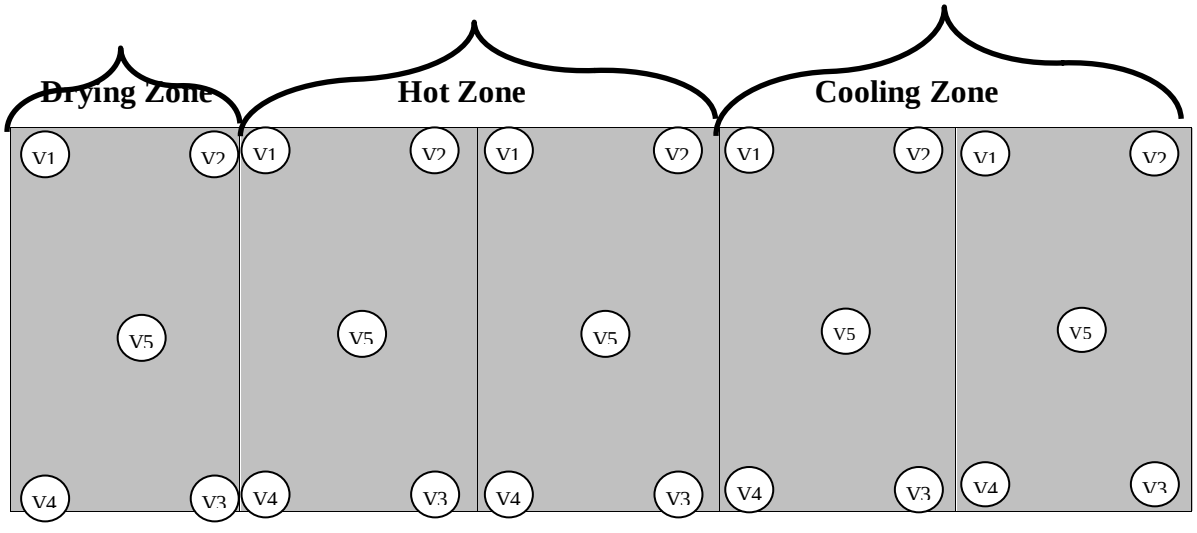
  To demonstrate that the system is capable of delivering Air Velocities as per the requirement and to maintain continuous Laminarity under the HEPA filter.

- **Equipment / Instrument Used:**

  Digital Anemometer

- **Method Applied:**

  Ensure that the Sterilization & Depyrogenating Tunnel blower is switch **"ON"** at least 30 minutes prior to the start of the observations. Measure the Air Velocity 150 mm below the grill, at 5 locations of each filters (Four Corners and Center shown in fig.) with the Digital Anemometer and record. Calculate the Average Velocity of air coming from Supply Grill.



Sampling Locations

- **Acceptance Criteria:**
  - Average velocity across the HEPA filter should be within the range as per design.
  - Average velocity variation should not be more than 5% of designed velocity.

Sr. No	Zone	Average Velocity
1.	Drying Zone	120 ft. / min. ± 20% (96 to 144 ft. / min.)
2.	Hot Zone	150 ft. / min. ± 20% (120 to 180 ft. / min.)
3.	Cooling Zone	120 ft. / min. ± 20% (96 to 144 ft. / min.)

- **Result Recording:**

  Measure the Air Velocity at Five Locations (Four Corners and Center) of each HEPA Filters & calculate the Average Velocity of Filter and record the results in the Performance Qualification Report.

- **Evaluation Of Result:**

  If velocity is not within the specified limit, check the Motor Blower Assembly and Differential Pressure across the each HEPA Filters for any Abnormal Condition. If the Minimum Velocity is not achievable, Filters should be changed, irrespective to other test complying with the acceptance criteria.

11.3 NON - VIABLE PARTICLE COUNT TEST:

- **Objective:**

  To establish that critical locations of Sterilization & Depyrogenating Tunnel meet the requirement for desired cleanliness.

