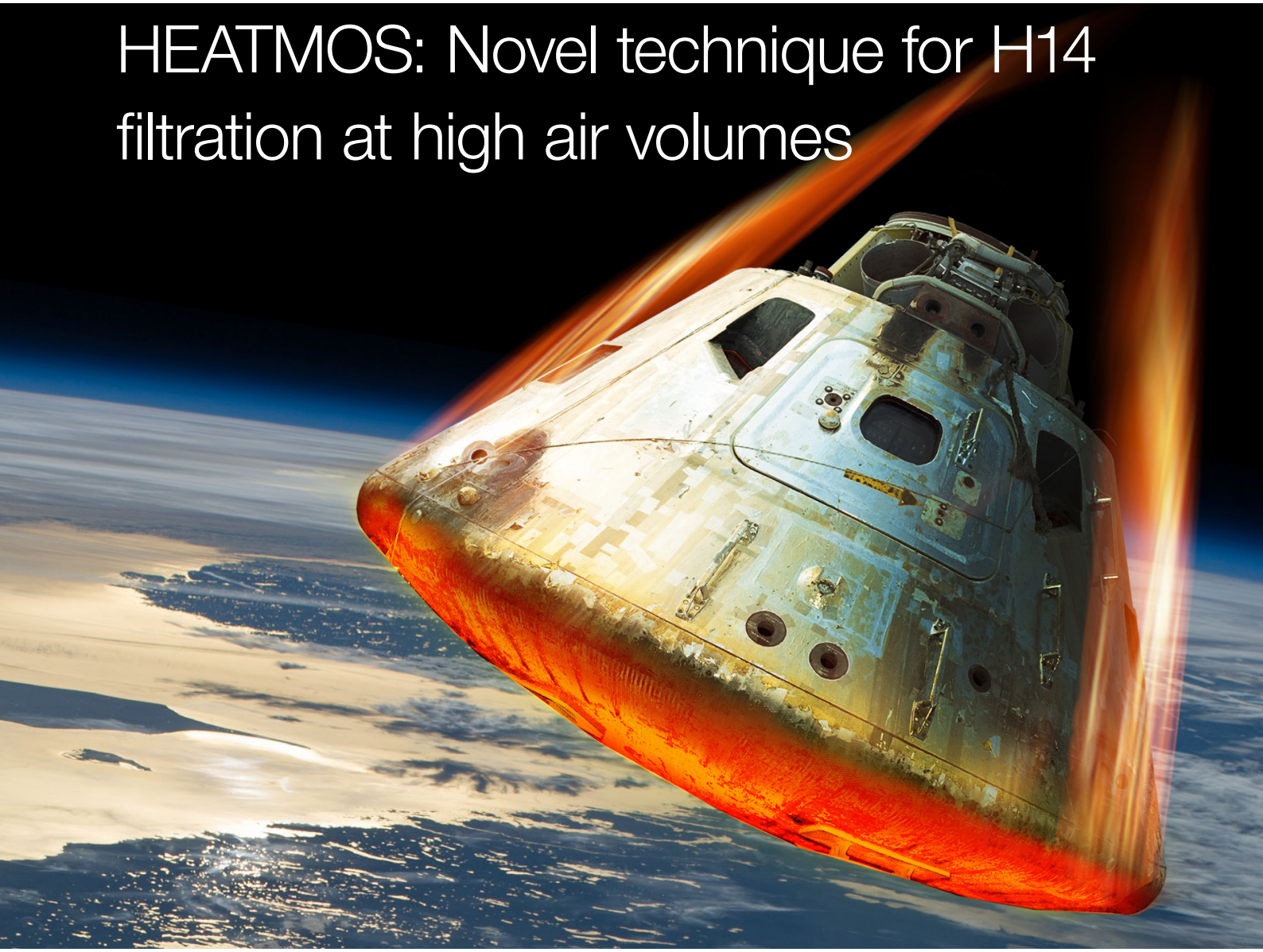
WHITEPAPER

The next step in filtration for dry heat sterilization applications

HEATMOS: Novel technique for H14 filtration at high air volumes



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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 ℃, operating conditions are challenging.

To control the challenges, and therewith not to affect manufacturing throughput, 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.

Supported by hundreds of test cycles, through which air filter durability and particle shedding were verified, an innovative filter design, HEATMOS, will be presented that resolves well-known issues with the traditional high temperature HEPA filter designs that have been serving the market so far, meeting H14 efficiency and facilitating ISO class 5 operating conditions throughout all process steps. The results were confirmed at extensive tests at renown sterilization equipment manufacturers.

The novel design offers the highest quality standard and ensures fulfillment of all technical specifications and requirements as stated by the guidelines of both FDA regulation 21 CFR-211.94 and EU-GMP Annex 1.

