Guideline for Sterilizing Filtration of Air and Other Gases in Aseptic Processing and Packaging of Food and Beverages

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Disclaimer

The Institute for Thermal Processing Specialists and its members present this information to the best of our current status of knowledge; we have exercised due diligence to make sure it is accurate and up to date. Users of this information should check for newer versions of the cited standards.

The following recommendations are voluntary guidelines, unless otherwise noted. While these recommendations do not preclude the application of other methods and equipment, this *Guideline* has been developed by consensus of the Institute for Thermal Processing Specialists and should be given serious consideration for adoption as methodology by individuals working with all aspects of aseptic air and gas filtration uniquely applicable to the food and beverage industry.

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Guideline for Sterilizing Filtration of Air and Other Gases in Aseptic Processing and Packaging of Food and Beverages

1 Introduction

Aseptic food and beverage production often includes processing and packaging steps that require gas (typically air) sterilization. There are several ways to sterilize gas such as by incineration, treatment with electron beams, plasma or sterilizing chemicals. In this *Guideline* we focus on the principles of sterilizing filtration. Air or gas (*e.g.,* nitrogen, carbon dioxide), when in contact with the product, packaging materials, or processing and packaging equipment surfaces must meet certain requirements for basic cleanliness and/or sterility, depending on the location of these contact points.

This *Guideline* has been prepared to assist processors, equipment suppliers, regulatory agencies and academic institutes in dealing with all aspects of aseptic gas filtration. While non-binding in scope, it is based on state-of-the-art filtration and good manufacturing practices.

The *Guideline* includes information about gas filter types used for aseptic filtration, selection criteria, mechanisms of gas filtration, installation, operation, and verification of performance. It also explains the validation protocols and verification tests carried out by filter manufacturers, equipment manufacturers, and food processors.

1.1 Importance of this *Guideline* for Aseptic Food and Beverage Production

Aseptic production consists of highly controlled and monitored manufacturing steps, to ensure the required quality and safety of the finished product. This includes establishment and maintenance of aseptic conditions to maintain product commercial sterility post-processing and prior to final package sealing. Failure of the aseptic filtration operation can result in contamination of the food product leading to spoilage and a potential public health hazard. Figure 4.1 (Chapter 4.1.1) shows the critical locations where sterile gas is utilized in the aseptic process.

This *Guideline* will provide the readers with understanding to design and manage the filtration system according to aseptic good manufacturing practices.

1.2 Intended Audience

This *Guideline* is intended for international use by:

- food and beverage manufacturers: QA, Production, Process and Systems Engineering, Management
- equipment manufacturers (OEMs): Consulting Engineers and Aseptic Specialists
- filter manufacturers
- process authorities and experts
- regulatory authorities

1.3 Scope of this *Guideline*

Authors' Note: Henceforth in this *Guideline*, we will use the term "air" to refer to any gases, excluding steam, used in aseptic production.

This *Guideline* aims to provide a food and beverage industry-specific document, which covers all points of relevance for these applications. It will only cover filtration of air post-processing and prior to final package sealing. It does not cover room air filtration, air filtration for non-sterile parts of the aseptic process, and air-conditioning/pretreatment prior to sterilizing air filtration, other than a discussion of supply air quality and an overview of its treatment in Chapter 2. However, successful aseptic filtration is dependent on these

other types of filtration.

Despite being outside the scope of this document, the minimum specifications of air quality before the sterile air filters must satisfy the filter manufacturers' recommendation to ensure delivery of the required sterilizing filter performance and efficiency.

1.4 Definition of Sterilizing Air Filtration

The purpose of this section is to give readers basic nomenclature and definitions about sterilizing filtration. Chapter 5 provides information on different morphologies of membrane and depth cartridges as well as HEPA/ULPA filters.

A comprehensive glossary is also given at the end of this document.

1.4.1 Hydrophobic Air Cartridge Filters

A sterilizing-grade air cartridge filter is defined as a filter which, when appropriately validated by the filter manufacturer, will reproducibly produce a sterile effluent, free of viable microorganisms in the filtered air. Further, when properly validated filters are installed, sterilized, operated, monitored and maintained according to filter manufacturer installation and operating instructions they will provide air free of viable microorganisms in aseptic applications.

The validation of air cartridge filters by filter manufacturers is performed by microbial challenge. A sterilizing-grade filter is defined as one that retains a challenge of at least 10^7 colony-forming units (cfu) *Brevundimonas diminuta (B. diminuta)* per cm^2 of effective filter area yielding sterile effluent. This definition is rooted in the Food and Drug Administration (2004) Guidance for Industry)[1] and the Parenteral Drug Association (PDA) (2005) Technical Report (TR) 40).[2] Further discussion regarding this definition is provided in Chapter 7.1. Details regarding relevant concepts and methods of filter microbial validation are provided in Chapters 7.2.1 and 7.5.1.

Chapter 7.5 describes the overall cartridge filter performance validation program so that a user can identify whether a filter cartridge manufacturer delivers compliant products and documentation.

1.4.2 High Efficiency Particulate Air (HEPA) / Ultra Low Penetration Air (ULPA) Filters

HEPA and ULPA are commonly used expressions to describe air filters with extremely high capture efficiency on submicron-sized particles in air. They are grouped into various filter classes depending on their efficiency against airborne particles of a specific size.

Authors' Note: In this *Guideline*, the term HEPA will be used as a general term to describe both HEPA and ULPA filters unless otherwise noted.

There are three international guidelines for the classification of HEPA filters:

- IEST-RP-CC001[3]
- EN 1822 (part 1)[4]
- ISO 29463 (parts 1-5)[5]

Further details are provided in Chapter 8.1. These standards utilize filter efficiency as the most relevant factor for retention performance, and they distinguish between HEPA and ULPA filters, where ULPA filters perform at an even higher level.

Both EN 1822 (part 1) and ISO 29463 (parts 1-5) use Most Penetrating Particle Size (MPPS, see Chapter 6.4) to calculate capture efficiency. In these guidelines, HEPA filters suitable for use in aseptic systems begin at 99.95% efficiency on MPPS and ULPA filters at 99.9995% on MPPS.

HEPA and ULPA filters, when appropriately validated by the filter manufacturer, will reproducibly provide filtered air free of viable microorganisms in accordance with their rated efficiency. Further, when properly validated filters are installed, sterilized, operated, monitored and maintained according to filter manufacturer and OEM installation and operating instructions, they will provide air free of viable microorganisms in aseptic applications in accordance with their rated efficiency.

The validation of these filters by filter manufacturers is performed by particle removal classification. Further discussion regarding these classifications is found in Chapters 8.1 and 8.2.1. Chapter 8.5 describes the overall HEPA filter classification validation program so that a user can identify whether a HEPA filter manufacturer delivers compliant products and documentation.

2 Supply Air Quality in Aseptic Production

The quality of the supply air to final sterilizing-grade cartridge filters or final HEPA filters in aseptic food and beverage equipment is a critical determinant of successful final, sterile filtration of air. It is extremely important to focus on purifying the air upstream of the final filters, whether it is supplied from a compressed air source or a blower. Purification equipment treats the air in order to reduce known contaminants to an acceptable level. Proper selection and use of air pretreatment equipment will assure the performance and extend the service life of final filters in the aseptic system.

An important part of purification is controlling the humidity of the air to reduce undesirable moisture condensation caused by temperature fluctuation or pressure changes. More importantly, drying the air prevents uninhibited microbial growth in air systems, especially in compressed air, which can result in contamination of products and processes or premature blockage of final filters.

Although supply air plays a critical role in aseptic production, its treatment tends to vary widely across food plants. A short overview about air pretreatment is provided here.

2.1 Compressed Air

Compressed air must be pretreated before it is filtered by final, sterilizing-grade filters.

2.1.1 Compressed Air Contamination

Compressed air contains many contaminants. In a typical compressed air system, at minimum there are ten contaminants coming from four different sources that are treated and reduced to acceptable levels for safety and efficiency. Figure 1.1 summarizes contaminant types and sources.

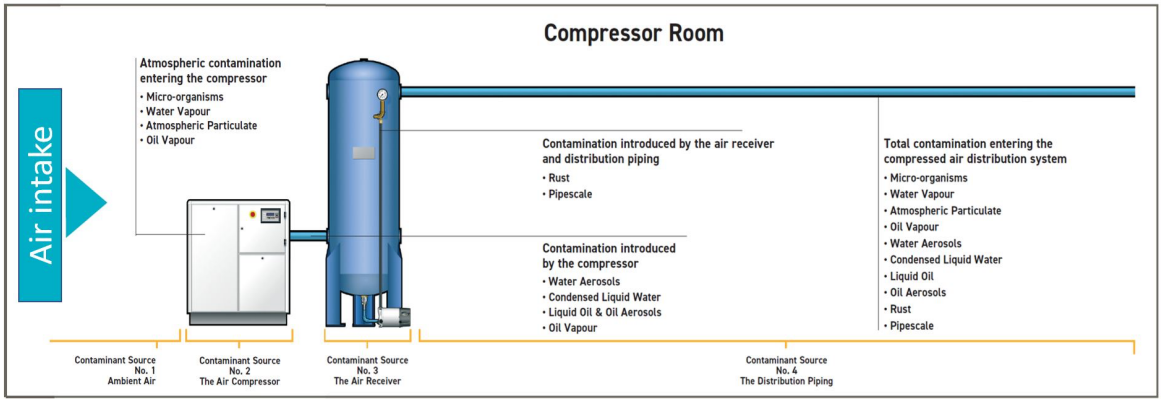

Figure 2.1: Sources of Air Contamination in a Compressed Air System
Source: Courtesy of Parker Hannifin

The process of air compression concentrates the contaminants in the ambient (intake) air, significantly raising the contaminant concentration per unit volume of compressed air. Subsequent transport of the air from the compressor to downstream equipment (air receiver) out to the distribution systems adds contaminants. Due to the very high concentration of microorganisms in compressed air, biofilms may form, which can have a negative effect on compressed air quality as well.

Contaminants should not be looked at as simply dirt, water and oil, as they are found in different phases. For example, water will be present as water vapor, liquid water and aerosols of water, as shown in Table 2.1.

Table 2.1: Contaminants in Compressed Air
Source: Courtesy of Parker Hannifin

Contamination Entering the Compressed Air System			
Water	**Oil**	**Particulates**	**Organic**
Water Vapor	Oil Vapor	Atmospheric Particulate	Microorganisms
Liquid Water	Liquid Oil	Rust	
Water Aerosols	Oil Aerosols	Pipe Scale	

2.1.2 Contamination Reduction Technologies

As contaminants are found in different phases, different purification technologies are required for their reduction. Table 2.2 summarizes the purification technologies required.

Table 2.2: A Solution for Every Contaminant / Purification Equipment Technologies for Compressed Air
Source: Courtesy of Parker Hannifin

Purification Technologies	Contaminants									
	Atmospheric Particles	Rust	Pipescale	Micro-organisms	Liquid Water	Water Aerosol	Water Vapour	Liquid Oil	Oil Aerosol	Oil Vapour
Water Separator					●			●		
Coalescing Filters	●	●	●	●		●			●	
Adsorption Filter										●
Refrigeration Dryer							●			
Adsorption Dryer (PDP ≤ -40°C)				●			●			
Dry Particulate Filter	●	●		●						
Sterile Filter				●						

Filtration alone is not enough. Water separators and dryers are additionally needed to handle liquid water, liquid oil, and water vapor, to control the humidity of the air. To inhibit the growth of microorganisms, compressed air should have a pressure dew point of < -26 °C (-14.8 °F), commonly delivered by correctly specified adsorption dryers (with dew point measurement by hygrometer, ISO 8573-3:1999[6]).

Adsorption dryers are typically designed to deliver pressure dew points as listed here, but not specifically that of < -26°C (-14.8 °F).

- ≤ -70°C (-94 °F) (ISO 8573-1 Class 1)
- ≤ -40 °C (-40 °F) (ISO 8573-1 Class 2)
- ≤ -20 °C (-4 °F) (ISO 8573-1 Class 3)

Therefore, to achieve a pressure dew point of < -26 °C (-14.8 °F), a Class 2 adsorption dryer (≤ -40 °C, -40 °F) should be specified. By selecting a Class 2 dew point, it ensures that the dew point is always past the point of where it would stop microbial growth (affording added security), even if the dryer were to be overflowed slightly and lost a little dew point.

Refrigeration dryers are not commonly able to achieve the required < -26 °C (-14.8 °F) dew point as correctly measured by hygrometer. In existing installations with refrigeration dryers, point of use adsorption dryers are available which can additionally be specified for aseptic applications.

Selecting compressed air equipment to address contaminant treatment in critical applications, as in aseptic food and beverage production, should be the role of the Quality Department, not Facilities Management. The Quality Department is best positioned to carry out a HACCP risk assessment or similar, based on a knowledge of the risk from microbial contamination and correct air purity required.

2.1.3 Compressed Air Network

Air pretreatment begins at the compressor intake, continues in the compressor room and air distribution system, and ends at the application points of use (Figure 2.2).

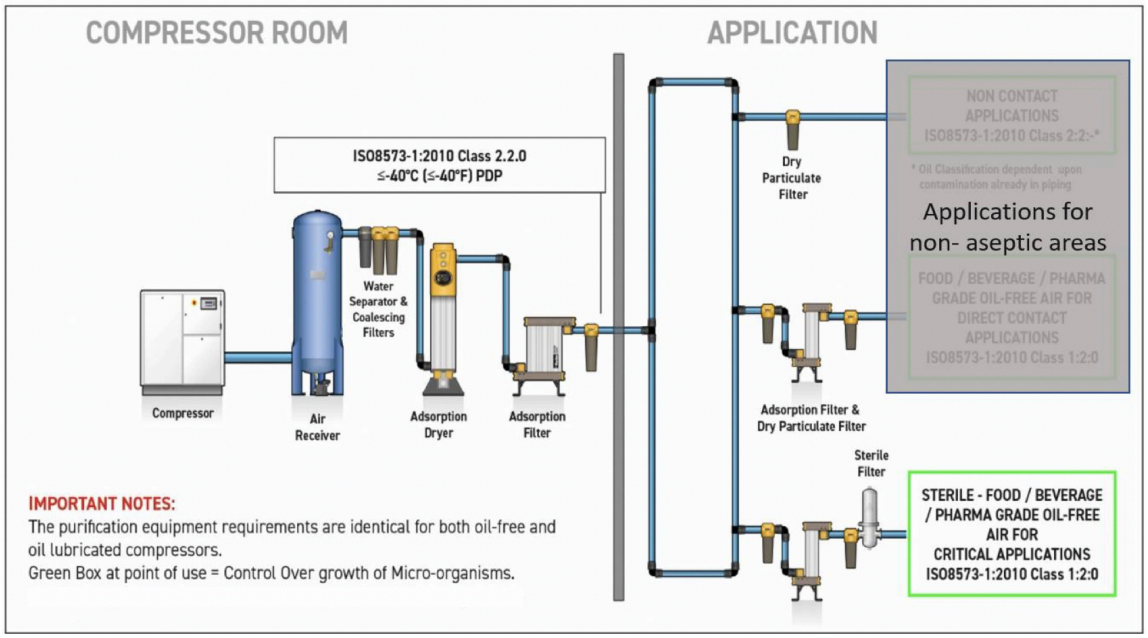

Figure 2.2: Schematic of a Compressed Air Network
Source: Courtesy of Parker Hannifin

Based on recommendations from compressor and filter suppliers, end users should ensure appropriate purification and relevant quality monitoring of compressed air.

2.1.4 Standards and Best Practice

2.1.4.1 GMP's

There are many GMP's available for manufacturers to follow. While such documents may mention the compressed air system, they are not very detailed and typically do not provide a usable specification for the plant to follow.

2.1.4.2 International Standards

ISO 8573 series is the international standard relating to compressed air purity. It is used globally and allows a compressed air user to test the compressed air system and classify the air purity found or alternatively, provide an air purity classification to equipment suppliers. It should be understood however, that the ISO standards do not make recommendations for air quality in specific industries or applications as this is the responsibility of the user.

2.1.4.3 Best Practice Guidelines

The British Compressed Air Society (BCAS) Best Practice Guideline 102-1[7] is a best practice guideline that provides a usable specification for compressed air used in the food, beverage and pharmaceutical industries.

2.1.4.4 Recommendation

The recommended requirement for the prefiltration of sterilizing-grade air cartridge filters is to achieve the ISO 8573-1:2010[8] Air Purity Classification 1:2:1 at minimum.

2.2 Blower Air

Blower air must be pretreated before it is filtered by final HEPA filters.

Blowers generally draw on ambient plant air immediately surrounding the aseptic system for intake air. Figure 2.3 is a schematic illustration of a blower air network.

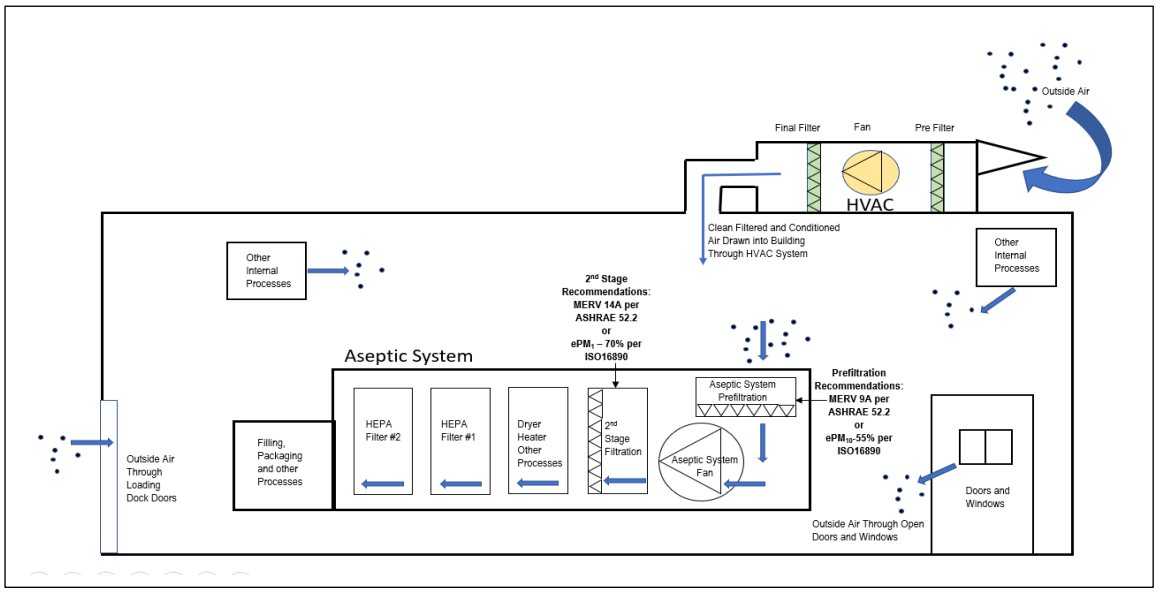

Figure 2.3: Schematic of Blower Air Installation
Source: Courtesy of Camfil

The ambient plant air is typically delivered through HVAC (heating, ventilation and air-conditioning) systems, which condition the air so that any moisture in the air does not later condense at point(s) of use. The air is directed through ventilation ducts into the facility. Air filters in the HVAC systems remove airborne contaminants from surrounding outdoor air. Contaminants can also enter open doors and windows, and other processes occurring within the building can generate contaminants. Air prefilters

contained within the aseptic system should be capable of removing larger contaminants to protect final HEPA filters in aseptic equipment. Care should be taken to ensure that exhaust air from the aseptic system is directed outside the building, as it may contain chemical sterilant residue from the container or machine sterilization processes.

Two widely referenced, similar but not identical test standards are used to indicate the particle capture efficiency for the types of air filters most likely to be used as prefilters:

- ASHRAE 52.2-2017 (with Appendix J)[9]: This test standard was developed by ASHRAE (American Society of Heating, Refrigeration and Air-Conditioning Engineers) and establishes the MERV (Minimum Efficiency Reporting Value) of an air filter using a scale of 1-16. The higher the MERV value, the more efficient the filter is at removing smaller particles.
- ISO 16890-1:2016[10]: This ISO test standard establishes air filter classification categories with numerous sub-ratings within each class. This standard utilizes particle classifications known as PM (Particulate Matter), with PM_1, $PM_{2.5}$ and PM_{10} as a basis for the rating scale.

The minimum recommendation for prefiltration efficiency in facilities housing aseptic processing systems based on the ASHRAE 52.2 Appendix J is a MERV 14/MERV-A 14A, and based upon the ISO 16890 standard is ePM_1-70%.

3 Regulatory Context

3.1 Historical Background

Aseptic food and beverage production originated in the 1950's and has experienced an exponential growth since the 1980's. Numerous types of processing and packaging equipment are used. In comparison to retort applications, product and packages are sterilized separately and must be stored, transported and "combined" under aseptic conditions. The storage of sterile product in aseptic pipelines and tanks, and the filling of sterilized packages with sterile product in specially shielded aseptic zones requires sterile air, for example generated by air filtration equipment, to prevent any microbial contamination and maintain the sterile condition of these zones.

Sterilizing air filtration has been addressed in a few industry documents put forth by the Food and Drug Administration and PDA. While both reference sterile drug products, the guidance can nevertheless be instructive for critical food industry applications such as the sterilizing filtration of air in aseptic production.

3.2 Regulations and Good Manufacturing Practice (GMP) Governing Air Filters in Aseptic Food and Beverage Processing and Packaging

The Food and Drug Administration (FDA) has established regulations to ensure that the production of aseptic low-acid canned foods is safe from potential public health hazards. The regulations stipulate that the product sterilizer and all product contact surfaces downstream of the sterilizer, such as an aseptic bulk tank, and container, filling and closing systems be brought to a condition of commercial sterility (21 CFR 113.40g).[11] This means that all of the operations of the aseptic processing system must work together so that at the end of the pre-production sterilization cycle the product contact surfaces and the aseptic zone of the filler are commercially sterile.

The FDA regulations also indicate that in order for the filler to produce product it must stay in a condition of commercial sterility. The regulation also stipulates that as soon as any part of the aseptic processing and packaging system enters a condition of non-sterility it must be brought back to a condition of commercial sterility before the system is put back into production mode. Also, if the filler was not stopped immediately when the sterile zone lost its sterility, any product that was produced during the deviation must be segregated and evaluated by a process authority.

For processes that incorporate a filtration system to sterilize air that enters the sterile zone, the filtration system must operate according to the established conditions that were set when the filler system was validated. If the filtration system fails, the integrity of the aseptic zone will be compromised and thus, the filler would need to be stopped and/or the product segregated. Since a failure of the filtration system would result in the loss of sterility of the sterile zone and the possible contamination of the food product, there must be a record that the filtration system was operating properly during the complete production cycle. 21 CFR 113.40g(2)(ii)(C)(4) stipulates that critical factors of an aseptic system must be measured at sufficient frequency to ensure that the critical limits are within those specified in the scheduled process. FDA has not indicated what it considers to be a proper frequency for integrity testing of filters for aseptic processing and packaging systems used in the production of low-acid aseptic foods. However, that portion of production packaged under non-sterile conditions (*i.e.,* the product produced since the last known check for proper operation of the filtration system) must be segregated and evaluated as a deviation. Unless this evaluation demonstrates that the product had been rendered free of microorganisms of public health significance, it must be fully reprocessed or destroyed (21 CFR 113.89).[12]

FDA Guidance for Industry for sterile drug products produced by aseptic processing recommends that filters be integrity tested periodically, including but not limited to these instances:

- installation
- end of use
- after activities that may damage the filter

Further, integrity test failures should be investigated, and filters should be replaced at appropriate, defined intervals.

Authors' Note: The preproduction sterilization cycle, also sometimes called equipment "pre-sterilization," refers to sterilization processes of product contact surfaces, including filter assemblies and aseptic zones. To facilitate understanding in this *Guideline*, we refer to all sterilization processes, whether they are for equipment, air, product or packaging materials, as "sterilization," understanding that this term, based on its context, can mean:

- pre-sterilization of equipment, including filter assemblies
- sterilization of air, product and packaging materials.

3.3 Food Contact Compliance Regulations

Sterilizing-grade air filters are intended for the sterilization of air used in food manufacturing processes and are classified as indirect food contact materials. In this context, the filters are exempt from the stipulations set out in food contact regulations such as FDA 21 CFR parts 170 – 199 and EC 1935/2004.[13]

The principle underlying the European Commission Regulation (EC) 1935/2004 is that any material or article intended to come into contact with food must be sufficiently inert to preclude substances from being transferred to food in quantities large enough to endanger human health or to bring about an unacceptable change in the composition of the food or deterioration in its organoleptic properties.

The European Commission Regulation (EU) No 10/2011[14] is specific to plastic materials and articles intended to come into contact with food and sets out the specific rules for plastic materials and articles to be applied for their safe use.

Food inevitably comes into contact with normal ambient air, so for the purposes of Regulation (EC) 1935/2004, air and its constituent gases cannot be considered a contact material and is therefore not covered under the scope of the Regulation. In addition, Regulation (EU) No 10/2011 specifies six liquid "simulants" which are designed to cover the variety of food types plastic materials may contact – however there is no provision for air and constituent gases. It is for this reason that certification to Commission Regulation (EU) No 10/2011 is unnecessary for sterilizing-grade air filters.

However, there is industry debate as to whether air c filters are exempt from these stipulations, due to industry observed deviations from standard customer use situations where tank contents come into contact with the filters. Thus, these industry parties believe sterile air filters should be constructed from materials that meet the food contact compliance regulations. Until such time as regulatory or auditing bodies come to agreement, it is up to end users to determine the right course of action for their own company.

4 Applications for Air Filtration in Aseptic Production

In general, we distinguish between aseptic/critical area and clean/controlled area applications for air filtration in aseptic production.

Although the focus of this *Guideline* is on filtration of air/gas for aseptic/critical area applications within the aseptic system, we briefly discuss clean/controlled area applications in Chapter 4.2.

4.1 Aseptic/Critical Area Applications

Aseptic/critical area air filtration applications are those in which air contacts the sterile product or sterile packaging environment after the sterilizing processes, and it is therefore a potential risk for microbial post-process contamination. Filtration of the air is considered to be critical to ensure commercial sterility. The filters must deliver sterile air per formal definitions of this standard of quality (Chapters 7.1, 8.1 and 8.2.1).

4.1.1 Typical Application Examples

Typical critical area air filtration applications (Figure 4.1) are:

- overpressure air in aseptic product tanks, to transport and secure the aseptic product during production
- overpressure cooling air introduced post-steaming into the aseptic environment
- overpressure or laminar (unidirectional) air within the sterile zone of the aseptic filling equipment
- air used for heating or drying of the packaging materials during package sterilization processes
- air injected into packages before, during or after filling
- air used for blowing in preform sterilization systems
- air used for blowing and transporting of sterile bottles

4.1.2 Filter Selections for Aseptic/Critical Area Applications

The two main choices for air filters commonly used on food and beverage aseptic/critical area applications are cartridge filters (membrane and depth) and HEPA filters.

Both sterilizing-grade air cartridge filters and HEPA filters are used to protect sensitive products and processes from microbial contamination in a variety of industries and environments. In the food and beverage industry, aseptic filtration, when validated, operated and maintained correctly, provides air free of viable microorganisms.

Cartridge filters are most commonly used for aseptic filtration of compressed air, such as found on aseptic tanks or aseptic packaging machines. Cartridge filters can also be used on low pressure air supply and low to mid-volume blower air as on some aseptic packaging machines. High volume blower air supplies can be filtered using cartridge filters, although economic considerations may limit their use.

HEPA filters are most commonly used for low pressure, high flow applications, in critical area air filtration on product filling and packaging machines or sensitive product preparation areas.

While cartridge or HEPA filters are specified in different types of aseptic filling machines often depending on air volume and supply pressure, there are instances of overlap in which either filter type may be applied.

In these cases, the equipment suppliers will base their selection on relevant filter attributes, equipment design, economics and risk assessment.

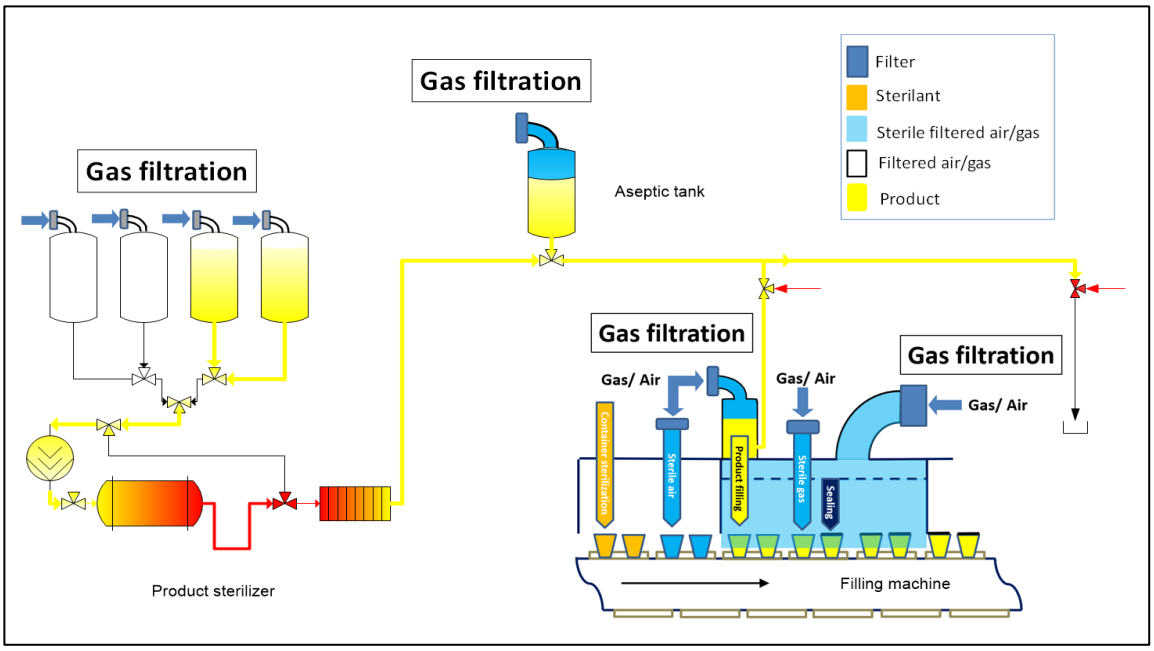

Figure 4.1: Diagram of Aseptic Production System Showing Aseptic/Critical Area Air/Gas Applications
Source: Courtesy of SIG Combibloc

4.1.3 Summary of Filter Attributes by Filter Type

Cartridge filters (membrane or depth) and HEPA filters used in aseptic production differ in many aspects that are relevant to aseptic equipment suppliers and end users; these attributes dictate their selection. The following summarizes major differences. Further detail can be found in Chapters 7, 8 and 10, as indicated.

4.1.3.1 Retention Performance

Table 4.1 summarizes retention capabilities of different filter types.

Authors' Note: Due to the different validation definitions and challenge test methods, these values are not directly comparable. The most important take-away for the reader is to understand based on the filter in use, what degree and type of retention the filter is capable of and what validation supports vendors' claims.

Table 4.1: Overview of Retention Capability and Removal Efficiency under Filter Validation Test Conditions

Filter Type	Filtration Efficiency Validation	Challenge Contaminant (by definition)	Challenge Level	Removal Efficiency	Contaminant Reduction (bacteria, particles)
Membrane Cartridge [A]	Liquid Bacterial Challenge	*B. diminuta* [C]	$\geq 10^7$ /cm^2 EFA	99.999999999% in liquid	$\geq 10^{11}$ in liquid, with sterile effluent [D] (bacteria)
Depth Cartridge [A]	Aerosol Bacterial Challenge	*B. diminuta* [C]	$\geq 10^7$ /cm^2 EFA	99.999999999% in dry air	$\geq 10^{11}$ in dry air, with sterile effluent [D] (bacteria)
HEPA Filter [B]	Aerosol Particle Challenge	0.1-0.2 µm or 0.3 µm particles (IEST)	depends on filter class	99.97% - 99.9999% [E] in dry air	$\geq 10^4 - 10^8$ in dry air (according to classification) (particles)
HEPA Filter [B]	Aerosol Particle Challenge	Test aerosol, evaluated at MPPS (EN/ISO Std.)	depends on filter class	99.95% - 99.999995% [E] in dry air	$\geq 10^4 - 10^8$ in dry air (according to classification) (particles)

[A] Refer to Chapter 7.2.1 for further details regarding microbial retention performance of cartridge filters.
[B] Refer to Chapter 8.2.1 for further details regarding particle retention performance of HEPA filters.
[C] These are minimum requirements. Cartridge filter vendors will typically validate removal of other contaminants, such as *B. subtilis* and/or *B. atrophaeus* spores and bacteriophage.
[D] Based on typical 10-inch cartridge with an effective filtration area (EFA) of 0.8 m^2 (8.6 ft^2).
[E] Typical maximum range used in aseptic production

4.1.3.2 Airflow Rate

Table 4.2 provides a qualitative comparison of filtration airflow rates of different filter types. However, one should check the actual sizing for each application with the filter manufacturers as there are many influencers to sizing.

Table 4.2: Qualitative Filtration Flow Rate Comparison

Filter Type	Filtration Flow Rate
Membrane Cartridge [F]	Lowest
Depth Cartridge [F]	Medium
HEPA Filter [G]	Highest

[F] Refer to Chapter 7.2.2 for further details regarding airflow rate and sizing of cartridge filters.
[G] Refer to Chapter 8.2.2 for further details regarding airflow of HEPA filters.

4.1.3.3 Hydrophobicity

Table 4.3 provides a qualitative overview of the hydrophobicity of different filter types.

Table 4.3: Qualitative Hydrophobicity Comparison

Filter Type	Hydrophobicity
Cartridge Filter (PTFE or PTFE-impregnated borosilicate microfiber) [H]	High
HEPA Filter [I]	Low

[H] Refer to Chapter 7.2.3.2 for further details regarding hydrophobicity of cartridge filters.
[I] Refer to Chapter 8.2.3.2 for further details regarding hydrophobicity of HEPA filters.

4.1.3.4 Sterilization Methods

Table 4.4 summarizes the most typical methods of *in situ* sterilization.

Table 4.4: Typical Sterilization Method Comparison

Filter Type	Typical Sterilization Method
Membrane Cartridge [J]	Steam in Place (SIP)
Depth Cartridge [J]	Steam in Place (SIP)
HEPA Filter [K]	Hydrogen Peroxide Gas

[J] Refer to Chapter 7.3.1 for further details regarding *in situ* sterilization of cartridge filters.
[K] Refer to Chapter 8.3.1 for further details regarding *in situ* sterilization of HEPA filters.

4.1.3.5 Filter Claims Validation

Table 4.5 summarizes available filter retention performance validation methods as they apply to different filter types.

Table 4.5: Retention Performance Validation Methods

	Retention Performance Validation			
Filter Type	**Bacteria Removal from Liquids**	**Bacteria Removal from Aerosols**	**Spore Removal from Aerosols**	**Particle Removal from Air**
Membrane Cartridge [L]	Possible	Possible	Possible	Possible
Depth Cartridge [L]	N/A	Possible	Possible	Possible
HEPA Filter [M]	N/A	N/A	N/A	Possible

[L] Refer to Chapter 7.5.1 for further details regarding retention performance validation of cartridge filters.
[M] Refer to Chapter 8.5 for further details regarding retention performance validation of HEPA filters.

4.1.3.6 Verification of Filter Integrity/Leak Tightness

Table 4.6 summarizes available methods for verifying cartridge filter integrity and HEPA filter leak tightness to ensure the expected retention performance.

Table 4.6: Test Methods

Filter Type	Bubble Point Test	Diffusional Flow Test	Pressure Hold Test	Water Intrusion Test	Aerosol Challenge Integrity Test	Leak Test	Global Efficiency Test
Membrane Cartridge [N]	Possible	Possible	Possible	Possible	Possible	N/A	N/A
Depth Cartridge [N]	N/A	N/A	N/A	N/A	Possible	N/A	N/A
HEPA Filter [O]	N/A	N/A	N/A	N/A	N/A	Possible	Possible

[N] Refer to Chapter 10.1 for further details regarding integrity testing of cartridge filters.
[O] Refer to Chapter 10.2 for further details regarding leak tightness verification of HEPA filters.