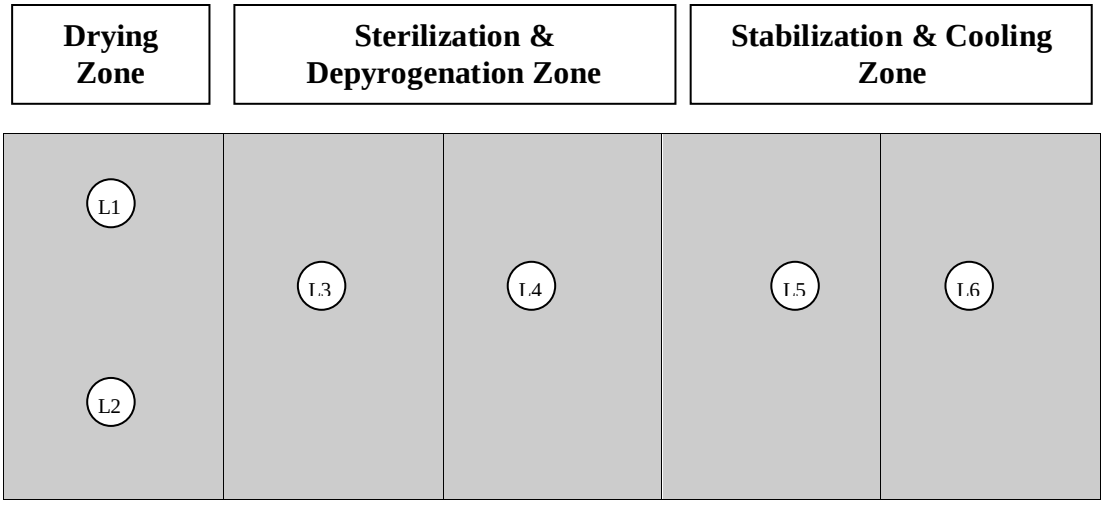
- **Equipment / Instrument Used:**

  Non- Viable Particle Counter

- **Method Applied:**
  - Start the Sterilizing and Depyrogenating tunnel as per respective SOP.
  - Ensure that the blower of the Sterilization & Depyrogenating Tunnel is running and Heater is not in "ON" condition.
  - Place the Probe of Non – Viable particle counter at the locations described below, approximately 60mm above the surface of conveyor and observes the readings.
  - Take the readings from different pre determined locations as per below mentioned table. Finally Average shall be calculated as per the guideline.
  - Three Consecutive Runs shall be carried out for Monitoring of Non - Viable Particle counting of Sterilizing & Depyrogenating tunnel.

a) Dimensions of the Tunnel are as below:

S.No	Zone Name	Total Area A=L X W in Meter	$\sqrt{A}$ in Meter^2	No. of Location For Non – Viable Particle Count
1.	Drying Zone	1.38 X 0.710	0.9898	02 Nos.
2.	Sterilizing Zone	1.490 X 0.910	1.1644	02 Nos.
3.	Stabilizing & Cooling Zone	0.710 X 0.710	0.710	02 Nos.



Sampling Locations

- **Acceptance Criteria:**

Grade	Maximum number of permitted particles per cubic meter equal to or above.	
	≥ 0.5 µm Particle	≥ 5 µm Particle
A	3520	29

- **Result Recording:**
  Measure the Non - Viable Particle Count at mentioned Locations & record the results in the Performance Qualification Report.

- **Evaluation of Result:**
  In case the particulate does not meet the requirement, investigation shall be carried out and proper action shall be taken. Non - Viable Particle Count shall be taken again after rectification.