This whitepaper will therefore provide new insights in how to mitigate process contamination risk by applying innovative material developments to the proven HEPA filtration technology. It will support the pharmaceutical industry to obtain a more stable, more reliable, and less risky dry heat sterilization process.

Key words: Dry heat sterilization, dry heat depyrogenation, high temperature HEPA filtration, filter design, filter durability, particle shedding, filtration efficiency, ISO14644, EN1822, ISO29463, FDA 21CFR-211.94, EU-GMP Annex 1

What's Inside

1 Introduction

1.1 Critical process step in sterile manufacturing

Short time-to-market and high production throughput, while meeting quality specifications and regulations and reasonable production costs are accompanying challenges in the pharmaceutical industry. In particular the 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 and EU-GMP guidelines Annex 1 [1] [2]. 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.

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. For the sake of simplicity, the term sterilization is used in the rest of the text to refer to dry heat sterilization and depyrogenisation.

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 [3].

Modern demands on sterilization processes, laid 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)” [4]. This demand contributed decisively to the development of safe, fast and efficient dry heat sterilization processes including unidirectional airflow with HEPA filtration.

The more stringent regulations are a motivation for product developments. Moreover, the risk of introducing impurities in the final process step of filling would jeopardize any purity efforts made in the manufacturing process.

The awareness of incalculable risks for patients, subsequent cost for claims and compensation, as well as the danger of a unquantifiable loss of reputation are major driving forces for continuous innovation efforts.

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.

The dry heat sterilization of glassware typically follows a three-step approach: infeed in the pre-heating zone, sterilization in the hot zone and cooling in the cooling zone.

High risk operations like aseptic filling have to be carried out in Grade A zones which require ISO class 5 cleanroom conditions [1] [2]. Therefore, in these areas any air admitted has to pass through a HEPA filter [2]. 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.

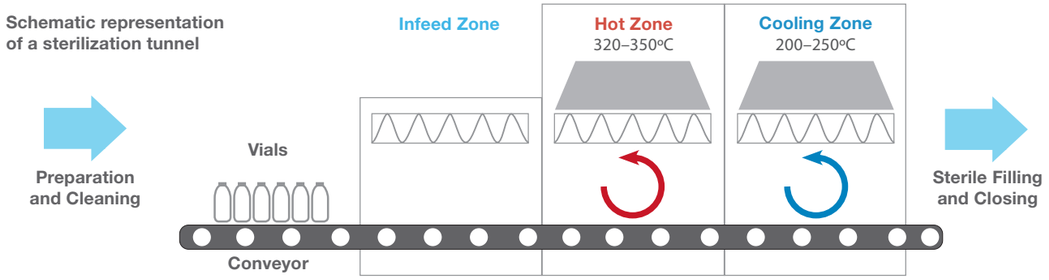


Figure 1: Schematic representation of a sterilization tunnel

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 [5].

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 [6].

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 shutdowns or interruption of power supply.

Controlling the challenges during exposure to high temperature and frequent heating and cooling cycles, is a demanding task 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.

EN-ISO 14644-1 2015: Classification by Particles

		Maximum Concentration Limits (Particles/m³)					
		0.1 µm	0.2 µm	0.3 µm	0.5 µm	1.0 µm	5.0 µm
ISO 14644-1 Classification Number (N)	1	10					
	2	100	24	10			
	3	1,000	237	102	35		
	4	10,000	2,370	1,020	350	83	
	5	100,000	23,700	10,200	3,500	830	
	6	1,000,000	237,00	100,200	35,200	8,320	298
	7				352,000	83,200	2,930
	8				3,520,000	832,000	29,300
	9				35,200,000	8,320,000	293,000

Table 1: Airborne particulate cleanliness classes to ISO 14644-1:2015 [7]

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 and tests conducted with renown 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.

2.1.1 Mechanical construction

A high stiffness and durability of construction should assure that the integrity of the HEPA filter is retained during elevated temperatures. Filter frames are generally produced from galvanized and for demanding applications stainless steel constructions. The assemblies necessary for a functioning filter are the filter frame, filter medium, spacer or separators, a casting material to form a bond between filter medium pack and filter frame, and a gasket for leak-free coupling to a connection surface.

The most often used filter media are generally glass fiber, sometimes even dual layer media. Depending on the application, ceramic materials, PTFE or when allowed silicon are the most frequently employed gasket materials.

Filter design and material selection should be such, that degradation does not occur, and thermal expansion and contraction do not create stress cracks. Unwanted particle release from the filter's components is also referred to as secondary particle generation or particle shedding.

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 14644-1:200515.

