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# **Qualification of Tunnel Sterilizing Machine**

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**Abstract:** Depyrogenation devices, such as tunnels, are used in the pharmaceutical industry to prepare components for aseptic filling. To qualify such devices, various pharmacopoeias require depyrogenation devices to be periodically challenged with high levels of bacterial endotoxin. Although the pharmacopoeias state the acceptance criteria, little consideration is given to the practical approach. This work discusses the theoretical concept of depyrogenation and the various tests performed for the qualification of Depyrogenation Tunnels. **Key words:** Depyrogenation, Bacterial Endotoxin, Performance Qualification.

# Introduction

Depyrogenation is an important part of the manufacture of pharmaceutical products and is distinct from sterilization. Sterilization refers to the destruction of living cells. However, the process does not necessarily destroy microbial by-products and toxins. Endotoxin is one toxin that is extremely heat stable and is not destroyed by standard sterilization cycles (e.g., autoclaving). If only sterilization is required to be demonstrated, this can be achieved using biological indicators impregnated with endospores from a heat resistant bacteria (e.g., Bacillus subtilis var. niger [often used for dry heat] or Geobacillus stearothermophilus [often used for moist heat, although the microorganism also has a high resistance to dry heat].<sup>2</sup>

Depyrogenation by dry heat for glass in the pharmaceutical industry is the primary endotoxin destruction method used. This process both sterilizes and depyrogenates and is mainly used for glass components. Dry heat involves subjecting the components to a high level of heat (normally between 180 and 250°C) for a defined time (the higher the temperature, the shorter the time required). The typical cycle is 250°C for not less than 30 minutes. For example, the European Pharmacopoeia in chapter 2.6.8 states two possible time-temperature combinations for depyrogenation: 60 minutes at 200°C or 30 minutes at 250°C. A quantity of endotoxin destroyed at 250°C for 60 minutes would not necessarily be totally destroyed at 200°C at 60 minutes, based on the non-linearity of the thermal destruction curve. Endotoxin destruction at low temperature is of the second-order.<sup>2</sup>

Depyrogenation dry heat devices include ovens and tunnel sterilizers. To operate, depyrogenation devices require a series of parameters to be controlled. These parameters include laminar airflow controlled by high-efficiency particulate air (HEPA) filters, with a specification for air velocity and particulates. Where the device is a depyrogenation tunnel, the rate of speed (e.g., minimum, maximum, and nominal) must be measured and verified. The key function for depyrogenation is temperature control. Such depyrogenation devices require qualifying as part of validation. This is performed along the familiar lines of design qualification, installation qualification, operational qualification, and performance qualification, as well as annual re-qualifications. A depyrogenation study is a test of the physical capabilities of a device to depyrogenate an article or device. It is demonstrated by physical measurements (including temperature) and biological (using bacterial endotoxin).<sup>2</sup>

As part of the validation, normally at the performance qualification stage, depyrogenation devices are biologically challenged using a known level of a high concentration of Escherichia coli endotoxin. The preparation used is a freeze-dried extract from the Gram-negative bacterial cell wall lipopolysaccharide (LPS). The preparation is similar to the control standard endotoxin (CSE) used for routine LAL testing, although the concentration, once reconstituted, is far greater.<sup>2</sup>

# Qualification<sup>3</sup>

# Design qualification

The first element of the validation of new facilities, systems or equipment could be design qualification (DQ).

The compliance of the design with GMP should be demonstrated and documented.

# Installation qualification

Installation qualification (IQ) should be performed on new or modified facilities, systems and equipment.

IQ should include, but not be limited to the following:

(a) Installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;

(b) Collection and collation of supplier operating and working instructions and maintenance requirements;

(c) Calibration requirements;

(d) Verification of materials of construction.

# **Operational qualification**

Operational qualification (OQ) should follow Installation qualification.

OQ should include, but not be limited to the following:

(a) Tests that have been developed from knowledge of processes, systems and equipment;

(b) Tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as "worst case" conditions.

The completion of a successful Operational qualification should allow the finalisation of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal "release" of the facilities, systems and equipment.

# Performance qualification

Performance qualification (PQ) should follow successful completion of Installation qualification and Operational qualification.

PQ should include, but not be limited to the following:

(a) Tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment;
(b) Tests to include a condition or set of conditions anonymous ing upper and lower operating limits.

(b) Tests to include a condition or set of conditions encompassing upper and lower operating limits.

Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ.

# Qualification of established (in-use) facilities, systems and equipment

Evidence should be available to support and verify the operating parameters and limits for the critical variables of the operating equipment. Additionally, the calibration, cleaning, preventative maintenance, operating procedures and operator training procedures and records should be documented.

# Process for flow of sterilization tunnel<sup>1</sup>

Washed glass vials Drying zone Sterilizing zone Cooling zone Filling table

#### **Test and Its Rationale**

#### Table-1: Tests performed and its Rationale

Sl.No.	Test	Rationale
1	Air flow Velocity	The purpose of this test is to measure airflow velocity and uniformity, and supply airflow rates through the HEPA filter.
2	Filter system leakage Test	The purpose of this test is to confirm that the filter system is properly installed and that leaks have not developed during use.
3	Tunnel Belt / Conveyor speed verification	To ensure the tunnel conveyor belt speed meets the requirements as specified by vendor.
4	Nonviable Particle Count	The purpose of this test is to provide acleanliness in the supplied air.
5	Heat penetration and Endotoxin challenge study	To ensure and establish the heat Penetration and endotoxin log reduction efficiency of the Tunnel Sterilizer

# Tests, Objective, Procedure and its Acceptance Criteria<sup>1,4</sup>

#### 1. Air velocity

#### 1.1 Objective

To determine that factors that affect cross-sectional air velocity distribution in tunnel-ventilated system and is capable of delivering air velocities, as per the requirement to maintain continuous laminarity of HEPA filter installed in tunnel.

