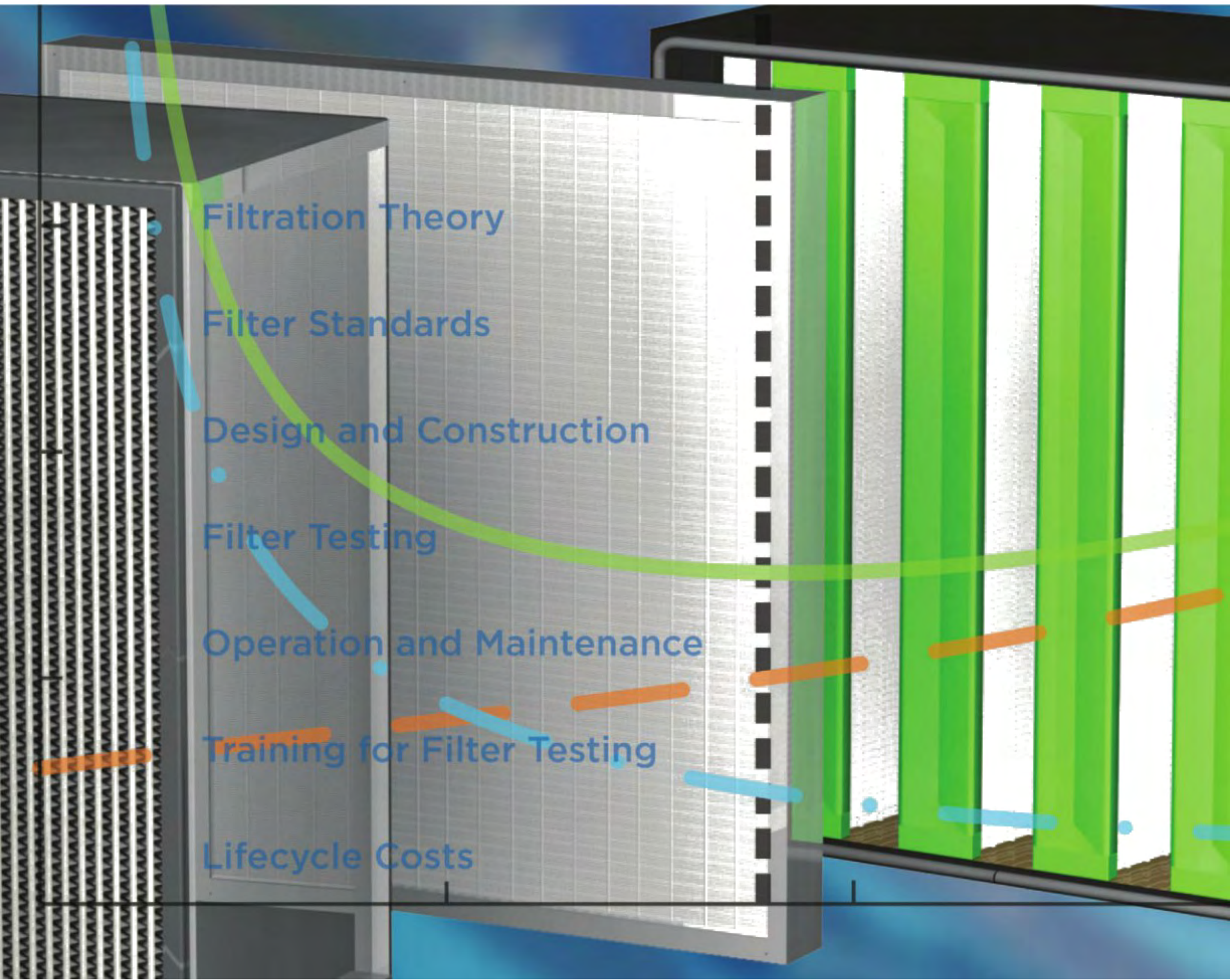
ISPE®

GOOD PRACTICE GUIDE:

HVAC and Process Equipment Air Filters



GOOD PRACTICE GUIDE:

HVAC and Process Equipment Air Filters

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Preface

Heating, Ventilation, and Air Conditioning (HVAC) systems can critically affect the ability of a pharmaceutical facility to meeting its objective of providing safe and effective product to the patient. The *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning (HVAC)*, published September 2009, provides excellent advice regarding the design of HVAC systems in the pharmaceutical industry. Among the key components of any pharmaceutical HVAC system are the types of air filtration incorporated into the system. The *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning (HVAC)* does address the subject of air filters, their specification, application and testing, and other important considerations. This Guide, the *ISPE Good Practice Guide: HVAC and Process Equipment Air Filters* delves much deeper into the subject of air filters in HVAC and process equipment applications and aims to be the definitive guide to air filters in the pharmaceutical industry, as used for:

- HVAC systems
- Pharmaceutical process equipment
- Laboratory equipment
- Containment systems

This Guide has been written by leading experts in the pharmaceutical industry on the subject of HVAC and air filters. This Guide is intended to be an indispensable reference on the selection, specification, testing, maintenance, and operation of filters in pharmaceutical applications. It is intended to be used to supplement guidance provided in the *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning (HVAC)* and the HVAC and process equipment sections in the various facility ISPE guides (*ISPE Baseline® Guide: Volume 3 – Sterile Product Manufacturing Facilities*, *ISPE Baseline® Guide: Volume 2 – Oral Solid Dosage Forms*, *ISPE Baseline® Guide: Volume 6 – Biopharmaceutical Manufacturing Facilities*, *ISPE Good Practice Guide: Packaging, Labeling, and Warehousing Facilities*, etc.).

This Guide also explains the principles, objectives, and methods of filter testing during manufacturing and on-site, and includes a suggested approach to evaluate the impact of lifecycle costs in filter selection.

This Guide is written considering the European, US and Japanese requirements (and other countries depending where the authors have relevant experience) on the basis that these regulations provide a reference for other country regulations.

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Table of Contents

1 Introduction

1.1 Background

In the pharmaceutical industry, the correct specification and application of air filters in HVAC systems and certain process equipment are critical to maintaining the environment at an appropriate cleanliness.

This Guide is intended to be used as supplement to the *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning (HVAC)* [1], providing detailed information as to the selection, specification, installation, operation, and maintenance of HVAC and certain process air filters in meeting and maintaining the required environmental cleanliness. This Guide also explains the principles and objectives of filter testing conducted during manufacturing and after installation. Guidance is also provided for air filters in process equipment applications.

1.2 Purpose

This Guide aims to be a valuable reference on the selection, application, specification, testing, and operation and maintenance of filters in the pharmaceutical industry as used for:

- HVAC systems
- Pharmaceutical process equipment
- Laboratory equipment
- Containment systems

The information presented in this Guide is intended to supplement existing ISPE Guidance Documents. The ISPE Baseline® Guide series [2] for pharmaceutical facilities and associated ISPE Good Practice Guides [3] discuss the clean environment required for different types of facilities and processes, and address some of the requirements for air filters. The *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning (HVAC)* [1] addresses the recommended selection and application of filters from a system perspective for different types of HVAC systems (for sterile products, Oral Solid Dosage (OSD), Active Pharmaceutical Ingredients (API), laboratories, warehouses, etc.). This information is not repeated in this Guide.

Filter technology advancements generally outpace regulatory guidances. This Guide describes current technologies and their application as it relates to the current guidance. The document is written primarily considering the European, US, and Japanese regulatory requirements [4, 5, 6] on the basis that these regulations provide a reference for most other country regulations. Regulations for other countries have been added where the authors of this Guide have relevant experience.

Note: It is recognized that several industry standards and regulatory reference documents listed in this Guide are in the process of being reviewed and revised. As of the Guide publication date, this Guide reflects an understanding of these final documents.

1.3 Structure of the Guide

The chapters in this Guide are structured to make it easy for the reader to find the relevant content:

- Chapter 2: How filters work
- Chapter 3: Industry standards and references for air filters
- Chapter 4: Filter design and construction
- Chapter 5: Applications of HVAC and process air filters
- Chapter 6: Filter testing
- Chapter 7: Verification (commissioning and qualification) of air filters
- Chapter 8: Operational and maintenance considerations of air filters
- Chapter 9: Training for filter testing
- Chapter 10: Lifecycle costs
- Chapter 11 (Appendix 1): Regulatory and other guidance for air filters
- Chapter 12 (Appendix 2): Example forms