2.1.2 Air flow rate

Removal of aerosols with the help of a particle filter is always synonymous with an additional expenditure of energy that is required to maintain the air volume flow. The flow resistance or pressure loss of the filter should be as low as possible without compromising the required separation performance.

Lower pressure drop also allows for upgrading from H13 to H14 filter efficiency without compromising the air flow rate while existing equipment and components can continue to operate without replacement. Compared to the air required to heat the air for sterilization, the energy requirement for filtration can be considered low.

Every saving in additional pressure loss, however, has a favorable effect on system components, in particular the fan and associated drive, prevents unnecessary wear and thus serves to maintain the entire system.

2.1.3 Heating rates

The heating rate with which the filter can be heated to the operational temperature is of great importance since this is a limiting step in production modes that rely on frequent changes in processing conditions, batch changes, cleaning activities and equipment set up.

The recommended heating rates differ depending on the product design and product manufacturer and vary from 1°C per minute to up to 10°C per minute. In order to allow for the even distribution of heat in the filter and to facilitate the thermal expansion, intermittent holding plateaus are recommended for older products.

Every slight increase in the heating rate means a reduction in the unproductive waiting or down time in a commercial process and an increase in overall productivity.

2.1.4 Particel efficiency

While the classification according to ISO14644 defines the cleanliness of a room by defining allowed numbers of particles in a cleanroom, the performance of HEPA filters is classified due to their efficiency in removing particles of a particular size from the supply air. The quality of the supply air is determined by the efficacy of the terminal HEPA-filter stage. HEPA filters can be classified according to internationally accepted standards as EN1822, which is also known as ISO29463 or as well as IEST-RP-CC001 [8] [9] [10].

Historically, testing of filter efficiencies was carried out at a particle size of 0,3 µm, but due to the improvement and economization of the measurement technology, tests can now be carried out in the range of the Most Penetrating Particle Size (MPPS) acc. to EN1822, which is in the range of 0,1 – 0,2 µm and thus below the 0,3µm.

For HEPA filters, efficiency values of 99.95 % and above are achieved which is also coined the term of “absolute filters” and commonly, filters of these efficiencies at 0,3 µm particle size are used in dry hot air sterilization.

The shift in efficiency to the lower particle size range of MPPS, which due to the characteristic shape of the filter's efficiency curve is equivalent to an even higher efficiency for the 0,3 µm particle size, can be seen as a significant improvement in the protection against contamination of high-value medicinal products.

Filters are not only tested for their efficiency against one particular particle size, but also have to meet leak free criteria, which is that unavoidable local variations in efficiency values must not exceed defined maximum values. An integral efficiency of 99,95 % at MPPS and the absence of local exceedances are the requirements for HEPA filters of filter class H13 and above according to EN1822.

Any improvement in filter efficiency to higher values is equivalent to a reduction in the risk of contamination and the associated risks. According to the test method according EN1822, the separation efficiency at the most penetrating particle size is used to determine the filter class and allows for the assignation of filter classes like e.g., H13 and H14.

The classification according IEST-RP-CC001 evaluates the filter's efficiency at the particle sizes 0,1 µm, 0,2 µm and 0,3 µm and filter classes are assigned with alphabetical letters ranging from A to K. The separation efficiencies of the filter elements used are generally 99.95 % and above.

With increasing quality awareness, the demands on the filter element have also increased, whose qualification as a full-fledged HEPA filter with defined integral and local minimum values must be proven before installation by means of acceptance certificates. Operating with H14 class filters facilitates a cleaner and safer process environment and also peace of mind of the process owners.

HEPA Filter Classification Comparison EN-1822 & ISO-29463

Group		EN-1822	ISO 29463	Integral Value		Local Value		Leakage Factor
				Efficiency at MPPS	Penetration at MPPS%	Efficiency at MPPS	Penetration at MPPS%	
Group	EPA	E10		≥85	≥15			
		E11	ISO 15 E	≥95	≥5			
			ISO 20 E	≥99	≥1			
		E12	ISO 25 E	≥99.5	≥0.5			
			ISO 30 E	≥99.9	≥0.1			
	HEPA	H13	ISO 35 E	≥99.95	≥0.05	≥99.75	≥0.25	5
			ISO 40 H	≥99.99	≥0.01	≥99.95	≥0.05	5
		H14	ISO 45 H	≥99.995	≥0.005	≥99.975	≥0.025	5
			ISO 50 H	≥99.999	≥0.001	≥99.995	≥0.005	5
	ULPA	U15	ISO 55 H	≥99.9995	≥0.0005	≥99.9975	≥0.0025	5
			ISO 60 U	≥99.9999	≥0.0001	≥99.9995	≥0.0005	5
		U16	ISO 65 U	≥99.99995	≥0.00005	≥99.99975	≥0.00025	5
			ISO 70 U	≥99.99999	≥0.00001	≥99.9999	≥0.0001	10
		U17	ISO 75 U	≥99.999995	≥0.000005	≥99.9999	≥0.0001	20

