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Review Article

QUALIFICATION AND VALIDATION OF DEPYROGENATION TUNNEL: A REVIEW

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ABSTRACT

Beyond the usual engineering aspects of validation with regard to specification, installation, commissioning, qualification, and calibration, the two important aspects of validation of dry heat processes are thermal validation and endotoxin validation. Sterility is the most important and absolutely essential characteristic of a parenteral product. Sterility means the complete absence of all viable microorganisms. This review will provide an overview of depyrogenation tunnel qualification and validation protocol with some of more application of it. 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, and methods little consideration is given to the practical approach. The review highlight the theoretical concept of depyrogenation and the various tests performed for the qualification of Depyrogenation Tunnels.

Key words: Depyrogenation, Bacterial Endotoxin, Qualification.

INTRODUCTION

Dry heat should be the method of choice for sterilization of heat-stable items that are damaged by moisture or are impervious to steam. It can serve one or both of two functions; it may serve as a method of sterilization and depyrogenation (destruction of bacterial endotoxin). Sterilization can be defined as any process that effectively kills or eliminates transmissible agents (such as fungi, bacteria, viruses) from surface, foods, equipment, medications or biological culture medium. [1]

A sterility assurance level (SAL) of 10^{-6} means that there is less than or equal to one chance in million that particular item is contaminated or unsterile following sterilization process. [2, 3]

Validation is establishing documented evidence which provided a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specification and quality characteristics" [4]

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^{0}C) for a defined time (the higher the temperature, the shorter the time required). The typical cycle is 250^{0}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^{0}C. A quantity of endotoxin destroyed at 250◦C for 60 minutes would not necessarily be totally destroyed at 200^{0}C at 60 minutes, based on the non-linearity of the thermal destruction curve. Endotoxin destruction at low temperature is of the second-order.

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).

QUALIFICATION

Design qualification:

The first element of the validation of new facilities, systems or equipment could be designed qualification (DQ). The compliance of the design with GMP should be demonstrated and documented. The sterilization tunnels have been designed to continuously sterilize dehydrogenated glass vial containers in class 100 and environment. The tunnel is comprised of the In feed chamber, Sterilizing chamber (Heating Phase) and Cooling chamber.

Heaters generate heat; the sterilizing time of the vials depends upon the temperature and air velocity. If the temperature is high and air velocity is available as required, then less time will be required for sterilization. After passing through the conveyor, the air taken up by a fan with continuous speed adjustment to required fH value.

Fig. 1: In feed chamber (where the vials enter) creates a thermal barrier between the vial washing room and the sterilizing chamber to protect the vials from contamination and to pre heat the vials.

Fig. 2: Sterilizing chamber

The sterilizing chamber is responsible for sterilization and depyrogenation. The sterilizing chamber is insulated with 120 mm fiber-glass filled walls.

The working temperature is 350-390°C for (3-4 min) and is generated by SCR-controlled heating elements.

Air is filtered by a high-temperature HEPA filter with an efficiency of 99.97% (at 3µ particulates). The air-velocity in the sterilizing chamber can be adjusted on the HMI and is typically set at 0.7-0.8m/s.

The cooling chamber, depending upon the tunnel size, comprises of one or two cooling coils, which assist in the cooling of the vials to ambient temperature. Regular chilled water may be used; vials stay in the cooling chamber for 15-20 minutes. [5, 6, 7]

(B) 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.

(C) 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 finalization of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal "release" of the facilities, systems and equipment.

(D) 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 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.

Different Parameters that are taking into consideration as follow:

Air velocity:

The purpose of this test is to measure airflow velocity and uniformity and supply airflow rates through the HEPA filter.

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

Fig. 3: Instrument: Hot air anemometer

Procedure: This test shall be performed by a trained person and training record should be attached to the report. Performed at least 30 minutes.