2 Fundamental Concepts in Air Filtration

2.1 Filtration Theory

2.1.1 Particle Collection

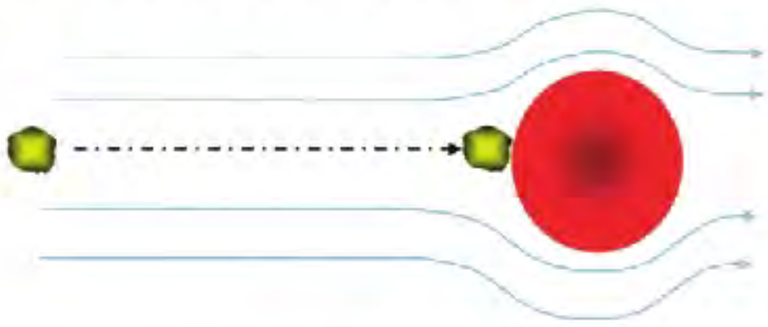
The ability of a filter to collect particles, i.e., the efficiency of a filter, is largely determined by various physical and mechanical phenomena such as diffusional, interception, inertia, and straining effects. These mechanisms of particle collection may not be intuitive since the effects of gravity and momentum become less significant as particle sizes approach micron and sub-micron sizes. Electrostatic effects between particles and fibers can also play a part in particle capture, but caution should be exercised when selecting a filter marketed for this feature. In many cases, the electrostatically charged behavior of the media is only temporary once the filter is put in use, and the added efficiency significantly decreases with time as a result.

In order to discuss and show the different filtration effects on a fundamental level, it is assumed that particles are spherical in shape with a known diameter. It is also assumed that if a particle touches a filter fiber, it will adhere to the fiber mainly due to van der Waals forces. Electrostatic forces also contribute to the adhesion. The adhesive forces are affected by the material, shape, surface roughness, and size of the particle. The following particle capture effects are discussed in the remainder of this section in an order that relates to their significance as the particle sizes of interest decrease.

2.1.2 Inertia Effect

The inertia effect comes into play when larger particles have too great a mass and inertial force to be able to follow the airflow when it curves around a filter fiber. The particles continue instead along their original path and stick to the face side of the fiber. The inertial force increases with increasing air velocity and increasing particle diameter. See Figure 2.1a.

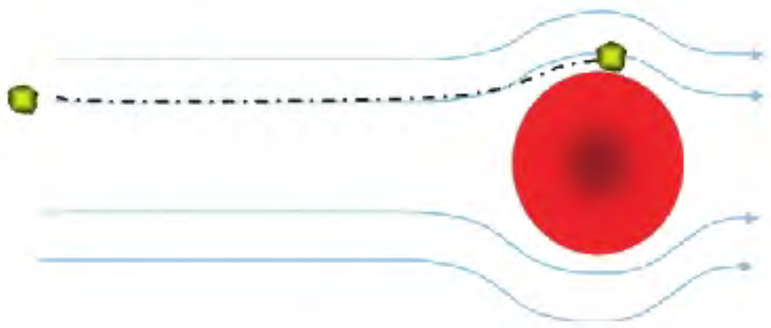
Figure 2.1a: Particle Collection Method – Inertia [7]



2.1.3 Interception Effect

Small, light particles follow the airflow around the filter fiber. If the center of the particle follows a flow path that comes within a distance to the fiber that is equal to or less than its radius, the particle is intercepted and attaches to the fiber. See Figure 2.1b. The interception effect is independent of the air velocity unless the variation is sufficient enough to alter the flow pattern around the fiber. The interception effect increases with increasing particle size, decreasing fiber diameter, and decreasing distance between the fibers. In order to have a good interception effect, a filter medium thus needs to contain a large number of fine fibers, usually with a diameter the same as that of the particles to be collected.

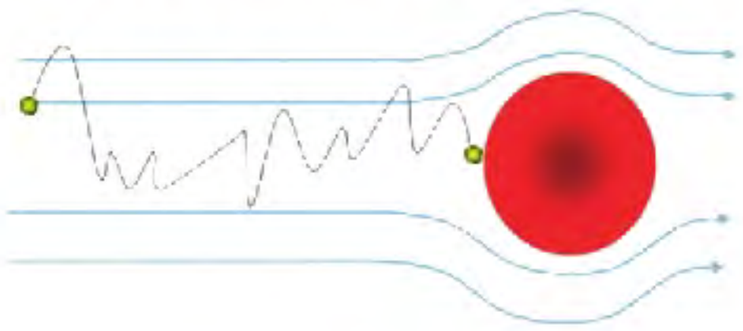
Figure 2.1b: Particle Collection Method – Interception [7]



2.1.4 Diffusion Effect

Particles in the order of 1 µm diameter in size and smaller do not follow typical airflow paths around a filter fiber because they are influenced by the Brownian motion of the air molecules surrounding them. The vibration of air molecules within close proximity of the particles can impact their motion, causing them to take a much longer and more random path through the filter media. This altered path increases their chance of coming into contact with a filter fiber. See Figure 2.1c. The probability of the particles coming into contact with the fibers increases as velocity, particle diameter, and fiber diameter decrease.

