High temperature HEPA filtration

Air filtration challenges
and answers for
dry heat sterilization tunnels

AAF INTERNATIONAL

Whitepaper

Preview

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Air filtration challenges and answers for dry heat sterilization tunnels

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Abstract

Dry heat sterilization is considered to be one of the most critical process steps in medicine manufacturing, by which to ensure sterility of pharmaceutical sterile and aseptic preparations. Inside such sterilization tunnels, HEPA filtration plays an indispensable role in protecting containers, such as vials or prefilled syringes, from contamination that might result in severe health risk for patients. Where the installed HEPA filter has to withstand frequent temperature fluctuations between ambient and up to 350 ˚C, operating conditions are challenging. To control the challenges, and therewith not to affect manufacturing throughput and product quality and safety, a careful selection of the high temperature HEPA filter is required. This whitepaper will describe the key challenges that have to be answered for dry heat sterilization processes, and will present two selection criteria that were found to be most important for a high temperature HEPA filter. The insights are based on extensive interviews that were conducted with both tunnel manufacturers and pharmaceutical end users. Supported by various test cycles, through which air filter durability and particle shedding was defined, a new filter design will be presented that resolves well-known issues with the dominating traditional high temperature HEPA filter design that has served the market since many years. The performance of the new filter design was proven by a field test in an existing dry heat sterilization tunnel, of which the results will be presented. This whitepaper will therewith provide new insights in how to mitigate process contamination risk by applying new, but proven, HEPA filtration technology. It will support the pharmaceutical industry to obtain a more stable and reliable dry heat sterilization process.

Key words: Dry heat sterilization, dry heat depyrogenation, high temperature HEPA filtration, filter design, filter durability, particle shedding, filtration efficiency

1 Dry heat sterilization and depyrogenation

1.1 Critical process step in sterile manufacturing

The pharmaceutical production of sterile medicine is subject to special requirements to minimize risks of particulate and microbial contamination. Stringent FDA and GMP guidelines are in place to limit exposure to such contamination, therewith preventing severe harm or life-threatening health risks to the patient.

Dry heat sterilization and depyrogenation are applied to ensure sterility of pharmaceutical aseptic preparations, as imposed by FDA regulation 21 CFR-211.94. For aseptic preparations, such as vials, ampoules, cartridges or prefilled syringes, terminal sterilization of the final container is not possible. The glassware therefore has to be rendered free from harmful contaminants that might affect the medicine, before filling.

"The identification of dry heat sterilization with depyrogenation imposed much more stringent demands on dry heat sterilization of glassware."

Dr.-Ing. Lothar Gail - VDI

Depending on the process, either dry heat sterilization or depyrogenation is applied. Sterilization is typically applied in the 160 - 180 °C temperature range, to render a product free from living microorganisms. Depyrogenation aims to remove or inactivate endotoxins for which higher temperatures are required in the bandwidth of 200 - 350 °C, taking place in either static ovens or in tunnels for automatized, continuous processes. Because of the increasing demand for pyrogen-free sterile packaging and for fast, safe and efficient processing, dry heat depyrogenation nowadays represents one of the most critical steps in the sterile medicine manufacturing process[1].

Pyrogen-free packaging material was originally demanded merely for the filling of large volume containers; meanwhile it became a standard for the whole field of sterile filling [1]. Modern demands on sterilization processes, layed down by the FDA, require temperature programs which demonstrate "that the endotoxic substance has been inactivated to not more than 1/1000 of the original amount (3 log cycle reduction)" [2]. This demand contributed decisively to the development of safe, fast and efficient dry heat sterilization processes including unidirectional airflow with HEPA filtration.

"Defined and homogenous conditions regarding particle concentration, airflow and temperature distribution are crucial for safe and reliable operation of sterilization tunnels. High temperature HEPA filters are playing a vital role for that."

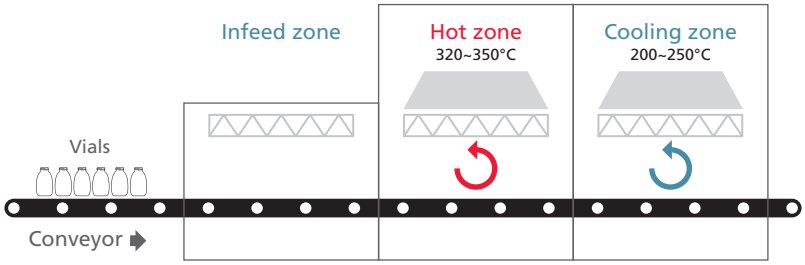
Dr.-Ing. Gerardo Fumagalli -
General Manager, Steriline s.r.l.

1.2 The protecting role of HEPA filtration

For protecting dry heat sterilized containers against particulate and microbial contamination, HEPA filtration has been introduced to such processing. Despite that the cleanliness in the environment of sterilized containers was considerably improved, a certain risk caused by released particles on the clean side of HEPA filters still has to be considered.