11.4 PROCEDURE:

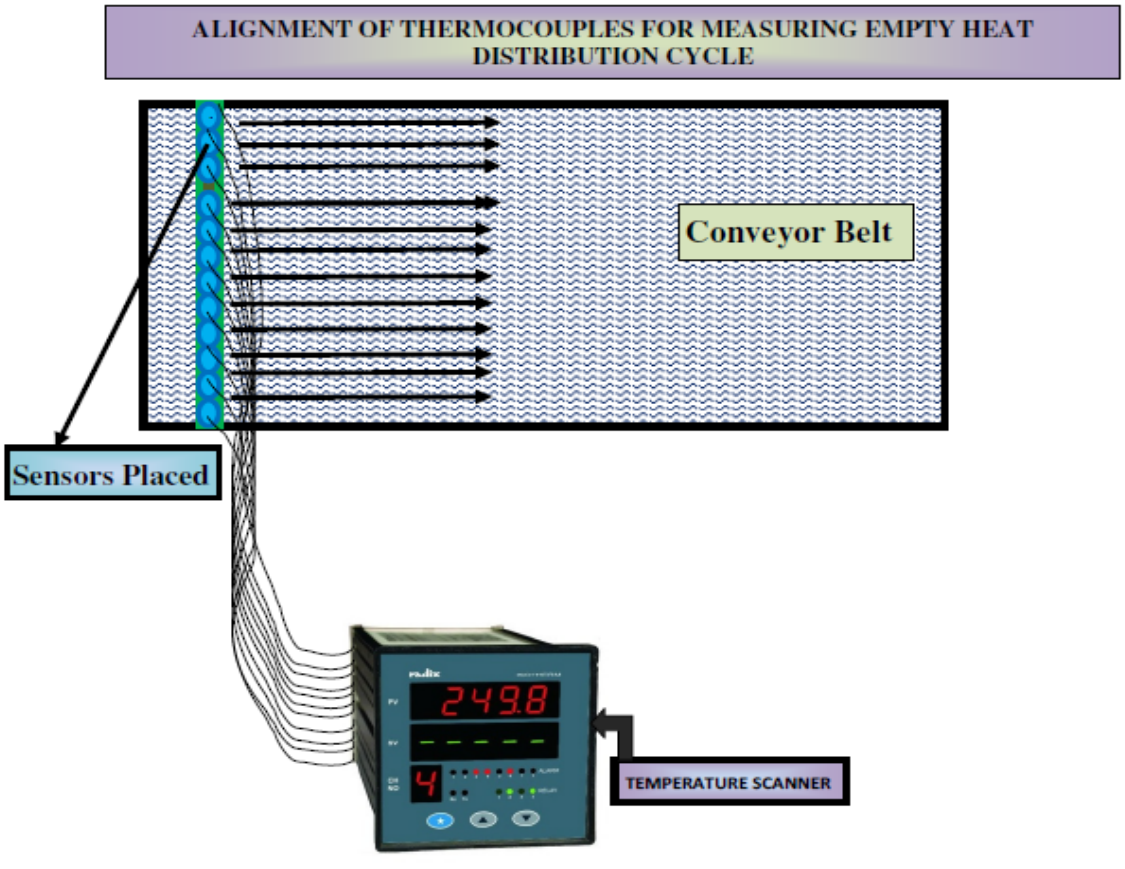
- **Pre & Post Calibration of Temperature Sensors:**
  - Pre & Post calibration shall be carried out before starting and after completion of Heat Distribution Cycle as well as Heat Penetration Cycle.
- **Preparation of Ice Bath:**
  - Prepare a container with Crushed Ice and add sufficient Purified Water to ensure a proper Slush Solution.
  - Allow the Temperature to Stabilize. Ensure to add Sufficient Crushed Ice to Maintain the Equilibrium State of Ice and Water.
- **Procedure:**
  - Temperature sensors which are to be used for Performance Qualification study shall be qualified in Ice Bath at approximately 0 °C and in oil bath at 50°C, 100°C, 150°C, 200°C, 250°C, 300°C, 350°C, & 400°C prior to its usage in the qualification.
  - Record the Temperature of all the sensors while putting it in ice bath. Record the data for at least five minutes after putting all the sensors to the ice bath there by allowing the temperature to stabilize.
  - Record the data for Five Minutes by data logger and attach the print out with report.
  - Put individual sensor to the slot of High Temperature reference block which is stabilized at different set of temperature. Record the readings after at least one minute after stabilization of temperature.
  - Record the Temperature for Five Minutes by data logger and attach the print out with report.
- **Acceptance Criteria :**
  - The mean of all the temperature sensors should not vary by ± 5°C from the Temperature recorded by the calibrated thermometer during data recording.

