Minimizing Aseptic Pharmaceutical Manufacturing Risks with the Inclusion of Depyrogenation Tunnels

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Introduction

Regulatory agencies prefer injectable products to be terminally sterilized. For some products, such as biological drugs, terminal sterilization is not possible because it will adversely affect the product. In these cases, the product must be aseptically filled in a class 100 or iso-5 environment. The vials must be washed, to remove particles, and then depyrogenated before filling.

Historically, if products were terminally sterilized, it was common practice to discharge vials from the washer directly to the filling room. However, the ISPE Baseline Guide volume 3: Sterile Product Manufacturing Facilities[1], published in April 2018, recommends that all vials be depyrogenated, even if the product is terminally sterilized.

Depyrogenation, as the name implies, is the process to remove pyrogens, including bacterial endotoxins from vial surfaces. There are several different ways to depyrogenate vials. One of the most common and effective is using dry heat. Exposure of the vials to temperatures above 250°C destroys the pyrogens. Most depyrogenation processes are designed to achieve at least a log three, and preferably, a log six reduction of endotoxin.

The two most common methods for depyrogenation are batch ovens and depyrogenation tunnels (see fig 1), but there are different risk levels associated with these two processes. The risks involved with installing a depyrogenation tunnel come primarily from the management of airflows within the tunnel. The risks associated with batch oven depyrogenation involve the manual manipulation of vials and the dwell time between depyrogenation and filling. This paper discusses these risks and the opportunities for mitigation.

Depyrogenation Tunnel *versus* Batch Oven

Vial depyrogenation can be accomplished using a batch oven or depyrogenation tunnel (see Figure 1)

When using the batch oven process, the vials are washed in the preparation area, typically a grade C or iso-7 cleanroom, placed on trays and manually loaded into the oven. The oven is situated at the interface between the preparation area and the filling line. Well-designed batch ovens have two doors, one to the preparation area and the other to the filling line isolator or cleanroom. Once the depyrogenation process is complete, the batch of depyrogenated vials is manually unloaded onto the filling line. It can be hours before some vials are filled. Haag[2] (2011) highlights the risk of contamination due to exposure of the internal surfaces of the container during the filling process, citing the increased risk associated with open vials, even those in a grade A environment. Vials processed in an efficient depyrogenation tunnel, experience a cooling process of approximately 15 minutes, and automatically feed the filling machine. Therefore, the risk of contamination is significantly less.

Figure 1: *Depyrogenation Tunnel*

Example:

Consider a batch size of 10,000 vials and a line speed of 50 vials per minute (with an assumed 80% line efficiency), the exposure time of an open vial from the time it leaves the depyrogenation tunnel until the time of stoppering is approximately eight minutes for a typical commercial filling line. On the other hand, the exposure time of the last vials of the same batch size for an oven is can be 250 minutes, or more. This greater exposure time creates a 30 fold increase in risk of contamination. This does not including risks associated with introducing an operator to the filling area for the manual transfer of the vials from the oven to the filling line.

In his opening comments at the 2019 ISPE Aseptic Conference, Rick Friedman (Deputy Director, Science and Regulatory Policy FDA/CDER) talked about making positive choices to minimize contamination risks and commented that all new aseptic filling line designs should incorporate depyrogenation Tunnels instead of Batch Ovens.

Risks Involved with Pre-sterilized Glass

Purchasing pre-sterilized glass is an alternative to an in-house depyrogenation process. In this case, the washing and glass sterilization is done at a remote site and the vials are double bagged and then shipped to the manufacturing site. The increase complexity of the supply chain brings with it, inherent risks.

For example, the glass supplier must be monitored to insure that they follow the proper quality standards throughout the sterilization and packing process. Preferably, the film used for double bagging the components is particle free and the washing, depyrogenation and packaging process is automated to reduce manual manipulation.

The next risk to consider arises from the delivery process where the movement of glass on glass during shipping can generate glass particles and chips that are difficult to identify before filling. Operators need to follow special sanitization procedures during the manual unwrapping process to insure that the contamination on the outside wrappings does not migrate into the vials.

Qualities to Evaluate when Selecting Depyrogenation Tunnels

A depyrogenation tunnel is easily justified for large batch applications. However, from a risk mitigation perspective, a depyrogenation tunnel should also be considered for smaller batch applications as well. Currently, vial washer and depyrogenation tunnel combinations specifically designed for small batch applications take up minimal space, occupying as little as 8 feet / 2.5m.