Measure the velocity above the conveyor for the different zone of tunnel sterilizer and measure the air velocity 6 inches below the filter. Take the velocity of air at five locations (on center and four corners) of each zones of sterilizer tunnel. Calculate average velocity for each filter · If the velocity is not within the limit, inform the manufacturer of the sterilizing tunnel for corrective action. Acceptance criteria: Air velocity should be maintained within 90 fpm ± 20% or 28 m/min ± 20% of mean unit velocity for even distribution of temperature.

2. Filter system leakage test:

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.

Fig. 4: Equipment: Aerosol generator, Aerosol photometer

Procedure: Place the aerosol generator to introduce an aerosol challenge upstream of the HEPA filter in zone wise manner in the concentration of 80-120mg/m^3 of air by opening an appropriate number of nozzles. Measure upstream concentration of aerosol by using zone wise upstream (in the 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 a transverse rate not more than 10ft/minute with sample flow rate of 1cft/min ±10%.

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%

Tunnel belt/conveyor speed verification

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

Equipment: VernierCalliper

Procedure: Mark the start position and an 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

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

Nonviable Particle Count

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

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.

A number of sampling location $N_L = \sqrt{A}$ whereas; the minimum number of sampling locations.

Switch on particle counter and place the iso-kinetic suction probes at a specified location under the filter of the conveyor belt of the tunnel and observe the reading, record in reports.

Figure 5: Non-viable Particle Counter

Take the particle counts for all zones of sterilizing tunnel.

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.

Table 1: Acceptance criteria of permitted Particles

Grade/class	Maximum permitted no. of particle/m3	
	0.5µm	5µm
A	3500	20

Heat distribution study (loaded chamber)

The sterilizing and depyrogenation tunnel, when operated with an empty chamber, is capable of producing the temperature profile as per temperature set point set in PLC of the equipment. The temperature distribution is uniform throughout the sterilization period.

Procedure: Place ten temperature indicating probes across the width of the conveyor of the tunnel, in such way that probes junction do not touch solid surfaces but remain in hanging condition inside the vials.

Use zig plate to hold vial with the probes (sensor) in place as it helps smooth travel through the tunnel. Attach the connecting cable of probes (sensor) to the data logger, which can scan the date, time and temperature of probes at every 10 seconds.

Set the temperature/cycle condition as per set parameter.

Record the set parameter for the sterilization cycle operated during the test.

Operate the tunnel as per the standard operating procedure and start the data logger to record the actual temperature within the sterilization zone of the tunnel through probes (sensor).

Allow the zig plate is having vials containing the external temperature probes (sensor) to travel along with other washed vials through the sterilization zone.

Operate vial washing machine continuously to fill the tunnel chamber back to back.

When the vials having probes cross the sterilization zone stop the conveyor belt of sterilizing tunnel, switch off the data logger and pull out the probes along with zig.

Take one validation run for loaded chamber heat distribution studies for each type of load.

Acceptance Criteria: All temperature measured in the chamber is ≥ 3000C. The recovery of endotoxin concentration after in sterilization and depyrogenation should at least 3 log reductions.

Thermocouple Calibration:

All thermocouples will calibrate within ± 0.5^0C of the reference temperatures before protocol execution and verify within ± 0.5^0C of the high reference temperature after protocol execution. 85% of thermocouples used must be operational upon completion of the study.

All critical thermocouples (i.e., thermocouples with specific acceptance criteria, such as cold spots or adjacent to a controller) must be operational upon completion of the study.

Heat penetration studies:

To ensure that heat is sufficiently penetrating into the inner most portion of the vial subjected to sterilization and depyrogenation to achieve the 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. [12]

Procedure: Get the nine spiked vials with approx. 10,000 EU/vial of bacterial endotoxin from microbiology. Place minimum 10 number of probes, one probe each inside the endotoxin spiked eight vials and three 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 the test.

Operate the tunnel and pass the spiked endotoxin 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 and Record the result of temperature observation of different location 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.