11.5 HEAT DISTRIBUTION STUDY FOR EMPTY CHAMBER

- **Objective :**
  - To ensure that the Sterilization & Depyrogenating Tunnel when operated with Empty Chamber is capable of producing the Temperature Profiles as per the temperature set points set in the PLC of the equipment.
  - To ensure that the Temperature Distribution is uniform throughout the Sterilization & Depyrogenating Period.
  - Consecutively three Run shall be performed to qualify the measurement of the Temperature throughout the Chamber by 12 Temperature Sensors during the Sterilization and Depyrogenating Cycle.

- **Equipment Required:**
  - Calibrated Data Logger with 12 Probes.

Figure-01 Thermocouples Placed Location Diagram for Empty Heat Distribution

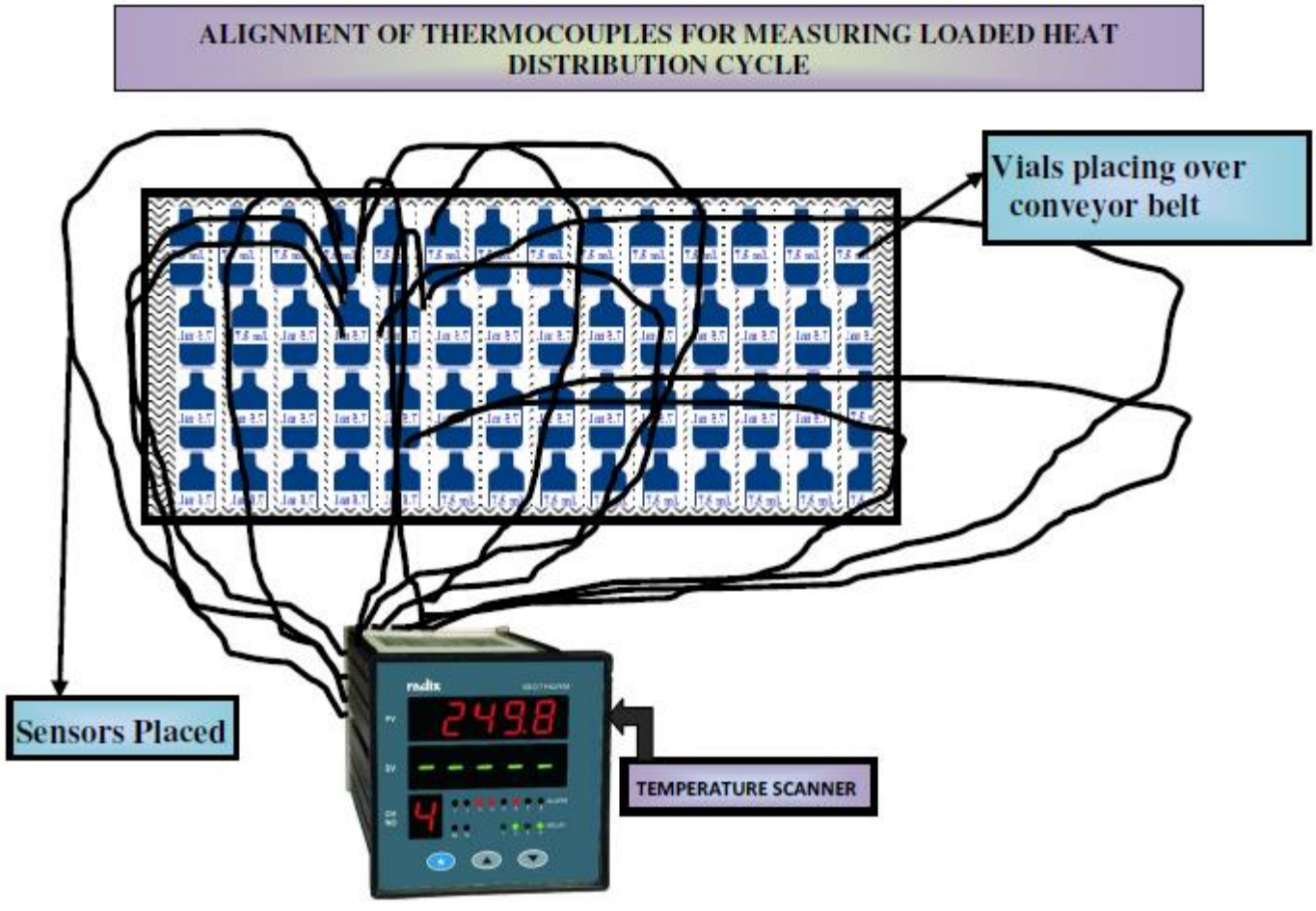


- **Procedure :**
  - Heat distribution studies are to be performed in order to determine temperature variation throughout the depyrogenating tunnel especially in the depyrogenation zone in running condition of the conveyor. Simultaneously start the data loggers to scan and record the temperature output from the 12 Thermocouple.
  - Allow to pass all the 12 thermocouples throughout the length of the sterilizing tunnel, into the cooling zone. Record the data throughout the cycle.
  - Set the 12 calibrated thermocouple inside the drying zone of the sterilizing tunnel (as per defined location in Figure-01).
  - Thermocouple should not touch the internal walls of the sterilizing zone.
  - Set the parameter of the Thermocouple in the data-logger. Also set the other parameter of the data loggers like
    - Scanning and recording interval time : 15 second
    - Probe numbering : Probe 1 to Probe 12
    - Date : As applicable
    - Data / cycle No. : As applicable
  - Operate the sterilizing tunnel and allow attaining temperature to 330^0C. In the sterilizing zone of the tunnel, keeping the entrance gate of the drying zone closed.
  - Start the data loggers to scan and record the temperature output from the 12 Thermocouple.
  - After attainment of the pre-set temperature of the sterilizing tunnel start the tunnel conveyor at a speed of 140 mm/minute and open the entrance gate of the sterilizing.
  - Down load the data recorded from the data loggers to the software and get the hard copy of the data.
  - Run three cycles and record the data.
  - Allow to pass all the thermocouples throughout the length of the sterilizing tunnel, into the cooling zone. Record the data throughout the cycle.

11.6 HEAT DISTRIBUTION STUDY FOR LOADED CHAMBER

- **Objective :**