4.2 Clean/Controlled Area Applications

Clean/controlled area air filtration applications are those that ensure general cleanliness of air at points in the process outside the aseptic environment. From the perspective that any product or package materials exposed to air in these areas will subsequently be sterilized by thermal, chemical, filtration or other treatment, these applications do not require sterilizing filtration.

Nonetheless, paying attention to minimizing microbial and particle counts in these applications is recommended.

4.2.1 Typical Application Examples

Typical clean/controlled area air filtration applications are:

- room air filtration in various zones of production
- tank vent filters for raw ingredient storage prior to product sterilization
- air used for blowing and transporting of bottles
- air used for removing physical impurities from packaging material before aseptic filler
- air pretreatment for oil, moisture, and particle removal

Of course, depending on the cleanliness of the surrounding environment and the level of acceptable risk, equipment vendors or end users may designate certain controlled area applications to be critical, and selection of air filtration equipment will follow accordingly. For example, applying sterilizing filtration to tank vents for raw ingredient storage minimizes the bioburden content of ingredients that will subsequently be sterilized. Similarly, ensuring facility intake air is adequately prefiltered will reduce the level of particles impacting downstream HEPA filters.

5 Air Filter Types for Aseptic/Critical Area Applications

5.1 Cartridge Filters

5.1.1 Membrane Filters

Disposable membrane cartridge filters typically consist of cast or stretched media, comprised of materials such as nylon, polyvinylidene fluoride (PVDF), polytetrafluorethylene (PTFE), polyether sulfone (PES), *etc.*

Due to the requirement for hydrophobicity of air filters (Chapter 7.2.3.2), the most common modern membrane media used for sterilizing air filtration is PTFE (Figure 5.1), which features the highest natural hydrophobicity in comparison to other typical membrane materials. Even with repeated steam sterilization cycling, the 100% PFTE membrane maintains its inherent hydrophobicity over time.

Membrane filters feature a fixed pore structure characterized by very fine pores and narrow pore size distribution, resulting in excellent retention capability under both liquid and aerosol challenge conditions. The media has thickness, generally speaking from ~40-150 µm. The membrane structure resembles more of a sponge than a simple screen or sieve, which is a complex matrix that creates a tortuous path to trap contaminants.

Membrane filters that meet the definition for a sterilizing-grade filter, described in Chapter 7.1, usually have an indicated pore size rating of 0.2 µm or 0.22 µm. These filter ratings are not materially different from each other, as these pore sizes are not indicative of all the pore sizes within the filter media. The actual pore sizes vary from smaller than to greater than 0.2 µm. In addition, there are multiple mechanisms of filtration at play other than size exclusion that result in contaminant retention (Chapter 6). Therefore, pore size rating should not be used to determine the efficacy of the membrane.

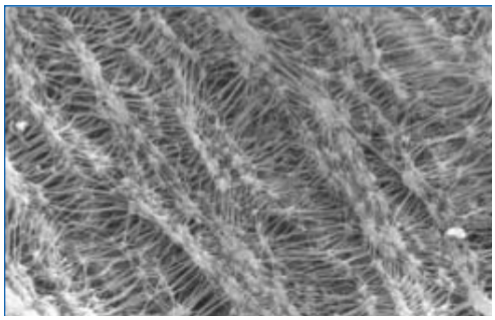

Figure 5.1: PTFE Membrane Media
Source: Courtesy of Pall Corporation

Rather, these filter ratings indicate the approximate size of the model bacteria, *B. diminuta,* which these filters are designed to remove. Filter retention performance must be demonstrated by bacterial challenge testing, in validation studies conducted by filter manufacturers (Chapters 7.2.1 and 7.5.1).

Sterilizing-grade membrane filter cartridges are validated to provide sterile air according to the definition, when challenged with high concentrations of bacteria both in liquid ("liquid bacterial challenge") and in aerosolized form in air ("aerosol bacterial challenge"). Further validation studies may also be carried out, such as for aerosolized bacterial spore and/or bacteriophage retention, however, passing liquid bacterial challenge is scientifically the most rigorous test for demonstrating microbiological retention by membrane filters at worst-case conditions.

5.1.2 Depth Filters

Depth media is made from a layer of fibrous material designed to combine a tortuous flow path with increased depth or thickness of material, from 1000-2000 µm. While depth filters are porous, they have no defined pore size or structure. Typical materials are borosilicate microfibers treated to enhance hydrophobicity (Figure 5.2).

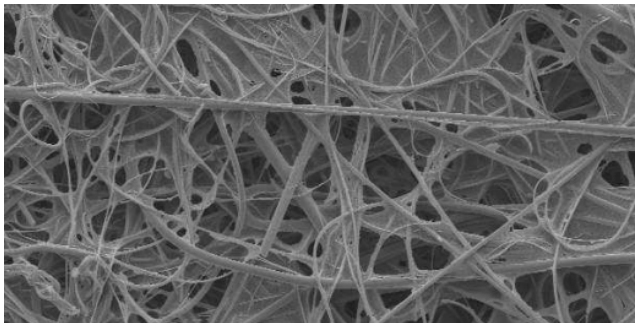

Figure 5.2: PTFE-Impregnated Borosilicate Microfiber Depth Media
Source: Courtesy of Parker Hannifin

Due to the large depth (thickness) of the filter material, depth filters provide a tortuous pathway to contaminants in air streams and offer excellent microfiltration retention capability. Filter manufacturers must validate sterilizing-grade depth filter performance according to the definition when challenged with high concentrations of bacteria in aerosolized form in air ("aerosol bacterial challenge") (Chapter 7.2.1 and 7.5.1.2). Additional validation studies to demonstrate filter performance and fit for purpose, such as aerosolized bacterial spore retention, may also be done. It should be noted that in applications which require validation of sterilization capability under liquid challenge conditions (Chapter 7.5.1.1), sterilizing-grade membrane cartridge filters should be used (Chapter 5.1.1).

Filters which utilize depth media generally have flow advantages over membranes, with approximately twice the flow rate per unit area, therefore allowing for smaller systems for given flow rates and subsequently reduced process costs.

Originally, the material was used in a wrapped construction, but this format has been optimized in more recent years through the advent of pleated formats to further enhance airflow rate per cartridge.

5.1.3 Cartridge Filter Construction

A disposable sterilizing-grade air filter cartridge consists of pleated filter media (*i.e.,* membrane or depth media), pleated support and drainage layers, and filter hardware which typically includes the outer support cage, inner tubular core, end caps, adaptor and locating fin (Figure 5.3).

Due to the critical nature of sterilizing air filtration, only single open-end (SOE) cartridges, which offer efficient and reliable sealing, should be used. SOE cartridges are ones which have a “blocked” end, and an open end, where the cartridge mates to the filter housing. SOE cartridges also offer an easier and more hygienic installation.

The pleated membrane or depth media is the most important component of the cartridge as it removes the contaminants. This filtration layer is sandwiched between the support and drainage layers.

The support and drainage layers are pleated along with the filtration layer; these three components are called the “pleat pack”. Support and drainage layers stabilize the filtration layer during pleating and installation into the cartridge. They keep the membrane or depth media structure intact and the pleats apart during filtration operation, avoiding compression of the pleats, which would otherwise result in the loss of available filtration area.

The cage is the outer cylinder, which encases the cartridge and protects the pleat pack. It provides stability to the cartridge in reverse flow operation and eases handling during installation.

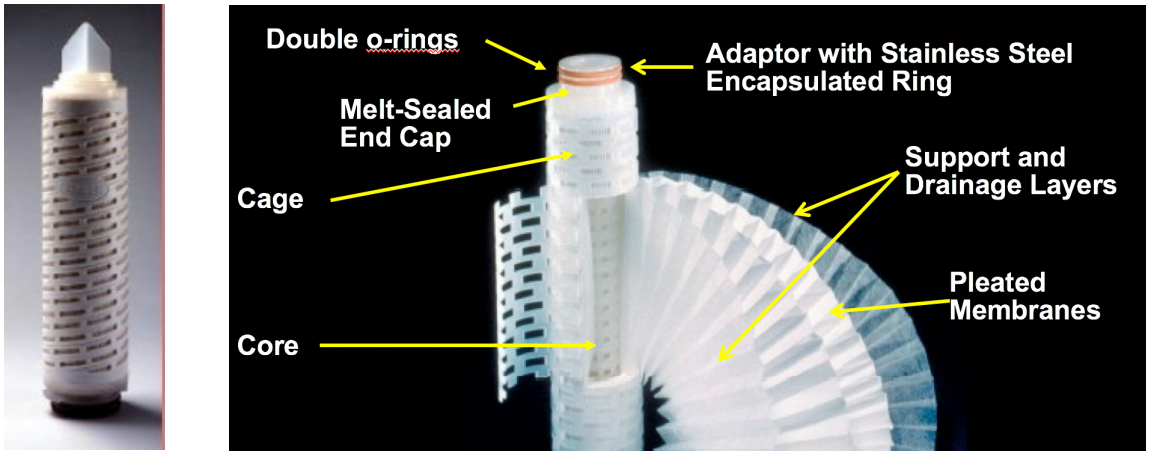

Figure 5.3a Figure 5.3b

Figure 5.3: (a) Typical Single Open-End Disposable Filter Cartridge – Upright View; (b) Cutaway View of Filter Cartridge / Inverted View
Source: Courtesy of Pall Corporation

The core is the inner tube, which supports the pleat pack. Its length determines the length of the cartridge. It has perforations through which the filtered air exits the pleat pack. The filtered air collects in the core and exits out of the filter housing (Figure 5.5).

The end caps are critical components as they hold the cartridge parts together. They are applied to ensure integrity of the attachment areas at either end of the cartridge, so there is no chance of bypass at those points during filtration.

The end cap on the open end of the cartridge is welded to the cartridge adaptor, which connects the cartridge to the housing (Figure 5.4). Adaptor design is critical, in order to ensure correct location and sealing within the filter housing and robustness during operation and steaming. These requirements are typically satisfied by the use of adaptors with double bayonet design that engage with the housing grooves in a “twist-lock” pattern, avoiding any risk of the filter cartridge dislodging; two O-rings for enhanced sealing; and internal stainless steel or polymeric rings for adaptor stability. Another important consideration

is the hygienic design of the adaptor and its mating point to the filter housing. The use of threaded connections for cartridge adaptors is not recommended.

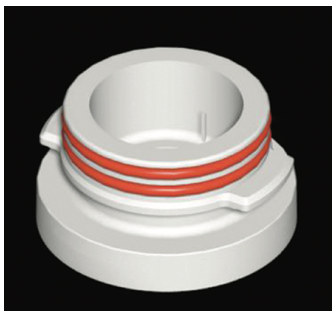

Figure 5.4: Preferred Adaptor Design – "Code 7"
Source: Courtesy of Parker Hannifin

The end cap on the blocked end of the cartridge is typically welded to a locating fin (also called "spear" or "bomb fin"), to ensure good location within the housing.

The typical airflow path through the cartridge is from "out to in", also known as forward flow direction, as filters are most robust in this flow mode (Figure 5.5). However, many cartridge filters are validated for both forward and reverse flow direction, both during normal operation and steaming.

Cartridge filters are supplied in different geometries (lengths, configurations) to enable sizing for different airflow rates. The user should familiarize themselves with available options by consulting the data sheets provided by filter manufacturers.

For more information about filter housing design, see Chapter 7.2.3.6.

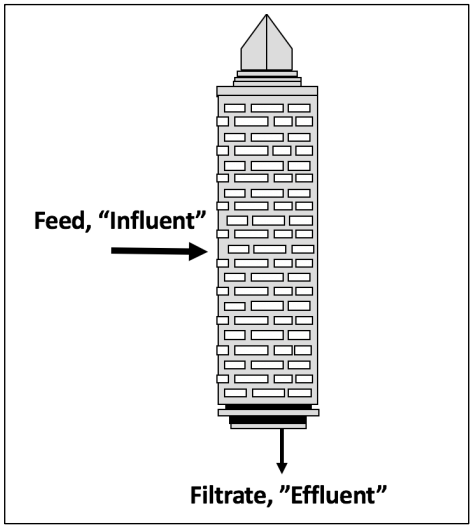

Figure 5.5: Schematic - Typical Forward Flow Direction of Air
Source: Courtesy of Pall Corporation

5.2 HEPA Filters

5.2.1 HEPA Filter Construction

HEPA filters have three key performance attributes which characterize their overall performance: particle capture efficiency, particle retention, and resistance to airflow. Numerous components work together to accomplish this, but there are three chiefly responsible for the overall performance of the filter (Figure 5.7):

- the filtration media
- the filtration media configured into a media pack
- the frame in which the media pack is sealed in place

Figure 5.7a: Filtration Media

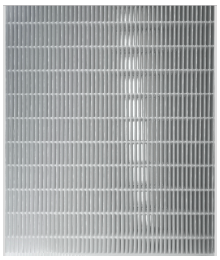

Figure 5.7b: Media Pack

Figure 5.7c: Frame

Figure 5.7 (a, b, c): Main Components of HEPA Filters
Source: Courtesy of Camfil 5.7a, b / Courtesy of Hengst 5.7c

5.2.1.1 Filtration Media

The base component of a HEPA filter is the filtration media, of which there are two established media technologies: microglass fiber and synthetic composites. When HEPA filters comprised of synthetic fibers (e.g. polypropylene) are used, it is important to ensure they are classified in a discharged state, as any benefit from an additional charged state deteriorates over time.

The filtration media in HEPA filters is typically a nonwoven fabric composed by entangling fibers to form a sheet. For these filters, there is a narrow range of fiber styles and sizes capable of capturing the smallest particles in air by the filtration mechanisms of diffusion and interception described in Chapters 6.2.1 and 6.2.2.

5.2.1.1.1 Microglass Fiber Media

The most common fiber for producing HEPA filtration media is microglass fiber. These fibers are entangled using a wet-laid nonwoven process in which fibers of different diameters are combined with an acrylic binder to create a filter media that can be used in the pleating process with minimal fiber shedding. There is no defined pore size or structure in glass fiber media.

Microglass fiber medias are considered to be depth filters as the structure can be considered three-dimensional. Consequently, the diffusional interception effect described in Chapter 6.2.1 has increasing retention effect on particles smaller than MPPS (Chapter 6.3) down to 2 nanometers (nm), which represents the limit of modern particle counting technologies.

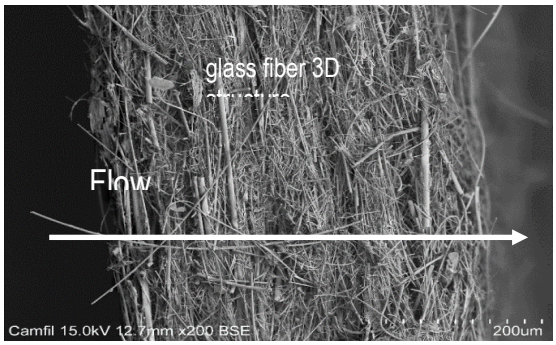

Figure 5.8: Microglass Fiber Media
Source: Courtesy of Camfil

5.2.1.1.2 Synthetic Media

Synthetic filter media typically consists of the following types of materials, which create strong composites that can be further processed:

- expanded PTFE membranes as a functional filter layer(s) with synthetic melt-blown carrier media that protects the membrane
- electrospun nanofibers as a functional layer applied to a synthetic carrier media that protects the nanofiber layer

In HEPA filters, synthetic fiber media delivers advantages such as physical robustness, chemical resistance, and a very low initial pressure drop. Limitations may exist in terms of service life due to the lower particle retention capacity of some synthetic media.

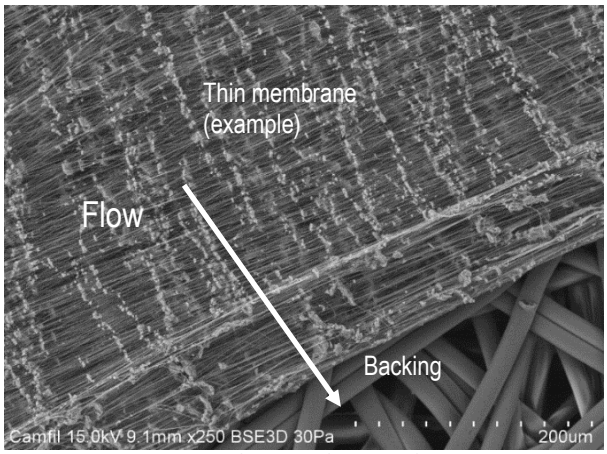

Figure 5.9: PTFE Membrane Filter Media
Source: Courtesy of Camfil

5.2.1.2 Media Pack

When produced as a flat sheet, filtration media typically has far too high resistance to airflow to make it usable as a filter so the media is configured into a media pack. The most common method is to pleat the flat sheet into a "V" shape which increases the available surface area thus lowering airflow resistance.

From this shape, two main methods are used for filter construction: aluminum separators and hot melt separators, *e.g.,* mini-pleat. Each style delivers different performance characteristics suitable for various applications.

5.2.1.2.1 Aluminum Separator

Traditional HEPA filter media were pleated by the means of aluminium separators to form a rigid filter media pack and later enclosed by a solid frame (Figure 5.10). Air filters with aluminium separator technology are typically selected for air handling units, ducted housings or safety housings with higher airflows, however, they are not suitable for use in aseptic/critical area air applications.

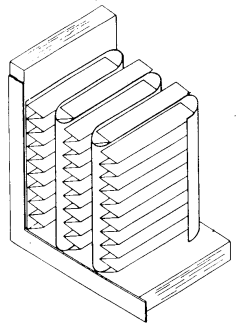

Figure 5.10: Aluminum Separator Pleat Pack, HEPA Filter
Source: Courtesy of Camfil

5.2.1.2.2 Mini-Pleat

For HEPA filters used in aseptic systems, the most common pleating technology incorporates hot melt beads to form a rigid pleat pack, commonly called "*mini-pleat*" (Figure 5.11). Compared to the traditional aluminium separator filters, this technology has some advantages such as the ability to build filter packs with larger dimensions, tighter pleat spacing and lower pressure drops. For higher airflow applications which require greater strength, mini-pleat technology provides an alternative to the aluminium separator filter by either creating deep pleat filter packs or arranging several low pleat packs into a V-bank filter construction.

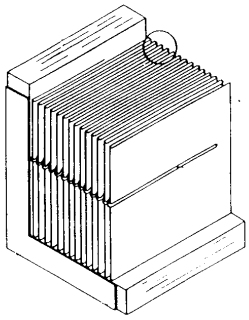

Figure 5.11: Mini-Pleat Filter Pack, HEPA Filter
Source: Courtesy of Camfil

5.2.1.3 Filter Frame Assembly

The frame assembly of a HEPA filter holds the filter media securely in place with no air bypass. The frame can be configured in a wide variety of shapes and sizes, to fit the intended application and deliver the desired performance characteristics. The material of construction will depend upon the intended application. Factors involved in frame selections include the configuration of the system, air throughput, chemical compatibility with the sterilization process and the intended format of disposal.

Various materials have been established for filter frames:

- galvanized steel
- stainless steel

- aluminum
- plywood
- fiberboard
- plastic

Depending on the intended field of use, the filter pack is glued into this frame by means of various bonding materials such as polyurethane, silicone or other polymers.

After assembling of the filter, gaskets are applied to create an airtight seal between the filter housing frame via the gasket and the filter frame to the filter media. There should be no possibility of bypass.

A variety of filter design types have been established depending on the individual needs of the respective applications. Following are some examples typically used in aseptic/critical area air filtration applications.

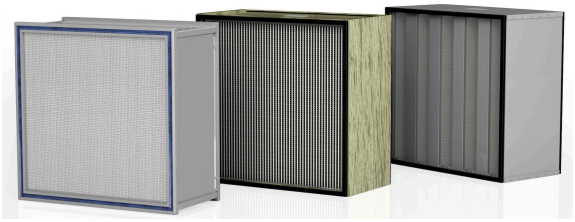

Figure 5.12: Box Style, HEPA Filters
Source: Courtesy of Camfil

Figure 5.13: Panel Style, HEPA Filters

6 How Air Filters Work

There are several mechanisms at work in air filtration, which enable filters to remove contaminants from air streams. Often the retention of the contaminants is due to a combination of one or more types of filtration mechanisms, depending on the size, mass and nature of the contaminants, air velocity, and filter structure.

When considering the effects of the filtration mechanisms, it is important to remember that different from a simple sieve or screen mesh, industrial filtration media has depth in varying degrees. Contaminants may be retained at the surface of the filtration media but more importantly, they are retained as they travel through a tortuous path within the filter media.

Most of the mechanisms described are common to both liquid and air filtration, however the primary mechanism of importance unique to air filtration is diffusional interception, due to the Brownian motion of suspended particles in the air, caused by bombardment by the air molecules.

6.1 Size Exclusion or Direct Interception

The mechanism of size exclusion (also called direct interception, sieve or mechanical retention, straining) occurs when contaminants in the air (as in liquids) are physically trapped when they are too large to pass through smaller pores of the filtration media. The largest contaminants may be trapped at the filter surface, but they are also trapped as they travel through a tortuous path of varying filter pore sizes within the filter media. As long as the contaminants are not deformable, the effect of size exclusion is independent of the air velocity.

Contaminants of larger sizes can also block the filter pores, such that bridging occurs, in which smaller-sized contaminants can no longer pass through.

While size exclusion is the major mechanism that takes place in filtration of liquids, its effect is less pronounced in air filtration. Retention by size exclusion is shown in Figure 6.1.

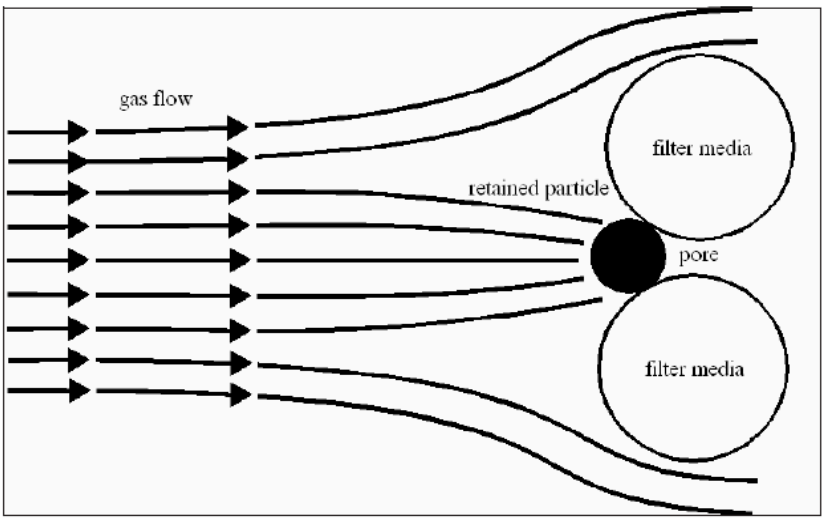

Figure 6.1: Particle Retention by Size Exclusion
Source: Courtesy of PDA

6.2 Retention of Small Particles

More prevalent in air than in liquid filtration, retention of contaminants many times smaller than the filter pore sizes occurs, primarily by diffusional interception, interception, inertial impaction, and electrostatic attraction. The binding force between the filter media and the contaminants is either molecular or electrostatic attraction, hence the contaminants must either impact the filter media or come into close proximity for retention to occur.

6.2.1 Diffusional Interception or Diffusion

Diffusional interception or diffusion takes place only in air filtration. It is the primary reason why contaminants of smaller size than the filter pores are retained.

Air molecules are in a state of constant movement. Contaminants in air streams that are extremely small are therefore constantly bombarded by the air molecules and knocked out of the stream of airflow in different directions. When the contaminants impact the surrounding filtration media, they are retained due to molecular attractive forces and effectively removed from the air stream. As one particle is attracted and captured, other particles diffuse into the area just vacated by the captured particle and themselves are captured.

Retention by diffusional interception is shown in Figure 6.2. Figures 6.3a-d further illustrate the concept, and also introduce the discussion about liquid removal *versus* aerosol removal performance.

Due to this filtration mechanism, small air particles five to ten times smaller or more than the size of the filter pores are retained. The phenomenon of diffusional interception explains why filters can have both a liquid and a gas removal rating. This is described in the following example:

A filter with a liquid removal rating of 0.2 µm would be expected to remove contaminants of 0.2 µm and larger from a liquid. The same filter, if used to remove contaminants from a dry air stream, would have a retention performance in air, or an air removal rating estimated at 0.02-0.04 µm or approximately five to ten times smaller than the 0.2 µm contaminants. The actual removal capability of the filter in dry air can be identified by filter vendors based on specific validation.

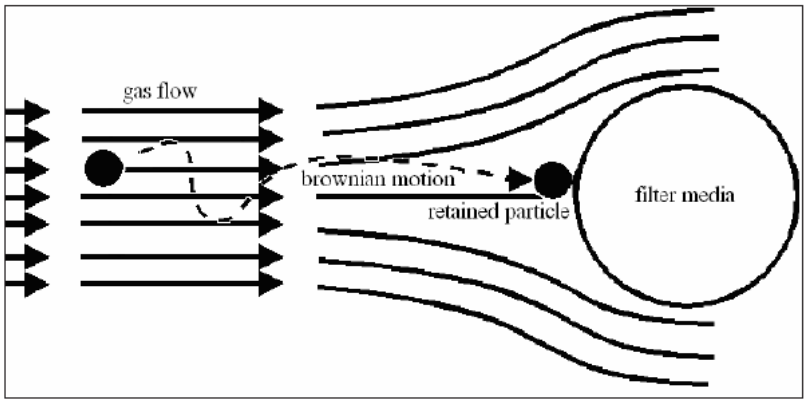

Figure 6.2: Retention by Diffusional Interception
Source: Courtesy of PDA

When air streams are dry, the effect of diffusional interception is pronounced. If there is moisture present, the degree of diffusional interception is reduced and the contaminants follow the streamlines of liquid flow (Figure 6.3d). In the presence of liquid in the air stream, filters revert to their liquid removal performance, which is more open. Brownian motion of the contaminants in air is the primary reason why it is easier for filters to remove contaminants from dry air than from liquids.

The efficiency of diffusional interception increases with smaller particle sizes. It exhibits its primary effect on contaminant sizes less than 0.1 to 0.3 µm.

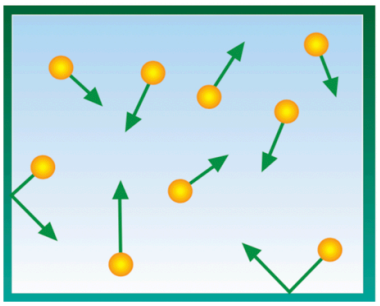

Fig. 6.3a: Air molecules are in a state of continuous random motion.

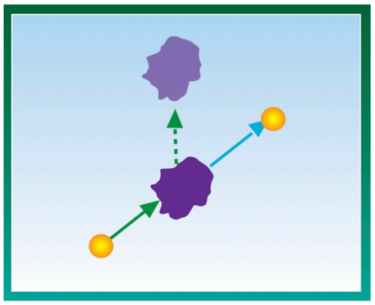

Fig. 6.3b: Small particles or aerosol droplets in the air are struck by the moving air molecules and displaced, causing Brownian motion.

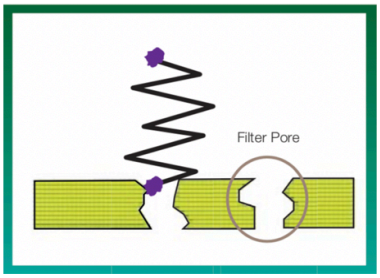

Fig. 6.3c: Due to Brownian motion, diffusional interception is the key filtration mechanism occurring in dry air. Particles many times smaller than the filter pore size are intercepted.

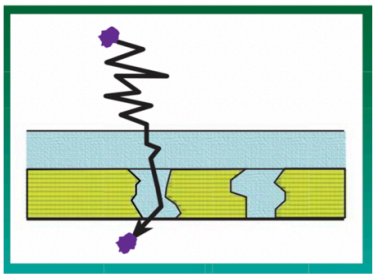

Fig. 6.3d: Diffusional interception does not work under wet conditions. The filter reverts to its more open, liquid removal rating.

Figure 6.3: Conceptual Drawing of Filter Retention in Dry and Wet Environments[15]
Source: Courtesy of Pall Corporation

6.2.2 Interception

Interception refers to contaminants carried along the streamlines of airflow becoming attached to or intercepted by filter media in their path. These contaminants are small, and light enough not to be removed due to inertial impaction.

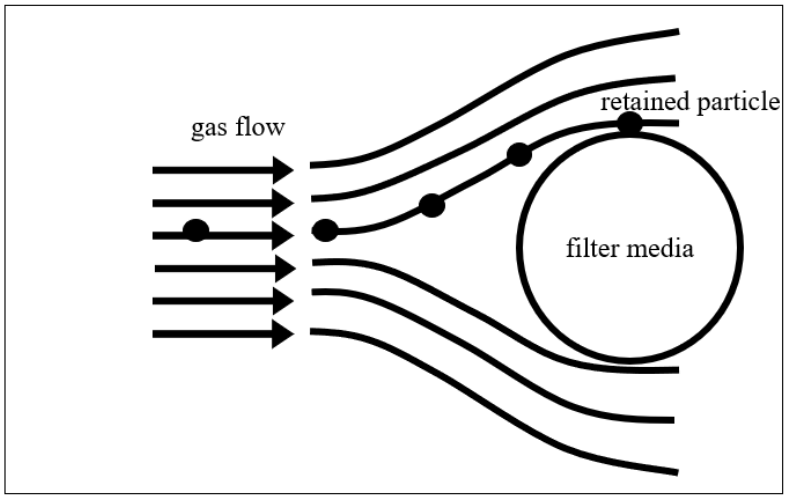

Figure 6.4: Retention by Interception
Source: Courtesy of SIG Combibloc

6.2.3 Inertial Impaction

Contaminants display inertia due to their mass and velocity. The filtration mechanism of inertial impaction occurs when contaminants in an air stream have momentum in a given direction, which deviates from the streamlines of airflow as it flows in a tortuous path within the filter media. When impacting the surrounding filtration media, they adhere to the media due to molecular attractive forces between the media and the contaminants and are effectively removed from the air stream. Retention by inertial impaction is illustrated in Figure 6.5.

This mechanism is more significant in air filtration than in liquid filtration and exhibits its primary effect on contaminant sizes greater than 0.5 to 1 µm.

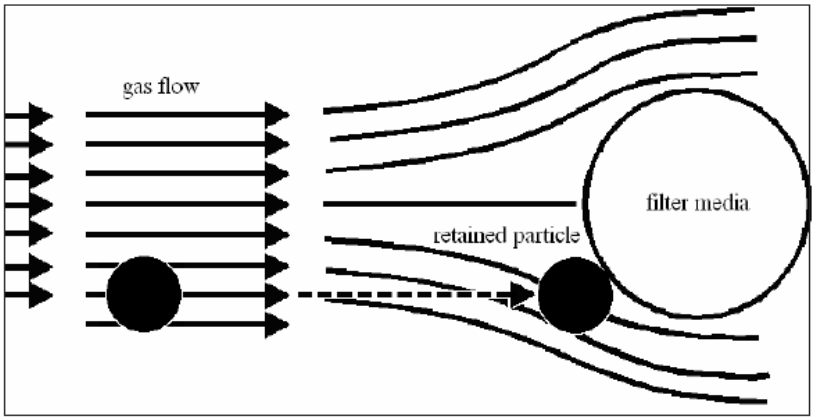

Figure 6.5: Retention by Inertial Impaction
Source: Courtesy of PDA

6.2.4 Electrostatic Attraction or Electrostatic Precipitation

Contaminants in air streams, which carry an electrostatic charge are retained by filtration media types that carry an opposite charge. Regardless of the size or mass of the contaminants in relation to the filter pore structure, the presence of the electrostatic attraction is what causes the contaminants to leave the airflow stream and be firmly retained.

The most practical example of this filtration mechanism is the case in which positively charged filtration media attracts contaminants that typically carry a negative charge, such as yeasts and bacteria.

The effectiveness of this mechanism is influenced by the air humidity, velocity and service life. The drier the air, the greater the degree of electrostatic attraction. The air velocity influences the contact time between the contaminants and the charged media so that retention may occur. The longer the service life, the greater the insulating effect of captured particles, which reduces the charge's ability to capture additional particles.

The extent to which the retention mechanism is effective in air filtration is limited by the saturation of the oppositely charged filter media.

While the above description relates to a natural electrostatic attraction between contaminants and filter media, some air cleaner systems utilize methods to actively create a charge on particulate contaminants, such that they are attracted to oppositely-charged collection devices.[16]

6.3 Gravitational Sedimentation

Similar to inertial impaction, contaminants of high density can leave the airflow path and impact the filter media due to gravitational sedimentation. This mechanism has its primary effect on larger particles.

This mechanism plays a less significant role in submicron filter media typically used in air filtration as the contaminants that would typically be retained by gravitational sedimentation far exceed the size of the filter pores and would first be retained by size exclusion.

6.4 Net Filtration Retention Efficiency in Air and Most Penetrating Particle Size (MPPS)

The net filtration efficiency in dry air filtration results from the combination of all filtration mechanisms at play when a particular filter is used on an air stream of a particular velocity, containing contaminants of particular size, mass, and characteristics.

At a given air velocity, the size of the particles influences the predominance of the filtration mechanism in action. Smaller contaminants are better removed by diffusional interception and interception. As the contaminant sizes increase, inertial impaction, size exclusion and gravitational sedimentation increasingly come into play. There is a contaminant size range at which none of the filtration mechanisms are particularly effective and the efficiency of the filter medium is at its minimum; this size is known as the Most Penetrating Particle Size (MPPS), illustrated by Figure 6.6. This phenomenon is usually the controlling factor in rating of filters for submicron air applications.

Air velocity through the filter also influences the MPPS, causing it to shift. High air velocity or pressure reduces the effect of diffusional interception because Brownian motion is less pronounced, whereas it does not as greatly affect inertial impaction.

6.5 Retention Performance and Filter Pore Size Rating

As discussed previously, the only air filtration mechanism that relates strictly to pore size and is generally independent of other factors is size exclusion. The ability of the filter to remove particles smaller than the

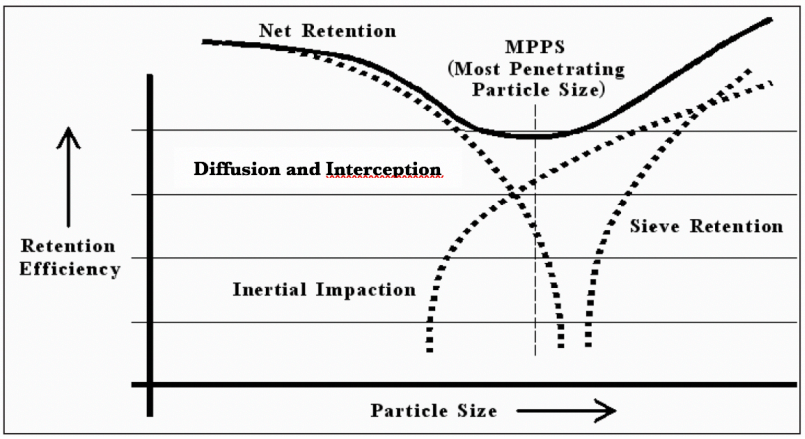

Figure 6.6: Conceptual Diagram / Effect of Various Retention Mechanisms of Contaminants Retained from a Dry Air Stream as a Function of Contaminant Size
Source: Adapted from PDA

filter pores hinges not on pore size but on other mechanisms at play. It is therefore important that pore size not be used as the main determinant for which air filter to select.

In sterilizing-grade air filters, the typical pore size nomenclature of 0.2 µm is a more or less arbitrary figure selected to reflect a size dimension close to the smallest size dimension of the model microorganism *B. diminuta,* which measures approximately 0.3-0.4 µm x 0.6-1 µm. Not all pore sizes within the filter are identical in size, but rather the pore sizes are distributed around a mean, with some pores smaller and some larger.

Rather than the numerical pore size rating, users should focus on the validation studies provided by filter vendors to prove that the air filter in question, when challenged by contaminants of known type and concentration, is able to provide the retention performance expected.