Figure 2.1c: Particle Collection Method – Diffusion [7]



2.1.5 Electrostatic Discharge

Electrostatic deposition is a mechanism to be considered in the capture of solid aerosol particles. For example, electrostatic precipitators are used industrially to remove solid particles, where an active high voltage corona discharge is used to charge the target particles. A high voltage with the opposite charge is applied to the collectors so that the particles are attracted to the surface of the collector. This type of active charging system can work as a filtration mechanism. However, more common in the pharmaceutical industry is the use of a passive electrostatic filter, where the fibers in the filter have an applied electrostatic charge. This mechanism can initially increase the separation efficiency. However, the designer needs to be aware there are published independent studies showing this passive electrostatic charge is often reduced or eliminated when the media/filter is exposed to atmospheric aerosol in actual service [9, 10]. Thus, ASHRAE 52.2-2017 [8] Appendix J provides a procedure with a specifiable Minimum Efficiency Reporting Value (MERV) designation, MERV-A, to give the user a more accurate filter efficiency. The Appendix J procedure is based on ASHRAE research [9]. It is also supported by the ASHRAE research work [10] into how filters perform when challenged with atmospheric aerosol. ISO 16890 [11] uses a different procedure, but with a similar result to the ASHRAE 52.2-2017 [8] Appendix J procedure to help the designer specify a filter efficiency value that more accurately reflects the filter performance when the filter is put into actual service.

2.2 Filtration Efficiency

Capture efficiency, or efficiency of a filter, is typically determined for a specific particle size or particle size range. The efficiency % represents the percentage of particles of the specified size or range that are captured within the filter compared to those entering the filter. The capture of particles occurs by different capture mechanisms as discussed in Section 2.1. It is typically defined by its relationship to filter penetration %, since the penetrating particles are those that are measured, and is defined as follows:

$$\text{Efficiency \%} = 100\% - \text{Penetration \%}$$

Penetration % represents the percentage of particles of the specified size or range that pass through the filter compared to those entering the filter and is defined as follows:

$$\text{Penetration \%} = 100 \times \frac{\text{Particles Penetrating Filter}}{\text{Particles Entering Filter}}$$

As the total efficiency of a high efficiency filter is determined by the sum of different filtration effects, it is natural to assume that the collecting efficiency has a definite minimum value under certain conditions. Both the interception effect and the inertial effect increase with increasing particle size, whereas the diffusion effect decreases with increasing particle size. This should therefore imply that there is a definite particle size which is the hardest to collect in a filter; this particle size is defined as the Most Penetrating Particle Size (MPPS) as shown in Figure 2.2.