  - To ensure that the Sterilization & Depyrogenating Tunnel when operated with Loaded Chamber of different-different size of vial is capable of producing the Temperature Profiles as per the temperature set points set in the PLC of the equipment.
  - To ensure that the Temperature Distribution is uniform throughout the Sterilization & Depyrogenating Period.
  - Consecutively three run shall be performed to qualify the measurement of the Temperature throughout the chamber by 12 temperature sensors during the Loaded of different-different size of vials.

Figure-02 Thermocouples Placed Location Diagram for Loaded Heat Distribution



- Suspend the probe in the chamber as zigzag position (Refer figure-2) in such a way that probes don't touch any metallic surface or vial. Record the position of the probe in a representative schematic manner.
- Connect the probes to suitable data logger, which can scan and print the actual temperature observed at different locations with respect to time.
- On the basis of three consecutively cycles run, Temperature profiling for specified vial size has been developed in-terms of minimum temperature and maximum temperature location can be identified by the running of heat distribution for loaded.
- Operate the Sterilizing & Depyrogenating Tunnel as per current version. Also start the data logger to record the actual temperatures with respect to time.
- After completion of Sterilization Cycle "Switch OFF" the data logger.
- Collect printout from the printer of Sterilizing & Depyrogenating Tunnel.
- Download the data from the data logger in the computer for the data analysis and printing enclosed the printout obtained from the data logger.
- Following formulas shall be used for Calculation of Conveyor Belt Speed & Sterilization:

$$\textbf{Belt Speed in mm} = \frac{\textbf{(Vial Diameter)}^2 \textbf{ X cos 30 X M/C Out put}}{\textbf{Tunnel Conveyor Width}}$$

$$\textbf{Sterilization hold time} = \frac{\textbf{Length of sterilization Zone}}{\textbf{Conveyor Belt Speed}}$$

- **Acceptance Criteria**
  - A Minimum Exposure Time of Total 03 minutes should be achieved at Depyrogenating temperature of 300 °C & above.
- **Observations And Results**
  - Record the temperature at various locations in Performance Qualification Report.
- **Evaluation Of Result**
  - Any location(s) where the Temperature Sensor is placed, achieving Minimum Sterilization & Depyrogenating Temperature of above 300°C during Sterilization and Depyrogenating Period shall be considered as Cold Spot.