7 Cartridge Filters

7.1 Definition of Sterilizing-Grade Air Cartridge Filter

A sterilizing-grade air cartridge filter is defined as a filter which, when appropriately validated by the filter manufacturer, will reproducibly produce a sterile effluent, free from viable microorganisms in the filtered air. Further, when properly validated filters are installed, sterilized, operated, monitored and maintained according to filter manufacturer installation and operating instructions they will provide air free of viable microorganisms in aseptic applications.

The validation of air cartridge filters by filter manufacturers is performed by microbial challenge. A sterilizing-grade filter is defined as one that retains a minimum challenge of 10^7 colony-forming units (cfu) of *B. diminuta*/cm^2 of effective filter area, yielding sterile effluent.

The FDA's Guidance for Industry states that the microorganism *B. diminuta* (ATCC 19146), when properly grown, harvested and used, is the common standard challenge microorganism for 0.2 µm rated air filters because of its small size (0.3 µm mean diameter). For these rod-shaped microorganisms, actual dimensions are approximately 0.3-0.4 µm x 0.6-1 µm.

The challenge microorganism detailed in older literature was *Pseudomonas diminuta*, however this microorganism has since been reclassified as *B. diminuta*.

As explained in Chapters 5.1.1 and 6.4, filter pore size ratings should not be used to determine the microbial removal efficiency of the filter.

Virus removal is typically exempt from the definition of a sterilizing-grade air filter. However, in applications where the presence of a virus (*e.g.,* bacteriophage) is considered to be a hazard, the same filter performance requirements apply, *i.e.,* 10^7 pfu/cm^2 of effective filtration area.

7.2 Filter Selection Criteria

Filters for aseptic systems are typically selected by equipment (OEM) suppliers and end users based on recommendations from filter vendors.

The goal of the application is to maintain commercial sterility of manufactured products by eliminating any post-process contamination by microorganisms in process air (*e.g.,* aseptic tank pressurization, aseptic zone air) (Chapter 4.1). To achieve this goal, the most important attribute with regard to cartridge filter selection is microbial retention performance, based on the definition of a sterilizing-grade air filter cartridge and a review of validation studies published by filter manufacturers.

The criteria for proper cartridge filter selection are summarized here:

- microbial retention performance
- airflow rate, sizing and throughput
- design features and attributes
    - application compatibility
    - hydrophobicity
    - durability
    - toxicity
    - geometry and hardware fit
    - filter housing design
- economics and cost of ownership
- disposal: While disposal is not a key criterion for filter selection, users should give careful consideration regarding local disposal and legal requirements.

Filter selection should be based on an assessment of risk of failure of performance, both during normal and worst-case scenarios or upset operation.

7.2.1 Microbial Retention Performance

Retention performance describes the ability of air filters to remove a defined level of contaminants from the unfiltered air (“influent”), yielding a certain level of contaminants in the filtered air (“effluent”).

Using a microbial challenge test for evaluating filter retention performance provides the highest degree of test sensitivity, as even very low counts of viable microorganisms can be detected in large filtrate volumes (Chapters 7.5.1.1 and 7.5.1.2).

In sterilizing air filtration with microbial rated cartridge filters, the following terms are important, and are illustrated in Figure 7.1.

- **Challenge Testing**: The rigorous testing which is carried out by filter manufacturers to characterize the microbial removal performance of filter cartridges. The filter is exposed to, or challenged with a defined amount of viable model microorganisms under defined test conditions, selected based on the definition of sterilizing-grade filter cartridges.

- **Liquid and Aerosol Challenge Testing**: A further distinction with regards to microbial challenge testing is the method of bacterial challenge, *i.e.,* whether liquid removal performance (influent is a liquid suspension, Chapter 7.5.1.1) or aerosol removal performance (influent is air, Chapter 7.5.1.2) is used.

- **Model Microorganism**: The standard microorganism used to conduct challenge testing, which the filter must be capable of removing. In sterilizing filtration, this microorganism is the bacteria *B. diminuta* (ATCC 19146).

  Different from test dusts, latex beads or other inorganic particles used for validation of particle removal filters, microbial challenge is the accepted challenge testing method for microbial-retentive filters. It represents the lowest level of risk in the application because it is based on actual microbial removal; in contrast, challenge testing which employs particles uses these as a surrogate for microorganisms (Chapter 7.5.1.4).

- **Validation Test Conditions**: Due to the mechanisms of air filtration (Chapter 6), the removal performance of an air filter is dependent not only on the type and size of contaminant, but also on parameters such as air velocity and air humidity. The selection of the challenge test conditions has a significant impact on the filter retention performance.

- **Challenge Level**: The number of contaminants in the unfiltered air. For microbial rated sterilizing-grade air filters, by definition the challenge level must be 10^7 cfu of the specified model microorganism/cm^2 of effective filtration area. For a 10-inch filter of approximately 0.8 m^2 (8.6 ft^2) of effective filtration area, a minimum of 8 x 10^{10} cfu of challenge organisms would be required; a slightly higher total challenge level of 10^{11} cfu in the unfiltered air is often chosen to meet this requirement.

  Challenge level has a significant impact on retention performance. The user should distinguish between the required area challenge level (*i.e.,* $10^7/cm^2$) and the resulting total challenge level based on the effective filtration area of the cartridge (*e.g.,* 10^{11} in the example above).

  The FDA's statement that sterilizing-grade air filter cartridges must withstand the area challenge level of *at least* $10^7/cm^2$ is interpreted by some to mean that a higher area challenge would provide even better safety margins. Such implications are unwarranted.[17] The challenge concentration used for validation is intended to provide a margin of safety well beyond what would be expected in production.

- **Sterile Effluent**: Zero contaminant counts found in the filtrate. In sterilizing air filtration, microbial filters challenged with 10^7 cfu/cm^2 of effective filtration area must yield zero counts of viable microorganisms in the filtered air, without exception.

- **Filter Retention Performance**: Because we are dealing with large numbers of microorganisms, we speak typically about titer reduction, LRV, or removal efficiency when describing filter retention performance. All three terms identify the degree to which a filter is capable of removing contaminants; they are simply different mathematical expressions of the same concept.
  - **Titer Reduction**: The titer reduction is the ratio of the number of contaminants upstream to number of contaminants downstream of a filter; it is a number without a dimension, calculated as follows:

    $$\text{Titer Reduction } (T_R) = \frac{\text{Number of Contaminants in Influent}}{\text{Number of Contaminants in Effluent}}$$

In the case of sterile effluent (zero count), it is not possible to divide by zero. Therefore, to express the titer reduction value, the number '1' is assigned as the effluent count and the resulting value is shown as greater than the indicated titer reduction.

- **Logarithmic Reduction Value**: Common logarithm of the titer reduction value; it is a number without a dimension, calculated as follows:

  Logarithmic Reduction Value (LRV) = Log (Titer Reduction)

- **Removal Efficiency**: An expression of the titer reduction ratio in percentage terms, calculated as follows:

$$\text{Removal Efficiency} = \frac{(\text{Titer Reduction} - 1) \times 100\%}{(\text{Titer Reduction})}$$

In conclusion, when evaluating microbial filter retention performance, it is important to consider not only the stated microbial titer reduction or published filter removal efficiency, but also the microbial challenge level, method of challenge (liquid or aerosol), type of test microorganisms used, and the specific test conditions employed during filter validation, as the resulting filtrate quality is highly dependent on all of these factors.

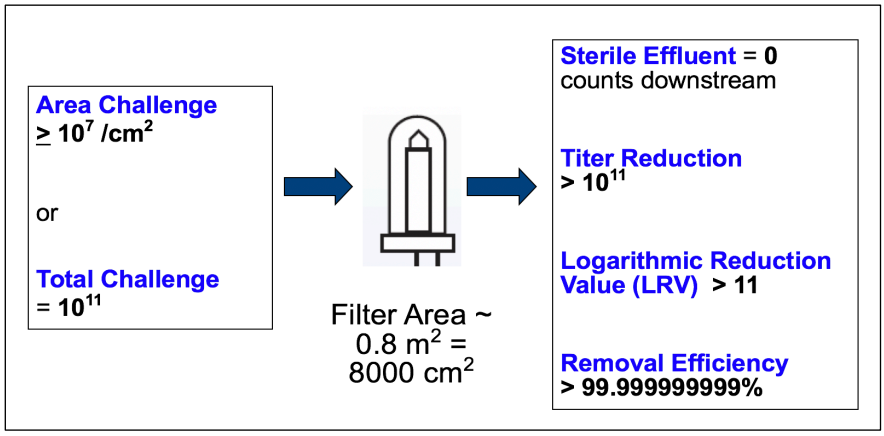

Figure 7.1: A sterilizing-grade air filter cartridge tested with a challenge level of 10^{11} model microorganisms *B. diminuta* must yield sterile effluent (zero viable counts) downstream, equating to a titer reduction of $>10^{11}$, a logarithmic reduction value of >11, and a removal efficiency of 99.999999999%. Due to the reason discussed in Chapter 7.2.1 (Challenge Level), a 10^{11} challenge level on a 0.8 m^2 cartridge actually results in a slightly higher area challenge level than $10^7/cm^2$ of effective cartridge area.
Source: Courtesy of Pall Corporation

7.2.2 Airflow Rate, Sizing and Throughput

7.2.2.1 Terminology and Principles

The following terms are described for common understanding:

- **Airflow Rate:** Refers to the filter manufacturer's published airflow vs. differential pressure data for a single filter unit, expressed in a graph. Airflow rates are inherently influenced by gas type, air velocity, supply pressure, and temperature. Airflow rate is used for sizing filters.

- **Filter Sizing:** Refers to the size of the total filter assembly recommended by the filter manufacturer based on the practical application, depending on the published airflow rate.

- **Total Throughput**: Refers to the total volume of air which passes the filter over the course of its service life. Highly dependent on the criteria for filter change-out and the quality of the influent air.

7.2.2.2 Filter Sizing

Cartridge filter assemblies, which consist of the filter(s) in the filter housing(s), are conservatively sized to achieve an initial low differential pressure and suitable linear velocity, in order to achieve long service life.

Sizing in air filtration is not linear as it is in liquid filtration. Type and design of filter media (thickness, porosity), retention characteristics, support and drainage materials, core losses within the filter cartridge, and filter housing design influence sizing. In installations of primarily single-round filter assemblies selected for smaller airflow rates, sizing is influenced mainly by filter media attributes. In large multi-round filter assemblies selected for higher airflow rates, sizing is influenced not only by filter media attributes but by assembly design. Housing design (swept bends and proper inlet/outlet pipe diameter) should be suitably selected to offer minimum restriction.

The higher the volumetric airflow, the greater the number of parallel filters that are required so that the overall assembly differential pressure remains low. Different filter manufacturers may vary in conservatism on their choice of allowed initial differential pressure:

- Undersizing the filter assembly by accepting a higher initial differential pressure results in premature shortage of filter life and high differential pressure across the assembly, which can negatively impact compressor energy cost.
- Oversizing the filter assembly results in excessive capital and operating cost especially when filters are not used to their full potential life

When comparing filters of like media, the determining aspect for sizing is the airflow/differential pressure behavior of the filters, not their absolute filtration areas. The filtration area will have a larger influence on filter life if filters are run to blockage.

Good prefiltration of compressed air prior to final cartridge filtration helps to prolong the filter's air throughput and resulting service life: without extreme particle blockage, the cartridge filter's main task is limited only to submicron particle and microorganism removal. Very often, cartridge filters in aseptic production are changed out on a conservative preventive maintenance schedule based on a certain number of steam sterilization cycles, so total air throughput is rarely limited by filter blockage. At minimum, end users should refer to filter manufacturers' recommendations for acceptable filter change-out frequency based on maximum steam sterilization cycle claims (Chapter 7.5.3.1).

7.2.3 Design Features and Attributes

7.2.3.1 Application Compatibility

All filter materials of construction, including polymeric materials and rubber materials used in the filter adaptor area must be compatible with the type, temperature and pressure of the gas. The filter's integrity and thus its performance are compromised if quality degradation were to occur over time due to incompatible materials or process conditions.

Typically, in aseptic production that generally uses air at ambient temperature, there are no major concerns regarding compatibility with common filter media and hardware materials (PTFE, polypropylene) or rubber materials (silicone, EPDM). It is a different situation when temperatures are excessively hot or cold, or oxygen-enriched air is in use.

In applications where chemicals such as hydrogen peroxide are employed, as in cases wherein hydrogen peroxide is used in conjunction with steam sterilization of cartridge filters, the filters must be able to withstand exposure to the chemicals at the temperatures, concentrations, and duration of use.

Biological persistence should be given by choosing components that do not support the growth of bacteria or mold, nor should they be degraded by their metabolic products.

7.2.3.2 Hydrophobicity

In the filtration of air, the use of media with highest possible hydrophobicity is of utmost importance. Hydrophobicity is the physical property of a material that repels water rather than absorbing it. For a more scientific description, see PDA TR 40.

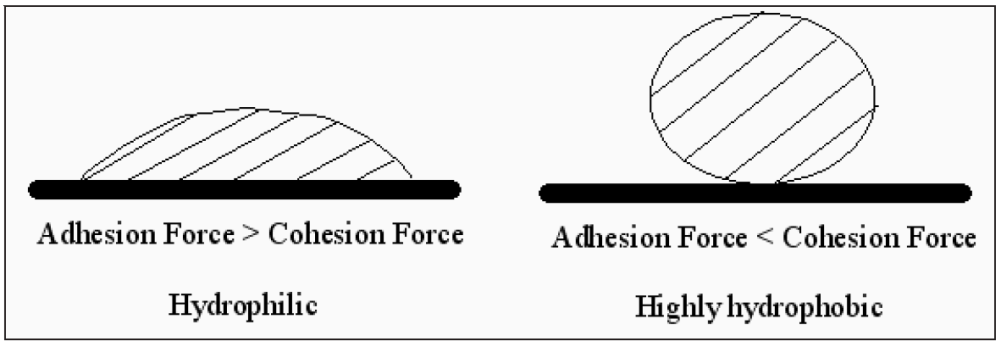

Figure 7.2: Interaction of Water with Hydrophilic and Hydrophobic Surfaces
Source: Courtesy of PDA

Of the popular materials PTFE, PVDF, polypropylene, and polyethylene, PTFE is the most hydrophobic and polyethylene the least, as can be seen from published critical surface tension values. This is why modern air cartridge filters are constructed of PTFE media, or in the case of depth filters, of PTFE-impregnated borosilicate microfiber media.

Employing hydrophobic filters reduces the risk of their wetting out when exposed to moisture in air streams, resulting in unrestricted airflow during filtration with associated low differential pressure across the filter. Small pressure drops in turn can contribute to compressor energy savings.

Hydrophobic filters also enable relatively quick blow down time, *i.e.,* the time it takes to cool and remove moisture from filter assemblies after steam sterilization, or after filter integrity testing, so that they are quickly put back into operation.

While it is best practice for the system to be designed and operated to minimize any moisture formation during production runs, the risk of upset conditions is minimized by employing hydrophobic filters. When the aseptic process is well controlled, the risk of upset conditions is low. OEMs and end users should be aware of the risks as they relate to filter performance and how to mitigate them.

Even the most hydrophobic filters can end up partially wetted under upset conditions. These can occur especially in compressed air streams, such as in these examples:

- Failure of an upstream compressed air dryer or condensate traps causes humid air to impinge on and pass the filter if filter bubble point is exceeded.
- Pressure surges especially in the presence of improperly drained steam condensate overcome the bubble point of the filter causing moisture to pass the filter. In a 0.2 µm filter the bubble point can be as high as 3.5 bar.
- Oils or solvent chemicals in compressed air or splashing chemicals from CIP fluids in tanks on aseptic tank vent filters reduce the surface tension of moisture in the air and result in hydrophilic

spots on the filter.

In all the above cases, the risk of compromising sterility exists, and it is minimized by using hydrophobic filters that are qualified for effective microbial removal under such wetted conditions (*i.e.,* liquid-challenged filters).

7.2.3.3 Durability

The durability or robustness of a cartridge filter is reflected in its ability to withstand multiple cycles of *in situ* steam sterilization, its forward and reverse flow steaming capability at different temperatures and pressures, its resistance to steaming and normal operating temperatures, and its oxidative stability in the presence of air over time. These attributes are demonstrated during validation work by filter manufacturers and described in relevant documents. Users should operate the filters within the limits specified by filter manufacturers.

Type, morphology and design of the filter media, selection of support and drainage layer materials, and hardware materials influence the robustness of the filter. Methods used to apply adaptors and end caps, as well as joining filter sections to achieve different lengths are also critical factors in determining how well a filter stands up to stressing forces while in operation. Filters encounter the greatest physical stress at elevated temperatures, *e.g.,* during steaming, or oxidative damage on exposure to hot air or oxygen-enriched air.

7.2.3.4 Toxicity

Undesirable substances should not be released from filter materials into the product or product-contacting areas during operation. Different from liquid filtration, the risk of extractable release is low in air filtration, especially when a hydrophobic final filter is present. Nevertheless, filter materials should comply with national and international food contact compliance regulations regarding suitable materials of construction. Aseptic manufacturers should verify compliance of filter manufacturers with these standards (Chapter 3.2).

7.2.3.5 Geometry and Hardware Fit

OEM equipment manufacturers will select suitable filter hardware geometry for installation on aseptic equipment. It is important to note, that sometimes there is a tendency to undersize filter housings in order to positively impact overall hardware cost and reduce machine footprint. However, end users will be faced with a higher cost of ownership due to the resulting more frequent need for disposable filter change-outs.

When cartridge filters are specified, their configuration is critical in order to achieve positive location, reliable and hygienic sealing within the filter housing and physical stability during all phases of operation and steaming. It is recommended that only SOE cartridges be used, with adaptors featuring a double bayonet design, two O-rings and internal adaptor rings. Filters are only as good as their hermetic connection to the filter housing therefore attention is given to sealing integrity.

7.2.3.6 Filter Housing Design

Cartridge filter housings meet several requirements to support an efficient filter sterilization process and leak-free filtration during aseptic operation. Figure 7.3 illustrates typical single-round air filter housings.

Air filter housings in aseptic filtration installations feature hygienic design, with smooth surface finish (minimum Ra = 0.8 micrometers/32 microinches), smooth welds, and sanitary (no threaded) connections. They are generally crevice-free. To withstand SIP pressures and temperatures and to reduce corrosion from CIP chemicals and product, they are typically constructed of DIN 1.4301 (AISI 316) or more corrosion-resistant DIN 1.4404 (AISI 316L) stainless steel. The use of other corrosion-resistant materials may also be considered.

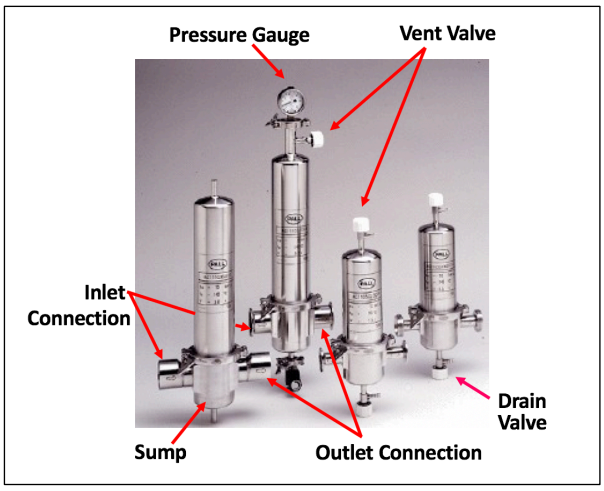

Figure 7.3: Typical Single-Round Air Filter Housings – featuring sump design, inlet/outlet connections, vent and drain connections, associated pressure gauge and vent/drain valves
Source: Courtesy of Pall Corporation

Air filter housings feature relatively large diameter inlet/outlet connections, in order to reduce pressure drop across the filter assembly during filtration operation and therefore enable cost-effective sizing. Housings are installed in pipelines in the allowed direction of airflow across the filter, which is typically "out to in", or "forward flow" direction, although reverse flow installations are also possible.

Air housings should be oriented in a vertical position, with the single open end of the filter pointed downwards, so that steam condensate can drain off from the filter core continually during steaming. Different from liquid filter housings, air housings feature a "sump" design on the housing head (base of housing) which enables condensate drainage from the upstream side of the filter especially during initial *in situ* steaming. Collection of steam condensate on the upstream side of the filter would block the available filtration area and eventually cause filter collapse due to excessive differential pressure across the filter, as it is hydrophobic and the condensate has nowhere to go. Condensate drain valve cycling sequences, steam traps or orifices enable continuous condensate removal from the sump.

The housing design should prevent incoming steam or air from directly impinging on the filter, which could cause damage.

Housings feature a high point vent, which enables purging the housing of air especially at the beginning of *in situ* steam sterilization. Purging air is necessary so that the desired steam sterilization temperature can be attained.

Any supplied monitoring devices such as pressure and/or temperature gauges and associated valves need to be tight, manufactured of similar materials, and of hygienic design.

The housing O-ring provides a tight seal between housing head and bowl. The adaptor area in the housing head mates with the corresponding filter cartridge adaptor to ensure a tight fit, to prevent not only air bypass during filtration, but to also ensure continued filter seal integrity during heating (steam sterilization) and subsequent cooling.

As cartridge filter assemblies are commonly used on compressed air, the housings are rated for pressure and vacuum, and O-rings must withstand steaming temperature and pressure.

Single- and multi-round housings which hold single or multiple filter cartridges enable filter assembly sizing to accommodate low to high airflow rates.

7.2.4 Economics and Cost of Ownership

Filter performance to maintain the appropriate level of filtration is always the highest priority. Assuming the filter performance is within requirements, economic considerations are made.

When evaluating filter hardware assembly and disposable filter purchase price, care should be taken not to overemphasize these costs. Good economic analysis should consider the true cost of ownership, including operational costs incurred over the filter's service life and the impact of filter quality on the cost of related operations. These often represent far higher expenses.

The following factors will impact cost of ownership:

- Conservative assembly sizing with low initial differential pressure drop will generate compressor energy savings and can result in longer filter service life.
- Robustness of filters, especially on prolonged exposure to oxidation and repeated steaming cycles can extend service life.
- Robust manufacturing quality control of filters ensures reliability in use, thus avoiding costly process interruptions.
- Availability of filter vendor service and troubleshooting support enables smooth operation.

7.3 Sterilization of Filter Cartridges

7.3.1 Steam in Place (SIP) or *In Situ* Steam Sterilization

Sterilizing-grade cartridge filters typically supplied to the food and beverage industry are not supplied in sterile condition. The most common method of rendering them sterile prior to use is to install them into the production environment and steam them in place (SIP) before operation. This is also known as *in situ* steaming. Steaming in place involves passing a continuous or cycled flow of saturated steam under pressure through the filter assembly, to achieve the required lethality on filter cartridges and filter housing surfaces. Using this method avoids risk of contamination that would occur if pre-sterilized installations were to be aseptically transferred (such as with autoclaving).

The filters are commonly used and re-sterilized multiple times over the course of their life. Filter manufacturers validate a number of repeated SIP cycles, which the filters will withstand. This information provides insight into a filter's robustness. In practice, filters are typically changed out on a preventive maintenance basis, selected by equipment suppliers and/or end users to reduce risk.

It is the user's responsibility to confirm for their process whether the required sterility assurance has been achieved.

7.3.1.1 Cartridge and Housing Design Requirements Related to *In Situ* Steam Sterilization

Aspects of filter housing design as they relate to *in situ* steaming are discussed in Chapter 7.2.3.6.

7.3.1.2 Installation

According to procedures supplied by filter manufacturers, the filter should carefully be removed from its packaging and correctly installed into the relevant filter housing located within the aseptic process or filling equipment. Correct filter installation is of paramount importance, as any leaks between the non-sterile and sterile side of the filter within the filter housing would later compromise sterility. O-rings on the filter cartridges must be checked for damage to ensure integrity of the seal between the filter and its housing. Housings and sterile side connections should be tightly sealed.

After installation into the housing, ideally a filter installation integrity test should be carried out, to confirm tightness of the assembly and integrity of the filter. Please see Chapter 10.1.4.2 for further discussion about practical application of this guidance.

7.3.1.3 SIP Process

7.3.1.3.1 Introduction of Steam and System Deaeration

Saturated steam of culinary quality is gradually, continuously introduced to the filter assembly.

The steam initially purges air from the assembly and replaces it with steam. High point vents enable air removal. In particular for filter housings of 10-inch length and greater, air must adequately be purged from the housing during the introduction of steam.

Steam condensate is drained or bled from the filter housing, to ensure the filter is continually exposed to dry steam. In addition, draining condensate from the filter assembly is critical and is facilitated by the housing design (Chapter 7.2.3.6).

Steam is introduced to the filter assembly either in forward or reverse direction. Generally speaking, the steaming operation is stressful to filters, as they soften with thermal exposure. Depending on filter manufacturer, cartridges may be validated for steaming performance only in forward ("out to in") or also in reverse ("in to out") direction. Filters themselves are more robust when steaming in a forward flow direction, hence from a filter cartridge perspective it is preferable to steam in this direction. The allowed differential steam pressure is lower in reverse direction and the probability of filter damage is increased. However, in many practical applications, steam is supplied in a reverse direction through the filter, *e.g.,* from a connected aseptic tank or filling system. For such cases, reverse flow performance validation is required from filter manufacturers to instruct the user on proper steaming procedure and predict filter robustness under these conditions.

Whether operating filter cartridges in forward or in reverse steaming direction, it is important to be aware of specific claims regarding maximum differential pressure and temperature during steaming, and operate them according to filter manufacturers' instructions (Chapter 7.5.3.1) to avoid overpressure and thermal shock.

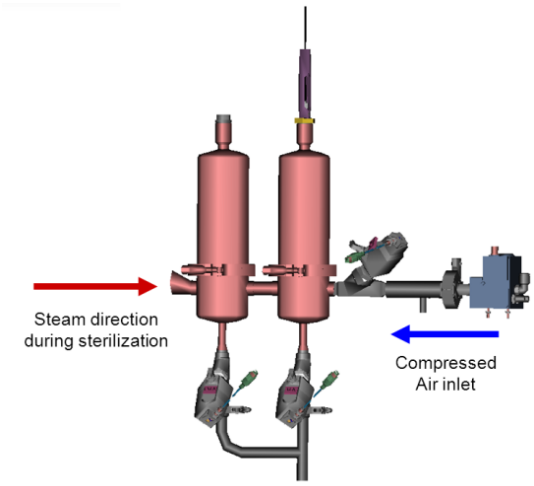

Figure 7.4: Schematic of a Steaming Installation - in which steam is introduced to the cartridge filters in an "in to out" direction or in reverse flow mode.
Source: Courtesy of SIG Combibloc

7.3.1.3.2 Sterilization Sequence

After the initial steam introduction phase, in which air and condensate are purged from the filter assembly, temperature monitoring at all critical areas is mandatory to ensure the defined time/temperature process. Following the International Pharmacopoeia recommendations provided for the sterilization of medical devices in autoclaves the minimum theoretical sterilization time of 15 min @ 121 °C (250 °F) at the "cold spots" is necessary to achieve sufficient lethality on equipment, such as filter housing surfaces and cartridges.[18] In practice, most producers use a minimum sterilization time of 30 min @ 121 °C (250 °F) to ensure adequate heat treatment of all system surfaces. Higher temperatures with shorter exposure times are possible as long as the required lethality is achieved.

In order to ensure the required time/temperature sequence is maintained throughout the filter installation, continuous removal of air and steam condensate is necessary.

Due to various filter housing designs and sizes, the equipment manufacturer should verify with adequate means, that the sterilization sequence renders the filter and housing sterile, with temperature monitoring devices installed at relevant "cold spot" areas. This might be on top of the filter housing (air bubble monitoring) or at the bottom (condensate control), depending on housing, filter, and process design. The use of temperature monitoring devices to verify cold spot areas is based on filter assembly validation studies (Chapter 9.2.2.2).

7.3.1.3.3 Depressurization and Ventilation

After the sterilization sequence is complete, depressurization is conducted via condensate traps, followed by the gradual introduction of prefiltered low pressure cooling air into the aseptic system. As filters used in sterile air filtration are hydrophobic and therefore not wetted out during steam sterilization, the cooling process should not be mistaken to be a drying process of the filters. The cooling air is passed first through the sterilized filter, as the now sterile filter sterilizes the air before it enters the rest of the system.

Especially during the first part of this cooling period, hot filters can easily be damaged, and condensate from collapsing steam can lead to water blockage on filter membranes and resulting high pressure drop. Therefore, the incoming air pressure should be limited to reduce mechanical stress on the filter. Initial cracking open of the vent and drain valves on the non-sterile side of the filter so that the air initially passes across the filter and not entirely through it is another option.

During cooling, air is supplied to avoid sudden pressure reduction due to collapsing steam, to avoid a vacuum and damage to equipment. Cooling air should flow in such a way that condensate is blown out of the system.

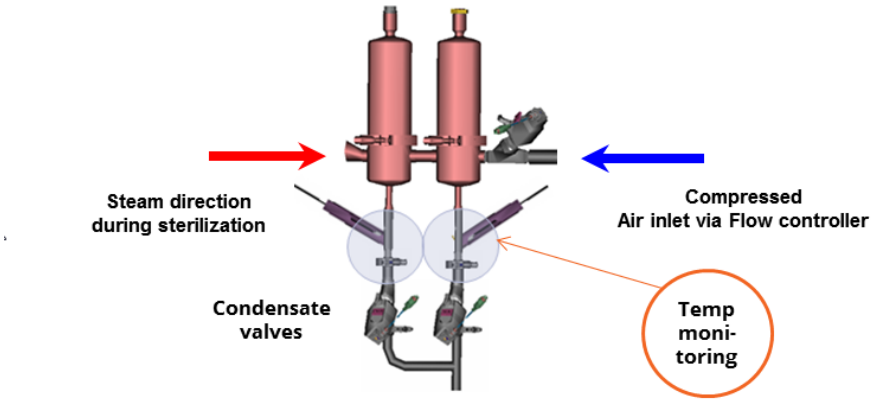

Figure 7.5: Illustration of Temperature Monitoring - at "cold spot"
Source: Courtesy of SIG Combibloc

7.3.1.4 Start of Filtration Operation

Once the system has cooled to operating temperature, filtration operation can begin. Air overpressure is always maintained across the filter and the allowed differential pressure across the filter should never be exceeded.

Within the aseptic zones of the system, air overpressure or flow barriers (where air overpressure is not measurable) are accepted protective means to avoid any chance of contamination from the outside environment.

At the end of operation, a filter integrity test can be carried out, to confirm integrity of the filter installation and for batch record documentation (Chapter 10.1.4.2).

7.3.2 Autoclaving

In very rare cases, filter assemblies in use on aseptic equipment may be separately autoclaved prior to certain types of use. Many filter manufacturers validate their filters for autoclave sterilization at temperatures of at least 121 °C (250 °F). Autoclaving of filters according to proper procedures provided by filter manufacturers is a viable option for filter sterilization. However, extreme care must be exercised to transfer the autoclaved filter assembly aseptically to the final installation, so as not to compromise sterility at the connection points.

It is the user's responsibility to confirm for their process whether the required sterility assurance has been achieved. Additional information is also detailed in PDA TR 40.

7.3.3 Hydrogen Peroxide Sterilization

Some machine manufacturers incorporate the use of hydrogen peroxide for system sterilization. In cases where the filter cartridges are sterilized by or exposed to this chemical, it is important that users ensure the filters' sterilization and chemical compatibility claims are validated and suitable for the concentration, exposure time, and temperatures at which the chemicals are used.

7.4 Other System Design Considerations

7.4.1 Redundant Filter Arrangements

FDA regulations stipulate that any portion of production packaged under non-sterile conditions must be segregated, and fully reprocessed or destroyed if an evaluation demonstrates that the product is not free of microorganisms of public health significance (Chapter 3.1).

In order to avoid potential product losses, double cartridge filter set-ups with two separate filter housings in series are highly recommended to provide redundancy in case of human or system error or filter defects, to reduce the risk of losing commercial sterility due to filtration failure. However, redundant filters are not an FDA requirement for aseptic production in the food industry.

Redundancy in filter layout requires a sequential sterilization process of both filter cartridges and housings. Each housing is equipped with a separate drain valve to facilitate condensate removal during SIP. This approach significantly reduces differential pressure across the entire filter assembly during steam sterilization because any condensate formed is removed at each filter.

Filter to filter seals need to have an intermediate flange to provide a defined sealing area for both attached filters.

Some users exchange filters installed in series at different intervals to minimize the failure probability of the filters at the same time. Usually, the switching point is one half of the total validated filter sterilization

cycles or less, so as never to exceed the allowed cycle maximum for each filter. New filters should be installed as the final filter in the series closest to point of use; after a predetermined number of sterilization cycles they are moved to the second (upstream) position and replaced by another new filter. Airflow direction indicators on filter housings assist with identifying upstream and downstream (final) filter positions (Figure 7.6). The rationale for installing the newest filter as the final filter is to minimize risk as it provides the final microbial barrier: the newest filter will have seen the least number of sterilization cycles and is the "cleanest" filter (no contaminant load) and therefore the most robust.

7.4.2 Water Blockage and Moisture Control

Air filters operate most efficiently and safely when they remain dry. The negative effects of condensate accumulation during SIP have already been discussed. During filtration operation, accumulation of moisture in the filter assembly due to insufficient air pretreatment restricts airflow and may also result in microbial growth on the upstream, non-sterile side of the filter, which is undesirable.

Accumulated water in a filter housing cannot pass through a hydrophobic filter; if condensation from moist air is not drained, a point is reached when the filter will collapse due to excessive differential pressure. In upset conditions when moisture may nevertheless pass the filter (Chapter 7.2.3.2), the risk of compromising sterility is minimized when liquid-challenged filters are in use.

Moisture in a compressed air system is removed either by drying or using liquid/air coalescing prefilters, or it can be continuously drained with condensate traps at low point drains in piping and filter housings. We have already discussed the benefits of using filter housings with a sump design, and vertical orientation of filter assemblies. It is possible to steam jacket or heat trace filter housings to keep moisture in vapor form, although extended exposure of the filters to air at elevated temperatures (over 80 °C, 176 °F) can speed up degradation of filter materials due to accelerated oxidation. Check the filter manufacturers' claims regarding service life at elevated temperatures.

7.4.3 Failsafe Design

OEM manufacturers ideally design their systems to provide adequate accessibility and convenience for filter change-outs. Ongoing filter change-outs by operators or service personnel must not compromise the originally validated system. Position marks or guides on the housing should enable a repeatable, correct positioning of filter elements. Flow direction should be displayed on the filter assembly so that incorrect installation is avoided. Simple visual verification of positioning by Poka-Yoke means is preferred to provide the same conditions as validated.

Figure 7.6: Airflow Direction Indicator on Air Filter Housing Head
Source: Courtesy of Parker Hannifin

Basic leakage testing on filter clusters needs special devices to detect gaps between seals and the housings. Fog generators can be used to visualize escaping air during operation under pressure.

Chapter 11 describes responsibilities of filter and OEM equipment manufacturers to facilitate proper filter change-outs and assembly by operators and service personnel.

7.5 Validation of Cartridge Filter Performance Claims

Air filters used in aseptic production must deliver the required performance to ensure desired outcomes reliably and repeatedly: namely, to achieve filtered air sterility, resulting in commercial sterility of manufactured products.

Filter manufacturers are responsible for validating filters under a range of different conditions of expected use, to ensure correct performance in field application. This validation test work can be destructive and should be done on a suitable selection/quantity of production filters, as no two production filters can be identical due to inherent variation. Data gathered is used to identify filter performance claims.

Different filter manufacturers will use varying protocols for production filter selection, test quantity, testing methodology, and levels of conservatism in data interpretation for creating the claims (applying different safety factors).

Reputable filter manufacturers will publish detailed information about this test work and results in a "Validation Guide", also called a "Technical Performance Document" or similar. While data sheets do indicate claimed filter performance data, the validation guide illustrates the nature and robustness of actual background test work. A review of the validation guide is a good way to compare and contrast claimed filter performance when selecting filters.

Once validation has been completed and claims published, it is the filter manufacturer's responsibility to monitor continued validity of the claims in production filters on an ongoing basis, to ensure that any changes in production techniques or modifications of filter raw materials or components do not cause changes in the claimed filter performance (Chapter 11.1.3).