Table 2: Filter efficiency and classification according EN1822

IEST RP-CC001 Classification

Filter Type	Particle Size for Testing	Overall Value Efficiency	Local Value Leakage
A	0.3*	≥99.97	
B	0.3*	≥99.97	
E	0.3*	≥99.97	
H	0.1-0.2 or 0.2-0.3**	≥99.97	
I	0.1-0.2 or 0.2-0.3**	≥99.97	
C	0.3*	≥99.99	1
J	0.1-0.2 or 0.2-0.3**	≥99.99	1
K	0.1-0.2 or 0.2-0.3**	≥99.999	1,6
D	0.3*	≥99.999	5
F	0.1-0.2 or 0.2-0.3**	≥99.9995	5
G	0.1-0.2 or 0.2-0.3**	≥99.9999	10

*Although the mass median diameter of thermally generated particles are approximately 0.3 micron, the count mean is under 0.2 micron or close to the MPPS.

Table 3: Filter efficiency and classification IEST-RP-CC001

2.1.5 Burning in procedure

The burning in procedure of a high temperature filter is a necessary process to remove any remaining organic material that originates from the manufacturing process of the filter. This is the first process step for a high temperature HEPA filter and is also referred to as filter tempering or prebaking procedure. During this step the filter is usually heated to a temperature which is equal or higher than the intended continuous operation temperature and has to be carried out strictly according to manufacturer's instructions.

The burning in procedure is usually accompanied by the generation of white smoke.The white smoke originates from the burning off of acrylic and latex binders from the filter media and other adhesives used in the manufacturing of the filter. During the burning in procedure adequate precautions have to be taken and the white smoke must be vented off.

After the burning in procedure the filter, in particular the filter media, has lost some mechanical strength due to the removal of the organic binder substances and the filter must be handled with outmost care to avoid any unnecessary impact of forces like e.g., vibration or accidental dropping. It is therefore advisable to burn in the filter element at the place of intended operation. Once the filter is burnt in it can be used for operation.

In some instances, the organic binder components are already removed during a pre-baking process step at the manufacturing of the filter. This might be deemed beneficial as it's eliminating a time-consuming step at the site of the filter user.

Whilst this offers an attractive time saving, it must be considered that the transport of fragile pre-baked filters must be done with outmost care, nevertheless carrying a risk of filter damage. The filters have thus to be transported outside the sterilizing equipment and the provision of replacement filters must also be taken into account.

2.2 Available solutions to the challenges

Historically seen, the number of options available to tunnel manufacturers and pharmaceutical end users for HEPA filters that can withstand temperatures up to 350 °C has been limited.

This section will compare the currently commercially available high temperature HEPA filter options, Type A, Type B, and Type C, with a reflection on the selection considerations as introduced before.

The first design, Type A, is a construction which has served the pharmaceutical industry for many years. This filter type does however possess some generally known deficits, directly attributable to its construction and the components used.

The second filter design, Type B, comes in a new design, which promises better results on the requirements of long-term durability and efficiency during operation.

Filter design Type C is a product that enables an improvement in filter quality by claiming the particle efficiency of H14.

The latest development step to date is the innovation to the HEATMOS filter design which facilitates the filter efficiency H14 with improved air throughput, while at the same time being capable of allowing high heating rates, ensuring highest cleanliness demands and shortest possible process times.

Type A HEPA filter with ceramic sealant and aluminum separators

The traditionally widely used but technically superseded filter option for sterilization tunnels comes with a ceramic sealant and fiberglass filter medium.

The medium is folded around aluminum separators, which in turn are placed in parallel in a stainless-steel frame. Because ceramic material is used to seal the aluminum separated media pack to the frame, this filter type is sensitive to the formation of stress cracks.

The cracks occur between the ceramic glue and the filter frame due to internal stresses created by process driven temperature cycles. In order to try to absorb the movement of the filter components during elevated temperatures, the filter is equipped with a compensation mat directly under the sealant. The stress cracks can cause leaks that result in bypass of unfiltered air.

Particle emission is created when the edges of a sealant crack are rubbing each other due to normal fan and motor induced vibration of the whole construction. Thus, the cracks also generate particles by themselves. Such uncontrolled shedding into the tunnel, which can be reinforced during even very small temperature fluctuations, results in contamination of the sterilization process.

The air filter industry has worked together with the tunnel manufacturing industry to look for an alternative solution to mitigate the risks from the occurring stress cracks. This has resulted in a so-called 'dynamic seal', in which spacers are positioned to the installed filter at the clean air side.