[1] *The remainder of the whitepaper will speak about dry heat sterilization as an umbrella term for both dry heat sterilization and dry heat depyrogenation.*

Figure 1: Schematic representation of a sterilization tunnel



The dry heat sterilization of glassware typically follows a three-step approach: infeed, heating and cooling. Though dry heat sterilizers are typically installed in GMP grade D areas, the industry imposes grade A demands on the whole glassware transportation line between washing and filling. Therefore, in these areas any air admitted has to pass through a HEPA filter [3].

In particular the heating process, taking place in the 'hot zone', poses high demands on HEPA filters at temperatures going up to 350 °C. But even in the 'cooling zone' the installed HEPA filters have to withstand temperatures between 200 - 250 °C in case of sterilizable cooling sections. Challenges in terms of filter durability and efficiency have to be mitigated to guarantee sterility of the containers that leave the sterilization tunnel.

"Modern demands on cleanliness, processing time and reliable control turned out to be met merely by unidirectional airflow with HEPA filtration."

Dr.-Ing. Lothar Gail - VDI

1.3 Challenges to be mitigated

Various studies have shown that performance improvement issues dominate the priority list of the pharmaceutical industry. Challenges related to reducing time to market, increasing manufacturing throughput, quality requirements on cleanliness, complying with applicable regulations and reducing costs are of high concern. The performance of a dry heat sterilization tunnel has a direct influence on all these critical issues.

The degree to which a sterilization tunnel is able to remove pyrogens from the washed glassware in an effective, efficient and repeatable manner, is in turn highly depending on the function of HEPA filtration [4]. Traditional dry heat sterilization equipment, performing e.g. IR (infrared) heating, showed deficits in cleanliness, equipment size, processing time and precisely controlled temperature programs. Unidirectional airflow with HEPA filtration was found to be the far more suitable technique for the various challenges of dry heat sterilization [5]. Final filtration of the circulated air stream enables a faster and more simultaneous heating up of the glassware. However, the air filter has to withstand integrity challenges caused by high variations in operating temperature during heating and cooling. Process contamination and resulting unscheduled downtime from bypass of unfiltered air, leaks or shedding of particles has to be prevented. The challenge to limit particle shedding can be particularly critical in cases of temperature fluctuations that arise from emergency shut-downs or interruption of power supply.

Controlling the challenges during exposure to high temperature and frequent heating and cooling cycles, is no sinecure for a HEPA filter. ISO 5 conditions are being stipulated and determined to demonstrate that HEPA filters are effective and free from cracks or other defects. An overview with the applicable particle limits per ISO cleanroom class is presented in table 1.

Table 1: Airborne particulate cleanliness classes to ISO 14644-1:2005

ISO classification number (*N*)	Maximum concentration limits (particles/m^3 of air) for particles equal to and larger than the considered sizes shown below					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1,0 µm	5,0 µm
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1.000	237	102	35	8	
ISO Class 4	10.000	2.370	1.020	352	83	
ISO Class 5	100.000	23.700	10.200	3.520	832	29
ISO Class 6	1.000.000	237.000	102.000	35.200	8.320	293
ISO Class 7				352.000	83.200	2.930
ISO Class 8				3.520.000	832.000	29.300
ISO Class 9				35.200.000	8.320.000	293.000

2 High temperature HEPA filtration

2.1 Considerations for selecting the right solution

Several characteristic requirements for high temperature HEPA filters can be identified that directly influence the productivity of a sterilization tunnel. From various in-depth interviews conducted with tunnel manufacturers and pharmaceutical end users, two HEPA filter requirements have been found most critical in especially the hot zone of a sterilization tunnel:

1. High stiffness and durability of construction;
2. Proven efficiency performance during operation.

A high stiffness and durability of construction should assure that the integrity of the HEPA filter is retained during elevated temperatures. Filter design and material selection should be such, that degradation does not occur and thermal expansion and contraction do not create stress cracks. Integrity breaches, caused by stress cracks, should be avoided at all times as these might result in bypass, particle shedding and process contamination.

A compliant efficiency performance of the HEPA filter should not only be confirmed from a factory test by the filter manufacturer, but moreover from real-life operation. A stable downstream efficiency is to be retained during multiple heating and cooling cycles, whereby the particle counts are compliant with the ISO Class 5 limits as set by standard ISO 14644-1:2005.

Considerations for hot zone

- Select air filter with long term durability of construction
- Select air filter with proven performance on efficiency during operation

"Many in-depth interviews with tunnel and medicine manufacturers have given us a perfect understanding of how HEPA filtration can optimize high temperature processes."

Dr.-Ing. Marc Schmidt - Business Development Manager Pharma, AAF International B.V.