The methods cartridge filter manufacturers use to generate and validate filter claims are explained in the following sections.

7.5.1 Retention Performance Validation

Retention performance testing has to do with the filter's ability to remove contaminants, *i.e.,* type, how many, and under what conditions.

Important distinctions to be made in evaluating retention performance testing are:

- whether a filter is liquid-challenged or aerosol-challenged: the first approach uses a liquid suspension and the second uses a nebulized suspension in air to determine filter removal performance.
- whether microorganisms or particles are used as the contaminants in a challenge test
- what test procedures are employed
- which filter configurations are tested

In microbial challenge testing of cartridge filters, a critical requirement is the correlation of claimed bacterial removal performance (from destructive tests) with integrity test values, as integrity testing is the only non-destructive method available to end users for confirming filter performance in operation (Chapter 10.1). Filter manufacturers will apply different safety factors when making this correlation.

As mentioned in Chapter 7.2.1, microbial challenge testing for evaluating filter retention performance provides the highest degree of test sensitivity and therefore safety in the application.

7.5.1.1 Liquid Bacterial Challenge Testing

Liquid bacterial challenge testing, or 'liquid challenge' is a destructive test to determine the filter's bacterial retention and its removal efficiency in a liquid. This testing approach reflects a worst-case scenario, which can occur if a hydrophobic air filter were to let moisture through due to process upset conditions or due to development of hydrophilic spots or partially wetted out pores (Chapter 7.2.3.2). This type of test can only be carried out on membrane cartridge filters, which uniquely provide liquid challenge claims.

Liquid challenge claims in sterilizing-grade filters represent the lowest risk in terms of bacterial removal performance because it is always more difficult for a filter to remove bacteria from a liquid than from dry air (Chapter 6.2.1).

A common procedure for the liquid challenge test, namely ASTM F838-20[19] (originally published as ASTM F838-83 with subsequent revisions) provides guidance for test execution. In principle, the filter assembly is initially steam sterilized and cooled, ensuring removal of all steam condensate. The test filter is then wetted with a low-surface-tension fluid (*e.g.,* alcohol solution). An aqueous suspension of minimum 10^7 cfu *B. diminuta* (ATCC 19146)/cm^2 of effective filtration area, equivalent to a challenge level of *e.g.,* >10^{11} cfu per 10-inch cartridge (Chapter 7.2.1) is passed through the test filter at a given flow rate for a period of time under standardized conditions. Downstream of the test filter, the entire filter effluent (*i.e.,* not just a slip stream portion thereof) passes through a 0.2 µm rated analysis membrane filter disc, which captures any microorganisms, even a single viable cell, that may have penetrated the test filter. The filter disc is subsequently incubated to determine the presence and quantity of any viable microorganisms in the effluent. Figure 7.7 illustrates a typical test set-up.

The test result is quantified as a titer reduction, as explained in Chapter 7.2.1, with:

- the number of contaminants in the influent referring to the number of bacteria in the influent (challenge suspension)
- the number of contaminants in the effluent referring to the number of bacteria in the effluent (on the analysis disc)

To prove sterilization capability of the test filter, the required outcome of this test is to find sterile effluent, or zero viable microorganisms on the filter analysis disc. For a sterilizing-grade filter, according to the above-mentioned description in Chapter 7.2.1, the T_R is therefore: > influent count or >10^{11} (10-inch test filter, also see Figure 7.1).

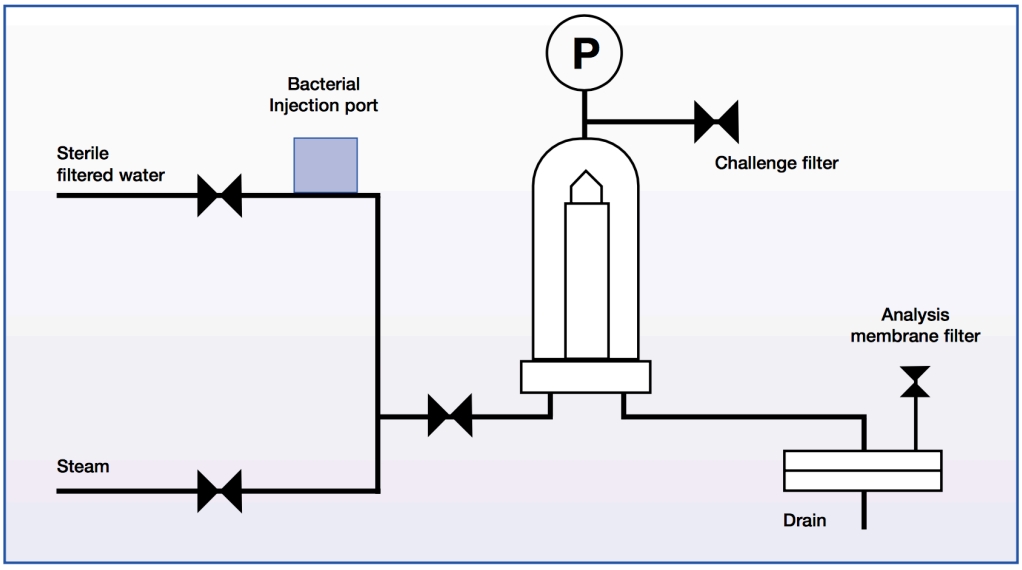

Figure 7.7: Schematic of Liquid Bacterial Challenge Test Set-Up (membrane test filter)
Source: Courtesy of Pall Corporation

7.5.1.2 Aerosol Bacterial Challenge Testing

Aerosol bacterial challenge testing, or 'aerosol challenge' is a destructive test to determine the filter's bacterial retention and its removal efficiency in air. This testing approach reflects filter performance in its most common operation, namely a dry air process in normal operation, *i.e.,* assuming negligible risk for process upset conditions, partial wetting out of hydrophobic air filters, or in non-hydrophobic filters. This type of test can be carried out on both membrane and depth cartridge filters, resulting in aerosol challenge claims.

Aerosol bacterial challenge testing should not be confused with ongoing performance monitoring by aerosol challenge *integrity* testing in the field (Chapter 10.1.2.5). The first is the method used to validate filter performance based on actual bacteria removal, while the second describes a method for filter integrity verification by end users under dry air conditions.

There are different methods used for aerosol bacterial challenge tests; some are carried out by filter manufacturers or by third party independent testing labs. It is important to be assured that the tests used are fit for purpose.

In principle the test procedure is as follows: The filter set-up is initially steam sterilized and cooled, ensuring removal of all steam condensate. A nebulized suspension of *B. diminuta* (ATCC 19146) in air at a concentration of minimum 10^7 cfu/cm^2 of effective filtration area, equivalent to a challenge level of *e.g.,* > 10^{11} cfu per 10-inch cartridge (Chapter 7.2.1), is passed through the test filter at a given flow rate for a period of time. The test is designed so that a concentration of bacteria is aerosolized using a nebulizer and then passed through the test filter. The filter effluent is passed through a collection device (*e.g.,* impingers, impactors) downstream of the test filter to capture any bacteria that pass through the filter. In a parallel stream, the aerosol is also passed directly through the test system without a test filter in line, and that "effluent" is also captured downstream in a separate collection device. The concentration of bacteria captured in the downstream flow without passage through a filter is compared to that captured post filtration and a titer reduction is calculated.

Most commercially available microbiological air samplers use the impingement or impaction collection techniques.

It is important to note that downstream of the test filter the entire filtered stream of effluent air (*i.e.,* not just a slip stream portion thereof) is passed through the air samplers, so that even a single viable bacteria cell that may have penetrated the filter would be recovered. Figure 7.8 illustrates a typical test set-up utilizing a Casella slit sampler, a type of impactor air sampling device.

The test result is quantified as a titer reduction, as explained in Chapter 7.2.1, with:

- the number of contaminants in the influent referring to the number of bacteria in the influent (challenge suspension)
- the number of contaminants in the effluent referring to the number of bacteria in the effluent (recovery buffer or agar plate)

To prove sterilization capability of the test filter, the required outcome of this test is to find sterile effluent, or zero viable microorganisms in the recovery buffer. For a sterilizing-grade filter, according to the above-mentioned description in Chapter 7.2.1, the T_R is therefore: > influent count or > 10^{11} (10-inch test filter).

In general, results from aerosol challenge tests are influenced by:

- air velocity
- air humidity
- microbiological techniques

- devices used

In addition to the above described aerosol challenge test, some filter manufacturers carry out extended aerosol bacterial challenge tests to reflect how a multi-use filter installed for a prolonged period (*e.g.,* 30 days) in between sterilization cycles continues to perform over time.

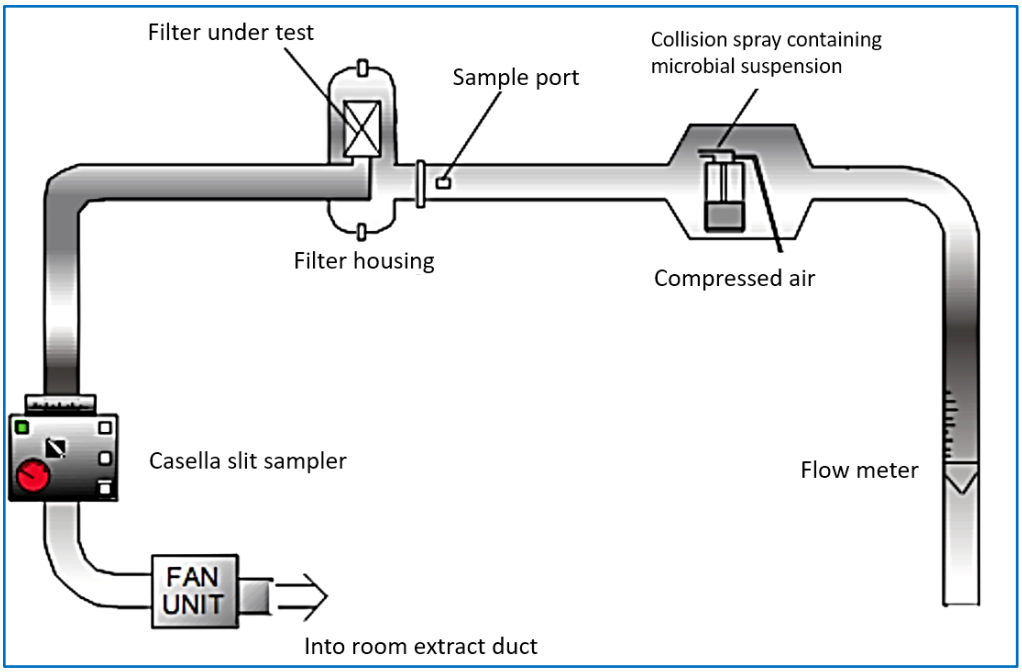

Figure 7.8: Schematic of Aerosol Bacterial Challenge Test Set-Up (membrane or depth test filter)
Source: Courtesy of Parker Hannifin

7.5.1.3 Aerosol Spore Challenge Testing
While not obligatory as part of the definition of sterilizing-grade cartridge filters, some filter manufacturers supplement their bacteria retention performance claims with claims regarding aerosol spore removal.

The microorganism typically used is *Bacillus atrophaeus* (historically referred to as *Bacillus subtilis* var. *niger*, *e.g.,* ATCC 9372) spores, with a dimension of roughly 1 x 0.7 µm. Basic methodology is similar to previously described aerosol testing. A titer reduction is calculated.

Bacterial spores can remain viable in otherwise damaging conditions and are transmitted easily in air. In addition, the size of spores is typically in the range which is challenging for air filters to retain (Chapter 6). Bacterial spores are a particularly concerning microbial hazard to aseptic packaging operations.

Some filter manufacturers also carry out extended aerosol spore challenge tests to reflect how a multi-use filter installed for a prolonged period in between sterilization cycles continues to perform over time.

7.5.1.4 Particle Challenge Testing
Particle challenge testing of sterilizing-grade cartridge filters is largely irrelevant because only actual microbial retention validation demonstrates microbial removal performance. Particles are not considered to be suitable surrogates for microorganisms, and particle removal does not represent microbial removal performance (Chapter 7.2.1). A filter which provides sterile effluent according to the definition will naturally display an extremely high level of particle removal, far beyond that of typical particle-rated filters.

Nevertheless, although more appropriate for air cartridge prefilters, some manufacturers publish particle removal efficiency data for sterilizing-grade air cartridge filters. What is ultimately important for the end user to understand is:

- Results vary based on test method, including types of particles used, method of nebulizing or other delivery mechanisms of the particles into the air stream, airflow rate, and type and sensitivities of particle counters or other downstream detection devices employed. It is difficult to compare particle removal performance amongst different air filters unless identical tests under identical conditions are used.

7.5.2 Airflow Rate / Differential Pressure Validation

Filter manufacturers publish the differential pressure characteristics of filters measured at different airflow rates and inlet pressures. These values influence assembly sizing and assembly pressure drop.

The values are typically shown in an airflow/differential pressure graph at 'vent' (atmospheric) and pressurized air conditions and ambient temperature. Several measurements are done on a quantity of selected production filters; from this validation data, suitable claims are generated.

Different filter manufacturers will use varying protocols for production filter selection, test quantity and levels of conservatism in data interpretation for creating the claims.

In principle, the measurement method consists of a test filter installed in an air filter housing on a test rig; clean compressed air is directed through the assembly at a range of flow rates, at either vent or pressurized air conditions. The differential pressure across the filter assembly is measured at different combinations of flow rates and supply pressures. Flow/pressure characteristics for the filter are calculated by subtracting housing-only results from assembly results.

7.5.3 Validation of Physical Robustness

Filter manufacturers publish claims regarding how filters will hold up to known stressor events during production, such as steam sterilization for cartridge filters, hydrogen peroxide exposure, and operating temperature exposure effects on the filters over time.

These stressors can damage filters if not controlled according to the limits set by filter manufacturers, potentially resulting in compromised filter integrity and retention performance.

7.5.3.1 Steam Sterilization

Exposure to steam weakens polymeric cartridge filters due to the combination of elevated temperatures and exposure time. Filter manufacturers validate the limits to which cartridge filters should be *in situ* steamed with saturated, condensate-free steam, or autoclaved.

For developing *in situ* steaming claims, a selected quantity of production filters is tested. Each test filter is installed into an air filter housing, initially integrity tested (pass value is required), steamed *in situ* typically at temperatures ranging from 121-142 °C (250-288 °F), held at temperature for a given time period at constant steam flow and differential pressure, and cooled with compressed air. This procedure is repeated for several cycles, with periodic integrity testing to reconfirm filter integrity, until the number of desired cycles is reached. The resulting, published number of successful steam cycles does not necessarily mean that filter integrity was compromised after that number of cycles was tested; rather it is commonly an arbitrary choice by the filter manufacturer, and typically serves to demonstrate filter robustness.

Different filter manufacturers will target different numbers of steaming cycles and different lengths of time exposure to demonstrate steaming robustness. Use of the filters beyond these values is at the discretion of the end user with ongoing filter integrity verification monitoring.

Some examples of steam cycling performance claims found in the industry are:

- 165 1-hour cycles at 142 °C (288 °F) @ maximum < 300 mbar (4.3 psi) differential pressure
- 225 ½-hour cycles at 142 °C (288 °F) @ maximum < 300 mbar (4.3 psi) differential pressure

Some filter manufacturers will validate *in situ* steaming in both forward and reverse filtration direction, to reflect expected use in the field. They may also provide validation data reflecting other conditions of use.

Some filter manufacturers validate autoclave resistance as well.

7.5.3.2 Hydrogen Peroxide Exposure

Filter manufacturers may provide validation data regarding cartridge filter resistance to hydrogen peroxide as some end users use a vaporized hydrogen peroxide in conjunction with steam.

In principle, a solution of hydrogen peroxide of a given concentration is introduced into a heated compressed air stream; it vaporizes on contact. This stream of hydrogen peroxide vapor in air is passed through the test filter assembly at a given flow rate for a given period of time. Downstream of the filter, the hydrogen peroxide is condensed and discarded. After a given exposure time, a filter integrity test is done to confirm no damage has occurred to the filter. The resistance data generated includes hydrogen peroxide concentration, air temperature, and exposure time.

7.5.3.3 Operating Temperature Resistance

Filter manufacturers publish claims regarding the resistance of filters to oxidation over time. Some filter components are sensitive to oxidative damage, which may exhibit physical degradation and negatively impact filter integrity and performance. In particular, exposure to high temperature air accelerates oxidation.

Validation testing centers around cycling hot air through test filters and checking them at periodic intervals for integrity and signs of degradation. From these tests, filter compatibility to different air temperatures can be calculated based on physical principles.

8 High Efficiency Particulate Air (HEPA) / Ultra Low Penetration Air (ULPA) Filters

8.1 Definition of HEPA and ULPA Filters

HEPA and ULPA are commonly used expressions to describe air filters with extremely high capture efficiency of airborne submicron-sized particles.

Authors' Note: We remind the reader that in this *Guideline*, the term HEPA is used as a general term to describe both HEPA and ULPA filters, unless otherwise noted.

As stated in Chapter 1.4.2, HEPA filters are grouped into various classes depending on their efficiency in removing airborne particles of a specific size. Filter classes range in efficiency from 99.95% to 99.999995%.

There are three international guidelines for the definition of these air filters:

- IEST-RP-CC001 (HEPA and ULPA Filters)
  This Recommended Practice (RP), IEST-RP-CC001, covers basic provisions for HEPA units as a basis for agreement generally between customers and suppliers in North America.

Under IEST-RP-CC001, HEPA and ULPA filters are tested using one or more method(s) as indicated below:

- HEPA and ULPA in an efficiency range of 99.97% to 99.999%: the filter may be tested in accordance with MIL-STD-282.[20]
- HEPA and ULPA in an efficiency range of 99.97% to 99.9995%: using particle counter technology in accordance with IEST-RP-CC007[21] (Testing ULPA Filters), the filter is classified based on the minimum efficiency of either the 0.1-0.2 μm or 0.2-0.3 μm particle size ranges.
- Super ULPA: in an efficiency range of greater than or equal to 99.9999%: using particle counter technology in accordance with IEST-RP-CC007, the filter is tested at the MPPS, determined in accordance with IEST-RP-CC021[22] (Testing HEPA and ULPA Filter Media).

Depending on the filter type, some are also scan tested for leakage in accordance with IEST-RP-CC034[23] (HEPA and ULPA Filter Leak Tests).

Based on IEST-RP-CC001, HEPA filter efficiencies range from 99.97% to 99.995%. ULPA filter efficiencies range from 99.999% to 99.9995% and Super ULPAs are $\geq$99.9999%.

HEPA (high-efficiency particulate air) filter: An extended-medium, dry-type filter in a rigid frame when tested at rated airflow having a minimum particle collection efficiency of 99.97% for 0.3 um mass median diameter of DOP when tested in accordance with MIL-STD-282.

ULPA (Ultra-low-penetration air) filter: An extended-medium dry-type filter in a rigid frame, having a minimum particle-collection efficiency of 99.999% (that is, a maximum particle penetration of 0.0010%) when tested in accordance with the methods of IEST-RP-CC007.

- EN 1822 (part 1) (High Efficiency Air Filters (EPA, HEPA and ULPA) – Part 1: Classification, Performance Testing, Marking)
  EN 1822 part 1 is a European norm for the definition, classification and manufacturers' qualification of EPA, HEPA und ULPA filter performance. Testing confirms the filters' retention efficiency against MPPS.

  HEPA includes filter classes H13 (min. 99.95% at MPPS) and H14 (min. 99.995% at MPPS)

  ULPA includes filter classes U15 (min. 99.9995% at MPPS), U16 (min. 99.99995% at MPPS) and U17 (min. 99.999995% at MPPS).

  Historically, EN 1822 parts 2-5 further described accepted test equipment and procedures, however in 2019 these were withdrawn and replaced by the adoption of ISO 29463 parts 2-5. Only EN 1822 part 1 was retained and continues to be valid as EN 1822-1:2019.

- ISO 29463 (parts 1-5) (High Efficiency Filters and Filter Media for Removing Particles from Air)
  This new international norm establishes an expanded classification of filters, test equipment and procedures based on EN 1822 part 1 and the now historical EN 1822 parts 2-5. The most important practical differences are:
  - Classification: Filters characterized by existing EN 1822-1 classifications E10-E12, H13-H14 and U15-17 are reclassified in ISO 29463 into smaller subgroups. See Table 8.3.
  - Test equipment and procedures: Regarding leak testing, ISO 29463 part 1 specifies five testing methods, while EN 1822 part 1 specifies three. Regarding efficiency testing, ISO 29463 includes provisions to allow for photometric testing while EN 1822-1 is limited to a particle counting method. Otherwise the methods outlined in ISO 29463 are similar to those of EN 1822.

Part 1 (ISO 29463-1): Classification, performance, testing and marking
This part defines 13 different filter classifications based on increasing retention efficiency performance.

Part 2 (ISO 29463-2): Aerosol production, measuring equipment and particle-counting statistics
Measurement devices such as laser particle counters with different channels and aerosol photometers are specified, but also particle generators creating defined dust and aerosols for filtration efficiency and leakage testing.

Part 3 (ISO 29463-3): Testing flat sheet filter media
This subpart defines the testing routine for filter media, including test sequences with monodisperse and polydisperse test aerosols to challenge filter flat sheet material. Particle detection by discrete optical particle counters is mandatory for polydisperse aerosols, while condensation nuclei counters can be used for monodisperse aerosol testing.

Part 4 (ISO 29463-4): Test method for determining leakage of filter elements
This test describes a leakage test for filter elements using a scan methodology, so local and global leak values are tested. The test is conducted under defined parameters for aerosol generation, particle detection and scanning speed. The filter element is tested at rated airflow, the pressure drop is recorded. Filter class depending on local or global leakage rates must be achieved.

Part 5 (ISO 29463-5): Test method for filter elements
This part describes the specific test set-up for efficiency testing of filter elements with mono- and polydisperse aerosols, including extra sections for membrane filters and charged filter elements. The test delivers a global efficiency value for the tested filter element, a pressure drop value at defined airflow and the corresponding filter class.

8.2 Filter Selection Criteria

Effectively removing microorganisms and other particulates from the gases that come into direct contact with aseptic products and packaging is the key function of any filtration strategy. This function or retention performance, (sometimes referred to as efficiency) is defined and categorized based on industry test standards (Chapter 8.1). It is typically the OEM's and end user's responsibility in agreement with filter vendors to select HEPA filters of appropriate classification that will deliver the required performance for aseptic/critical area filtration (Chapters 11.3 and 11.4).

Additionally, application requirements such as maintaining specified airflow during operation (resulting in a specified pressure drop), usable service life of the filters, and compatibility with the intended sterilization process must be considered.

The criteria for proper HEPA filter system selection are summarized here:

- filter classification according to relevant norms
- efficiency (particle retention performance)
- airflow volume and initial pressure drop
- design features and attributes
    - application compatibility
    - hydrophobicity
    - durability
    - toxicity
    - particle shedding
    - geometry and hardware fit
    - filter housing design
- economics and cost of ownership

- disposal: While disposal is not a key criterion for filter selection, users should give careful consideration regarding local disposal and legal requirements.

Filter selection should be based on a risk assessment of performance failures both during normal and worst-case scenarios.

8.2.1 Efficiency (Particle Retention Performance)

Retention performance describes the ability of air filters to remove a defined level of contaminants from the unfiltered air ("influent"), yielding a certain level of contaminants in the filtrate ("effluent").

Retention performance of HEPA filters is directly linked to the efficiency rating in accordance with the regionally accepted standard.

In EN 1822-1, all filter classes are defined by their overall efficiency against MPPS particles (Table 8.1). The Most Penetrating Particle Size must be determined individually before any efficiency testing. MPPS describes the particle size at which the filter exhibits its lowest retention capability, as a result of several particle capture mechanisms that vary in effectiveness depending on both particle size and air velocity (Chapter 6.4). Thus, it can be assumed that for particles smaller and larger than the MPPS, the efficiency will be higher.

In North America HEPA filters are described by the Recommended Practice (RP) IEST-RP-CC001. It describes eleven levels of filter performance and six grades of filter construction. When used in conjunction with other RPs, including IEST-RP-CC001, IEST-RP-CC002, IEST-RP-CC006, IEST-RP-CC007, IEST-RP-CC021, and IEST-RP-CC028, or other parts of EN 1822 or ISO 29463, these standards may be used to define the basis of an agreement between customer and supplier in the specification, procurement and testing of HEPA filters.

No direct comparison can be made between filters classified in accordance with EN 1822-1 and the IEST recommended practices. Table 8.2 provides a relative performance comparison only and is not intended to indicate any equivalence.

Table 8.1: HEPA Filter Classifications Based on EN 1822-1:2019

Filter Group	Integral value		Local value [a] [b]	
Filter Class	Efficiency (%)	Penetration (%)	Efficiency (%)	Penetration (%)
E 10	≥ 85	≤ 15	---[c]	---[c]
E 11	≥ 95	≤ 5	---[c]	---[c]
E 12	≥ 99,5	≤ 0,5	---[c]	---[c]
H 13	≥ 99,95	≤ 0,05	≥ 99,75	≤ 0,25
H 14	≥ 99,995	≤ 0,005	≥ 99,975	≤ 0,025
U 15	≥ 99,9995	≤ 0,0005	≥ 99,9975	≤ 0,0025
U 16	≥ 99,99995	≤ 0,00005	≥ 99,99975	≤ 0,00025
U 17	≥ 99,999995	≤ 0,000005	≥ 99,9999	≤ 0,0001

[a] See 7.5.2 and FprEN 1822-4.

[b] Local penetration values lower than those given in the table may be agreed between supplier and purchaser.

[c] Group E filters (classes E10, E11 and E12) cannot and must not be leak tested for classification purposes.

Table 8.2: Relative Performance Comparison of IEST-RP-CC001, EN 1822 and ISO-29463 Practices

IEST-RP-CC001, EN1822 & ISO-29463 Comparison

IEST-RP-CC001			
		Global Value	Local Value
Filter Type	Particle Size for Testing	Collection Efficiency %	Multiple of Global Efficiency %
		-	-
		-	-
		-	-
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**	>9.97	-
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**	>99.995	1.6
D	0.3*	>99.999	5
F	0.1-0.2 or 0.2-0.3**	>99.9995	5
G	.1-.2	>99.9999	10

EN1822 Classification			
		Global Value	Local Value
Filter Class	Particle Size for Testing	Collection Efficiency %	Multiple of Global Efficiency %
E10		>85	-
E11		>95	-
E12		>99.5	-
H13	MPPS	>99.95	5
H14	MPPS	>99.995	5
U15	MPPS	>99.9995	5
U16	MPPS	>99.99995	5
U17	MPPS	>99.999995	20

ISO-29463 Classification			
		Global Value	Local Value
Filter Class (Group)	Particle Size for Testing	Collection Efficiency %	Multiple of Global Efficiency %
			-
ISO 15 E	MPPS	>95	-
ISO 20 E	MPPS	>99	-
ISO 25 E	MPPS	>99.5	-
ISO 30 E	MPPS	>99.9	-
ISO 35 E	MPPS	>99.95	5
ISO 40 E	MPPS	>99.99	5
ISO 45 E	MPPS	>99.995	5
ISO 50 E	MPPS	>99.999	5
ISO 55 E	MPPS	>99.9995	5
ISO 60 E	MPPS	>99.9999	5
ISO 65 E	MPPS	>99.99995	5
ISO 70 E	MPPS	>99.99999	10
ISO 75 E	MPPS	>99.999995	20

* Mass median diameter particles (or with a count median diameter typically smaller than 0.2 µm as noted above).
** Use the particle size range that yields the lowest efficiency.

Table 8.3 shows the comparison between EN 1822-1 and ISO 29463-1 filter classifications.

Table 8.3: HEPA Filter Classifications in EN 1822-1 compared with ISO 29463-1

	EN 1822-1			ISO 29463-1			EN 1822-1 / ISO 29463-1	
Filter group	Filter class	Global/Integral value		Filter class	Global/Integral value		Local value	
		Efficiency (%)	Penetration (%)		Efficiency (%)	Penetration (%)	Efficiency (%)	Penetration (%)
EPA	E10	≥ 85	≤ 15				-	-
	E11	≥ 95	≤ 5	ISO 15E	≥ 95	≤ 5	-	-
				ISO 20E	≥ 99	≤ 1	-	-
	E12	≥ 99.5	≤0.5	ISO 25E	≥ 99.5	≤ 0.5	-	-
HEPA				ISO 30H	≥ 99.9	≤ 0.1	-	-
	H13	≥ 99.95	≤ 0.05	ISO 35H	≥ 99.95	≤ 0.05	≥ 99.75	≤ 0.25
				ISO 40H	≥ 99.99	≤ 0.01	≥ 99.95	≤ 0.05
	H14	≥ 99.995	≤ 0.005	ISO 45H	≥ 99.995	≤ 0.005	≥ 99.975	≤ 0.025
				ISO 50U	≥ 99.999	≤ 0.001	≥ 99.995	≤ 0.005
ULPA	U15	≥ 99.9995	≤ 0.0005	ISO 55U	≥ 99.9995	≤ 0.0005	≥ 99.9975	≤ 0.0025
				ISO 60U	≥ 99.9999	≤ 0.0001	≥ 99.9995	≤ 0.0005
	U16	≥ 99.99995	≤ 0.00005	ISO 65U	≥ 99.99995	≤ 0.00005	≥ 99.99975	≤ 0.00025
				ISO 70U	≥ 99.99999	≤ 0.00001	≥ 99.9999	≤ 0.00001
	U17	≥ 99.999995	≤ 0.000005	ISO 75U	≥ 99.999995	≤ 0.000005	≥ 99.9999	≤ 0.00001
Filtration efficiency measured at MPPS (most penetrating particle size)								

It is important to mention that HEPA filter class selection is determined both by the filtered air quality requirements for the aseptic application and the supply air quality to the filters. With appropriate air pretreatment according to manufacturers' and/or OEM recommendations, the minimum requirement for final filtration is to use the H13 filter class.

For an indication of suitable air pretreatment, see Chapter 2.2 and Figure 2.3.

8.2.2 Airflow Volume and Pressure Drop

Initial differential pressure serves as an indicator for correct assembly of filters at specified airflow. Specified and verified values are published by filter vendors for individual filter types. Operating ranges typically include an initial differential pressure (typically values of new filters at operating conditions) and a defined limit indicating the filter replacement.

HEPA filters are typically selected in aseptic systems due to their ability to handle a large volume of air at a low supply pressure and low initial "clean" pressure drop. The initial pressure drop at a given air velocity is an important performance characteristic. This information is typically listed in either pascals at an air velocity in cubic meters/hour (Pa @ m^3/h) or inches of water gauge (wg) at an air velocity in cubic feet/minute (wg @ CFM). The initial pressure drop is calculated from the difference of static pressure before and after the filter element at the rated airflow without particle load.

Initial pressure drop will vary based on retention performance. Generally speaking, the higher the retention, the higher the initial pressure drop. However, the overall design configuration of the HEPA filter plays a significant role in the resulting initial pressure drop (Chapter 5.2).

OEMs consider the contribution of the HEPA filter's resistance to the overall system static pressure when selecting the fans and motor that draw air through the filter. The initial pressure drop of HEPA filters is important to design an economic air fan operation. The resistance of a HEPA filter will be at its lowest when first put into service and will increase as particles are captured. To compensate and maintain desired airflow, variable frequency drive fans regulate airflow to maintain adequate velocity.

OEM machine manufacturers provide pressure drop ranges depending on design of airflow, piping and specified filter types. Maximum limits for pressure drops are given by filter manufacturers and should not be exceeded. When selecting replacement HEPA filters, do not exceed the OEM's design specifications for initial pressure drop.

8.2.3 Design Features and Attributes

8.2.3.1 Application Compatibility

All the raw materials used in the construction of the filter's components, including polymeric and rubber materials used in the gaskets, must be compatible with the type of gas, temperature and pressure of the production and sanitation process. The filter's physical integrity can be damaged over time due to continued exposure to incompatible materials or conditions.

Typically, in aseptic production that generally uses air at ambient temperature, there are no major concerns regarding compatibility with common filter media and hardware materials (glass fiber, PTFE, polypropylene, aluminum, stainless steel,) or rubber materials (silicone, EPDM, polyurethane). It is a different situation when temperatures are excessively hot or cold, or oxygen-enriched air is in use.

In applications where chemicals such as hydrogen peroxide are employed for the sterilization of HEPA filters, the filter elements must be able to withstand exposure to the chemicals at the temperatures, concentrations, and the anticipated duration of use.

All the raw materials used in the construction of the filter's components should not support the growth of bacteria or mold nor should the filter's performance be compromised by their metabolic byproducts.

8.2.3.2 Hydrophobicity

HEPA filters can be designed to operate in high-moisture environments close to 100% relative humidity but should not be subjected to direct contact with water or cleaning fluids. Wet filters should be dried as soon as possible and the conditions that caused the filter to become wet corrected.

While the component materials of the filter may not support the growth of bacteria or mold, filters that are wet for 48 hours or more could be subject to mold within the body of the media. Note: Filters that are allowed to dry after being wet may have a higher pressure drop when compared to their pressure drop before they were wet.

8.2.3.3 Durability

The service life of a HEPA filter depends upon the operating conditions of the system in which it is installed and is not a predetermined length of time. Assuming retention performance remains within specification and no weakening of the structure of the filter is observed, a common rule of thumb is to operate the filter until the differential pressure has increased to twice the initial pressure drop at rated airflow.

HEPA filters in systems with high efficiency prefilters can safely remain operational for years using this criterion. However, HEPA filter manufacturers should also publish a final pressure drop for their filters which should not be exceeded.

Notwithstanding the above, the service life of a HEPA filter may also need to be determined by sterilization cycles as outlined in Chapter 8.3.

The risks posed by repeated exposure to high temperature, pressure or chemicals have the potential to weaken components of the HEPA filter. Determining if the integrity of the filter is compromised by the number of sterilization cycles can be accomplished by testing individual components of the filter. Either the HEPA manufacturer or a qualified testing facility can offer guidance. In this situation, the service life of a HEPA filter would be measured by the number of cycles and not an increase in pressure drop or achieving maximum recommended final pressure drop.

8.2.3.4 Toxicity

HEPA filters in aseptic systems are not intended to come into direct contact with the product and therefore do not fall under the requirements of FDA 21 CFR 170[29] (Chapter 3.2).

EC 1935/2004 regulates all materials intended for direct and indirect food contact. For indirect food contact, as is the case with air, there are no test procedures and migration limits defined.

Notwithstanding the above, some HEPA filter manufacturers do provide direct or indirect food contact information in reference to EC 1935/2004, where applicable for their products. Overall migration tests should be done and reasonable limits defined to address carryover from gas-extracted substances into the food. Absence of harmful chemical components like phthalates, BPA, and/or formaldehyde is recommended.

8.2.3.5 Particle Shedding

The first line of defense in eliminating the possibility of particle and/or fiber shedding is to ensure that the actual airflow velocity is within the parameters of the filter.

Operating the system at an airflow velocity higher than specified can lower the retention performance due to particle shedding.

Similarly, operating a HEPA filter at temperatures higher than specified can weaken the effectiveness of the components of the filter, such as the potting adhesive that seals the media pack to the frame. Filter manufacturers should publish the continuous recommended operating temperature and include a higher ‘spike’ temperature rating acceptable for short durations.

The fibers which make up the body of the filter media should be bound together with a durable resin binder to minimize fiber shedding. The edges of the filter media, cut during production, should be embedded in the potting adhesive which prevents release.

8.2.3.6 Geometry and Hardware Fit

A filter's performance depends on correct installation. The HEPA filter's pressure drop causes air to seek a pathway less resistant than that of the filter media. When not installed properly, such as not seating the filter into the frame securely, a pathway for air to avoid passing through the filter media becomes available. The smallest pathways can allow dangerous particles to bypass the filter.

A gasket may be part of the housing but is typically attached to the filter as it is a rather inexpensive but critical component which should be exchanged after the filter's service life is complete. OEM manufacturers ideally design their systems in a way to provide adequate accessibility and convenience for the filter exchange. In case of dry gasket applications, a clamping mechanism should enable a uniform distribution of the clamping pressure to compress the gasket in a way that ensures long-term air tightness.