Figure 2.2: Efficiency Varies with Particle Size

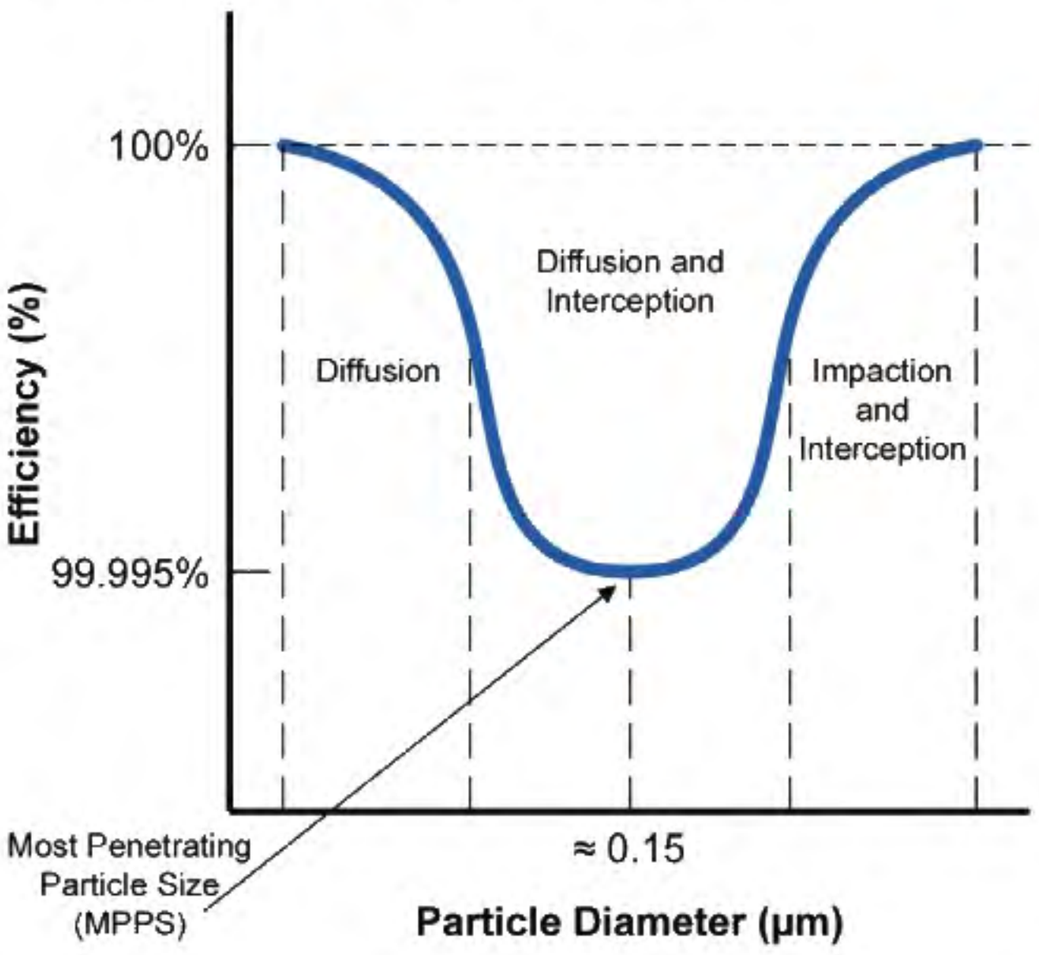


Figure 2.3 shows the collecting efficiency curve of a given filter operating at full airflow and at 50% of that rated flow. The filter collection efficiency has a minimum for particles that are 0.15 µm to 0.25 µm in diameter. At a lower velocity through the filter, the curve shifts to the right, resulting in a slightly larger MPPS. It can also be seen that the minimum collecting efficiency would also rise since a lower velocity through the filter increases the time particles will spend in the filter media. The latter phenomenon is a consequence of the fact that the interception effect is independent of the velocity, whereas the diffusion effect increases with decreasing velocity. Conversely, if the velocity increases, the diffusion effect decreases and the curve will shift left, moving the MPPS towards smaller particles.

Note: By reducing the airflow velocity through the filter media by 50%, the overall efficiency increases 10-fold, i.e., an H-13 filter becomes an H-14 filter.