    If Depyrogenating temperature (More Than 300°C) is not achieved throughout the cycle, then

Temperature Set Points Adjustment, Modifications or Repair shall be performed and the Heat Distribution Studies shall be repeated.

11.7 HEAT PENETRATION STUDY FOR LOADED CHAMBER:

- **Objective**

- To ensure that, heat is sufficiently penetrating into the innermost portion of the vials subjected for sterilization & Depyrogenating to achieve desired temperature i.e. more than 300°C during the sterilization & Depyrogenating cycle.
- Loaded chamber Heat Penetration Studies shall be conducted for consecutively three cycles with Temperature Probes for Different vials size i.e. 5ml, 10ml & 20ml vials.
- To ensure that, Heat is sufficiently penetrating into the innermost portion of the vial subjected for Sterilization & Depyrogenating to achieve desired Temperature i.e. More Than 300°C using Endotoxin Challenge Test.
- Endotoxin Challenge Test shall be conducted all heat penetration cycles which are going for Validation.
- The recovery of Endotoxin Concentration after exposing to Sterilization & Depyrogenating Tunnel should show more than 3 log reduction.
- Three run shall be performed to qualify the measurement of the Temperature throughout the tunnel by 12 Temperature Sensors during the sterilization cycle.

- **Equipment Required**

- Calibrated Data Logger with 12 Probes.

- **Procedure**

- Conduct the study with loaded chamber for three consecutively cycle with Calibrated Temperature probes of each vial size.
- Suspend the minimum 05 Temperature Sensors (including hot & cold locations) inside the vials and put into tunnel for Heat Penetration Study.
- Record the position of the probes in a representative schematic form.
- Insert 3 Endotoxin vials (Marked Vials) having 10000 EU each along with the temperature sensors in each cycle.
- Connect the probes to suitable data logger, which can scan and print the actual temperature observed at different locations with respect to time.
- Operate the Sterilizing & Depyrogenating Tunnel as per SOP.

- Also start the data logger to record the actual temperatures within the Tunnel with respect to time.
- After completion of sterilization cycle collect printout from tunnel printer.
- Download the data from the data logger in the computer for the data analysis and printing enclosed the printout obtained from the data logger.
- Seal the exposed Endotoxin vials and wrap the exposed Endotoxin Challenge vials aseptically with sterile Aluminum foil and identify suitably. Send the exposed Endotoxin Challenge vials to microbiology laboratory for testing. Microbiologist shall analyze the exposed Endotoxin Challenge Vials and recovery of Endotoxin.
- Calculate the F_H Value as per following formula :-

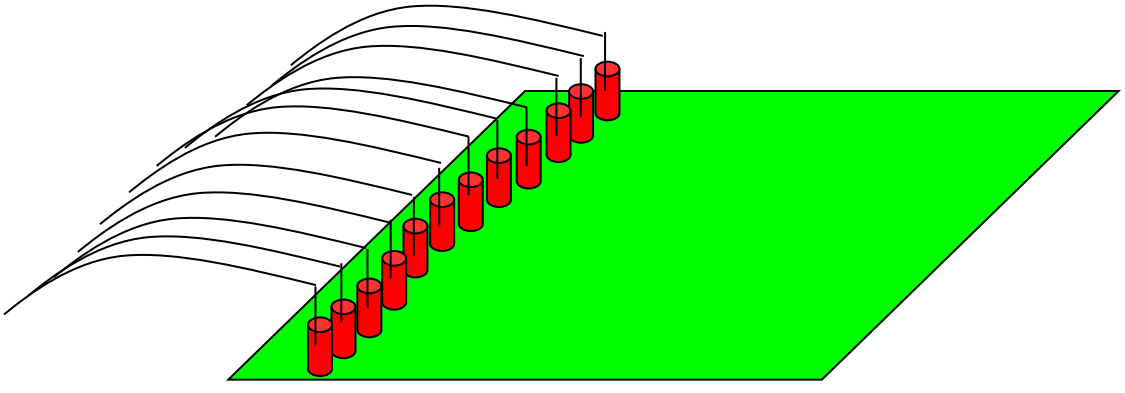
$$F_H = \Delta t \times 10^{(T-300/Z)}$$