There should be sufficient distance upstream and downstream of the filter to avoid strong turbulence and uneven airflow distribution which could create bypass conditions or even damage the filter media.

8.2.3.7 Filter Housing Design

Filter housings must meet several requirements to support an efficient filter sterilization process and leak-free filtration during aseptic operation. Figure 8.1 illustrates a typical filter/housing installation.

Housing air inlet sections should provide a flow optimized design to distribute the incoming air on the full surface of the HEPA filter element evenly. If air is delivered only to small regions of the filter at high speed, the local air velocity can exceed the designed maximum air velocity for the filter element, resulting in a lower particle retention capability than specified.

Filter housing materials are chosen according to mechanical requirements and chemical resistance against the sterilization media of choice. State-of-the-art housings are made of stainless steel, such as DIN 1.4301 (AISI 316) or more resistant steel qualities such as DIN 1.4404 (AISI 316L). Surfaces should be smooth and designed to be sterilized with vaporized or atomized chemical sterilants such as hydrogen peroxide.

The housing needs the mechanical strength necessary to accommodate the pressure required to seal the filter to the frame by compressing the gaskets. HEPA manufacturers should provide the pressure amount required to ensure an adequate seal around the perimeter of the filter. Adjustable clamping devices are typically used which include mechanical stops to protect from excessive pressure damaging the gaskets and allowing bypass.

Filter housings should provide guiding elements for filters to facilitate replacement and positioning. Connections for monitoring devices such as pressure or flow monitoring need to be tight and manufactured from inert materials as they will be exposed to sterilizing agents as well.

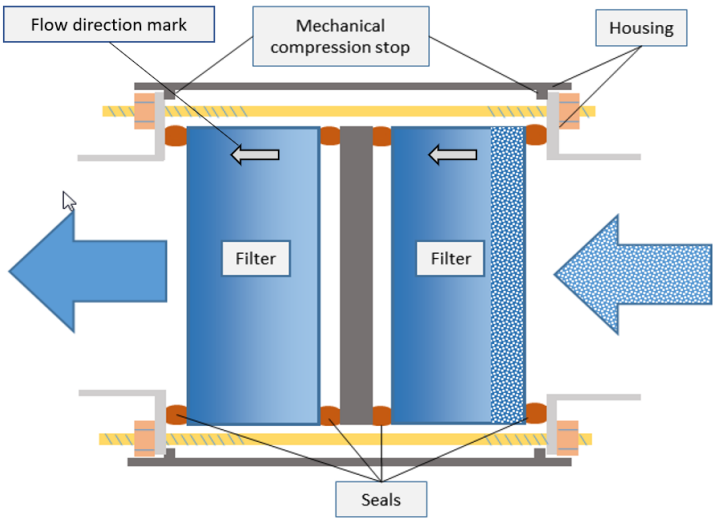

Figure 8.1: Typical HEPA Filter/Housing Installation
Source: Courtesy of SIG Combibloc

8.2.4 Economics and Cost of Ownership

HEPA filters are among the most expensive classes of air filters. They are typically manufactured in controlled environments, made of high-quality raw materials, undergo time consuming individual testing/certification and are shipped in protective cartons. As such, utilizing the full service-life capability of the filter is suggested to obtain maximum value.

Chapter 8.2.3.3 outlines several parameters for determining the usable service life of a HEPA filter based upon pressure drop or number of sterilization cycles, which varies according to the process utilized for individual applications. Sufficient research should be undertaken to arrive at the maximum service life that satisfies the acceptable level of risk.

That research should include calculating the additional cost of energy consumed to achieve the required airflow when using HEPA filters with high initial pressure drop. Additionally, Chapter 8.2.2 mentioned aseptic systems are often designed with variable frequency fans that maintain adequate airflow by increasing the RPM of the fan. With each increase in RPM, more energy is consumed. Selecting HEPA filters with the performance characteristic of a slow loading curve is desirable.

8.3 Sterilization of HEPA Filters

8.3.1 Chemical Sterilization

HEPA filters are built based on glass fiber layers or other inert materials, as described in Chapter 5.2.1.

Because of the filter media's three-dimensional structure, sterilant must penetrate completely throughout the media. The sterilization is always designed as "*in situ* sterilization" meaning the filters are not removed but remain securely latched in place as they are during production. During this sterilization sequence, the air ventilation ductwork is likewise exposed to the sterilant.

Aerosol or gas sterilization with chemical agents is a common technique for sterilizing HEPA filters.

The general sterilization principle may include several spraying steps, where a chemical with sufficient sterilizing properties is sprayed on the filter surfaces, or evaporated before contacting the filter. From there, the sterilant is either pressed through the filter material with the help of compressed air or an air fan, in the direction of the filtration pathway or in reverse direction.

After application of the sterilant, the process needs some reaction time for completion, followed by a gas flushing to remove remaining residues. It is critical, that all filters are penetrated with the sterilant during the process. It may be necessary to install separate injection ports before, after or in between single filters of a filter cluster.

While the use of sterilants like formaldehyde, chlorine gas, n-propanol or others is still a common practice in the pharmaceutical industry, most filter sterilization applications on HEPA-protected systems in the food industry are conducted with hydrogen peroxide due to its excellent penetrating properties, worldwide availability and low environmental footprint.

8.3.1.1 Hydrogen Peroxide Sterilization

Hydrogen peroxide is widely used for HEPA filter inline sterilization, either mixed with air and vaporized or sprayed as mist at ambient temperatures or at slightly elevated temperature. The elevated temperature provides a possibility for higher amount of sterilant in the gas phase due to higher vapor pressure.

The sterilization effect increases with temperature while hydrogen peroxide decomposition is accelerated as well, especially in contact with metal surfaces or organic material. Figure 8.2 illustrates the decomposition of the hydrogen peroxide.

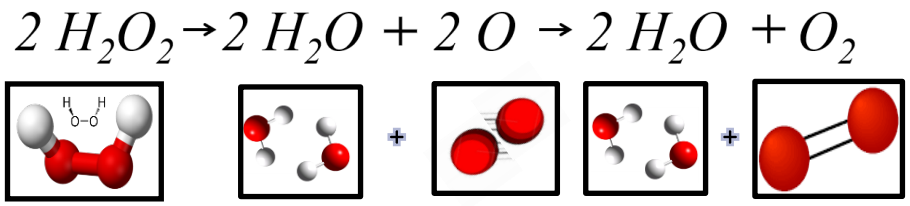

Figure 8.2: Decomposition of Hydrogen Peroxide
Source: Courtesy of SIG Combibloc

Hydrogen peroxide vapor is generated by evaporation or aerosolization of concentrated (*e.g.,* 30–35%) aqueous hydrogen peroxide solution through conductive heating or mixture with heated air.

Some processes (at low peroxide vapor concentrations & temperatures) require initial dehumidification prior to introducing the peroxide vapor into the space. While some processes allow micro-condensation to occur, accumulation of condensation should be avoided since the condensate could be very concentrated and the concentration of peroxide in the air could drop as a result of condensation.

In pure vapor phase sterilization at high peroxide concentration (*e.g.,* 1-10%), the application temperature should be securely above the dew point of the gas mixture, so the peroxide stays in the vapor phase and is able to penetrate the filter material together with the vaporized water.

In vapor phase hydrogen peroxide can rapidly penetrate biological cells collected on filter material fibers, frame or seals.

Using hydrogen peroxide at lower concentration in vapor phase, the application temperature can be reduced according to the peroxide saturation curve, but the reaction time must be increased to

compensate. The typical duration of hydrogen peroxide sterilization cycles is between 10 and 30 minutes, followed by adequate ventilation.

The same applies for any sterilization by peroxide mist, generated from liquid peroxide. For these processes, a reduced penetration speed through the filter and the distribution probability of small droplets in the perpendicular direction to the flow direction must be considered. Since liquid peroxide solutions contain 65% water, the pressure resistance on the wetted filter material must be considered for penetration transport through the filter package.

The advantage of a liquid application is a negligible thermal impact on filter and seal materials during sterilization. It is known that over time, hydrogen peroxide adsorbs onto exposed surfaces and desorbs during aeration (or ventilation).

Special attention must be paid to the ventilation steps after completion of the sterilization process. The removal of remaining hydrogen peroxide from filters and filter housing can be facilitated by heated gas flow through filters but will take some time depending on the applied peroxide amount, the gas flow volume and gas temperature, especially for liquid spray sterilization.

If filter, bonding or seal materials are used, which are capable of absorbing hydrogen peroxide of significant quantity, it must be ensured, that the sterilant is removed before start of commercial production, so the aseptically filled product contains less than 0.5 ppm according to 21 CFR 178.1005.[30]

It should also be noted, that hydrogen peroxide specification is important, as stabilizer components and impurities which may be present may plug the HEPA filters depending on filter size, stabilizer type and quantity.

8.4 Other System Design Considerations

8.4.1 Redundant Filter Arrangements

Typically, double filter set-ups are used to provide redundancy in case of filter defects and reduce the risk of loss of commercial sterility due to filter failure. As an additional benefit, overall efficiency is enhanced by sequential filtration as the filter closest to point of use is receiving sterile filtered air. It is common practice to exchange filters installed in series at different intervals to minimize the failure probability of the filters at the same time. Usually, the exchange occurs when a portion of the full expected lifetime of the filter is reached, based on the differential pressure rise across the filter, which indicates the degree of contaminant loading. New filters should be installed as the final filter in the series closest to the point of use; the previously used final filter is moved to the second (upstream) position. The rationale for installing the newest filter as the final filter is to minimize risk as it is the “cleanest” filter (no contaminant load) and therefore the most robust.

Filter to filter seals need to have an intermediate flange to provide a defined sealing area for both attached filters. Position marks or guides on the housing should provide a repeatable positioning of filter elements. Filter elements have a flow direction, which is displayed on the filter frame and needs to be respected during assembly of filters into the housing (Figure 8.1).

Dedicated training or clear instructions need to be prepared by filter vendors or OEM equipment manufacturers to facilitate filter changes by operators or service personnel. Simple visual verification of positioning by Poka-Yoke means is preferred to provide the same conditions as validated.

Leak testing on filter clusters needs special devices to detect gaps between seals and the housing. Fog generators can be used to visualize escaping air during operation under pressure.

8.5 Validation of HEPA Filter Classification and Performance Claims

Air filters used in aseptic production must deliver the required performance to ensure desired outcomes reliably and repeatedly: namely, to achieve filtered air sterility, resulting in commercial sterility of manufactured products.

There are detailed norms and test methods for identifying and validating the classification of HEPA filters (Chapter 8.1). These norms vary with regard to aerosol generation and detection methods, and there are many papers written on the subject. For purposes of simplicity, we limit ourselves here to describing validation according to the ISO 29463 standard.

See Chapters 8.5.1 and 8.5.2 for validation of flat filter material and filter elements to satisfy the norm.

Each filter element that is claimed to meet the validated standard must be tested by manufacturers to prove leak tightness. In addition, manufacturers may choose to provide a global efficiency value. Chapter 8.5.3 describes the scan test that confirms and documents the filter's leak tightness as part of its quality release criteria. Documentation is provided on shipment or upon request. It is not recommended to install a filter without first reviewing this documentation.

The claims generated from validation and manufacturing release testing comprise:

- filter classification according to relevant norm
- efficiency (airborne particle retention performance)
- leak tightness according to relevant norm
- initial pressure drop
- rated airflow

8.5.1 Validation of Flat Filter Material

During the first development phase of filter elements the fractional efficiency of the foreseen flat sheet filter medium is measured with polydisperse aerosols, and the particle size at which minimum efficiency occurs (MPPS) is determined to ensure that it can be used for future testing with monodisperse aerosols.

The MPPS mainly depends on the type of filter media in use; particle sizes between 0.1 and 0.2 µm are typical for glass fiber media, while PTFE membranes show the lowest retention in the area below 0.1 µm.

This testing procedure delivers the filter material's global efficiency (particle retention) and the MPPS, which is then used as reference for future testing of filter elements made from this material.

In practice, representative sections of the flat filter material are evenly loaded with an aerosol of solid or liquid particles at very high level under defined air flow, temperature and humidity, and the upstream particle load and size is measured. The same or a second counting device connected to the downstream side of the filter measures the amount and size of particles passing the filter. This data yields the classification of the flat filter material. It is important to mention, that during any aerosol overloading of filters, the concentration at the sampling points must be within the linear range of the detectors. Typically, upstream particle loads are diluted in several steps to be in this range, while downstream of the filter a statistically significant number of particles must be present at the detector.

These tests, according to ISO 29463-3 are repeated several times to achieve meaningful results: test conditions, aerosol generation and detection records are kept as validation documentation.

8.5.2 Validation of Filter Elements

Filter elements incorporate the flat filter material and are configured in dimension, shape, layer thickness, surface area and orientation to meet application requirements (see Chapter 5.2).

During development, validation of filter element performance includes tests of global efficiency and pressure drop at rated airflow under conditions of overloading the filter beyond full retention. These tests, according to ISO 29463-5 are performed on a defined number of identical filter elements for classification purposes, delivering compliance data with the norm.

8.5.3 Manufacturing Leak Testing of Filter Elements

To document the leak tightness of manufactured filter elements manufacturers typically use a non-destructive scan test described in ISO 29463-4. Due to the nature of this test it cannot practically be duplicated in aseptic food and beverage equipment at OEM or end user sites.

The leak test test is used for quality release of each filter element; a compliance statement to ISO 29463-4 indicates that the filter is leak-free.

The global efficiency can be calculated from the scan test value. The global value confirms each filter's removal efficiency (and conversely its penetration efficiency), which defines its classification. The term "global value" is also expressed as "overall value" or "integral value."

8.5.3.1 (Leak/Scan) Test

The purpose of a leak/scan test is to identify individual leaks in HEPA filters, which can affect the overall retention performance. The basic concept of leak testing is, under rated airflow with a defined and measured particle concentration in the influent (upstream) air, to scan the effluent (downstream) side of the filter element with overlapping strokes over the face of the filter. Connected to the scanner is a measuring device such as a particle counter or photometer looking for any localized particle penetration that exceeds the acceptance criteria.

The Recommended Practice (RP) IEST-RP-CC034 and two standards, EN 1822-4 (historical) and ISO 29463-4 cover definitions, equipment, and procedures for leak testing of HEPA filters in the factory as they are produced.

While HEPA filters must pass one of the five leak test methods described in ISO 29463-4, ULPA filters must be tested exclusively using the scan method. Practical alternative leak testing methods are the oil thread leak test, the efficiency leak test (0.3-0.5 µm) and the photometer leak test.

The results from the scan test deliver data about leak tightness, as well as local efficiency, global efficiency, and pressure drop at rated airflow.

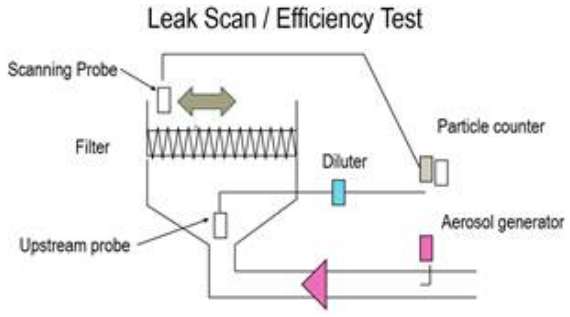

Figure 8.3: Diagram of a Typical Leak/Scan Test for HEPA Filters
Source: Courtesy of Camfil Corporation

8.5.3.2 Global Efficiency Test

A classified filter element is tested for compliance with the required retention rate by a Global Efficiency Test under rated airflow. Test execution includes measurement of the upstream and downstream particle concentration at defined MPPS using a photometer or an optical particle counter. From this data the global (overall or integral) particle removal efficiency can be calculated. HEPA filters are overloaded with mono- or polydisperse particle aerosols according to their designed efficiency class to ensure detection of statistically significant particle numbers passing the filter at MPPS.

There is a Recommended Practice (RP), IEST-RP-CC007 along with two standards, EN 1822-5 (historical) and ISO 29463-5 that cover all the details concerning Global Efficiency Testing, including but not limited to definitions, equipment, and procedures for efficiency testing HEPA filters in the factory as they are produced. It should be noted that both EN-1822-5 and ISO 29463-5 include allocations to allow for the calculation of a filter's global efficiency utilizing the local efficiency (leak/scan) testing data.

When a Global Efficiency Test is desired at the end user site, some OEMs add test ports on the aseptic machine before and after the filters to enable carrying out the test.

8.5.4 Pressure Drop Claim at Rated Airflows

During the validation work (flat material, filter elements) or manufacturing scan testing described in Chapter 8.5, documentation of pressure drop at the established rated airflow is mandatory, as particle retention is influenced by the air velocity. The pressure drop claim is derived from this data.

9 Validation of Air Filters in Aseptic Systems

Chapters 7.5 and 8.5 discussed the filter claims validation work done by filter manufacturers, to ensure that filters meet performance requirements and stated claims.

This chapter describes the design, qualification, and validation steps undertaken by aseptic equipment manufacturers and the end users to ensure a correct and functioning aseptic/critical area filtration process.

To facilitate better understanding, Figure 9.1 provides a conceptual overview of the different aspects of validating air filters in aseptic systems. Individual approaches may vary.

Authors' Note: We remind the reader that to facilitate understanding in this *Guideline*, we refer to all sterilization processes, whether they are for equipment, air, product or packaging materials, as "sterilization," understanding that this term, based on its context, can mean:

- pre-sterilization of equipment, including filter assemblies
- sterilization of air, product and packaging materials

9.1 Process Design and Machine Process Validation

Process design includes filter selection and integration into the aseptic equipment. Selection of filter types, and integration with machine components such as tanks, aseptic zones or other functional areas determines the sterilization and operation process design according to state-of-the-art aseptic principles.

This design phase can either be implemented by the OEM or in close collaboration by OEM and end user at the machine manufacturer's facility. Another option is the implementation of these steps at the end user's facility.

In any case, a Design Qualification after completion of process design is mandatory to ensure fit for purpose integration of filters into aseptic machine equipment and controls.

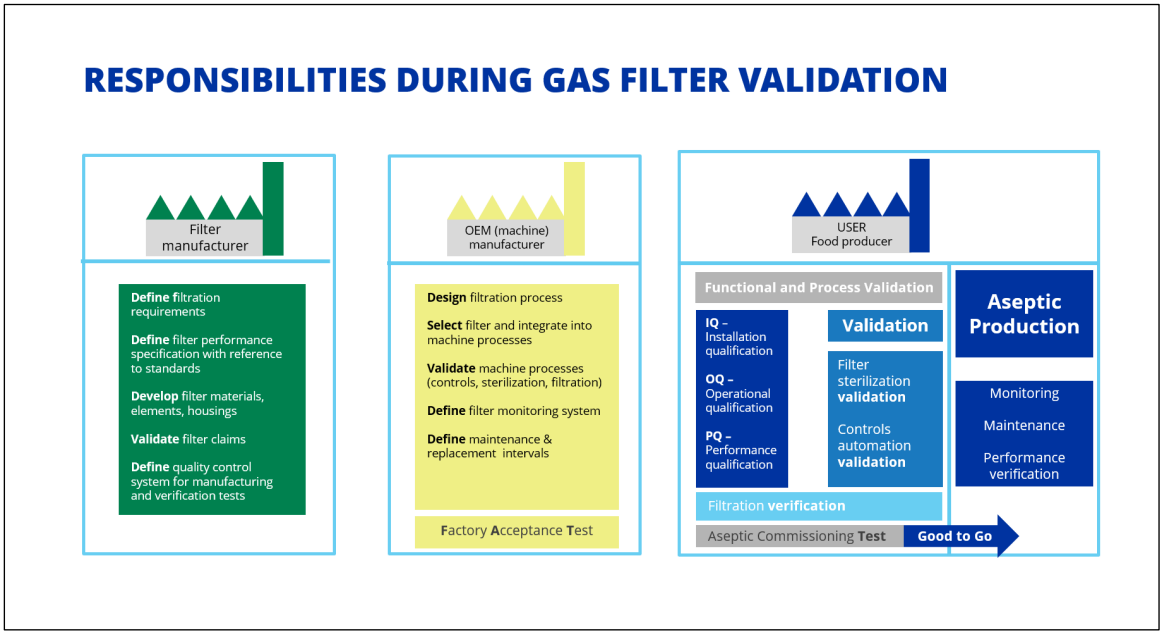

Figure 9.1: Conceptual Overview of Responsibilities During Air Filter Validation
Source: Courtesy of SIG Combibloc

As part of the Design Qualification, visual checks of filter-related components for the aseptic equipment must include:

- filter housings: type, dimension, quality of welding seams, smoothness of filter locking system in housing, sealing areas with mechanical stop for defined seal compression
- filter cartridges: clean, undamaged condition; correctness of fit into housing; assembly in correct flow direction
- drain valves, condensate traps: position, feedback sensors
- temperature and pressure sensors: type, position, identification label, calibration certificates, proper resolution and sensitivity according to operating range
- sterilization agent supply: type, position, feedback sensors on valves

In some cases, a machine process validation may be conducted at the equipment manufacturer's site; this is considered to be a prevalidation. Such an approach would mainly include an Automated Control System Validation (Chapter 9.2.2.1) and a Filter Sterilization Validation (Chapter 9.2.2.2).

While pre-validated systems are supplied to the end user with a complete documentation of specified filters, sterilization sequence and microbiological validation data under challenge limit conditions, systems which have not been validated before commissioning need to undergo this step at the end user site before proceeding with any aseptic commissioning runs.

During Factory Acceptance Tests (FAT) at the equipment manufacturer's site, a design qualification can be carried out involving a review of programmed process steps during sterilization, production, cleaning, and during transitions and ramp-up phases to ensure that filters are kept within the specified operating range during sterilization and filtration processes.

If systems are not pre-validated, sterilization and filtration program sequences are defined at the end user site to adequately sterilize the filter assembly and operate the filters according to filter manufacturers' instructions. Further, a full-blown functional and process validation (Chapter 9.2) must be carried out.

9.2 Functional and Process Validation

User Requirements (UR), Functional Requirements (FR) and Design Requirements (DR) for aseptic equipment form the basis against which Functional and Process Validation is executed at the end user site. This includes Qualification steps concurrent to Validation activities.

9.2.1 Qualification Steps

Qualification is a process undertaken at the end user facility, by the equipment manufacturer and the end user. It is primarily concerned with verifying facility and system aspects that can impact product quality. It is done during installation of an aseptic system at first start-up, to ensure the system delivers the expected performance. It includes several mechanical and microbiological tests of the overall aseptic system, but for the purpose of this *Guideline*, only the parts related to qualification activities for aseptic air filtration will be considered.

Execution of procedures described in this document does not allow simplification of the overall equipment validation, as we are focusing here primarily on filter-relevant topics.

With regards to sterilizing air filtration, Qualification refers to activities that generate data and evidence that the filtration system is able to:

- operate according to design specifications
- deliver the predicted sterilization results when operating under design and/or challenge conditions
- deliver consistent and repeatable filtration results when operating under design and/or challenge conditions

This work focuses especially on equipment and processes necessary to sterilize, operate and monitor air filtration units.

Qualification includes:

- Installation Qualification (IQ)
- Operation Qualification (OQ)
- Performance Qualification (PQ)

Qualification also includes commissioning activities ensuring that facilities, systems, and equipment meet established design requirements and stakeholder expectations. Commissioning is completed with an Aseptic Commissioning Test prior to commercial production.

9.2.1.1 Installation Qualification (IQ)

Installation Qualification verifies and documents that the equipment and system is installed per approved specifications.

The OEM should install each individual component of the system in a manner that complies with the supplier recommendations, technical specifications, standards, codes, and regulations. Proper installation of the equipment must be verified. This will help ensure the safety of personnel, minimize risk of damage to the equipment, and allow for a quicker start-up.

Specifically, regarding filtration, attention should be given to installation details such as:

- Before installing filters in the housings, make sure they are clean and not damaged.
- When installing, do not use lubricating oil or grease as these compounds can harbor dirt and microorganisms.
- Verify that correct parts are installed.
- Verify proper fit of the filters in the housings: A loose fit can be a sign of improper installation, an issue with the filter element, or even with the filter housing itself.
- Verify proper orientation of the components for flow as well as drainage of condensate.

- Confirm installation of all instrumentation necessary for monitoring the sterilization and performance of the filters; these sensors should be checked for proper position, functionality and calibration.
- Complete integrity testing (cartridges, Chapter 10.1), or leak tightness testing (HEPA filters, Chapter 10.2) to verify not only proper performance of the filter, but also that no issues were created during the installation such as damaged O-rings or gaskets and everything is tight.

9.2.1.2 Operational Qualification (OQ)

Operational Qualification verifies and documents that the system or sub-system operates properly as intended, and is capable of repeated operation within the limits defined by the Functional Specification.

Start-up and commissioning work is typically part of the initial stages of OQ or a prerequisite for OQ depending on end user preferences. Depending on the application, some of this work may be completed at the equipment suppliers manufacturing site. During this initial work, the system is run through multiple repetitions of various steps as defined in the Design Qualification. For filtration, these are typically sterilization, drying, and filtration operation.

During each operational phase, minimum and maximum ranges for parameters such as temperature, pressure, and time for each phase should be evaluated and compared to the filter suppliers' recommendations. While the filter suppliers' recommendations are a good target, it is not always practical to precisely meet those recommendations. Because of this, it is important to understand filter claims validation (Chapters 7.5 and 8.5).

It is recommended that integrity testing of cartridge filters and leak tightness evaluation of HEPA filters be performed during OQ. Methods for implementing these activities in the field are described in Chapter 10. This will build a history of performance for the specific application as well as identify issues with system performance which may lead to physical modifications of the system, programming changes, or even a change in filter supplier to correct. Some common issues that may shorten the life of the filter are:

- inadequate condensate removal
- temperature/pressure abuse
- improper cooling/drying of filters
- poor filter quality

9.2.1.3 Performance Qualification (PQ)

Performance Qualification is the last step in the Qualification process. It is carried out after OQ at the end user location, with or without the involvement of the OEM depending on contractual agreement, once the aseptic system has been released to produce commercial product.

PQ deals mainly with demonstrating the performance of the system using similar variations of product recipes or packaging materials or sizes. For example, if the system was validated on whole milk, a similar product would be 2% milk. Or if the system was validated on liter-sized containers, a similar package would be a 200 ml-sized package. Another aspect of PQ is measuring overall equipment efficiency to determine whether the equipment is performing as designed. System adjustments can be made as a result of PQ.

PQ may additionally be done on a regular basis over a period of time, based on legally required or internally defined routines, to monitor and verify ongoing performance in production. It is necessary to evaluate both the overall system and finished product performance over longer production runs. Additional sampling and testing is usually a requirement, but varies depending on the policies of the end user. This testing verifies that all aspects of the system work together to provide a commercially sterile finished product and package.

Performance testing may include, but is not limited to:

- finished product testing for commercial sterility

- integrity testing of filters
- particle count testing within the sterile zones of the equipment
- monitoring filter pressure drop over time

9.2.2 Validation Activities

Validation is a method of establishing documented evidence that shows that the stakeholders have a high degree of assurance that the manufacturing process will consistently yield a product of predetermined quality. Specifically, the Process Authority will be responsible to ensure proper validation methods.

Validation activities include both Automated Control System Validation and Microbiological Validation. This work is intended to prove the system can deliver sterilized air within the aseptic system in a consistent and repeatable manner.

Further guidance on process validation considerations, critical factor determination, microbiological challenge testing techniques and interpretation of results can be found on IFTPS Document G.005.V1 (IFTPS-A-V Guideline).[31]

9.2.2.1 Automated Control System Validation

Automated Control System Validation should be completed before Microbiological Validation of the system. This testing will ensure the equipment can operate appropriately and deliver all critical parameters impacting container sterilization, filling system and aseptic zone surface sterilization, and sterility maintenance. These must be challenged against the critical limits defined in HACCP and/or the Functional Specification. Automated Control System Validation should follow NFPA Bulletin 43-L[32] and for filtration focus on sterilization and production parameters and related transitions between sequences.

Aseptic lines and associated individual units like product sterilizers, aseptic tanks or filling machines are operated and controlled by designed program sequences, stored and integrated in independent or connected PLC units. Operating parameter settings, critical limits, program sequences for sterilization, production and cleaning are part of these programs as well as interface communication signal modules to secure safe operation during all operating states of individual units. It is common practice to adapt program sequences to interface with existing equipment or integrate equipment into Manufacturing Execution Systems (MES). These changes need to be validated prior to commercial production.

During Automated Control System Validation, each critical sensor is tested for its functionality to the intended use and the appropriate corrective action is taken by the automated system when necessary. Tested limits and logic for filtration may include, but are not limited to:

- temperature
- time
- sterilizing media chemical concentration
- sterilizing media flow rate
- sterilizing media residence/contact time
- filter counters controlled by the automated system including the prevention of sterilization if the number of sterilizations has exceeded the maximum defined in HACCP and/or Functional Specification
- abort processes, re-sterilization sequences
- manual override options

Aside of checking relevant program sequences, Automated Control System Validation should challenge signals, equipment states and limits:

- Challenge program transitions, critical factor set-points, alarm and limit values.
- Check monitoring of critical factors during sterilization and operation phases (*i.e.,* air pressure, sterilizing media temperature, valve positions, filter exchange cycles).

- Challenge abort processes, re-sterilization sequences, manual overriding options.

Documentation of program versions together with challenged functions and parameters is necessary to verify existing sequences against the specification.

9.2.2.2 Microbiological Validation / Filter Assembly Sterilization Validation

Microbiological Validation is conducted after Automated Control System Validation and answers the question: does the process, defined by program sequence, signals, parameters and controls, render the system commercially sterile?

Microbiological Validation for filters primarily involves proving and documenting that installed filter assemblies can be appropriately sterilized (Filter Assembly Sterilization Validation). In some cases, end users additionally validate the sterility of the filtered air, however most rely on the Filter Claims Validation supplied by filter vendors (Chapters 7.5 and 8.5).

As already indicated, equipment manufacturers might have already validated filter sterilization during Factory Acceptance Tests (FAT) prior to commissioning or provided validation data of identical equipment with the same process. At minimum, this prevalidation data is useful to provide assurance the system can perform before shipment of the equipment. Typically end users rely on this data and forego carrying out a further full-blown validation, replacing it instead with simpler verification steps, provided accuracy, repeatability and integrity criteria for validation data are met. Others consider it of critical importance that the system is fully validated as installed on site at the end user location and run a microbiological sterilization validation for installed filter arrangements.

Filter Sterilization Validation can be performed with Biological Indicator (BI) microorganisms. It should be mentioned, that microbiological validation is at the discretion of the OEM and/or end user; other methods such as time/temperature validation approaches for saturated steam sterilized systems can be implemented. These include checking the installation and verifying that the cold spot indicators are indeed at the cold spots, and required time/temperature exposure is reached.

For preparation of microbiological validation, BI microorganisms are either inoculated directly on filter or housing surfaces or on aluminum or paper strips, which are taped on the mentioned surfaces or inserted inside the filter or filter housing, surrounding pipework and downstream aseptic zones (Figures 9.2a, 9.2c, 9.3a, 9.3b). Spore strips will indicate spore survival after a time/temperature or chemical exposure to the sterilizing agent. An appropriate protocol must be developed for this testing which defines suitable microbiological challenge locations (Chapter 9.2.2.2.1).

For cartridge filters, the typical indicator for saturated steam sterilization is *Geobacillus stearothermophilus.* For HEPA filters, a typical indicator for chemical sterilization is *B. atrophaeus.* For further information, refer to IFTPS Document G.005.V1 (IFTPS-A-V Guideline).

Microbiological Validation must be conducted under worst-case conditions to challenge the process efficacy and demonstrate adequate reduction of microorganisms. An appropriate protocol must be developed for this testing which defines critical limits to reflect worst-case conditions (Chapter 9.2.2.2.2). An example of a critical limit is steam temperature, wherein the lowest acceptable time/temperature values must not be exceeded *(e.g*., 121 °C, 250 °F). Temperature charts must be kept to complete validation process documentation (Figure 9.2b).

In addition to spore strips, autoclave strips may be used as temperature indicating devices (TID) (Figure 9.2c). The strips change color when the defined steam temperature is reached.

A minimum of three successful and sequential repetitions are required on this step. For the filters, the following parameters should be challenged:

- cartridge filters (where sterilizing agent is typically steam)
    - sterilizing agent temperature and application time: (*e.g.,* minimum 121 °C (250 °F), for 15 min) (Chapter 7.3.1.3.2)
    - deaeration and depressurization phase
- HEPA filters (where sterilizing agent is typically hydrogen peroxide)
    - sterilizing agent chemical concentration, flow rate, application time, residence/contact time, and phase characteristics (*e.g.,* vapor, liquid, spray, fog or mist)

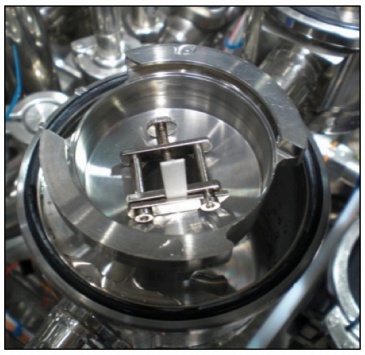

Figure 9.2a

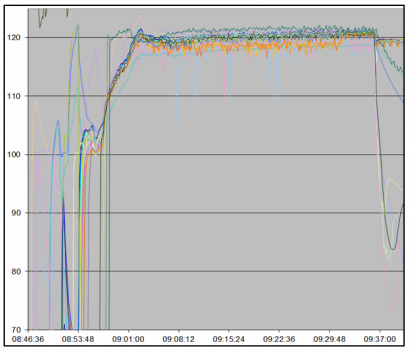

Figure 9.2b

Figure 9.2c

Figure 9.2: (a) Interior Bottom of Filter Housing, with spore strip; (b) Steam Sterilization Temperature Diagram, part of validation documentation, showing maintenance of minimum steam temperature (worst-case condition) of 121 °C (250 °F); (c) Interior Top of Filter Housing, with spore strip and autoclave strip
Source: Courtesy of SIG Combibloc

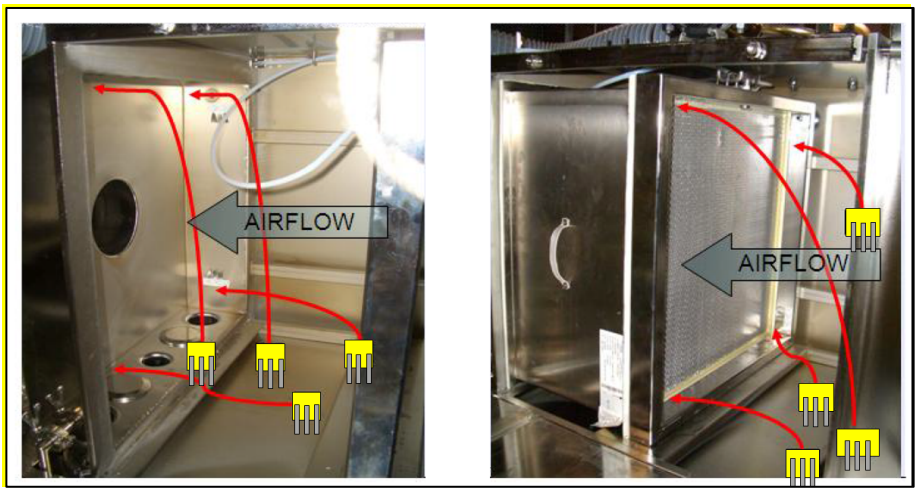

Figure 9.3a

Figure 9.3b

Figure 9.3: (a) Interior HEPA Filter Housing, with spore strips; (b) Spore strips between redundant filters
Source: Courtesy of SIG Combibloc

9.2.2.2.1 Microbiological Challenge Locations

Since it is impractical to submit the entire surface of the filters and housings to the microbiological challenge, it is critical to identify locations that are most likely to receive a minimum or worst-case process.

This identification must be based on an understanding of the sterilization process. For filter sterilization, the decision factors include, but are not limited to:

- temperature distribution, uniformity, stratification
- steady-state and transient contact times
- sterilizing agent concentration, phase, make-up rate
- sterilizing agent flow
- heat transfer characteristics
- filter media properties
- presence of wells or closed ends
- geometric restrictions
- preferential paths for sterilizing agent flow
- shielding/shadowing of surfaces from sterilizing media
- materials of construction, fabrication and layout

Preliminary testing may be necessary to define where the appropriate cold spots and shadow zones actually are for the challenge tests.