With this counter measure, the filtered air (which can include bypass air and released ceramic particles) is taken out from the overpressure situation in the oven to the under pressure situation outside the oven. Although this counter measure seemed to reduce the problem, it is not a structural solution to the intrinsic issue with the filter design itself: for a sustained result, the issue should be solved at the source.

The same is true for installing a fine mesh immediately downstream of the (clean) filter outlet. Such a mesh shall protect clean glass containers on the conveyor belt from being contaminated by larger particles, released from the installed filter and applied gasket.

Figure 2: Filter design A

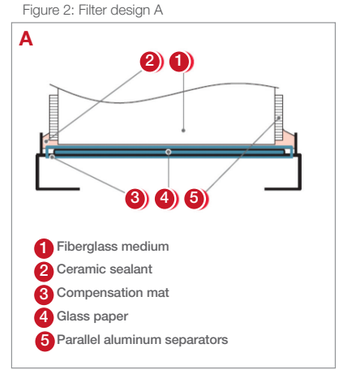
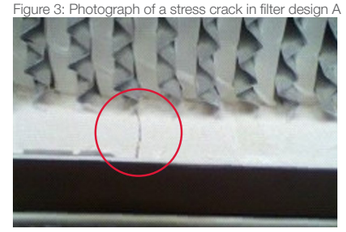


Figure 3: Photograph of a stress crack in filter design A



Type B HEPA filter with elastic fiberglass sealant and stainless steel separators

Similar to filter design A, filter design B comes with a stainless-steel frame, a fiberglass media pack and is free of silicones. The important differences are in the applied separator and sealant material.

Filter design B is equipped with corrugated stainless-steel separators and with stainless steel support bars and stays. This construction gives a high overall durability, which is less prone to oxidation. Risk of oxidized particles to shed off the separators on the air leaving side is reduced.

The separators are placed in staggered position to increase the media pack stiffness and to prevent the separators from nesting. Applying integrated stainless steel stiffener plates and stays prevent winding of the bottom of the pleats. In addition to stainless steel separators and stiffeners, filter design B includes an elastic fiberglass sealant in contrast to the vulnerable ceramic sealant of filter design A.

Figure 4: Filter design B

With the inclusion of an elastic fiberglass sealant, the HEPA filter is better able to compensate the forces from heat stretching of components. Integrity breaches from stress cracks are prevented.

Type C HEPA filter with inorganic polymer sealant and stainless steel separators

Filter Type C represents the further development of Type A by replacing the casting compound with an inorganic polymer and the use of stainless-steel separators inside a robust stainless-steel housing. The realization of filter class H14 is made possible on the expense of a relatively high pressure resistance and a limited air flow rate.

HEATMOS HEPA filter with novel glass fiber wool ceramic compound

The HEATMOS filter design represents the most recent innovation step. It is based on the successful filter Type B construction with stainless steel housing and a sophisticated separator technology of corrugated stainless steel sheets positioned in an staggered fashion, which allows most even air passage while avoiding detrimental compression of the filter medium.

Figure 5: HEATMOS filter

The innovative step is to seal the pleat pack of the filter to the frame with a new type of mechanically flexible glass-fiber-wool-ceramic composite material that enables a completely leak-free design over the duration of hundreds of operating cycles. The use of a high-technology glass fiber-based filter medium meets the enormous requirements of the filter class H14 at high temperatures and astoundingly low pressure loss .

Universal coupling of the filter to the sterilization equipment can be facilitated by either utilizing the filter's flush metal surface or by employing a glass fiber media gasket. The entire frame construction is designed to provide a maximum possible mechanical strength as to resist the expansion and contraction forces that occur during the thermal application process.

This ensures perfect dimensional stability for the safety of the fragile filter media package and for safe and leak-free coupling of the filter to the equipment.

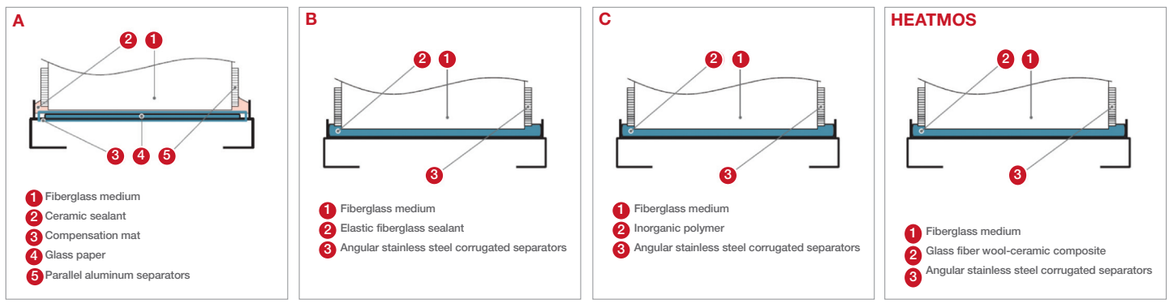


Figure 6: Available high temperature HEPA filter designs

3 Performance demonstration

To demonstrate the performance of the HEATMOS product innovation, a filter sample had to undergo a rigorous test regime.