Where

T= Observed Temp. During sterilization

Z= 46.6°C

t = Time Interval



Schematic Diagram of Sterilization and Depyrogenation Tunnel with Probe Location

Preparation Procedure of Endotoxin Indicator placed Vials:

- Take 1,00,000 EU/ml Endotoxin indicator vial.
- Reconstitute the vial in 1 ml of LRW, vortex for 1 min every 10 minutes for 30 minutes.
- Transfer 0.1 ml each into 10 Vials of 5, 10 and 20ml as per cycle. The Vials must be identical to the Vial used in the sterilizing tunnel.
- Dry the Endotoxin indicator placed inside the Vial in a LAF hood overnight. Each Vial now contains Endotoxin as 10000 EU/ml.
- One Vial per De-Pyrogenation cycle shall be retained as a positive control (Do not pass through sterilizing tunnel). Mark this Vial as PPC.

- Rest 9 Endotoxin indicator Vials shall be marked as NPC-1, 2, 3, 4, 5, 6, 7, 8 & 9 be placed along with "harness" during heat penetration cycle for each load.
- Record /Attach the all print-outs of the Bacterial Endotoxin challenge test studies.
- After the cycle is complete, carefully collect the Endotoxin indicator Vials from sterilizing tunnel and bring all of them to the Microbiology lab. Carry out the Endotoxin test on the De-Pyrogenates Vials and check the log reduction.

- **Acceptance Criteria**
  - Throughout the dwell time, all temperature measured in the chamber should be ≥ 300°C.
  - The recovery of Endotoxin concentration after exposing in Sterilization and De-Pyrogenation Tunnel should show at least 3 log reduction.
  - The Calculated minimum F_H value should be more than 30 minutes.
- **Observations and Results**
  - Record the temperature at various locations in Report**.**
- **Evaluation of Result**
  - If Sterilization Temperature is not achieved throughout the cycle, then Temperature Set Points Adjustment, Modifications or Repair shall be performed and the Heat Penetration Studies shall be repeated.

12.0 REFERENCES:

The Principle References are as following:

- Validation Master Plan.
- SOP for “Operation & Cleaning of Sterilization & Depyrogenating tunnel”.
- Health Technical Memorandum 2010, Part 3 Validation and Verification.

13.0 DOCUMENTS TO BE ATTACHED:

- Operation and Maintenance Manual.
- Copy of SOP’s.
- Raw data of Filter Integrity , Air Velocity ,Air Flow Pattern , Pressure Differential , Temperature , RH , Non-viable and viable counts.
- Any other relevant document.

14.0 NON COMPLIANCE:

All the Non-compliances of procedure, specifications, sampling, analysis and documentation activities shall be monitored & recorded.

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 operation as well as on performance of the machine & 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 operation as well as on performance of the machine & prepare final conclusion.

17.0 ABBREVIATIONS:

No.	:	Number
WHO	:	World Health Organization
FDA	:	Food and Drug Administration
CFR	:	Code of Federal Regulations
cGMP	:	Current Good Manufacturing Practices
QA	:	Quality Assurance
mm	:	Millimeter
Amp.	:	Ampere
DQ	:	Design Qualification
IQ	:	Installation Qualification
OQ	:	Operational Qualification
PQ	:	Performance Qualification
SOP	:	Standard Operating Procedure
Kg	:	Kilogram
MOC	:	Material of Construction
NLT	:	Not Less Than

HP	:	Horse Power
KW	:	Kilo watt
SS	:	Stainless Steel
ID.	:	Identification
mm	:	Millimeter