9.2.2.2.2 Worst-case Conditions

Testing conditions for the sterilization process must be based on critical factors, operational ranges defined in HACCP and the Functional Specification. It is important to remember that the worst-case/challenge condition is typically not the critical limit and must be clearly defined for each parameter. These are typically chosen to provide a level of safety for normal operation. The following defines some of this:

- Operational Set Point: the target for a parameter during operation in normal steady state
- Critical Limit: the limit which once exceeded, will deviate the process from a sterile or aseptic condition
- Challenge Condition or Worst-case Condition: a limit applied during Microbiological Validation to deliver a lower sterilizing effect than what would be expected at the Critical Limit

9.2.3 Aseptic Commissioning Test

Commissioning is a methodical, documented process undertaken at the end user facility to ensure that facilities, systems, and equipment meet established design requirements and stakeholder expectations. Commissioning verifies the following:

- What was specified was installed.
- The equipment functions properly.
- The equipment was successfully turned over to the user.

Aseptic Commissioning Test is an incremental part of the on-site Qualification program typically carried out between OQ and PQ and before any commercial production. The production line is run under validated conditions to confirm that the line is capable of meeting the required acceptance criteria for commercial sterility and sustaining these results with statistical repeatability. This test allows implementation of challenge conditions and provides evidence the system complies with the Functional Specifications in all main operations:

- equipment sterilization
- product sterilization
- package material sterilization
- sterility maintenance

This test verifies the performance of sterile air filters during equipment sterilization and generation of sterile air to maintain sterility of the line components during production.

Ideally three successful and sequential repetitions are required on this step. Some companies will do less, but will do sampling of initial production to verify required criteria are met. The number of samples and incubation conditions should be defined upfront to confirm the commercial sterility of the aseptic product.

The Aseptic Commissioning Test should be executed with the equipment adjusted to operational conditions and with product similar to the one expected to be produced. This can be a simulant product, within the same pH range, that would behave similarly to the actual product in terms of microbial growth, or an actual product.

After an equipment sterilization process, the simulant or actual product is sterilized in the product sterilization system and sent to the downstream aseptic equipment eventually ending up at the aseptic filler. The sterile product is then aseptically filled into the prescribed number of containers and the containers sealed.

Downstream aseptic equipment may include an aseptic tank used as a buffer between the sterilization system and the aseptic filler. Compressed air (or nitrogen) may be introduced into the aseptic system; it maintains a sterile overpressure in the tank. The air is sterile-filtered via a cartridge filter cluster connected to the top of the aseptic tank or in the valve cluster next to the aseptic tank. The product is conveyed from the tank to a pre-sterilized filler, by air pressure or by an aseptic pump downstream of the aseptic tank.

When aseptic tanks are in use, further challenge conditions could include forced air transport through the filters by changing the setpoints for tank pressure, one method to simulate changing pressure or tank breathing situations during emptying and filling aseptic tanks during production. Not all systems include an aseptic buffer tank.

It is common practice, that some product is kept for more than 24 hours inside the sterile zones of the process and filler, either standing still or filled in small sequences with longer breaks in between to challenge the maintenance of sterility over the typical production cycle.

For HEPA-supplied zones, the sterile overpressure or airflow setpoint can be set to low limit conditions and back to normal setpoint in order to simulate variations during operation. Start/stop conditions, forming containers *versus* not, splicing material, or even manually adjusting set points are some of the additional relevant scenarios that could be tested.

Other challenge conditions can be defined to simulate a wide range of expected production situations.

Filled containers are kept as samples and incubated at growth temperatures/times chosen to maximize the likelihood of detection of relevant microorganisms in the specific product.

The sterility of each sample is confirmed by one or a combination of inspection methods such as plating product samples on microbial growth media, detection of acid formation by pH measurement, adenosine triphosphate (ATP) bioluminescence-sensing assays, visual inspection, sensory assessment, *etc*.

10 Verification Methods for Filter Integrity/Leak Tightness

This chapter describes non-destructive test methods that are used to verify filter retention performance. The tests can be used by filter manufacturers as part of their manufacturing release criteria, during OEM system validation, start-up and performance qualification, during ongoing operation, and as part of field service events to prove the continued efficacy of the filtration.

Various factors can cause or contribute to filter damage. In order to reduce the impact of processing with a damaged filter, any filter failure needs to be detected as soon as possible. Currently, sterile air filter

systems are engineered to provide extended service lifetimes to suit the demand for increased process efficiency and reduced operational costs required by aseptic food processes. An increase in service lifetime of the filter further drives the need for routine filter performance verification testing, so that the performance of the filter system can be assured throughout its complete operational life cycle.

Verifying and documenting filter retention performance in aseptic processing and packaging operations is critically important, as sterilizing-grade air cartridge filters and HEPA filters generally qualify as a critical control point (CCP) in the site's HACCP plan. Continuous performance monitoring procedures are required to ensure the CCP is operating within the set limits. Examples of monitoring procedures that would indicate probable or possible loss of filter retention performance are focused on whether the maximum range of allowed parameters of filter operation are exceeded such as: number of filter sterilization cycles, supply and differential operating pressures, and steaming or operating temperatures. Loss of filter retention performance should be handled as a deviation of the established process.

10.1 Physical Integrity Testing of Sterilizing-Grade Air Cartridge Filters

10.1.1 Correlation of Microbial Removal Performance with Integrity Testing

The ability of sterilizing-grade filter cartridges to provide sterile air must initially have been validated by the filter manufacturer (Chapter 7.5.1). Typically, this will have been done through extensive bacterial challenge testing, which is a destructive test.

Therefore, a non-destructive physical integrity test correlated by filter manufacturers to data from bacterial challenge tests must be available to verify claimed filter performance on an ongoing basis. Integrity testing is a means of verifying that a filter meets its stated bacterial removal performance both as a manufacturing release criterion prior to shipment, and by OEMs and end users. When cartridge filters are damaged, they are termed as having "lost their integrity". Reputable cartridge filter manufacturers will have carried out an integrity test for each filter as part of their quality release criteria and should provide relevant documentation on shipment or upon request.

10.1.2 Types of Cartridge Filter Integrity Tests

There are various integrity test methods available to determine the integrity of sterilizing-grade air filters:

- Bubble Point
- Diffusional or Forward Flow
- Pressure Decay or Pressure Hold
- Water Intrusion
- Aerosol Challenge

There are advantages and disadvantages of each test method listed above and some methods are only applicable to certain filter types. No one method is applicable to every installation. It is imperative therefore to seek advice and support from the filter manufacturer when deciding which method to use. In addition, each test should only be performed by staff who have been specially trained and have a detailed understanding of the test procedures and dynamics which can affect the accuracy of the results. Finally, the use of these devices for *in situ* integrity testing should be evaluated for safety in the plant environment.

The following sections describe the principle of each test method.

10.1.2.1 Bubble Point Integrity Testing

Bubble point integrity testing is typically suited to sterilizing-grade air filters that utilize a hydrophobic membrane as the filter medium.

During bubble point integrity testing, the test filter is "wetted out" with a suitable low-surface-tension liquid to ensure all the pores of the membrane contain liquid. For sterilizing-grade air filters, a low-surface-

tension liquid would be required to overcome the hydrophobic nature of the membrane and wet the pores of the filter. Typically, a mix of isopropyl alcohol (IPA) and water is used for this purpose.

When the filter is fully wetted and the pores of the membrane hold liquid, the filter will resist the flow of air until a sufficiently high air pressure is reached to expel the wetting liquid from the largest pores. The pressure at which the wetting liquid is expelled from the largest pores to allow significant air flow through the membrane is called the "bubble point." In general terms, a filter with a high bubble point typically indicates a tight pore structure and therefore high retention efficiency, although other factors can also influence retention performance.

The minimum bubble point specification (air pressure) is provided by the filter manufacturer. In practice, once the minimal bubble point is reached, there is no need to go further as it may cause filter damage.
If the bubble point is measured to be below this value during integrity testing, there is a high probability that the test filter has a defect, is not fully integral, and will not perform as a sterilizing-grade air filter in the process application.

A common method of identifying the bubble point during an integrity test is a visual judgment of the presence of a constant stream of bubbles on the downstream side of the filter. This method is highly subjective and should not be used for verifying filter integrity in critical aseptic applications. Where automated instrumentation is available, users should ensure the measurement method is validated against microbial challenge tests for assessing filter integrity.

For a typical 10-inch filter system, the time required to perform bubble point testing is influenced by the requirements of wetting the filter out, draining the filter housing, pressure stabilisation and measurement phases of the test, and drying the filter out before it is put back into service. As such, the time required to perform the bubble point test can typically be in the region of 30 minutes per single-round filter housing. For multi-round filter housings, this time would not be expected to change much.

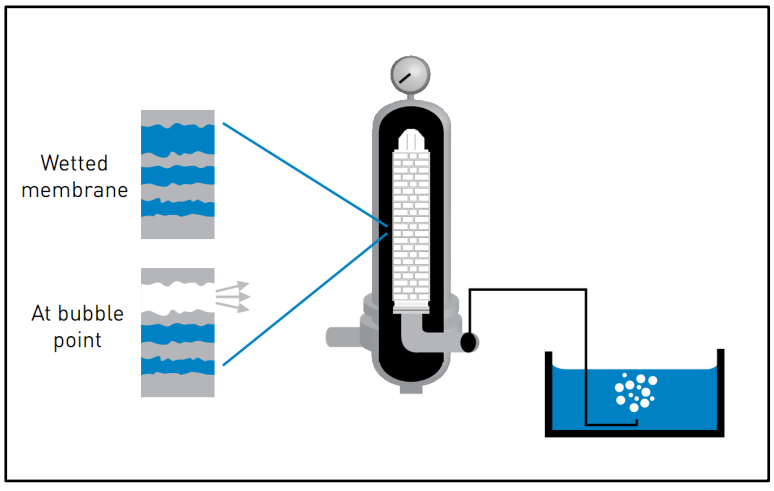

Figure 10.1: Diagram of a Typical Bubble Point Integrity Test Set-Up
Source: Courtesy of Parker Hannifin

It is highly recommended to contact the filter manufacturer for guidance when integrity testing multi-round housings.

10.1.2.2 Diffusional Flow Integrity Testing

Diffusional flow (or forward flow) integrity testing is typically suited to sterilizing-grade air filters that utilize a hydrophobic membrane as the filter medium. “Pass” results confirm a filter’s liquid challenge claims and the filter’s acceptable removal performance under moist or dry conditions.

During diffusional flow integrity testing, the test filter is wetted out with a suitable low-surface-tension liquid, typically a mix of IPA and water, to ensure all the pores of the membrane contain liquid as described in bubble point testing. The upstream side of the filter system is pressurized to a set test pressure for the particular test filter, typically with compressed air or nitrogen.

The diffusional flow integrity test operates on Fick’s law of diffusion in that air molecules will diffuse through the wetted pores of the membrane from the upstream pressurized side of the filter, into the downstream non-pressurized side. The rate of air diffusion is dependent upon the surface tension of the wetting liquid, the test pressure applied to the upstream side of the test filter and the porosity of the membrane.

The rate of airflow can be detected with a sensitive air flowmeter or mass flow transducer. A measured diffusional flow value, which is higher than the upper specification for the test filter at the appropriate test pressure will typically indicate a defect and a loss of filter integrity.

Parameters for the diffusional flow test, including test pressure and maximum allowable diffusional flow limits are provided by the filter manufacturer.

For a typical 10-inch filter system, the time required to perform diffusional flow testing is influenced by the requirements of wetting the filter out, draining the filter housing, pressure stabilization and measurement phases of the test, and drying the filter out before being put back into service. As such, the time required to perform the diffusional flow test can typically be in the region of 30 minutes per single-round filter housing. For multi-round filter housings, this time would not be expected to change much.

It is highly recommended to contact the filter manufacturer for guidance when integrity testing multi-round housings.

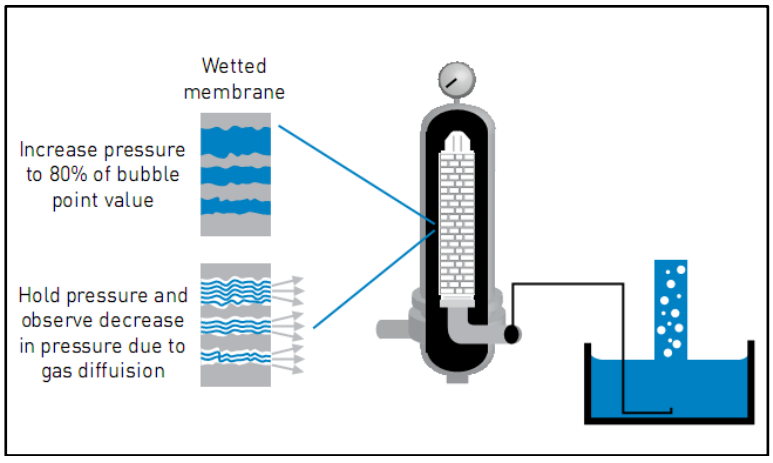

Figure 10.2: Diagram of a Typical Diffusional Flow and Pressure Decay Integrity Test Set-Up: In Diffusional Flow (Chapter 10.1.2.2), the rate of air diffusion through the membrane is measured; in Pressure Decay (Chapter 10.1.2.3), the pressure loss in the sealed upstream volume is measured.
Source: Courtesy of Parker Hannifin

10.1.2.3 Pressure Decay Integrity Testing

Pressure decay (or pressure hold) integrity testing is typically suited to sterilizing-grade air filters that utilize a hydrophobic membrane as the filter medium. “Pass” results confirm a filter’s liquid challenge claims and the filter’s acceptable removal performance under moist or dry conditions.

Pressure decay integrity testing operates on the same principle as diffusional flow integrity testing (Figure 10.2), however rather than measuring the air diffusion rate through the membrane, the pressure lost in the sealed upstream volume is measured and recorded as air diffuses through the wetted pores of the test membrane.

During pressure decay integrity testing, the filter is wetted out with a suitable low-surface-tension liquid, typically a mix of IPA and water, to ensure all of the pores contain liquid, and the upstream side of the filter system is pressurized to a set test pressure, typically with compressed air or nitrogen. When the correct test pressure is reached, the upstream system is isolated and the pressure within the upstream side is monitored over time. The test operates on Fick’s law of diffusion in that air molecules will diffuse through the wetted pores of the membrane from the upstream pressurized side of the filter, into the downstream non-pressurized side. The rate of air diffusion causes the pressure to decrease in the sealed upstream volume and this is measured as a pressure decay reading.

Parameters for the pressure decay test, including test pressure and maximum allowable pressure decay limits are provided by the filter manufacturer. It is very important for the accuracy of the test to correctly account for the upstream volume, *i.e.*, the volume of filter housing and piping between the filter cartridge and the test instrument.

For a typical 10-inch filter system, the time required to perform pressure decay testing is influenced by the requirements of wetting the filter out, draining the filter housing, pressure stabilization and measurement phases of the test, and drying the filter out before being put back into service. As such, the time required to perform the pressure decay test can typically be in the region of 30 minutes per single-round filter housing. For multi-round filter housings, this time would not be expected to change much.

It is highly recommended to contact the filter manufacturer for guidance when integrity testing multi-round housings.

10.1.2.4 Water Intrusion Integrity Testing

Water intrusion integrity testing is typically suited to sterilizing-grade air filters that utilize a hydrophobic membrane as the filter medium. “Pass” results confirm a filter’s liquid challenge claims and the filter’s acceptable removal performance under moist or dry conditions.

The use of the water intrusion test eliminates the need to wet hydrophobic filters with an alcohol solution. To perform the test, the upstream side of the filter assembly is filled with water (which does not wet the filter) and a predetermined air test pressure is applied. Under this condition, water vapor naturally “evaporates” through the membrane pores. In an integral filter, this evaporation rate does not exceed a certain limit, whereas in a defective filter, water breaks through the membrane.

The integrity test instrument makes a direct measurement on the upstream side of the filter of the evaporative water flow through the membrane and compares the result with the acceptable limit of water flow. After the integrity test, the water need only be drained from the housing, without a need to dry the filter.

Parameters for the water intrusion test, including test pressure and maximum allowable water flow limits are provided by the filter manufacturer.

For a typical 10-inch filter system, the time required to perform water intrusion testing is influenced by the requirements of filling the filter housing with water, pressure stabilization and measurement phases of the test, and draining the filter housing before being put back into service. As such, the time required to perform the water intrusion test can typically be in the region of 30 minutes per single-round filter housing. For multi-round filter housings, this time would not be expected to change much.

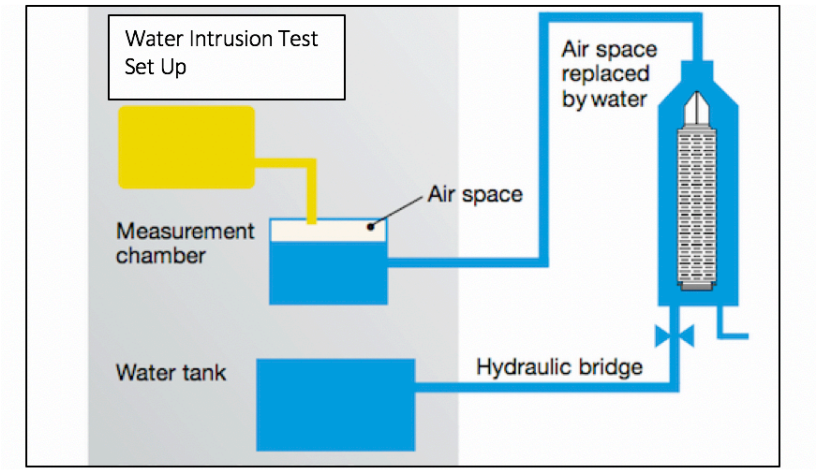

Figure 10.3: Diagram of a Typical Water Intrusion Integrity Test Set-Up
Source: Courtesy of Pall Corporation

10.1.2.5 Aerosol Challenge Integrity Testing

Aerosol challenge integrity testing, similar to Dispersed Oil Particulate (DOP) testing, can be used with hydrophobic membrane or depth filters claiming to be capable of sterilizing dry air. "Pass" results confirm a filter's aerosol challenge claims and the filter's acceptable removal performance in dry air conditions.

Unlike the previous integrity test methods, there is no need to wet the filters in alcohol or introduce water into the filter housing. During the aerosol challenge integrity testing, the upstream side of the test filter is exposed to a high concentration of food grade aerosolized mineral oil droplets within the 0.2-0.3 µm size range. This size is considered the MPPS for a sterilizing-grade air filter, as retention mechanisms in air are also influenced by diffusional interception, interception, inertial impaction, and electrostatic interactions, aside from size exclusion (Chapter 6).

The aerosol challenge integrity test simulates an aerosolized bacterial challenge test under high loading, worst-case conditions. Any aerosol, which passes through the filter to the downstream sterile side is directed through a particle counting device which directly detects the presence of any aerosol and calculates a percentage penetration value. On this basis, a pass or fail result for the test filter is established.

A downstream connection is required for this test, but as the system will always be steam sterilized after testing, this should not need to be a consideration in terms of achieving commercial sterility.

The integrity test device manufacturer should provide documentation to show that all traces of oil from the test are removed by the subsequent steam sterilization, in order to ensure that microorganisms cannot survive during steaming due to inadvertent protective effects of the oil.

For a typical 10-inch filter system, the time required to perform aerosol challenge integrity testing is influenced by the requirements of ensuring the test filter is completely dry prior to testing and connecting the integrity test machine to the filter housing. As such, the time required to perform the aerosol challenge

integrity test can typically be in the region of 5 minutes per single-round filter housing. For multi-round filter housings, this time would not be expected to change much.

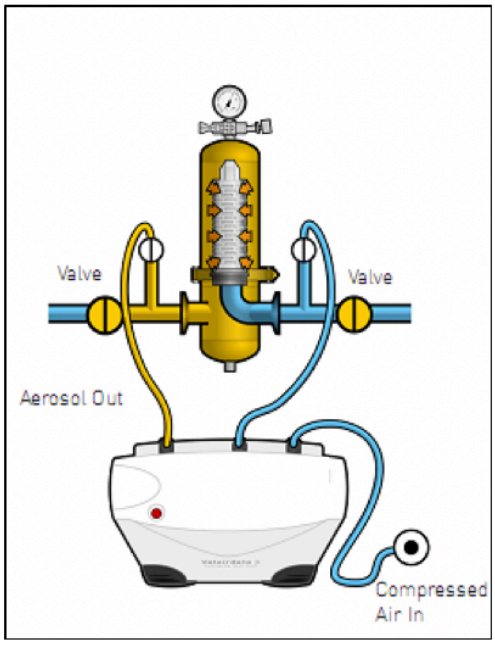

Figure 10.4: Diagram of a Typical Aerosol Challenge Integrity Test Set-Up
Source: Courtesy of Parker Hannifin

The aerosol challenge integrity test can be an attractive proposition for systems operating under time constraints. It can also be a practical option when testing multi-cartridge systems to avoid the use of large amounts of alcohol.

10.1.2.6 Summary

There are a variety of integrity tests available to document filter cartridge retention performance. They differ based on their principle of operation and test procedure, whether they are suitable for use on membrane and/or depth filters, whether they confirm liquid and/or aerosol bacterial challenge claims, and the time it takes to run the test. In all cases, these tests must be correlated to relevant bacterial challenge test data, which enables their use as a non-destructive quality control tool.

We stress that each type of integrity test has its advantages and disadvantages, and their selection should be done in close consultation with filter manufacturers. One or more of the methods could be used in combination, based on the production demand and on the level of risk acceptable to the facility.

10.1.3 Automated Integrity Test Instruments

Most integrity test methods can be carried out manually. However, due in part to operator subjectivity or external variances which can impact upon the test result, manual methods are characterized by a lack of accuracy and precision. It is recommended that automated integrity test instruments are always used.

Use of an automated integrity test instrument by a trained operator will increase the sensitivity of the test significantly, and reduce the risk of processing with a defective sterile air filter, which could compromise sterility. In addition, an automated instrument provides both hard and electronic documentation of the integrity test, thereby enabling accurate records to be kept for quality audit purposes.

Integrity test instruments must be properly calibrated and serviced throughout their use.

10.1.4 Considerations for Integrity Test Practices

10.1.4.1 Selection of Integrity Test Methods

The previous sections outline the underlying principles for typical integrity testing methods for sterilizing-grade air cartridge filters. Table 10.1 compares each method against some operational considerations, assuming that each method is used with an accurate, calibrated test instrument and is correlated to the test filter's bacterial retention ability.

Table 10.1: Comparison of Integrity Test Methods

Integrity Test Method	Positive Aspects	Negative Aspects
Bubble Point	Challenges the filter under liquid conditions to determine retention capability in moisture-containing air or if partially wetted filter pores are present. Good test for a new filter. Typical test time is 30 minutes for a 10-inch cartridge.	Requires wetting the filter properly with a suitable liquid, and subsequent drying prior to use. For used (partially blocked) filters, minimum bubble point should not be exceeded.
Diffusional Flow	Increased sensitivity for large systems. Challenges the filter under liquid conditions to determine retention capability in moisture-containing air or if partially wetted filter pores are present. Typical test time is 30 minutes for a 10-inch cartridge.	Requires wetting the filter properly with a suitable liquid, and subsequent drying prior to use. Test accuracy may be influenced by temperature fluctuations.
Pressure Decay	Relatively easy test. Challenges the filter under liquid conditions to determine retention capability in moisture-containing air or if partially wetted filter pores are present. Typical test time is 30 minutes for a 10-inch cartridge.	Requires wetting the filter properly with a suitable liquid, and subsequent drying prior to use. Test accuracy may be influenced by temperature fluctuations.
Water Intrusion	Wetting the filter with wetting fluid is not required, so no drying is required prior to use. Challenges the filter under liquid conditions to determine retention capability in moisture-containing air or if partially wetted filter pores are present. Typical test time is 30 minutes for a 10-inch cartridge.	Test accuracy may be influenced by temperature fluctuations. False positives may result due to contamination on the filter, which could cause localized hydrophilic spots. These can be removed by an alcohol flush, and the integrity test result reconfirmed.
Aerosol Challenge	Challenges the filter in air to simulate retention capability in dry air. Quick test as no wetting or drying required. Typical test time is 5 minutes for a 10-inch cartridge.	Requires a downstream (sterile side) connection to perform the test, which is subsequently sterilized during SIP. Introduces aerosolized mineral oil droplets onto the filter.

10.1.4.2 Frequency of Integrity Testing

In applications employing filter cartridges, strong consideration should be given to the need for filter integrity testing, given that properly functioning filters are critical to the overall success of the operation.

The sources of potential damage to sterilizing-grade air cartridge filters are:

- Manufacturing: Reputable filter manufacturers will implement integrity testing as part of their manufacturing release criteria for each filter shipped from their facility. These results should be documented and traceable.
- Transport and storage: Filter damage may occur within the distribution chain.
- Filter installation: Improper handling of the filters prior to or during installation can damage filters. A common example is filter O-ring damage during installation, which creates a leak between the upstream and downstream side of the filter.
- Filter sterilization (SIP) and cooling: Steam sterilization is the most critical stressor to filter integrity, as polymeric filter materials soften at high temperature and are most susceptible to damage at those conditions. A common problem arises when hydrophobic filters collapse due to improper drainage of steam condensate from filter housings, pipelines, and valves upon cooling. Filter manufacturer guidelines for SIP, including maximum number of steaming cycles must be followed.
- Filter operation: Conditions of use outside allowed limits, such as excessive differential pressure and temperature, can result in filter damage.

Based on the above, filter manufacturers recommend that integrity testing should be carried out with regular frequency:

- Pre-use (before steam sterilization):
  This recommendation is intended to verify incoming filter quality, non-damage during transport/handling and correctness of the filter installation including non-damage to O-rings. When filters are reused, this recommendation also verifies that filters are still integral after previous use.
- Post-use (after filtration operation):
  This recommendation is intended to verify the filter was integral throughout the filtration process, for batch sterility confirmation at end of operation. This information is entered into batch records.

It should be mentioned that the above recommendations for integrity testing pre- and post-use are in line with those put forward by FDA Guidance for Industry regarding aseptic production of pharmaceuticals. However, the FDA regulation for the food and beverage industry simply stipulates that the equipment and containers used for aseptic processing and packaging must be commercially sterile (21 CFR 113.3(2)).[33] Therefore, from the FDA regulatory perspective for the food and beverage industry, currently there is no specific recommendation regarding integrity testing.

As there will generally be multiple sterile air filters to test in any given facility, a balance should be struck between when the filters are tested, how and at what frequency. This is why integrity testing practices vary from process to process. The decisions as to what method to use and the frequency of testing are driven by understanding the relative risk to the process operations, with factors such as process schedules and downtime, process variations and number of SIP cycles being taken into consideration. Guidance from the filter manufacturer should be sought when making decisions about integrity testing practices.

End users in the food and beverage industry should be aware of the potential sources of filter damage and the risks associated with having such damage go undetected, then determine for themselves the practicalities regarding application and frequency of integrity testing. Many end users implement regular integrity testing, but some choose not to do so. Some end users choose to decrease their frequency of integrity testing over time because they have developed historical data, which demonstrates a high level of confidence in delivered filter quality, non-problematic filter installation, and successful repeated filter reuse.

Further guidance regarding the responsibilities of end users regarding cartridge filter integrity testing is found in Chapter 11.4.3.

10.1.4.3 Integrity Testing Redundant Filters

Where redundant filters are used, any integrity testing should be conducted on each filter. Ensure that record keeping for each filter position is accurate.

10.1.5 Troubleshooting Integrity Test Failures

If a filter fails an integrity test, it could either be damaged, or there may be other causes for the failure that include incorrect assembly (incomplete sealing) and incomplete wetting.

To distinguish between actual filter damage and false failures ("false positives") due to possible test problems, Table 10.2 summarizes the following verification steps:

Table 10.2. Summary of Troubleshooting Criteria for Sterile Air Filter Integrity Testing

Bubble Point, Diffusional Flow, Pressure Decay and Water Intrusion Integrity Tests	**Aerosol Challenge Integrity Test**
Correct test parameters have been used.	Correct test parameters have been used.
Correct wetting fluid and wetting procedure have been used (excluding water intrusion test, which only requires water).	The filter is dry.
There are no leaks in the test system.	There are no leaks in the test system.
Test set-up has been properly assembled and functions properly.	Test set-up has been properly assembled and functions properly.
Equipment has been properly calibrated.	Equipment has been properly calibrated.
Filter assembly temperature has remained stable and within specification during testing.	
Correct filter type (membrane) has been installed and correct test selected.	

Liquid integrity test (bubble point, diffusional flow, pressure decay) false failures are generally caused by insufficient wetting of the filter which allows pressurized air to flow through the filter membrane without resistance. Incomplete wetting is mainly due to inadequate flushing to wet out all the pores. In some cases, adsorbed contaminants or other formulation components that can change the surface wetting characteristics of the filter membrane may cause localized hydrophobic spots on the membrane, however generally, exposure to the wetting fluid used during the integrity test would eliminate those issues.

Water intrusion test false failures are generally caused by compromised hydrophobicity of the filters, which allows water to flow through the filter membrane without resistance. These problems are mainly caused by adsorbed contaminants that create localized hydrophilic spots on the filters. This issue can be corrected by flushing the filters with an alcohol solution, thus restoring the filter to its original hydrophobic condition, and redoing the integrity test to reconfirm the filter's condition.

False failures with aerosol challenge integrity testing can occur if anything other than the challenge aerosol is detected by the integrity test machine, which is then incorrectly recorded as penetration through the filter. This can typically occur if the test filters are not completely dry, or if there is debris in the test system. Typical counter actions are to purge the test system with compressed air to remove debris and to facilitate drying of the test filters.

10.2 Leak Tightness Verification of HEPA Filter Assembly and Air Distribution System

The retention performance of HEPA filters to substantiate their particle removal efficiency claims must have been originally confirmed by the filter manufacturer. Typically, this will have been done by means of the leak test as required by the norm (Chapter 8.5.3).

HEPA filter assemblies should be tested after installation to ensure the gaskets, seals and frames are secure and there is no air bypass around filter media at these points. These tests should be carried out after the first machine sterilization cycles to account for any possible thermal effects on the filter housing and sealing materials. This will also identify any damage to the filter media after factory testing such as those caused by shipping and handling. Further, testing should be carried out on an ongoing basis during operation to verify and document continued suitable assembly tightness.

OEMs and end users use various methods to verify absence of leaks after installation and in operation. This chapter describes at least three approaches to verify leak tightness of HEPA filter assemblies and air distribution systems. Depending on end user leak testing requirements, additional aseptic machine access ports may be incorporated to assist.

End users may use these in full or create variations to suit their individual situations. Another option is to contract with third party cleanroom certification services. Ultimately, it is the responsibility of the end user to select methods that verify absence of leaks.

On equipment start-up after installation completion, Installation Qualification first requires testing to ensure fulfilment of air pathway tightness (distribution system/piping, aseptic chamber, *etc.*) surrounding the HEPA filter installation as a mandatory precondition for all subsequent functional and process validation (Chapter 9.2).

Leaks are detected by presence of particles downstream of the assembly, detected by a particle counter. If particles are detected, a smoke test can identify the location of the leak. Finally, microbiological capture tests provide an additional option to determine the presence of serious contamination.

10.2.1 Particle Counting / Principle and Method

In an optical particle counter, the particles are led individually through an intensively illuminated measuring volume. When passing through the measuring volume, the particle scatters light, which is detected at a defined spatial angle by a photo detector and transformed into an electrical pulse. The level of this pulse corresponds to the size of the particle, and the number of pulses per unit time with the particle concentration in the air volume analyzed.

According to ISO 29463-2, minimum performance parameters for particle counters are:

- compliance requirements of optical particle counters (ISO 21501-4[34])
- measuring range for particle sizes of 0.1 µm to 2.0 µm (50% counting efficiency) providing at least one channel at a mean size smaller than the MPPS of the tested filter (preferred: half the size of the MMPS)
- for **filter medium** testing: minimum five size classes between 0.1 and 0.3 µm
- for **filter element** testing: minimum two size classes between 0.1 and 0.3 µm (channel size ranges of 0.1 to 0.2 µm and 0.2 to 0.3 µm are common to many commercial counters)
- zero count rate: <1/min (sampled from particle-free gas based on the detection range)

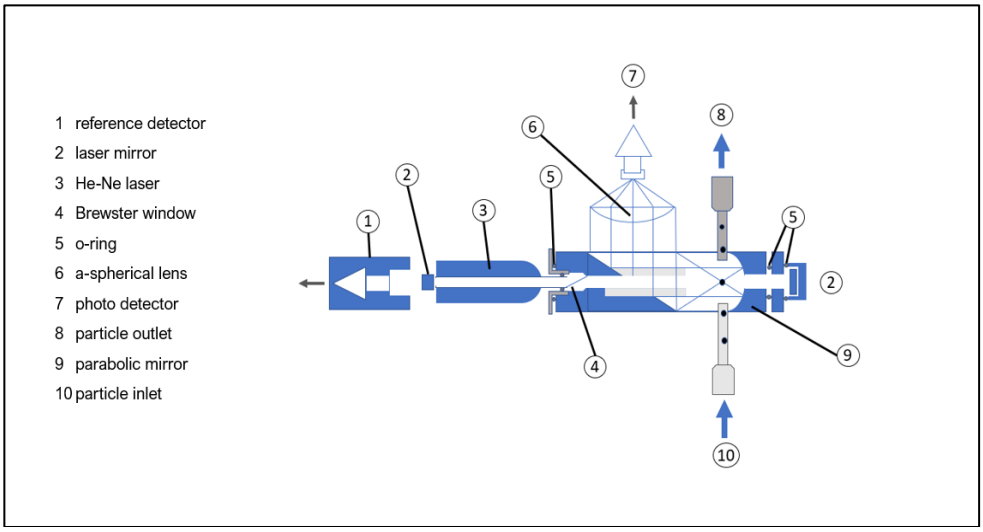

Figure 10.5: Schematic Principle of Laser Particle Counter (ISO 29463-2)
Source: Courtesy of SIG Combibloc

The method for testing particle retention of installed HEPA filters under simulated production conditions can be conducted using a laser particle counter, connected to the aseptic piping or chamber downstream of the HEPA filters. Preproduction sterilization and ventilation time must be completed before such testing can be started.

The presence of residual sterilant or loose particles in the piping or distribution system might disturb such testing, so tests should not be started earlier than 30 minutes after completion of any sterilization sequence.

Particle counting should be carried out in triplicate on 0.3 and 0.5 µm channel to generate representative data. Results should comply with the specified performance of the filters in use. The expectation for HEPA filter retention for aseptic systems is 0 counts/28.3 Liter (0 counts/cubic foot) on 0.5 µm channel downstream of the filter, repeated in triplicate.

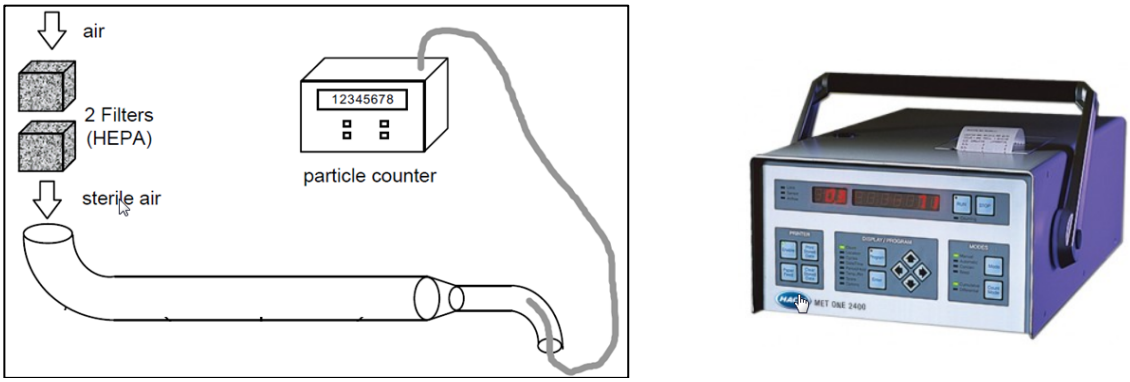

Figure 10.6: Schematic and Photograph of Particle Counting Test for HEPA Filter Retention Performance
Source: Courtesy of SIG Combibloc

If counts are found, smoke tests can be used to locate the leak.