The main purpose of a depyrogenation tunnel is to attain the required log reduction of endotoxin. When considering a tunnel manufacturer, it is critical to evaluate the manufacturer's airflow designs to ensure that pressure fluctuations within the clean room and washroom do not impact the depyrogenation process.

The highest air quality area is the filling suite. This area should always be at a higher pressure relative to the lower grade areas in order to preserve the air quality. However, this pressure cascade does fluctuate when, for example, doors open or close and the air handling systems modulates due to the hysteresis between set points.

These pressure changes may affect the performance of a poorly designed depyrogenation tunnel. Some tunnels are designed to cascade pressures from the filling suite to the cool zone. In other words, each zone (cooling zone, hot zone and infeed zone), has air entering from the filling room direction and exiting towards the preparation area (see Fig 2). Fluctuations in filling area static pressures can increase the ingress of cold air into the hot zone from the cold zone, thus preventing the heat absorption necessary to achieve the log 3 or 6 reduction in endotoxin.

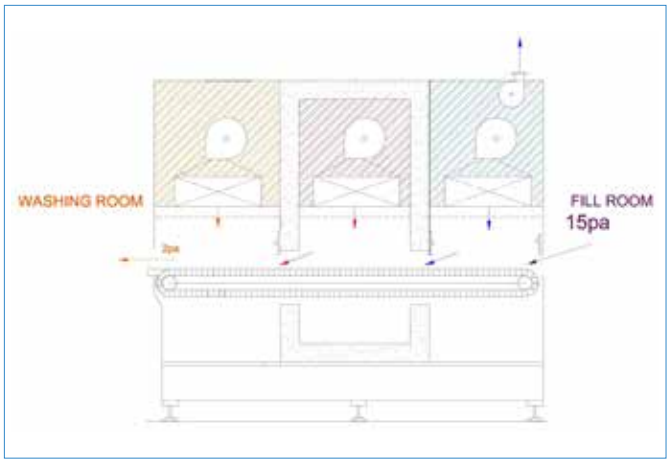


Figure 2: *Cascading air from the Clean Room to through the hot zone. Blue Zone = cooling zone, Red Zone = Hot depyrogenation zone, Orange Zone = pre-heat zone*

More sophisticated tunnel designs over pressurize the hot zone in relationship to the infeed and cool zone of the tunnel, thus insuring that the vials will always be exposed to the proper temperature for the correct duration (see Fig 3). Such designs have a vial conveyor return underneath the hot zone which creates an air pathway from the cool zone directly to the infeed zone. In addition, some have a fan that drives fresh air from the preparation room through a pre-filter into the hot zone. This airflow is monitored and the fan speed varied to counter any increase in pressure from the filling room. The best designed tunnels with the over pressurization of the hot zone can control the process with filling room cascades of 70 Pascals while less sophisticated units typically only control between 10 and 15 Pascals.

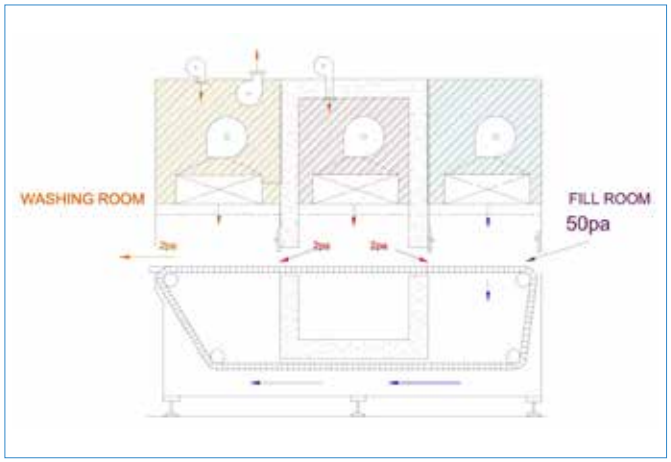


Figure 3: *Over Pressurized Hot Zone. Blue Zone = cooling zone, Red Zone = Hot depyrogenation zone, Orange Zone = pre-heat zone*