### 1.2 Equipment used

Hot air anemometer

#### **1.3 Procedure**

- This test shall be performed by trained person and training record should be attached in report. Performed at least 30 minute.
- Measure the velocity above the conveyor for the different zone of tunnel sterilizer and measure the air velocity 6 inches below filter.
- Take the velocity of air at five locations (on centre and four corners) of each zones of sterilizer tunnel. Calculate average velocity for each filter
- If velocity is not within the limit, inform the manufacturer of the sterilizing tunnel for corrective action.

### 1.4 Acceptance criteria

Air velocity should be maintained within 90 fpm  $\pm$  20% of mean unit velocity for even distribution of temperature.

# 2. Filter system leakage test

## 2.1 Objective

To verify the integrity of HEPA filter installed in the sterilization and depyrogenation tunnel. HEPA filter installation has been done properly and qualifies the filter integrity test.

# 2.2 Equipment used

Aerosol generator

Aerosol photometer

# 2.3 Procedure

- Place the aerosol generator to introduce an aerosol challenge upstream of the HEPA filter in zone wise manner in concentration of 80-120mg/m3 of air by opening appropriate number of nozzles
- Measure upstream concentration of aerosol by using zone wise upstream (in feed zone, hot zone 1, hot zone 2 and cooling zone)
- Adjust the photometer gain/span control for full scale deflection on 100% range
- Scan the downstream side of the HEPA filter, its perimeter, the seal between the filter frame and grid structure including its joints using overlapping strokes with the photometer probes
- The photometer probes should move at transverse rate not more than 10ft/minute with sample flow rate of 1cft/min  $\pm 10\%$
- If any leak is more than the specified limit, the above test should be repeated after taking the recommended corrective action

# 2.4 Acceptance criteria

Photometer reading downstream of the HEPA filtration unit caused by the leakage should be less than 0.01% of the upstream challenge concentration of the aerosol 100%

### 3. Tunnel belt/conveyor speed verification

### 3.1 objective

To ensure the tunnel conveyor belt speed meets the requirements as specified

### 3.2 Equipment used

Vernier calliper

### 3.3 Procedure

- Mark the start position and advance signal of the conveyor belt
- Start the conveyor belt
- Start the stopwatch when advance signal reaches the start position and run for 1 minute

# 3.4 Acceptance Criteria

Conveyor speed shall not vary more than 3% of the set speed

## 4. Nonviable Particle Count

### 4.1 Objective

To establish that at different location within the tunnel, count size of particle per cubic meter is within the limit.

# 4.2 Procedure

The particle count test should be performed by qualified or trained person

- Start blower of the sterilizing tunnel
- Calculate the number of location by the following formula
- Number of sampling location NL =
- Whereas; the minimum number of sampling locations
- Switch on particle counter and place the iso-kinetic suction probes at specified location under the filter of conveyor belt of tunnel and observe the reading, record in reports
- Take the particle counts for all zones of sterilizing tunnel

# 4.3 Acceptance Criteria

The particle counts taken under the HEPA filter in the different zones of sterilizing tunnel should meet the requirement of ISO 5/class A.

# 5. Heat penetration and Endotoxin challenge study

### 5.1 Objective

To ensure that heat is sufficiently penetrating into the inner most portion of the vial subjected for sterilization and depyrogenation to achieve desired temperature during the sterilization and depyrogenation cycle. The recovery of endotoxin concentration after exposing to depyrogenation tunnel should show more than 3 log reduction.

# 5.2 Procedure

- Get the 9/10 spiked vial with approx. 10,000 EU/vial of bacterial endotoxin from microbiology
- Place minimum 10 number of probes, one probe each inside the endotoxin spiked 8 vials and 3 without spiked vials at the junction of the bottom of the container and side wall. The containers inner surface should be in contact with the probe because for sterilization and depyrogenation of the inner walls of the container as well as inner space. Tie the probes firmly with the vial and place these vial inside the washed vial load
- Use zig to hold the spiked vials containing probes in place, as vial travel through the tunnel
- Set the temperature/cycle condition as per set parameter
- Record the set parameter for the sterilization cycle operated during test
- Operate the tunnel and pass the endotoxin spiked vials along with the washed vials as per standard operating procedure and start the data logger to record the actual temperature inside within the sterilization zone
- When the vial attached with temperature indicating probes cross the sterilization zone, stop the conveyor belt of sterilizing tunnel, switch off the data logger and pull out the probes. Wrap the exposed endotoxin indicator vials with aluminum foil and label properly
- Send the exposed vials to microbiology lab for testing of residual endotoxin in the vials after sterilization as per standard procedure
- Record the result and take validation run for each set of vial normally used in routine production with complete load and re-validation one run on rotation for different type of vial size
- Record the temperature observation at different location.

# 5.3 Acceptance Criteria

All temperature measured in the chamber is  $\geq$  3000C. The recovery of endotoxin concentration after in sterilization and depyrogenation should at least 3 log reductions

# Conclusion

Depyrogenation forms part of a critical process in many pharmaceutical production facilities, particularly where glass vials and bottles are required for aseptic filling operations. The number of validation runs is commonly set at three in order to demonstrate reproducibility, but this number is not fixed. The frequency of re-validation is to be determined by the user based on risk assessment.

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