10.2.2 Smoke Test / Principle and Method

Smoke generators (Figure 10.7) are generally used to determine the presence of leaks from the inside of the sterile zones of the filler (zones under overpressure or laminar flow) to the outside environment, or conversely, leaks from surrounding environment into the sterile zones.

Smoke is generated either from a liquid which is aerosolized by spraying or vaporization followed by condensation (smoke generators using fluids like diethylene glycol or water), or by emission of chemicals such as SO_3, followed by formation of H_2SO_4 mist in contact with surrounding air containing water vapor (smoke generating tubes).

In a first approach, high amounts of smoke particles are generated around each potential leak area such as around the HEPA filter installation, piping seals and connections (gaskets), along the complete route from the filters to the aseptic zone*, i.e.,* around any separating barrier between the sterile zone and the non-sterile surrounding zone. Any visually detectable deflections of the smoke fog, disturbed by air escaping through a leak from the internal pressurized sterile zone is observed. For this testing the fan is switched on creating the scheduled air flow through the sterile zone air distribution system. This method identifies the location of bigger leaks.

In a second approach, the smoke test can also be used in combination with particle counting where even small leaks can be detected (Figure 10.8). For this procedure, the particle counter probe is arranged at different places inside the sterile zone while smoke is applied outside, around the HEPA filter installation, piping seals and connections (gaskets), along the complete route from the filters to the aseptic zone*, i.e.,* around any separating barrier between the sterile zone and the non-sterile surrounding zone. This overloading of the surrounding environment raises the density of particles around potential leaks, so that particles intruding into the sterile zone can be detected.

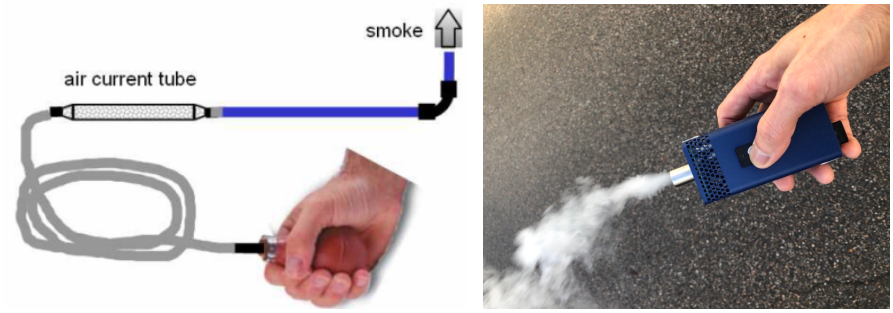

Figure 10.7: Schematic and Photograph of Smoke Generator
Source: Courtesy of SIG Combibloc

If leaks are present, small portions of smoke are sucked into the pressurized sterile zone by venturi effects and can be measured by the particle counting device indicating the location of a leak upstream of the sampling position.

Depending on the location of the leaks found, the cause could be either be identified as an assembly or filter element issue. The first case can usually be corrected; a non-integral filter element must be replaced.

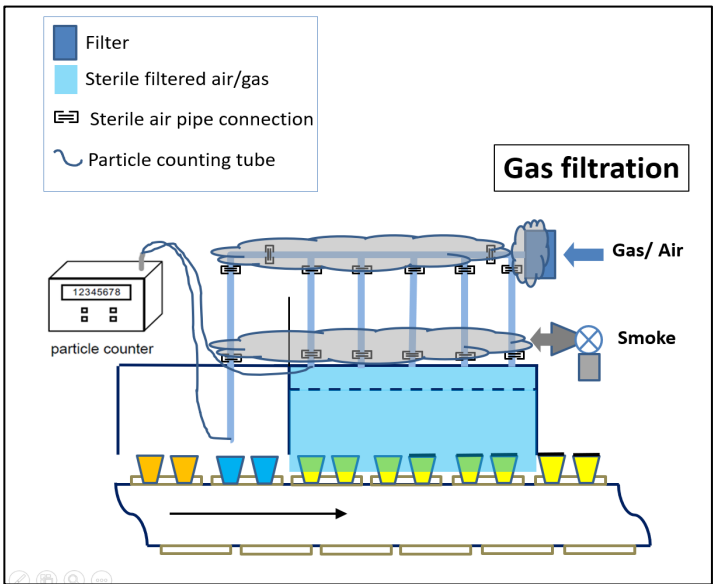

Figure 10.8: Schematic and Photograph of Smoke Generator Test in Conjunction with Particle Counting
Source: Courtesy of SIG Combibloc

10.2.3 Microbiological Capture Tests

Microbiological testing can be used to rule out intrusion of microorganisms into the sterile zone, although it can be stated, that only severe contamination can be detected because of the unfavorable ratio between the amount of filtered air and sampling volume.

10.2.3.1 Set Plates

Microbiological media that provides suitable growth conditions for expected airborne bacteria is prepared under sterile conditions, transferred to the sterile zone and exposed to the filtered air. During a predefined time, potential microbes are allowed to settle on the media surface. After transferring the closed set plates to an incubator for a sufficient incubation time, the amount of collected microorganisms can be obtained by counting the colonies on the plate.

This method is indicative and cannot be used to derive conformity with any cleanroom classification, but often serves as a method to confirm maintenance of sterility in aseptic zones, if absence of microorganisms can be demonstrated over time.

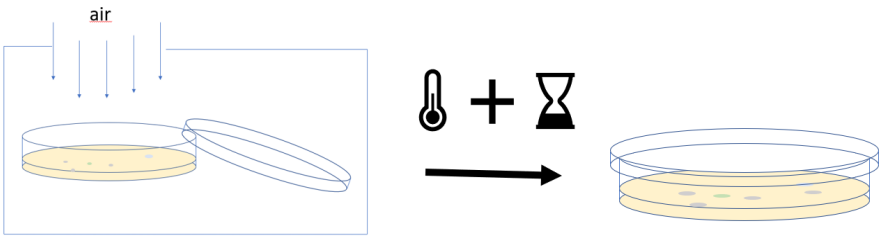

Figure 10.9: Schematic and Photograph of Set Plate Principle
Source: Courtesy of SIG Combibloc

10.2.3.2 Microbiological Air Sampling

Microbiological air sampling techniques can also be used to transfer defined portions of filtered air to a suitable growth media, such as solidified agar or liquid broth.

While different devices exist to transfer a defined volume of air to the media in a certain time, none of these solutions is capable of guiding the total volume of HEPA filtered air in- or onto the media. Therefore, any of these tests should be recognized as a fractional result, but nevertheless, they can deliver additional confirmation on the absence of bacteria in aseptic zones.

Special attention must be paid to the preparation of these tests as every device must be sterilized before being brought into the aseptic zone.

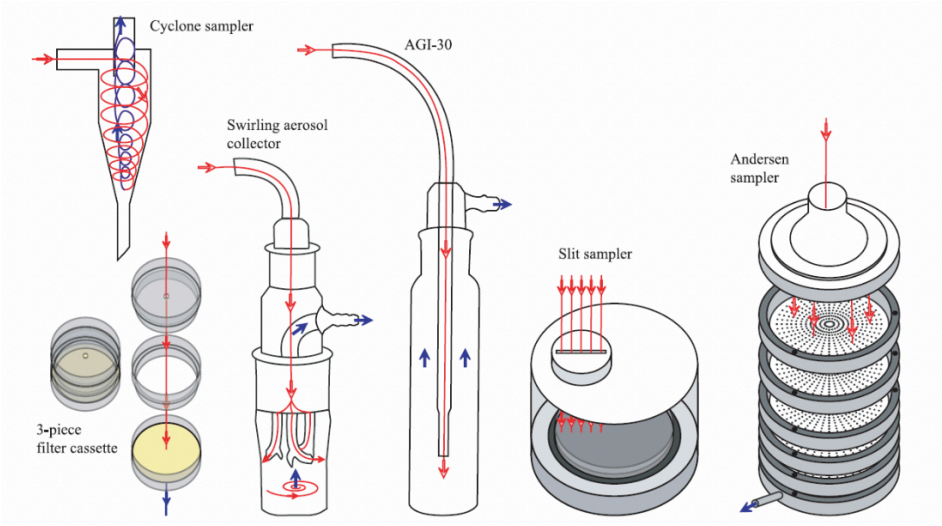

Figure 10.10: Diagrams of six different bioaerosol samplers (broth, plate). Red lines and arrows represent the airflow into the sampler. Blue arrows represent airflow out of the sampler. These drawings are simplified representations.
Source: Microbiology and Molecular Biology Reviews[35]

10.3 Comparison Summary

Filter retention performance verification varies according to filter types. The tests are based on different test conditions and are correlated to different levels of filter performance claims. The user should always consult with filter manufacturers to ensure that the test results satisfy their quality control and risk assessment needs. Table 10.3 summarizes filter types and performance verification attributes.

Table 10.3: Comparison of Filter Types and Performance Verification Attributes

Filter Type	Applicable Filter Performance Verification Tests	Test Conditions	Correlation to Claimed Filter Performance
Membrane Cartridge Filter	Forward Flow, Pressure Decay, Water Intrusion Integrity Test	Liquid challenge	Microbial *B. diminuta* removal in liquid
	Aerosol Challenge Integrity Test	Aerosol challenge	Microbial *B. diminuta* removal in dry air
Depth Cartridge Filter	Aerosol Challenge Integrity Test	Aerosol challenge	Microbial *B. diminuta* removal in dry air
HEPA Filter	Various leak tests according to end user practice	Aerosol challenge	Particle removal in dry air

11 Responsibilities of Involved Parties

The successful outcome of aseptic air filtration hinges on the fulfillment of responsibilities by all key stakeholders.

11.1 Cartridge Filter Manufacturers

11.1.1 Design Fit for Purpose

Sterilizing-grade air filters must meet industry and regulatory requirements for effective application. Expected performance claims and features should include:

- microbial removal performance
- sterilization by *in situ* steam, autoclave or other practical methods
- hydrophobicity
- high mechanical and thermal resistance
- high throughput at low differential pressure
- compatibility with the proposed applications (*e.g.,* high temperature air; oxygen service)
- suitable materials of construction, satisfying relevant food contact compliance and chemical compatibility requirements. It is the user's responsibility to determine which requirements apply.
- integrity testability with a non-destructive test correlated to microbial removal efficiency

11.1.2 Filter Claims Validation

Filter manufacturers are expected to conduct robust validation work, to qualify the filters for their intended function and use, and to provide documented performance claims. Such work should ultimately be done on a suitable quantity of filter units from different production lots. Validation includes:

- bacterial challenge testing (liquid and/or aerosol removal performance) with required model microorganism at required bacterial challenge level, resulting in sterile effluent
- multiple-cycle sterilization by *in situ* steam at defined temperatures (number of cycles, length of cycles, steam flow direction, allowed differential pressure during steaming, bacteria removal performance after multiple cycles)
- allowed differential pressures in airflow direction during normal operation
- expected filter life at ambient or high temperature operating conditions
- airflow rates based on vent and compressed air conditions
- definition of integrity test values consistent with data generated during bacterial retention studies
- suitable materials of construction satisfying relevant food contact compliance regulations

A detailed Validation Guide (also called Technical Performance Document) shows the validation testing conducted and results achieved.

11.1.3 Quality Assurance Program

Filter manufacturers are expected to implement a robust quality assurance program to ensure that filter design specifications and performance claims can be met on an ongoing basis. Manufacturing release includes an integrity test to confirm filter integrity prior to shipment. Filters are serialized to enable traceability. Filter manufacturers should have capabilities to provide full test reports for individual filters upon demand. The program should include a robust management of change program, *i.e.,* should material suppliers make changes in raw materials, to rule out potential changes to filter performance. There should be a mechanism in place for addressing customer complaints due to performance issues in the field.

11.1.4 Installation and Operating Procedures

Filter manufacturers should provide:

- installation guidelines
- airflow indicator
- sterilization recommendations and pressure/temperature/steam cycling limits

- operating recommendations and pressure/temperature limits,
- guidelines for filter change-out frequency
- dedicated training or clear instructions to facilitate filter change-outs by operating or service personnel
- suitable integrity test procedures, integrity test values (pass/fail limits), recommended integrity test frequency education and training

11.1.5 Service and Support

Service and support functions should be provided to address any issues occurring in the field. These typically could include:

- clarifying operational procedures
- troubleshooting possible causes of integrity test failures
- troubleshooting integrity test methodology, to rule out false failures or false positive results
- service life analysis

11.2 HEPA Filter Manufacturers

11.2.1 Design Fit for Purpose

HEPA filters must meet industry and regulatory requirements to ensure proper product selection based on specific end user applications. Expected performance claims and features should include:

- filter classification by particle removal efficiency using regionally accepted norms
- particle removal capability according to filter classification until end of lifetime
- high throughput at low initial differential pressure
- sterilization options by chemical sterilants (*e.g.,* hydrogen peroxide) or other practical methods
- mechanical and thermal robustness
- compatibility with the proposed applications, *e.g.,* process temperature, sterilant chemicals
- suitable materials of construction satisfying relevant food contact compliance regulations
- gasketing options to ensure proper installation in housings or frames for zero particle bypass

It is the user's responsibility to determine appropriate efficiency, throughput, compatibility and proper fit.

11.2.2 Filter Claims Validation

Filter manufacturers are expected to conduct robust validation work, to qualify the filters for their intended function and use, and to provide documented performance claims. Such work should ultimately be done on a suitable quantity of filter units. Validation includes:

- identifying particle removal efficiency for classification purposes at rated airflow
    - flat filter material
    - filter element
- leak testing
- pressure drop at rated airflow

11.2.3 Quality Assurance Program

Filter manufacturers are expected to implement a robust quality assurance program to ensure that filter design specifications and performance claims can be met on an ongoing basis. Every HEPA filter should be individually tested, certified and labeled prior to packaging and shipping as follows:

- categorization/documentation of filter class and retention efficiency based on regionally accepted norms (Certificate of Compliance, Letter of Certification, test report, *etc.,* confirming the claimed filter class)
- absence of leaks according to scan test or other method according to regionally accepted norms
- date of testing
- initial differential pressure at rated airflow

- flow direction indicator mark
- serial number and product code
- manufacturer information

Filters are serialized to enable traceability. Filter manufacturers should have capabilities to provide full test reports for individual filters upon demand. There should be a mechanism in place for addressing customer complaints due to performance issues in the field.

11.2.4 Installation and Operating Procedures

Filter manufacturers should provide:

- airflow indicator to ensure proper orientation during installation
- operating temperature range
- recommended final pressure drop
- filter, frame and gasket material information

11.2.5 Service and Support

Service and support functions should be provided to address any issues occurring in the field. These typically could include:

- localized customer support
- failure analysis for structural issues, chemical compatibility or high temperature damage
- service life analysis

11.3 Original Equipment Manufacturers (OEMs)

Equipment manufacturers choose filter solutions from filter vendors according to their experience with filter properties, performance and manufacturing quality.

Equipment manufacturers design air filtration applications by combining process knowledge with capabilities of specialized filter systems. It is the responsibility of OEMs to define preproduction sterilization methods, sequences and critical parameters followed by standard operating conditions and replacement intervals.

While HEPA filters are not necessarily delivered with specially designed housings, a reliable combination of cartridge filters with an adequate housing is important for cartridge filter systems. Although most filtration processes show a high degree of automation, maturity in design of the filter system provides the necessary safety for daily performance during aseptic processes, because manual handling during maintenance and replacement of filter cartridges by end users is also part of aseptic food production.

When integrating filters into equipment, OEMs rely on filter performance specifications and filtration capabilities claimed by filter vendors. Recommended handling, monitoring of critical parameters and also spare parts lists are provided to end users as an integrated part of the equipment operation manual or separate documentation.

It is the responsibility of the OEMs to either validate the scheduled sterilization processes or provide suitable documentation for 3rd party process authorities to conduct such steps at the customer site.

Automated processes providing steam supply for sterilization, draining of condensate, monitoring of sterilization temperature or regulating airflow or sterile air pressure are programmed and integrated as part of the overall equipment automation program. These program sequences must be validated for proper execution under normal and abnormal operating conditions.

Filter sterilization (temperature, cycles) and pressure drop limits depend on system and process design, therefore must be provided by the OEMs.

11.4 End Users

11.4.1 Risk Assessment

The goal of every aseptic system is to achieve commercial sterility for the finished product and container. It is each end user's responsibility to make sure this goal is achievable and assess the associated risks. These risk assessments should drive compliance with government regulations such as 21 CFR Part 117[36] (FSMA) and be used in the development of HACCP plans. Whenever possible, risk assessments should start during the equipment design process where engineering solutions may be applied to ensure that all relevant hazards are significantly minimized or prevented.

Ultimately it is the end user's responsibility to demonstrate the integrity and performance of the filter throughout its lifetime. A strategy should be developed for how this will be addressed. Validation information provided by the filter manufacturer and/or outside consultants is a starting point for evaluation.

The useable life for the filter is an important part of an assessment as well as ongoing operations. The more a filter is sterilized and used, the greater the risk of failure. The end user determines whether they will use the supplier recommendation of how frequently to replace filters, develop data on their own to substantiate the life, or consider one-time use of filters. It should also be determined whether filter elements will be rotated between primary and secondary locations to make sure each filter is at different stages of the life cycle to minimize risk of system failure while balancing the impact that moving a filter may have to performance.

If automated filter counters are used to track cycles, thought must be given to when these counters actually log a change. Will it log after a sterilization is complete, when the start button is pressed, or somewhere in between? Early in the process can help minimize risk to filters, but could increase the frequency of replacement. Too late and issues with completing sterilization can make it so counters do not adequately represent filter life cycles. Not all equipment manufacturers apply the same logic and some do not even apply logic consistently across a machine.

Integrity test frequency and inspection must also be evaluated. These tools can help determine the true life of the filter as well as performance of the system. The longer the duration between testing and inspection, the greater the amount of product potentially at risk when an issue is identified. While this testing is meant to minimize certain risks, it can also introduce risk. Every time a filter is removed and re-installed, damage could occur to the filter element or seals. If filters are tested in the production housings, leaks can occur at the connection points after testing during production. The benefits need to be balanced with the additional risks of testing.

11.4.2 Proper Installation and Operation

The air supplied by the end user to the filtration system must meet the requirements of the filter manufacturer and the OEM, as this is a critical factor in operation and life. Air quality data should be generated demonstrating operational conditions are in line with designed use.

Proper installation and operation of filtration systems is necessary to prolong the life of the filters and ensure product safety is not compromised. Supplier recommendations should be used as a starting point and transformed into Standard Operating Procedures (SOPs) as well as automation limits (SIP, Cool Down, Differential Pressure Control, Maintenance).

Modification of these recommendations may be necessary based on the actual performance as determined during the qualification process and ongoing testing.

Training is a necessity so all those involved understand the importance and are able to follow a standardized and consistent approach during operation.

Once validated, any changes made must follow a Management of Change process to evaluate the impact of the change to performance. These changes may include, but are not limited to:

- change of filter supplier or manufacturing location
- automation changes
- operating parameters or critical limits
- standard operating procedures

Depending on the outcome of the Management of Change process, additional validation work may be necessary.

11.4.3 Securing Filter Retention Performance in Operation

Verification of filter retention performance generally qualifies as a critical control point (CCP) in the site's HACCP plan. End users are responsible for ensuring commercial sterility of their products, taking into consideration the recommendations of filter suppliers and OEMs, while addressing the practicalities involved.

Regardless of whether cartridge filters or HEPA filters are in use, it is recommended that end users verify filter retention performance frequently during qualification of a new system, at initial start-up, when qualifying new procedures, processes or filter suppliers, and during related field service and troubleshooting events. This will help to define and substantiate the operational limits and true cycle life for the filters. As the confidence of performance goes up as this data is collected, the frequency of the verification tests can be adjusted accordingly with the Management of Change process.

During operation, end users should evaluate the need for ongoing verification of filter retention performance, knowing the typical stressors that could cause filter failures. This evaluation should be balanced against any potential additional risks to frequent integrity testing of cartridge filters or verification testing of HEPA filter performance during operation that are identified during the Risk Assessment and HACCP Plan development.

Who will perform the testing is another topic that should be evaluated, considering the types of filters being tested and the equipment and training necessary. This information can be used to determine if testing should be completed in-house or if it makes sense to have a third party handle this work. Completing testing in-house requires the purchase and maintenance of the appropriate equipment as well as having trained individuals. Where this could make sense for a facility with multiple lines or plan for frequent testing, it may not for one with few filters or the need for infrequent testing. Even if a third party does the work, the responsibility still lies with the Food and Beverage Manufacturer to make sure testing is completed according to industry standards.

11.4.3.1 Cartridge Filters

End users should evaluate the choice of the integrity test (Chapters 10.1.2, 10.1.3, 10.1.4.1), integrity testing frequency (Chapter 10.1.4.2), and/or potential implementation of substitute measures that may reduce, but not eliminate the risk of cartridge filter failure. However, none of the following substitute measures provide a guarantee of confirmed filter integrity.

- Visually inspect seals and filter appearance during assembly and exchange of filter elements for signs of obvious physical damage. Note that damage to filters is not always visible!
- Follow manufacturer instructions for installation of filters into filter housings, steaming and normal operation, and change-out frequency.
- Monitor steaming cycle frequency with sterilization cycle counters.

- Monitor and record temperature and filter differential pressure continuously, with system alarming (stopping the line, meaning loss of sterility) if out of specification.
- Sample air from the sterile zone of the aseptic filler to demonstrate sterility of the air.
- Build a base of experience with the filters to determine reliability and robustness of the filters over time.

Post-process, some end users incubate product for a period of time to determine batch non-conformance. Should microbiological issues arise, end users will address the potential sources of contamination in the overall aseptic system based on type and quantity of microorganisms found and numbers of containers affected. Such review includes an investigation of the filters along with other investigations, depending on relevance to the specific issue.

11.4.3.2 HEPA Filters

Ultimately, it is the responsibility of the end user to select methods that verify HEPA filtration retention performance during normal operation. Following are some examples.

- Monitor and record filter differential pressure continuously, with system alarming (stopping the line, meaning loss of sterility) if out of specification.
- Sample air from the sterile zone of the aseptic filler to demonstrate sterility of filtered air.
- After each filter replacement, perform leakage testing with particle counter at several positions inside the aseptic zone.
- Change out filters yearly or more frequently based on OEM recommendations and sensitivity of products produced.

11.4.4 Preventive Maintenance and Service

Maintenance is a crucial part of the operation to keep the system functioning properly. Standard Operating Procedures (SOPs) and Training must be developed for Preventive Maintenance (PM) and Service activities.

The SOPs should be detailed enough to guarantee tasks are completed consistently regardless of which individual performs the work. The following are examples that may be included in SOPs:

- Calibrate sensors (temperature & pressure) and integrity test equipment.
- Do filter integrity testing.
- Identify actions in case of O-ring damage during integrity testing: is the filter not useable or is the O-ring replaced?
- Properly inspect filter elements and housing gaskets for signs of defects and failures.
- Identify actions when maximum cycle count is reached: are filters inspected then discarded, or can some be rotated from a primary location to a secondary location?
- Identify actions to take when an issue is detected.

11.4.5 Documentation

Documentation is critical for all systems and even more so for aseptic systems due to their complexity. This documentation should include a baseline of information for how the system was set up, functioning at start-up and validated. Ongoing documentation collected from daily operations and testing can be compared against this baseline to verify proper operation and assist in troubleshooting when the need arises.

11.4.5.1 Validation Documentation

Validation and change control are part of a continuous process through the life of each food process system, and consequently, all the validation information kept in binders or files should be retained until that system has reached the end of its useful life. Validation documentation must be stored and available at the factory level. It describes what was done, why it was done in a certain way, and the results. This allows others to review and recreate the validation work if necessary.

The validation documentation on file should include any Qualification, Automated Control System Validation, and Microbiological Validation work.

The output of the validation work should be documentation that clearly states what the critical factors are and the associated limits to deliver the required performance during sterilization and operation.

11.4.5.2 Record Keeping

Records are necessary to document the performance of the system and help identify affected product when an issue is found. The necessary documents should be identified in the HACCP Plan. Management of Change documentation for evaluation of changes should be organized and easy to follow.

The scheduled process should include the critical factors identified for filtration and the records should prove the filters are being used in accordance with the specifications provided by the filter manufacturer and/or those developed and documented during the validation process.

All documents associated with Preventative Maintenance and Service should include, but may not be limited to:

- date
- technician performing the work
- standard used (calibration or integrity testing)
- filter serial numbers and location where the filter is/was used on the equipment
- documentation of filter replacements (as required on FDA Aseptic Audit Form)
- clear identification of comments and any corrective actions

If filters are rotated, a method to track where a specific filter was used in the system and at what time is necessary. Validation paperwork/COA that is provided with new filter elements should be kept on file as well for documentation and traceability purposes (*e.g.,* global efficiency, scan test, initial pressure drop data, *etc*.)

11.4.6 Filter Failures and Resulting Corrective Actions and Product Disposition

Even with all the upfront work to prevent issues, a filter failure is likely to happen at some point the longer an overall system is in service. It is important to identify different scenarios where conditions go beyond control and/or a deviation occurs which could impact product before they happen. Possible scenarios are shown here.

- One filter in a redundant system fails. If the second filter passes integrity testing is everything good? Are extra product samples inspected?
- What will the procedure be if the second filter fails as well? Is all the product considered bad? Can an increased sampling plan be used to release product?
- False integrity test failures are caused by equipment issues or even “wet” filters depending on the test equipment. What will be the procedure to identify this as a possible cause?
- High temperature or pressure alarm occurs during sterilization.

SOPs developed for these types of issues should be clear in how the situation will be handled and who will be notified. Alignment is critical between Operations, Maintenance, Quality, and the Process Authority to ensure the appropriate actions are taken in a timely manner. This can reduce the amount of product impacted by an issue. Product disposition will typically follow a risk assessment-based approach considering the type of product, end consumer, and any additional testing results.

Filter failures must be identified and documented detailing the root cause and corrective actions taken. Adequate record keeping can aid the process. Review of records for General Production, Maintenance and Testing, and Management of Change documentation can help pinpoint the cause or highlight an area for further review.

Common types of failures include temperature abuse, high pressure differential, exposure to CIP chemicals, improper handling/installation. It is important to use the root cause information from a failure to identify future prevention opportunities.

12 Glossary

Authors' Note: Definitions of important terms and acronyms from this *Guideline* are provided in the context of their use in this document.

ADAPTOR:
Component of a filter cartridge: hardware which connects the cartridge to the filter housing.

AEROSOL:
A dispersion or suspension of very small liquid droplets in air.

AEROSOLIZED:
In the form of liquid droplets dispersed or suspended in air.

AEROSOL BACTERIAL CHALLENGE TESTING:
In microbial filter validation, a method in which a known concentration of bacteria is finely dispersed or aerosolized in dry air and passed through the filter, to determine microbial filter retention performance under dry air conditions. Upstream bacteria counts are compared with downstream bacteria counts to determine the degree of titer reduction.

AEROSOL CHALLENGE INTEGRITY TEST:
A filter integrity test similar to a DOP test, which mimics an aerosol bacteria challenge. It can be used on both membrane and depth cartridge filters. A known concentration of finely dispersed food grade oil droplets is passed through the filter, to determine oil droplet filter removal performance under dry air conditions. Oil droplet removal is correlated with microbial removal in dry air conditions.

AEROSOL SPORE CHALLENGE TESTING:
In microbial filter validation, a similar test to aerosol bacteria challenge testing methodology, typically using the test organism *B. atrophaeus* (historically referred to as *Bacillus subtilis* var*. niger*) spores.

AIR:
In this *Guideline*, we use the term "air" to refer to any gases used in aseptic production, excluding steam.

AIRFLOW RATE:
Refers to the filter manufacturer's published volumetric airflow rate for a single filter unit, typically expressed in normal cubic meters per hour (Nm^3/hour) or standard cubic feet per minute (scfm). This flow rate is inherently influenced by air type, supply pressure, and temperature. In sizing, the airflow rate is selected to result in a low initial ("clean") differential pressure across the filter.

AIR VELOCITY:
The rate of air movement measured in distance traveled per unit of time. Air velocity is commonly measured in meters per second (m/s) or feet per minute (ft/min).

By multiplying air velocity by the cross-section area of a pipe, one can determine the volumetric airflow rate past a point in the pipe per unit of time. *Volumetric flow* is usually measured in cubic meters per hour(m^3/hour) or cubic feet per minute (ft^3/min). See Filtration Flow Rate.

AISI:
American Iron and Steel Institute. A membership Institute that advocates for and educates about a sustainable American steel industry. https://www.steel.org

ASEPTIC COMMISSIONING TEST:
The Aseptic Commissioning Test is part of Qualification. It confirms that the aseptic line is capable of meeting the required acceptance criteria for commercial sterility and sustaining these results with statistical repeatability. This test allows implementation of challenge conditions and provides evidence the system complies with the design specifications in all main operations.

ASEPTIC PROCESS:
The processing and packaging of a commercially sterile product into sterilized containers, followed by hermetic sealing with a sterilized closure in a manner that prevents viable microbiological recontamination of the sterile product.

ASEPTIC PRODUCT/PACKAGE:
A product and/or package which is commercially sterile at normal conditions of storage and distribution, and which has been produced by an aseptic process.

ASHRAE:
American Society of Heating, Refrigeration and Air-Conditioning Engineers. A worldwide membership organization which focuses on sustainable technologies in the built environment. It focuses on building systems, energy efficiency, indoor air quality, refrigeration and sustainability. Provides research, standards writing, publishing and continuing education. https://www.ashrae.org

ASHRAE 52.2:
"Method of Testing General Ventilation Air-Cleaning Devices for Removal Efficiency by Particle Size" is a standard which establishes a test procedure for evaluating the performance of air-cleaning devices as a function of particle size. It established the MERV value of an air filter. It is similar but not identical to ISO 16890. Of particular importance to the long-term particle capture efficiency of these filters is the test method described in Appendix J, which is indicative of continued maintained MERV efficiency throughout the life of the filter.

ASTM:
ASTM used to stand for American Society of Testing and Materials. However, today it is ASTM International, a body of international members who develop voluntary consensus standards, related technical information and services which are widely used around the world in many applications. These standards go far beyond the original scope of materials, and today promote public health and safety, the environment and overall quality of life. https://www.astm.org

ATCC:
American Type Culture Collection. A nonprofit organization which collects, stores, and distributes standard reference microorganisms, cell lines and other materials for research and development. It is the world's largest biological culture repository. https://www.atcc.org

AUTOCLAVE:
A chamber for sterilizing filters or equipment by using saturated steam at constant high temperature and pressure, at minimum of 121 °C (250 °F), 1 barg (14.7 psig).

AUTOMATED CONTROL SYSTEM VALIDATION:
A methodical and documented approach to provide a high level of assurance the automated system performs as designed in a repeatable manner. This includes the identification, corrective action, and recording of issues that can impact the sterility of the system.

BACILLUS ATROPHAEUS (B. ATROPHAEUS):
Typical microorganism used in spore form as a biological indicator to demonstrate successful chemical (hydrogen peroxide) sterilization of HEPA filters or to demonstrate aerosol bacterial spore retention by cartridge filters. Formerly known as *B. subtilis* var. *niger* strains, which have been reclassified as *B. atrophaeus*. Both names may be seen in literature.

BACILLUS SUBTILIS (B. SUBTILIS)* VAR *NIGER:
Typical microorganism used in spore form to do aerosol bacterial spore challenge testing, now reclassified as *B. atrophaeus.* Both names may be seen in literature.

BACTERIA:
Bacteria are microscopic living organisms, usually one-celled, that can be found everywhere. They can be dangerous, such as when they cause infection, or beneficial, as in the process of fermentation (such as in wine). They have a cell wall and characteristic shape (*e.g.*, round, rod-like, spiral or filamentous), lack a defined cell nucleus, and reproduce by cell division. Some bacteria form spores highly resistant to heat, dehydration, radiation and chemicals.

BACTERIAL CHALLENGE:
Term used when testing the bacterial retention of a microbial rated filter.

BACTERIOPHAGE:
A virus that lives within a bacterium, replicating itself and eventually destroying the bacterial cell.

BCAS:
British Compressed Air Society. UK trade association for compressors, air treatment and vacuum products. Plays a key role in setting standards and Codes of Practice, including "Food and Beverage Grade Compressed Air Best Practice Guideline 102-1." https://www.bcas.org.uk

BIOBURDEN:
The load or level of microorganisms in a substance to be filtered. Natural microbial flora present in a fluid.

BLOW DOWN TIME:
Amount of time required for drying of cartridge filters after steam sterilization or after integrity testing, so they can be put back into operation.

***BREVUNDIMONAS DIMINUTA (B. DIMINUTA)*:**
Model bacteria used to challenge sterilizing-grade cartridge filters, to determine their microbial removal efficiency. At a defined challenge level of $10^7/cm^2$ of effective filtration area for sterilizing-grade air filter cartridges, sterile filtrate (with zero viable counts) must be achieved. *B. diminuta* (ATCC 19146) measures approximately 0.3-0.4 µm x 0.6-1 µm.

BRIDGING:
One of the mechanisms involved in the filtration mechanism of size exclusion. Occurs when multiple contaminant particles collect on a filter pore, causing pore blockage due to their combined size. Can prevent contaminants smaller than the pore from passing through.

BROWNIAN MOTION:
The continuous, random zigzag motion of minuscule particles or microorganisms suspended in air. The motion is caused by impact of the molecules of the air upon the particles.

BUBBLE POINT INTEGRITY TEST:

A filter cartridge integrity test used on membrane filters, based on the air pressure required to expel a wetting fluid from the largest filter membrane pores. If the test pressure is lower than the minimum allowed bubble point pressure specification, this is an indication of a defect and a loss of filter integrity.

BUBBLE POINT PRESSURE:
The air pressure at which a wetting fluid (usually an alcohol/water mix) in a wetted, hydrophobic air membrane filter is pushed out of the largest filter pores and a steady stream of air bubbles is emitted from the filter into a downstream liquid-filled receptacle.

CAGE:
Component of a filter cartridge: outer hardware cylinder, which encases the cartridge and protects the pleat pack.

CARTRIDGE:
Typical cylindrical configuration of disposable filters.

CFU (COLONY-FORMING UNIT):
See Colony-Forming Unit.

CHALLENGE CONDITION:
See Worst-case Condition.

CHALLENGE LEVEL:
In cartridge filter testing methodology, refers to the number of contaminants which are in the unfiltered fluid. Expressed as an 'area challenge' (*i.e.,* number of contaminants per effective filter surface area), or as a 'total challenge' (*i.e.*, total number of contaminants per cartridge). A comparison of the challenge level upstream of the filter *versus* the number of contaminants found in the filtrate downstream of the filter determines the retention efficiency of the filter.

CHALLENGE MICROORGANISM:
The microorganism which is used to determine filter retention efficiency. A model bacterium is typically used as a standard, and in sterilizing-grade cartridge air filtration this bacterium is *B. diminuta.*

CHALLENGE TEST:
The rigorous testing which is carried out by filter manufacturers to characterize the microbial removal performance of filter cartridges. The filter is exposed to, or challenged with a defined amount of viable model microorganisms under defined test conditions.

CHALLENGE TEST CONDITIONS:
Test parameters used in filter claims validation: size, mass and nature of contaminants, air velocity, air humidity. Has significant impact on filter retention performance.

CLAIMS VALIDATION:
Validating the filter's claimed properties and performance. This is the filter manufacturer's task.

CLEANING IN PLACE (CIP):
Procedure by which the interior surfaces of food manufacturing equipment, pipes, vessels and other associated fittings are cleaned and sanitized at the end of production runs. Such cleaning is automated and occurs without disassembly of the installation. It involves the use of water, chemicals, and heat.

COLONY-FORMING UNIT (CFU):
A unit used to estimate the concentration of viable bacteria or fungal cells (*e.g.*, mold, yeast) in a sample. Viable is defined as the ability to multiply under the controlled conditions. After culturing the microbes on

an agar plate, the number of visible colonies (cfu) present can be multiplied by the dilution factor to provide a cfu/ml result.