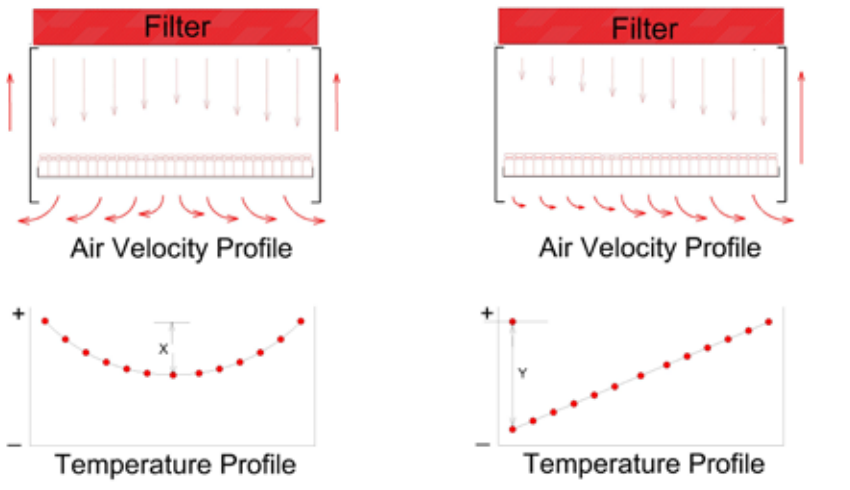
A secondary benefit to over pressurization of the hot zone is the natural temperature gradient that occurs as hot zone air mixes with the cooler air from the adjacent zones. This provides a gradual temperature change that minimizes the risk of glass cracking caused by thermal shock.

Another feature to consider in tunnel designs is the air velocity profile across the vial transfer belt. Air velocity is directly proportional to temperature, so it is important from a quality perspective to minimize the temperature variation during the thermic process. Tunnels that have uniform control of air velocity across the transfer belt have better process control and batch homogeneity.

Tunnels with air returns on both sides of the tunnel (as opposed to single-sided returns) generally have less variation in air velocities across the transfer belt (see Figure 4).

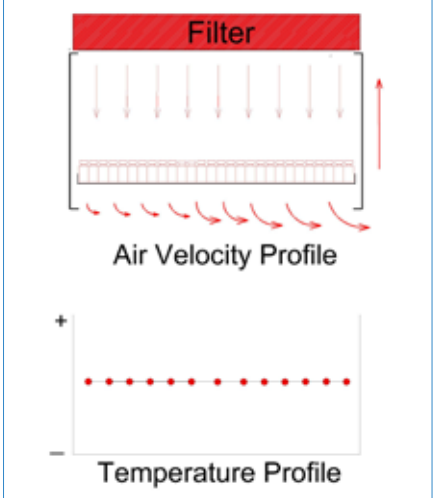
Some single sided return tunnel designs incorporate airflow controls that compensate for this pressure gradient and produce a very consistent airflow across the width of the belt (see Fig. 5). This design offers the best results and will eliminate cold spots, and provide consistent depyrogenation results.

Finally, consideration should be given to in situ monitoring for nonviable particle counts in the depyrogenation tunnel. Most depyrogenation tunnel designs provide for particle counting in the infeed and cooling zones. However, to date, only one manufacturer offers the ability to monitor the nonviable particle counts in the hot zone. The air collected from the hot zone travels to the particle counter via a heat exchanger in order to avoid damaging the sensor. The process typically records particle counts for 5 seconds in the cool zone, 5 seconds in the hot zone and 5 seconds in the infeed zone, and then repeats the cycle throughout the batch. This solution offers a full in situ particle monitoring of all three zones for optimum, in process, quality control.



Double-sided return ***Single-sided return***

Figure 4



Single-sided return with Velocity Compensation

Figure 5

Summary

Patient safety must always be the primary focus when producing injectable products. The drug manufacturing and packaging process is complex but the industry has made significant advancements in reducing the risks of product contamination.

Personnel are the most common source of particles and contamination in an aseptic process. Automation has greatly reduced the contamination risk from personnel. The introduction of automation is easily justified for large-scale production processes, however; smaller batch sizes historically have been produced with more manual processes and therefore susceptible to contamination risk.

With the increase in development of biologic medicines and more personalized drugs driving down batch size requirements, equipment suppliers have responded by offering isolated robotic filling equipment for slower line speeds.

Similar quality concerns must be considered, when selecting the supply of washed and depyrogenated vials for slow speed applications. Automatic vial washers and depyrogenation tunnels are now available to accommodate these high-value small batch size applications. When selecting equipment, size, throughput, and especially, air handling designs are key considerations to provide appropriate sterility assurance.

References

1. Baseline Guide Vol 3: Sterile Product Manufacturing Facilities, April 2018, ISPE. https://ispe.org/publications/guidance-documents/sterile-product-manufacturing-facilities-third-edition
2. Mattias Haag, 2011, Calculating And Understanding Particulate Contamination Risk. Pharmaceutical Technology Europe, Volume 23, Issue 3