Acceptance criteria: All temperature measured in the chamber is ≥3000C.

The recovery of endotoxin concentration after in sterilization and depyrogenation should at least 3 log reductions [1, 8, 9, and 10].

The equation to Calculate Heat Penetration:

Width of conveyer/ Diameter of vial = n No. of vial in each row (This is used when capacity is calculated)

Now,

The numbers of rows of vials are moving = speed of conveyer/ Diameter of vials = n No. rows will be mover per minutes.

Residence time is the width of heating zone/conveyer speed = n minutes.

Temperature Mapping [11]

During the mapping period, the temperature readings for the temperature recording chart and the average chamber temperature for Tunnels at 250^{0}C and greater are consistently ± 15.0^{0}C of each other throughout the study.

Temperature range among thermocouples for Tunnels at 250^{0}C and greater, for each five-minute interval is ± 15.0^{0}C of the average temperature throughout the study. The average temperature for Tunnels at 250^{0}C and greater at each interval is ± 15.0^{0}C of set point temperature Calculation of tunnel speed and cycle timing is an important issue during validation of Sterilization and Depyrogenation tunnel.

We can solve with an easy two steps mention below.

Temperature Mapping, Specific Loads: To determine cold spots.

Monitor Tunnel differential pressure during the depyrogenation period.

Pressure Balancing

Positive Air flow from the filling room to the washing room.

Minimum heat loss.

The ability to validate the tunnel.

When the air pressure in the filling room fluctuates, the air pressure in the three chambers changes proportionally.

This is accomplished by two pressure differential sensors and two fan motors

ΔP between the cooling chamber and the washing room

ΔP between the infeed chamber and the washing room

CONCLUSION

Depyrogenation is 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 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. The different parameters such as air velocity, heat distribution and penetration with different thermocouples methods and aerosol test evaluated as per pharmacopoeias.

It is based on observation it was concluded that result of the entire equipment performance test was found meeting the acceptance limit and all load pattern. Hence sterilization tunnel is successfully validated.

REFERENCES

1. Sultana Y. Pharmaceutical Microbiology and Biotechnology, Sterilization Method and Principle, 2007; Jamia Hamdard, Hamdard Nagar, New Delhi
2. American Society for Healthcare Central Service Professionals, Training Manual for Central Service Technicians, 2006; 5: 25-27.
3. Ninemeier J.D. Central Service Technical Manual, International Association of Healthcare Central Service Material Management. 2003; 06: 26-28.
4. Guidance for Industry – A Sterile Drug Product Produced by Aseptic Processing, Current Good Manufacturing Practice. 2004; US.FDA:1-63.
5. Akers M.J., Ketron K.M., Thompson B.R., F Value Requirements for Destruction of Endotoxin in the Validation of Dry Heat Sterilization/Depyrogenation Cycles, Parenteral Drug Association. 1982; 36: 23-27.
6. Hecker D., Witthaeurand D., Staerk A. Validation of dry heat inactivation of bacterial endotoxins. PDA, Journal of Pharmaceutical Science and Technology, 1994; 48: 197-204.
7. A Work Group of Scottish Quality Assurance Specialist Interest Group, Guideline on Test Method for Environmental Monitoring for Aseptic Dispensing, 2004: 35-40.
8. Thomas C, John P.J, Principles and Methods of Sterilization in Health Sciences, 1983; 2: 32-34.
9. Fabritz H, Autoclave Qualification and Validation, Expert reff ; 2007: 14
10. Validation of Steam Sterilization Cycles, Technical Monograph No.1, Parenteral Drug Association, Inc., Philadelphia: 5-6.
11. European Committee for Standardization, Sterilization of Medical-Devices Validation and Control of Sterilization by Moist Heat Sterilization, 1994; 554: 264-269.
12. Tim S., A Practical Approach to Depyrogenation Studies Using Bacterial Endotoxin. J GXP Compli. 2011; 15(4): 90-96.