COMMERCIAL STERILITY:
The condition achieved by the application of heat, chemical sterilants, filtration or other appropriate treatment that renders the food, aseptic equipment and containers free from viable microorganisms or spores that can reproduce under normal, non-refrigerated storage and distribution conditions or that have a public health significance (21 CFR113.3e[37]).

COMMISSIONING:
A methodical, documented process by which an equipment, system or facility (which is installed, is complete or near completion) is tested to verify if it meets and functions according to established design requirements, specifications and stakeholder expectations.

COMPATIBILITY:
Term used in relation to the non-reactivity of filter materials with the substance to be filtered, or any substances which come into contact with the filter.

CONTAMINANTS:
Microorganisms, particles or other undesirable materials that can be removed by filtration.

CORE:
Component of a filter cartridge: inner tube, which supports the pleat pack.

COST OF OWNERSHIP (in filtration):
Overall cost for the filtration process, based on disposable filter and filter hardware cost, filter service life, filter-related maintenance, *etc.*

CRITICAL AREA FILTRATION:
Meaning those areas of the aseptic process in which air comes into contact with product or packaging material after it has been rendered commercially sterile.

CRITICAL CONTROL POINT (CCP):
FDA defines a critical control point as a step in the production process at which control can be applied and is essential to prevent or eliminate a food safety hazard or reduce it to an acceptable level.

CRITICAL LIMIT (SET POINT):
The limit which once exceeded, will deviate the process from a sterile or aseptic condition.

CULINARY STEAM:
Steam quality suitable for exposure to food, packaging materials, filters, or equipment surfaces which contact the food. Steam of culinary quality is free of undesirable physical debris, oils and other organic volatile substances.

DEPTH FILTER:
A matrix of randomly distributed fibers creating a tortuous path which may have pores of undefined size and shape. Pores may be fixed or unfixed.

DESIGN SPECIFICATION (or DESIGN REQUIREMENTS):
Defines the equipment/system based on the User Requirements Specification (URS) and Functional Requirements (FR) Specification This provides the detail necessary to actually build the system.

DESTRUCTIVE TEST:
In cartridge filter performance monitoring, a microbial challenge test which evaluates filter integrity in such a way that the filter is no longer usable after the test. Result is correlated to a non-destructive test (integrity test) for routine cartridge filter monitoring. See also non-destructive test.

DIFFERENTIAL PRESSURE (air):
The difference in pressure between the upstream and downstream sides of equipment components, such as filters, valves, *etc.*, caused by the resistance of the component assembly to airflow. Also referred to as pressure drop. Measurement units are bard (metric) or psid (English). The term is further described with modifiers such as “applied,” “available,” “clean,” “dirty,” “initial,” or “maximum.”

DIFFUSIONAL INTERCEPTION (or DIFFUSION):
A filtration mechanism only found in air filtration, due to Brownian motion of suspended particles or microorganisms in air. This mechanism enables the capture of very small contaminants < 0.1-0.3 µm, which are smaller than the pore sizes of the filter. The contaminants leave the air stream lines of flow, impact the filter medium, and are retained. The effect of diffusional interception is highest at lower air flow rates and dry air.

DIFFUSIONAL FLOW INTEGRITY TEST:
Also known as Forward Flow Integrity Test. A filter cartridge integrity test for membrane filters, based on the measurement of the rate of air diffusional flow through the pores of a wetted hydrophobic filter membrane. A measured diffusional flow value, which exceeds the upper specification limit for the test filter at the appropriate test pressure will typically indicate a defect and a loss of filter integrity.

DIRECT INTERCEPTION:
See Size Exclusion.

DOP:
Acronym for Dispersed Oil Particulate. The name is based on dioctyl phthalate, a plasticizer that can be aerosolized to particles of extremely uniform size of the order of 0.3 µm. In the DOP test, retention of DOP aerosol is used as standard procedure for aerosol challenge testing of air filters. As DOP is classified a suspected carcinogen an FDA approved natural mineral oil is usually substituted.

DOWNSTREAM (OUTLET) SIDE (of filter):
The filtrate or effluent side of the filter *(i.e.,* where the filtered fluid exits the filter).

DRAINAGE LAYER:
Component of a filter cartridge: pleated polymeric material, which supports the filter media on its downstream side.

DURABILITY:
In filters, refers to robustness in operation, *i.e.,* how the filter holds up to typical stressors during operation, such as temperature, sterilization exposure, and differential pressure.

EC 1935/2004:
EU's framework regulation for materials and articles that are expected to come into contact with foods under normal and foreseeable use conditions; it sets out general requirements for all food contact materials (FCMs).

EFFECTIVE FILTRATION AREA (EFA):
The surface area of the filter media that the fluid flows through during the filtration process.

EFFLUENT:
Also called Filtrate. The fluid which has passed through a filter.

ELECTROSTATIC ATTRACTION (or PRECIPITATION):
A filtration mechanism which takes place in both liquid and air filtration. Contaminants are attracted to the filter media due to opposite electrostatic charges. In air filtration, charged contaminants are attracted to oppositely charged filter media.

EN 1822 (PART 1): A European Norm for the definition, classification and manufacturers' qualification of Efficient Particulate Air (EPA), High Efficiency Particulate Air (HEPA) and Ultra Low Penetration Air (ULPA) filters. Testing confirms the filters' removal efficiency against MPPS. EN 1822 part 1 (Classification, performance testing, marking) still applies. EN 1822 parts 2-5 have been superseded by ISO 28463 parts 2-5.

END CAP:
Component of a filter cartridge: flat hardware pieces that are thermally welded to both ends of the cylindrical cartridge to seal them.

EPA:
Acronym for "Efficiency Particulate Air" filter. An extended-medium, dry-type filter in a rigid frame when tested at rated airflow having a minimum particle collection efficiency of 85 – 99.5 % for MPPS particles.

EPDM:
Acronym for Ethylene-Propylene Diene Monomer. A synthetic rubber which is suitable for use in a diverse array of applications, such as O-ring material.

EU 10/2011:
The Commission Regulation (EU) No 10/2011 is a specific measure regarding plastic materials and articles intended to come into contact with food, as mentioned in the European Framework Regulation EU 1935/2004.

EXTRACTABLES:
Chemicals which may be leached from a filter during a filtration process, typically by exposure to liquid; usually tested for by soaking in liquid model simulants under controlled conditions. Food contact compliance standards may require that certain levels of extractables not be exceeded.

FACTORY ACCEPTANCE TEST (FAT):
The Factory Acceptance Test (FAT) is a process that evaluates the equipment during and after the assembly process by verifying that it is built and operating in accordance with design specifications. FAT ensures that the components and controls are working properly according to the functionality of the equipment itself.

FALSE FAILURE:
Also called False Positive. An integrity test result which indicates a defective filter, although the filter is in fact integral.

FALSE POSITIVE:
See False Failure**.**

FDA:
United States Food and Drug Administration. An agency within the U.S. Department of Health and Human Services. Protects public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. Also responsible for the

safety and security of the US food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products. https://www.fda.gov

FDA 21 CFR:
Title 21 of the USA Code of Federal Regulations (CFR). Title 21 is reserved for rules of the US Food and Drug Administration.

FICK'S LAW:
Adolf Fick, 1855. Describes physical laws that govern the diffusion of molecules.

FILTER (noun):
A device for removing contaminants (microorganisms, particles, others) from fluid (air or liquid) streams. Consists of the filtering medium and surrounding polymeric or hardware components.

FILTER (verb):
To pass a fluid (air or liquid) containing undesirable contaminants through a filter medium whereby the contaminants are removed from the fluid.

FILTER CLAIMS:
Expected filter performance published by the filter manufacturer, based on standardized tests run under controlled conditions. Such claims may include expected microbial or particle retention performance, differential pressure and temperature stability, chemical compatibility, robustness under steaming conditions, and other aspects which are relevant to the typical application of the filter.

FILTER MEDIA (or MEDIUM):
The permeable material that removes contaminants from a fluid being filtered.

FILTER HOUSING:
The holder into which the filter cartridge or HEPA filter is installed. Typically made of stainless steel and connected to surrounding pipework, tanks*, etc*.

FILTER RETENTION PERFORMANCE:
Describes the ability of air filters to remove a defined level of contaminants from the unfiltered air ("influent"), yielding a certain level of contaminants in the filtrate ("effluent").

FILTRATE:
See Effluent.

FILTRATION:
The process by which contaminants are removed from a fluid by passing the fluid through a permeable, filtering material.

FILTRATION EFFICIENCY:
Also called Removal Efficiency. A measurement of how well a filter retains contaminants. An expression of the titer reduction ratio in percentage terms.

FILTRATION SIZING:
Refers to the size of the whole filter assembly recommended by the filter manufacturer based on the practical application, depending on the published airflow rate.

FILTRATION THROUGHPUT:
Refers to the total volume of fluid which passes the filter over the course of its service life.

FLUID:
In filtration, either air or a liquid that passes the filter.

FORWARD FLOW INTEGRITY TEST:
See Diffusional Flow Integrity Test.

FRAME:
Component of a HEPA filter assembly: the rigid assembly that holds the filter media pack securely in place with no air bypass.

FSMA:
Food Safety Modernization Act, found in FDA 21 CFR Part 117, where key requirements for Good Manufacturing Practice, Hazard Analysis and Risk-Based Preventive Controls for human food are defined. FSMA is transforming the US food safety system by shifting the focus from responding to foodborne illness to preventing it. It gives the FDA new authority to regulate the way food is grown, harvested and processed.

FUNCTIONAL SPECIFICATION REQUIREMENTS (or FUNCTIONAL REQUIREMENTS):
A description of the product to be supplied in terms of the functions it will perform and facilities required to meet the user requirements defined in the User Requirement Specification (URS). The Functional Specification should be written in a way that both the supplier and user understand it. This portion of the documentation is used to support the Operational Qualification (OQ) phase of system validation.

GASKET:
Material inserted between contact surfaces of a joint to ensure a fluid-tight seal. Depending on configuration, can also be referred to as an O-ring.

GAS REMOVAL PERFORMANCE:
Gas filter retention performance in dry gas. Different from the same filter's retention performance in liquid.

***GEOBACILLUS STEAROTHERMOPHILUS* (*G. STEAROTHERMOPHILUS*):**
Typical microorganism used in spore form as a biological indicator to demonstrate successful steam sterilization of cartridge filters.

GLOBAL EFFICIENCY TEST:
A test method used to measure particle removal efficiency of HEPA filters. The basic concept of a Global Efficiency Test is, under rated airflow, to measure the upstream particle concentration and either simultaneously or sequentially measure the downstream particle concentration utilizing a particle counter or photometer. From this data, the global efficiency can be calculated.

GRAVITATIONAL SEDIMENTATION:
A filtration mechanism which takes place in both liquid and air filtration. Contaminants of high density can leave the air flow path, impact the filter media due to gravity, and are retained.

HAZARD ANALYSIS AND CRITICAL CONTROL POINT (HAACP):
A management system which aims to analyze, control and document the chemical, biological, and physiological processes involved in the production of raw materials to the consumption of the final product. The primary purpose of this management system is to ensure the production of safe food products.

HEPA:
Acronym for “High Efficiency Particulate Air” filter. In this *Guideline*, the term HEPA is used as a general term to describe both HEPA and ULPA filters unless otherwise noted.

HYDROGEN PEROXIDE:

A chemical which is widely used for HEPA filter *in situ* sterilization, either mixed with air and vaporized or sprayed as mist at ambient or at slightly elevated temperature.

HYDROPHILIC:
Having an affinity for water; a filter membrane or media which will wet with aqueous solutions.

HYDROPHOBIC, HYDROPHOBICITY:
Literally, fearing water; a filter membrane or media which cannot be wetted by and repels aqueous and other high surface tension fluids; requires pre-wetting with low-surface-tension fluid, such as an alcohol solution, so that the filter pores can be wetted. Hydrophobicity is a measure of the degree to which a hydrophobic filter repels wetting with an aqueous solution; it is expressed in dynes/cm^2.

IEST:
Institute of Environmental Sciences and Technology. A nonprofit, membership organization that provides expert technical guidance through International Standards, Recommended Practices (RP), and education programs. https://www.iest.org

IEST-RP-CC001, -CC002, -CC006, -CC007, -CC021, -CC028, -CC034:
These Recommended Practices (RP) cover basic provisions for HEPA and ULPA filters as a basis for agreement between customers and suppliers.

- IEST-RP-CC001: HEPA and ULPA Filters
- IEST-RP-CC002: Unidirectional Flow, Clean Air Devices
- IEST-RP-CC006: Testing Cleanrooms
- IEST-RP-CC007: Testing Cleanrooms
- IEST-RP-CC021: Testing HEPA and ULPA Filter Media
- IEST-RP-CC028: Minienvironments
- IEST-RP-CC034: HEPA and ULPA Filter Leak Tests

IFTPS:
Institute for Thermal Processing Specialists. A nonprofit organization established exclusively for the purpose of fostering education and training for those persons interested in procedures, techniques and regulatory requirements for thermal processing of all types of food or other materials, and for the communication of information among its members and other organizations. https://www.iftps.org

IMPINGER AIR SAMPLERS:
Impinger samplers use a liquid medium for particle collection, and make use of the principle of impingement. Particle-laden air is passed at high velocity onto a wetted glass surface, captured on the surface and resuspended in the surrounding fluid. In microbial aerosol challenge, impinger sampling involves passing a known volume of air through the impinger containing a specific liquid, such as a recovery buffer, that captures and suspends the microorganisms. Using the input and effluent concentrations, filter retention levels may be determined.

IMPACTOR AIR SAMPLERS:
Impactor samplers use a solid or adhesive medium, such as agar, for particle collection. Air is drawn into a sampling head by a pump or fan and accelerated, usually through a perforated plate (sieve samplers), or through a narrow slit (slit samplers). When the air hits the collection surface any suspended particles impact onto the collection surface. After a defined air volume passes through the sampling head, the agar plate can be removed and incubated. After incubation, the number of visible colony-forming units in the sampled air is counted.

IN SITU:

Latin for "in place." Sterilization or integrity testing of a filter in its location within the system rather than as an ancillary operation such as steaming a filter in an autoclave or testing its integrity using an offline integrity test stand.

INERTIAL IMPACTION:
A filtration mechanism which takes place in both liquid and air filtration. Even as the air stream lines flow in a tortuous path through the filter, the carried contaminants continue in a straight line due to their inertia, impact the filter media, and are retained. Effective primarily for particles about 0.5-1 µm and larger.

INERT:
Chemical inactivity; totally unreactive.

INFLUENT:
The contaminated fluid which has not yet passed through a filter; unfiltered fluid.

INITIAL PRESSURE DROP:
A measure of airflow resistance through a new and unused filter.

INLET PRESSURE:
The pressure of the fluid on the inlet side of the filter. Also called upstream pressure, line pressure or supply pressure.

INSTALLATION QUALIFICATION (IQ):
Installation Qualification is an important part of Qualification. It verifies and documents that the equipment and system is installed per approved specifications.

INTEGRITY TEST:
A non-destructive test which is used to predict the microbial retention performance of a cartridge filter. The valid use of this test requires that it be correlated to a standardized bacterial retention test. Examples: Bubble Point Test, Diffusional Flow (Forward Flow) Test, Pressure Hold (Pressure Decay) Test, Water Intrusion Test (WIT), Aerosol Challenge Integrity Test.

INTERCEPTION:
A filtration mechanism which takes place in both liquid and air filtration. Small contaminants follow the streamlines of airflow, impact the filter media in their path, and are retained.

ISO:
International Organization for Standardization**.** An independent, non-governmental international organization made up of members from 165 national standards bodies. It develops voluntary, universally-recognized standards agreed on by experts. These standards promote safety and effectiveness of products, services, systems and technologies in government, business and technical sectors. https://www.iso.org

ISO 8573 (PARTS 1-9):
"Compressed Air" is a collection of international compressed air standards, consisting of 9 parts. Part 1 specifies the purity of compressed air required in the compressed air system. Parts 2-9 specify test methods for testing specific contaminants in the compressed air system.

- ISO 8573-1: Contaminants and purity classes
- ISO 8573-2: Test method for oil aerosol content
- ISO 8573-3: Test methods for measurement of humidity
- ISO 8573-4: Test methods for solid particle content
- ISO 8573-5: Test methods for oil vapor and organic solvent content
- ISO 8573-6: Test methods for gaseous contaminant content

- ISO 8573-7: Test method for viable microbiological contaminant content
- ISO 8573-8: Test methods for solid particle content by mass concentration
- ISO 8573-9: Test methods for liquid water content

ISO 16890 (PARTS 1-4):
"Air Filters for General Ventilation" is the relatively new international standard for testing and classifying air (HVAC) filters according to their particle removal efficiencies, based on well-defined common testing methods. Published in 2016, the new test standard was intended to harmonize the two main world standards which were currently in existence, namely EN779 (Europe), and ASHRAE 52.2 (USA). Other regions of the world typically followed one of these two standards.

ISO 16890 provides information for testing filter efficiency (at clean and conditioned efficiency), pressure drop and test dust capacity.

- ISO 16890-1: Technical specifications, requirements and classification system based upon particulate matter efficiency (ePM)
- ISO 16890-2: Measurement of fractional efficiency and air flow resistance
- ISO 16890-3: Determination of the gravimetric efficiency and the air flow resistance *versus* the mass of test dust captured
- ISO 16890-4: Conditioning method to determine the minimum fractional test efficiency

ISO 29463 (PARTS 1-5):
"High Efficiency Filters and Filter Media for Removing Particles in Air" is a new global standard for EPA, HEPA, and ULPA filters. It was developed using the European norm EN 1822 (parts 1-5) as the basis, with revisions to accommodate the practices of other national standards from the U.S., Japan and others. It was developed to correct the problem of a lack of equivalence between current standards. Defines 13 different filter classes. Parts 1-5 describe different aspects of the standard.

- ISO 29463-1: Classification, performance, testing and marking
- ISO 29463-2: Aerosol production, measuring equipment and particle-counting statistics
- ISO 29463-3: Testing flat sheet filter media
- ISO 29463-4: Test method for determining leakage of filter elements
- ISO 29463-5: Test method for filter elements

ISOPROPYL ALCOHOL (IPA):
Typical low-surface-tension wetting fluid used in a defined concentration to wet hydrophobic membrane filters for purposes of integrity testing.

LEAK TEST:
A test method used to measure particle retention performance of HEPA filters. The basic concept of leak testing is, under rated airflow with a known/measured particle concentration, to scan a probe with overlapping strokes over the face of a HEPA filter, that is connected to a measuring device such as a particle counter or photometer looking for particle penetration that exceeds the acceptance criteria.

LIQUID BACTERIAL CHALLENGE TESTING:
In microbial filter validation, a method in which a known concentration of bacteria in a liquid is passed through the filter, to determine microbial filter retention performance under liquid conditions. The upstream bacteria count is compared to the downstream bacteria count to determine the degree of titer reduction after filtration. Represents worst-case filtration conditions.

LIQUID REMOVAL PERFORMANCE (in air filters):
Air filter retention performance in liquid. Different from the same filter's retention performance in air.

LIVE STEAM STERILIZATION:

Sterilization by flowing saturated steam through a vented vessel or system, at minimum of 121 °C (250 °F) and 1 barg (15 psig) (but can be performed at higher temperatures and corresponding saturated steam pressures).

LOCATING FIN:
Also called Spear or Bomb Fin. Component of a filter cartridge: hardware piece at closed end of the cartridge, that helps maintain the filter position within the filter housing.

LOCATING TABS:
Component of a filter cartridge: plastic tabs which assist, by a 'twist-lock' motion, in properly securing a filter cartridge into the filter housing.

LOGARITHMIC ("LOG") REDUCTION VALUE:
Also called LRV. Common logarithm of the titer reduction value. This value indicates the filtration efficiency of the filter. The logarithm to the base 10 of the ratio of bacteria in the feed fluid to bacteria in the filtrate. Also used as a ratio of in/out bioburden in other sterilization methods such as autoclaving.

LOW-ACID FOOD AND BEVERAGES:
Any foods, other than alcoholic beverages, with a finished equilibrium pH greater than 4.6 and a water activity (aw) greater than 0.85 (21 CFR113.3n[38]). These products are considered highly sensitive to the growth of potentially harmful microorganisms, and they are therefore subject to more stringent regulation. These products require a more rigorous thermal process in order to be rendered shelf-stable.

MACHINE PROCESS VALIDATION:
In the context of filtration on aseptic systems, this refers to conducting Automated Control System Validation and Filter Sterilization Validation, either at the OEM or at the end user site.

MANAGEMENT OF CHANGE (MOC) PROCESS:
A program which broadly addresses the impacts of changes to processes, systems, materials, or personnel. It consists of standardized methods and procedures to address changes efficiently and promptly. It implements necessary steps to minimize the impact of change-related incidents, including any potential needs for revalidation to ensure the operation returns to a stable status quo.

MANUFACTURING EXECUTION SYSTEM (MES):
An information system that connects, monitors and controls complex manufacturing systems and data flows on the factory floor. The main goal of an MES is to ensure effective execution of the manufacturing operations and improve production output.

MEDIA:
See Filter Media. Also, the nutrient-containing solutions in which cells or microorganisms are grown.

MEDIA PACK:
The package of filter media, typically pleated, that is the primary filtering medium in a HEPA filter.

MEMBRANE CARTRIDGE FILTER:
In disposable filter cartridges, a type of filter consisting of a cast or stretched material with a continuous fixed matrix with pores of defined size. Typical example of membrane material used in air filtration is PTFE.

MERV:
Acronym for Minimum Efficiency Reporting Value. A measurement scale designed by ASHRAE to report the effectiveness of air filters, which is helpful in comparing the performance of different filters. It reports a filter's ability to capture larger particles between 0.3 and 10 µm. The higher the MERV value, the better the filter is at trapping specific types of particles.

MICROBIOLOGICAL VALIDATION:
A validation step carried out at the end user facility on an installed aseptic system as part of Qualification. It verifies that the process that is defined by the equipment program sequence, signals and controls will render the system commercially sterile. Microbiological Validation for filters primarily involves verifying and documenting that installed filter assemblies can be appropriately sterilized (Filter Sterilization Validation).

MICROFILTRATION:
Separation of particles ranging from 0.1µm to 10µm from a fluid by passing the fluid through a filter.

MICRON (µm):
Also called Micrometer. It is a 1/1,000,000 of a meter (1µm = 0.000039 in); 25.4µm = 0.001 inch; 40 µm = approximately the limit of visible detection by the human eye; 60µm = approximately the diameter of a human hair.

MIL-STD-282:
United States Military Standard. This standard covers the methods used in the routine testing and inspection of filter units, protective clothing, gas mask components and related products.

MODEL MICROORGANISM:
The standard microorganism used to run microbial challenge testing, which the filter must be capable of removing. In sterilizing filtration, this microorganism is the bacteria *B. diminuta* (ATCC 19146).

MONODISPERSE AEROSOL:
Aerosol containing one defined size of droplets/particles, *i.e.*, the MPPS.

MOST PENETRATING PARTICLE SIZE (MPPS):
In air filtration, generally between 0.1-0.2 µm in size, although this value can shift based on air flow rate and pressure. This general benchmark is the contaminant size range at which a filter is least efficient in its removal performance, due to the overlapping interaction of the filtration mechanisms of diffusional flow and inertial impaction.

NET FILTRATION RETENTION EFFICIENCY:
Filtration retention performance result based on the combination of all filtration mechanisms at work during air filtration.

NON-DESTRUCTIVE TEST:
In filter quality monitoring, a test which evaluates filter integrity (cartridge filters) or leak tightness (HEPA filters) without damaging the filter. See also destructive test.

OEM:
Acronym for Original Equipment Manufacturers. They design and build machinery for food production. In the case of aseptic equipment, they select and integration filters for the machines.

OPERATIONAL QUALIFICATION (OQ):
Operational Qualification is an important part of Qualification. It verifies and documents that the system or subsystem operates as intended and is capable of repeated operation within the limits defined in the specifications used to design the system. Proves system operation under normal and challenge conditions.

OPERATIONAL SET POINT:
The target for a parameter during operation in normal steady state. Limit set points differ from operational set points to allow parameter fluctuation.

OUTLET PRESSURE:
The pressure of the fluid exiting the outlet side of the filter. Also called downstream pressure.

PARTICLE, PARTICULATE:
Any discrete unit of material structure; a discernible mass having an observable length, width, thickness, size and shape. In filtration, a type of contaminant.

PDA:
Parenteral Drug Association. An organization that develops technical information and expertise to serve the pharmaceutical and biotechnology industries. https://www.pda.org

PERFORMANCE QUALIFICATION (PQ):
Performance Qualification is an important part of Qualification. It verifies and documents that a system performs as expected under simulated real-world conditions.

PFU (PLAQUE-FORMING UNITS):
Plaque-forming units are a measure of the quantity of viruses that are capable of lysing host cells and forming a plaque. Virus counts are based on the fact that each virus will form a plaque on an agar completely covered with bacterial colonies. Because the virus is killing the bacteria, each plaque corresponds to one virus.

The concept of plaque-forming units of virus is equivalent to the concept of colony-forming units of bacteria.

PLEAT PACK:
Component of a filter cartridge: package consisting of pleated filter media, support and drainage layers.

POKA-YOKE:
Japanese term. A Poka-Yoke is any mechanism in any process that helps an equipment operator (*yokeru*) avoid mistakes (*poka*). Its purpose is to eliminate product defects by preventing, correcting, or drawing attention to human errors as they occur.

POLYDISPERSE AEROSOL:
Aerosol containing droplets/particles of sizes between 0.04 and 0.8 ppm, generated by one or multiple aerosol generators.

PORE and PORE SIZE:
A pore is the opening through which the fluid to be filtered flows from the upstream to the downstream side of the filter. Membrane filters are characterized by fixed (defined) pore structure, very fine pores that are tightly packed together, and narrow pore size distribution. Pore size is not necessarily an indicator for microbial filter retention performance.

On the other hand, depth filters are porous however they have no defined pore size or structure. Fluids to be filtered flow in a tortuous path through a fibrous matrix and contaminants are captured throughout the entire depth of the medium.

PREFILTER:
Stage(s) of filtration prior to the final stage. Typically have lower filtration efficiency than the final stage(s).

PREMATURE BLOCKAGE (filter):
Situation in which a filter is plugged due to buildup of particulate contaminants more quickly than expected, creating excessive differential pressure across the filter and a reduction in fluid flow. May occur due to insufficient prefiltration or unexpected presence of upstream particles.

PRE-STERILIZATION:
A term sometimes used to refer to the process of sterilizing equipment (filters, aseptic zones) prior to aseptic production (also known as pre-production sterilization), in order to render it free of viable microorganisms or commercially sterile. In this *Guideline*, we refer to pre-sterilization of equipment as "sterilization." See also Sterilization.

PRESSURE DECAY INTEGRITY TEST:
Also called Pressure Hold Integrity Test. Pressure decay integrity testing operates on the same principle as diffusional flow integrity testing, however rather than measuring the rate of air diffusion through the membrane, the pressure lost in the sealed upstream volume is measured and recorded as air diffuses through the wetted pores of the test membrane. A measured pressure decay value, which exceeds the upper specification limit for the test filter at the appropriate test pressure will typically indicate a defect and a loss of filter integrity.

PRESSURE HOLD INTEGRITY TEST:
See Pressure Decay Integrity Test.

PRESSURE DROP:
The difference in static pressure measured at two points in a dynamic fluid stream, whether liquid or gas. In a gas stream, pressure drop is a measure of airflow resistance through a filter.

PROCESS AUTHORITY:
An individual, group, or expert in the development, implementation and evaluation of thermal and/or aseptic processes (IFTPS Document WP.002.V1[39]).

PSEUDOMONAS DIMINUTA:
Model microorganism previously used in filter claims microbial validation testing. It has been reclassified as *B. diminuta.*

PTFE:
Acronym for Polytetrafluoroethylene. An example of this material is Teflon™. Highly durable and resistant to a broad range of temperatures and chemicals. PTFE is highly hydrophobic and is typically used as the filtration media material in membrane cartridge filters.
Teflon is a registered trademark owned by E.I. Dupont de Nemours & Company.

QUALIFICATION:
A process that is primarily concerned with verifying facility and system aspects that can impact product quality. It involves testing or challenging a component or process against its specification. It includes the record of performance tests documenting and determining conformance to requirements (IQ, OQ, PQ) and is carried out concurrently with Validation activities

REDUNDANT FILTRATION:
The practice of putting two filters with the same removal performance in series.

REMOVAL (RETENTION):
Ability of a filter to retain contaminants suspended in a fluid. When referring to filter performance, both terms are used interchangeably in this document.

REMOVAL (RETENTION) EFFICIENCY:
See Filtration Efficiency.

RETENTION (REMOVAL):
Ability of a filter to retain contaminants suspended in a fluid. When referring to filter performance, both terms are used interchangeably in this document.

SATURATED STEAM:
Also called "live steam," saturated steam is created by raising water to the boiling point, then additionally heating it to vaporize it (addition of latent heat of vaporization). Saturated steam is a condition in which steam and water are in equilibrium, meaning both steam and water are at the same temperature. Saturated steam has a much higher heat transfer capacity than superheated steam, and is recommended for *in situ* steam sterilization. Saturated steam condition is obtained by specific combination of steam pressure and temperature. See also Live Steam Sterilization.

SINGLE OPEN END (SOE):
Filter cartridge configuration in which one end is closed, and the other end, where the filter cartridge mates with the filter housing, is open. SOE filters are the filter configuration of choice for critical filtration tasks because the risk of bypass at the mating points with the housing is greatly minimized.

SITE ACCEPTANCE TEST (SAT):
Site acceptance testing of the system is performed based on the procedures approved by the client. The entire system is tested to determine if the requirements of a specification or contract are met.

SIZE EXCLUSION:
Also called Direct Interception, Sieving, or Straining. A filtration mechanism which takes place in both liquid and air filtration. It is based on the phenomenon of contaminant removal due to their size being larger than the filter pores, mimicking a sieving action. Some particles smaller than the pores may be removed due to bridging.

SOP:
Acronym for Standard Operating Procedures.

SPECIFICATION:
Defining the characteristic properties of a component or process.

SPORE:
Spores are usually unicellular dormant bodies produced by plants, algae, fungi and bacteria that are resistant to environmental conditions, and that can grow under the right conditions into a new organism. Bacteria change into spore form in order to survive harsh conditions. Bacteria spores are highly thermally resistant, and if present, must be eliminated by physical (thermal, irradiation) or chemical (hydrogen peroxide, peracetic acid) processes.

STABILIZATION:
At the initiation of an integrity test, this is the period of time during which the test system comes to an equilibrium prior to test begin.

STANDARD OPERATING PROCEDURES (SOP):
Standard Operating Procedures comprise established or prescribed methods to be followed routinely for the performance of designated operations or in designated situations.

STEAMING IN PLACE (SIP):
A procedure of sterilizing equipment (including filters) in which saturated steam is passed over said equipment *in situ, i.e.,* in their normal location within the system. This approach avoids chances of recontamination which would be the case if equipment were to be sterilized offline.

STERILIZATION:
In this *Guideline*, "sterilization" refers to preproduction sterilization ("pre-sterilization") of equipment (*e.g.* filters, aseptic zones) as well as sterilization of air, product, and packaging materials to render them commercially sterile.

STERILIZATION IN PLACE (SIP):
SIP is also widely used as an acronym for Sterilization in Place, relating to both chemical and thermal sterilization.

STEAM CYCLE:
The time duration during which a filter cartridge is exposed to saturated steam for the purpose of sterilizing the filter. Includes heat-up time, time at desired temperature, and cooldown time.

STERILE, STERILITY, STERILIZATION:
To make or be free of any viable microorganisms. Demonstrated by testing to show the absence of microorganisms.

STERILIZING AGENT:
The medium or method by which sterilization of filters takes place*, e.g.,* steam, hydrogen peroxide, *etc*.

STERILIZING-GRADE CARTRIDGE FILTER:
In air filtration, a cartridge filter which, when challenged with 10^7 model microorganisms *B. diminuta* per cm^2 of effective filtration area, yields sterile effluent in which no viable microorganisms are present. Usually accepted as a 0.2 µm rated *microbial* filter, although the pore size in and of itself does not guarantee the required microbial removal. The only valid method to confirm the performance of a sterilizing-grade filter is not by pore size, but by bacterial challenge validation at defined challenge levels and with proof of sterile effluent downstream.

SUPPORT LAYER:
Component of a filter cartridge: pleated polymeric material, which supports the filter media on its upstream side.

SURFACE TENSION:
Also "interfacial tension." Tendency of the surface of a liquid to contract to the smallest area possible due to cohesive forces among liquid molecules. In the case of hydrophobic filters used in air filtration, water with its high surface tension does not wet these filters. Only low-surface-tension fluids, such as an alcohol solution, can be used to wet the filters out, as is done during integrity testing.

TANK VENT FILTERS:
Tank vents are required to maintain tanks at equilibrium pressure. Under atmospheric conditions, air flows into the tank as the liquid level is lowered, and it flows out of the tank when the tank is filled. Filters mounted on these tanks ("tank vent filters"), particularly in clean/controlled areas reduce contaminants from the air passing into or out of the tanks.

Filters are sized for such applications under what is known as "vent conditions", based on the airflow rate at allowed differential pressure under atmospheric supply pressure conditions.

TECHNICAL PERFORMANCE DOCUMENT:
See Validation Guide. It fulfills the same function as the Validation Guide.

TITER REDUCTION:
Ratio of the number of contaminants upstream to number of contaminants downstream of a filter.

TORTUOUS, TORTUOSITY:
In the case of filtration, defines the twisting, winding path of a fluid through a filter medium, from the upstream side to the downstream side. Tortuosity describes the state of being tortuous.

TOXICITY:
Refers to components of materials which are toxic or poisonous.

ULPA:
Acronym for "Ultra Low Penetration Air" filter. In this *Guideline*, the term HEPA is used as a general term to describe both HEPA and ULPA filters unless otherwise noted.

UNDERSIZING:
The insufficient sizing of a filter assembly such that the initial differential pressure in operation is too high, thus compromising the service life of the filter.

UPSTREAM (INLET) SIDE (of filter):
The feed side of the filter *(i.e.,* where the fluid to be filtered enters the filter).

USER REQUIREMENTS SPECIFICATION (URS):
The requirements of the end user which detail how the system is supposed to perform and what it needs to deliver. This may include the "must haves" for the end user as well as the "nice to haves". These requirements are used during Performance Qualification to evaluate performance.

VALIDATION:
Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce product meeting its predetermined specifications and quality attributes. Validation confirms that requirements can be consistently fulfilled.

VALIDATION GUIDE:
Also called Technical Performance Document. Illustrates the validation work (actual background test work) performed by cartridge filter manufacturers to support claimed filter performance and to establish performance specifications.

VARIABLE FREQUENCY DRIVE:
Controls device that varies voltage and frequency to electric motor based upon present conditions. Often used to adjust airflow through a HEPA filter when accumulating dirt increases pressure drop.

VENTURI EFFECT:
Relative fluid pressure drop in a constricted section of a pipe, which allows a surrounding second fluid to be injected into the stream of the first fluid by this relative underpressure.

VERIFICATION:
The procedures by which the proper functioning of the commissioned equipment is continuously verified in day to day operation. Comparing a component or process with a specification to test whether the tested component or process is equal to the specification. Verification confirms that requirements have been fulfilled.

VIABLE MICROORGANISM:
A microorganism that is capable of growth, given the right conditions.

WATER INTRUSION INTEGRITY TEST:
A filter cartridge integrity test for membrane filters, based on the evaporative water flow rate in vapor form

through the pores of the hydrophobic filter membrane. In an integral filter, this evaporation rate does not exceed a certain limit, whereas in a defective filter, water breaks through the membrane.

WETTING AGENT:
Also called a wetting fluid. A low-surface-tension fluid (such as an alcohol solution) applied to a hydrophobic filter membrane to assure wettability by a high surface tension fluid such as water, useful in filter integrity testing.

WORST-CASE/CHALLENGE CONDITION:
During Microbiological Validation of installed equipment, this is a limit applied to deliver a lower sterilizing effect than what would be expected at the Critical Limit.

13 End Notes

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