A filter was prepared and burnt in before being tested for mechanical integrity in a pressure test and in up to 300 process cycles.

Particle shedding experiments at high temperature were conducted to complement the standard factory efficiency and leakage tests.

3.1 Flow rate and pressure drop

The Pressure drop of the HEATMOS filter was tested at the nominal flow rate as well as the filter efficiency was tested with a full scan test.

The HEATMOS filter was found to exhibit the lowest pressure drop in comparison to commercially available competitor products, while at the same time fully satisfying the filter class H14.

	Filter type			
	Type A	**Type B**	**Type C**	**HEATMOS**
Filter dimensions (WxHxD: mm)	610x610x292			
Flow rate (m^3/h)	1.960	2.100	1.960	2.100
Pressure drop (Pa)	250	250	290	270
Efficiency class	H13	99,95 % (0,3 µm)	H14	H14

Table 4: Performance parameter of various high temperature HEPA filters

3.2 Heat cycle and pressure drop test

The suitability of the filter design D is tested by assessing the response of the filter construction to a prolonged period at elevated pressure. The filter element undergoes a full burning in cycle from room temperature up to 350 °C for one hour before cooling down to room temperature.

After this thermal stress, a volume flow is applied to the filter element so that a pressure drop of 2,700 Pa is reached over the filter element and which is kept for the duration of one hour.

Pressure drop and particle efficiency are determined before and after thermal and volume flow loading, which allows for the evaluation of the filter design for its mechanical suitability.

The results show no change in the respective performance parameter and demonstrate the suitability of the design in principle. Merely a slight discoloring of the stainless-steel frame material as result of oxidizing processes during the thermal loading phase can be observed.

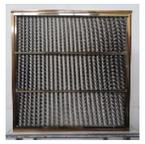
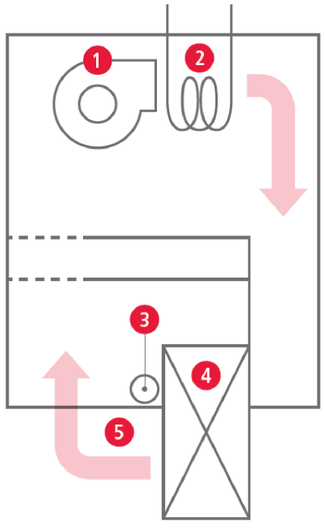
	Pressure test	
	Pre-test	Post-test
Filter dimensions (WxHxD: mm)	610 x 610 x 292 mm	
Flow rate (m^3/h)	2.100	
Pressure drop (Pa)	240	238
Efficiency at MPPS (%)	≥ 99,995	≥ 99,995
		

Table 5: Pressure test; pressure drop and particle efficiency test results (HEATMOS filter)



1. Fan
2. Electro-thermal heater
3. Temperature control point
4. Tested air filter
5. Particle measuring point (laser particle counter)

Figure 7: Illustration of particle release test rig

3.3 Filter efficiency performance

The performance of the filters is verified in a test according to EN1822. When the test aerosol is applied, the entire surface of the filter is scanned with a sampling head in order to determine the separation efficiency and to discover any leakage points.

The test was carried out using an automated test rig and employing a RION KC-24 particle counter. The efficiency for the HEATMOS filter was determined as ≥ 99,995 % at MPPS with the absence of any local excess penetration values, qualifying the filter element as “true” H14 according to EN1822.

3.4 Particle release test

In order to evaluate the particle release, a HEATMOS filter was subjected to a burning in process from room temperature to 400 °C and a holding phase at 400 °C for 1 h duration at its nominal flow rate of 2.100 m^3/h.

The filter was then set into a circulation-type test rig which allowed for the continuous monitoring by means of an optical particle counter with heated air being feed through the filter element (Figure 7).

The temperature of the air was increased from room temperature to 350 °C at a rate of 4,3 °C /min. The temperature level of 350 °C was kept constant for the duration of 1 h before the air temperature was reduced to room temperature again.

During each process step, the number of particles down stream of the filter was determined. Particle counting was carried out for particles with a diameter of ≥ 0,5 µm.

The result of this examination is displayed in the graph below and shows the observed number of particles for each step of the HEATMOS filter in comparison to a Type B filter (Figure 8).

The average particle count for the novel HEATMOS filter does not exceed the value of 100 particles/cf (= 3.520 particles/m^3) in both the heating and the cooling phase that were monitored with the particle counting system, which is safely creating ISO 5 conditions.

In comparison to the release of particles of a filter Type B, this is a significant reduction of particles being generated during the heating and cooling phases.

It is noteworthy that the release of particles can predominantly be observed during the ramping up of temperature and during the cooling phase of the filter, indicating that the particle shedding is indeed caused by the thermal expansion of materials and subsequent abrasion due to friction.

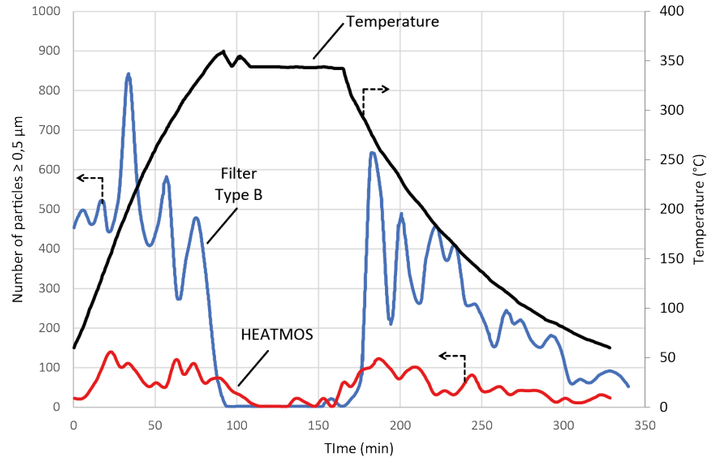


Figure 8: Particle release test during operation cycle for novel HEATMOS filter and filter Type B

3.5 Heat cycle test for 300 cycles

In order to simulate the requirements of a real-life application, the HEATMOS filter was subjected to 300 process cycles, consisting of heating, holding, and cooling phases, and then evaluated.

The heating cycle started at 40 °C and the filter was heated to 350 °C. A subsequent holding phase at 350 °C was kept for 30 min before the filter was allowed to cool down to 40 °C again before the next cycle commenced which is illustrated in Figure 9.

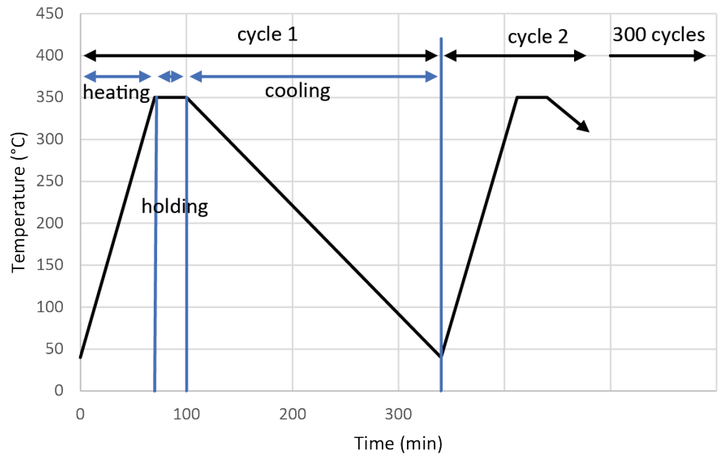


Figure 9: Cyclic temperature program for 300 heat cycle test

The pressure loss and particle efficiency of the filter were determined before and after the test procedure.

As expected, there was no difference visible in the filter's performance after the completion of the 300 heat cycles.

	300 heat cycle test	
	Pre-test	Post-test
Filter dimensions (WxHxD: mm)	610 x 610 x 292 mm	
Flow rate (m^3/h)	2.100	
Pressure drop (Pa)	236	236
Efficiency at MPPS (%)	≥ 99,995	≥ 99,995
		

Table 6: HEATMOS filter Performance data before and after 300 heat cycle test

3.6 Burning in process and temperature ramps

The HEATMOS filter requires the burning in at the intended operation temperature in order to drive off any organic construction compound and residues from the manufacturing process. This process usually takes 1 hour but can also be extended when required.

The recommended rate of temperature increase for ramping up the burning in procedure is limited to 5 °C/min which is also the rate with which the filter can be operated in the standard production.

This is an extremely attractive property since the elimination of holding steps during the ramp up phase is a considerable time saving and gain in productivity. A comparison of heat rates for various high temperature HEPA filters is illustrated in Figure 10.

After the burning in procedure the filter, in particular the filter media, has lost some mechanical strength due to the removal of the organic binder substances.

The filter has now to be handled with a large degree of care so avoid any unnecessary impact of forces like e.g., vibration or accidental dropping.
The novel glass fiber wool and ceramic compound allows for the availability of burnt in filters already being available from the factory, which equates to a substantial simplification of filter installation on site.

Further information on the optionally burnt in filter products is available on request.

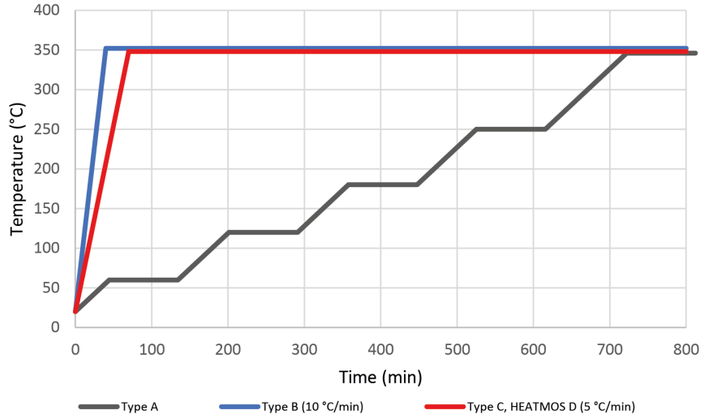


Figure 10: Heating rates for high temperature HEPA filters

3.7 Tests conducted with Leading Sterile Tunnel Manufacturers

HEATMOS filters of certified H14 filter efficiency were tested at globally renown sterile tunnel manufacturers on site. Operating temperatures were up to 350 °C continuously.

During multiple tests for all three cycles of heating, holding, and cooling, it was confirmed that the HEATMOS filter's mechanical construction did not show any temporary or

permanent deformation. Although a lighter filter construction in direct comparison to Filter Type B, the HEATMOS filter shows superior resilience and stability under duress and significantly reduces the potential of particle shedding during thermal expansion and contraction.

The visual inspection of the sterilization zone after every cycle shows a clean area, as no visible particles can be found nor are any structural weaknesses to be seen in the HEATMOS' sealing material, media, or frame.

Additional scan tests conducted after each cycle prove a repeated fulfilling and exceeding of the H14 rating in accordance with the EN1822 standard, therefore guaranteeing safety for the process at the currently highest level of filter efficiency for high temperature applications. The experiences of the manufacturers also include that the product is easier to handle and install than previous versions due to the robust construction and yet light weight.

The confirmation of the mechanical stability of the HEATMOS filter in the arduous tests, steady H14 efficiency, absence of particle shedding, and easier handling, provide convincing arguments for its use in sterilization tunnels.

4 Conclusion

The exposure to elevated temperatures during dry heat sterilization sets stringent requirements on high temperature HEPA filters. With high durability of construction and proven efficiency during operation being identified as the two most critical requirements, any failure in these areas will affect the sterilization process directly. Risk of process contamination from bypass, leaks or particle shedding needs to be mitigated.

ISO class 5 conditions are to be met, demonstrating that the high temperature HEPA filter is effective and free from cracks or other defects. Filter design A, with ceramic sealant and aluminum separators, has served the pharmaceutical industry for many years but is technically superseded. Nevertheless, this design does possess some generally known deficits that lead to a loss of integrity from stress cracks between the sealant and the frame.Increased risk of process contamination and premature filter replacement are the result.

Gradual improvements in product design have resulted in filters that meet H14 requirements, but at the cost of a higher differential pressure, a complication for easy and uncomplicated upgrading and retrofitting.

Multiple heat cycle, strength and pressure tests have demonstrated that the HEATMOS filter with an innovative glass fiber wool-ceramic composite and stainless-steel separators, offers an improved durability and stiffness of construction.

From a comparative particle shedding test between filter designs Type B and HEATMOS it can be concluded that the HEATMOS design offers a better and more consistent filtration efficiency performance at considerably higher levels during heating and cooling, meeting both, H14 efficiency level and facilitating ISO class 5 operating conditions. Because of absence of stress cracks, particle shedding is minimized.

The durability and performance of the element has been confirmed in a realistic 300 cycle test , as well as in tests at world-renowned manufacturers, proving the suitability for industrial applications.

The novel design of the HEATMOS filter offers the highest quality standard and ensures fulfillment of all technical specifications and requirements as stated by the guidelines of both, FDA regulation 21 CFR-211.94, and EU-GMP Annex 1.

A dry heat sterilization application can be considered as being one of the most critical pharmaceutical process steps in sterile manufacturing.

This whitepaper has given an analysis of the main challenges that have to be mitigated from an air filtration perspective.

It has provided a report on the historic filter development and new insights in how to answer to the integrity challenges of high temperature HEPA filters, by which to mitigate process contamination risk and protect product quality and safety.

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