Figure 2.3: Effects of Media Air Velocity on Efficiency and MPPS
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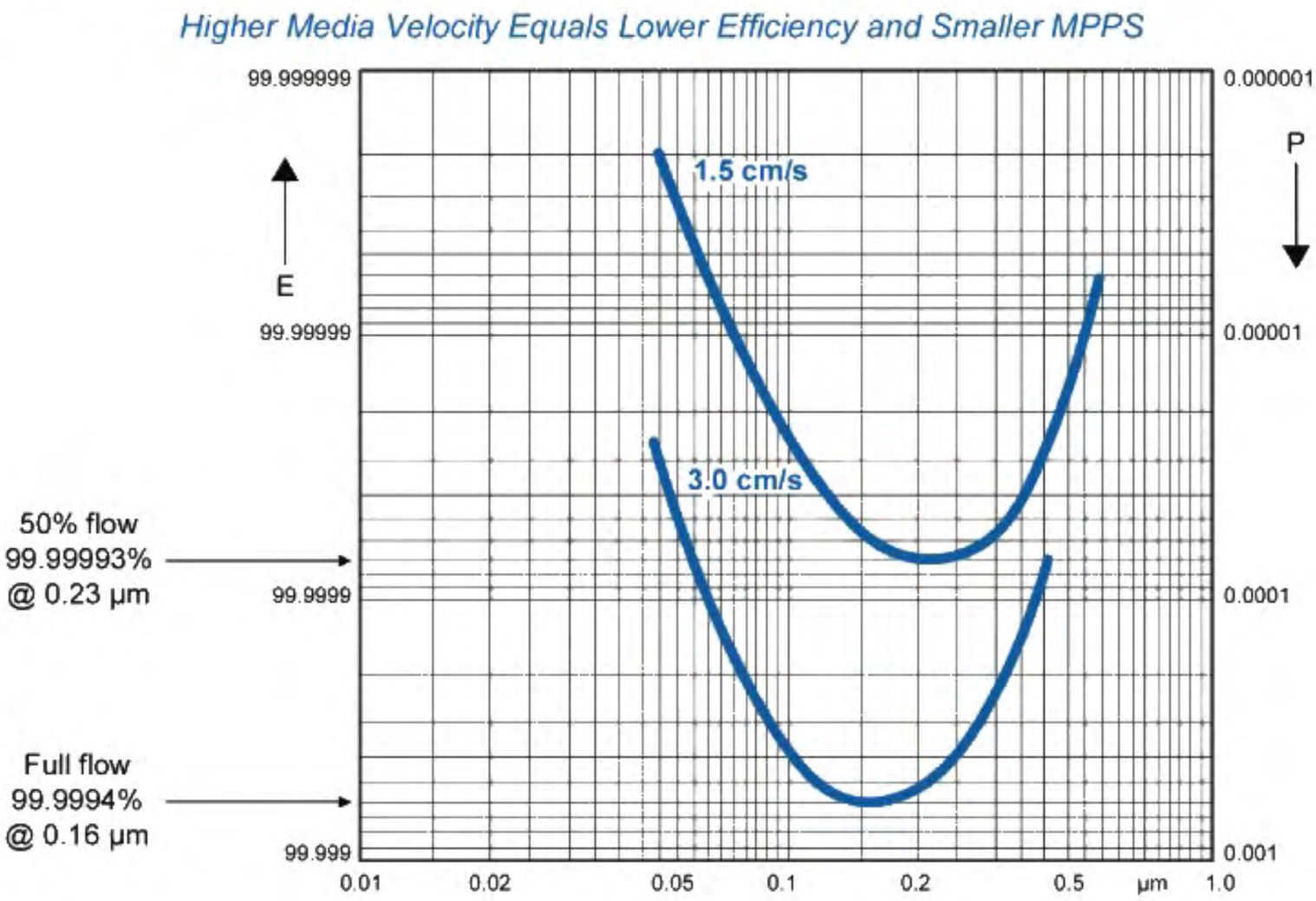

2.3 Air Filtration Characteristics

Air filtration can occur on the surface of filter media as well as within the filter media. These two behaviors are referred to as surface and depth filtration, respectively.

2.3.1 Surface Filtration

Surface filters capture particles on the surface of the medium in the form of a cake; the thickness of the cake increases as filtration proceeds. This buildup layer of particles also aids in the filtration process as this layer provides additional structures for new particles to adhere to. Certain chemical operations involve reuse of the cake as it has value, and recovery of the cake is also required. Surface (or cake) filtration usually occurs due to the straining effect (surface loading) where the diameter of the particles exceeds the pore size of the challenged medium. Although the surface layer can aid in the filtration process, the thickness of the surface layer typically has a significant impact on the pressure drop across a filter. The significance of pressure drop is discussed in Chapter 8. Examples of media for surface filtration include woven meshes, screens, and membranes.

2.3.2 Depth Filtration

As particle sizes decrease, depth filtration becomes more prominent and the effects of inertial impaction, interception, and diffusion begin to play a larger role. HEPA (High Efficiency Particulate Air) filters mainly rely on depth filtration to serve their purpose. Since surface loading can lead to undesired increases in pressure drop across the HEPA media, prefilters are commonly installed. Lower-rated prefilters are designed to remove larger particles and fibers by surface filtration, resulting in lower levels of depth filtration which extends the operational life of the terminal HEPA filter. As in the case of surface filtration, depth filtration can also improve with time as particles are captured and new structures are created within the filter media. Because of this phenomenon, the efficiency of an installed HEPA filter will improve with time.

2.3.3 Pressure Drop

Pressure drop directly relates to the energy consumption of a filter or filter media. It is the resistance offered by the filter to airflow. Pressure drop is measured in inches of water gauge (in wg) or Pascals (Pa). It is important to note that the filter's resistance or pressure drop is proportional to the airflow volume passing through the filter. When a filter resistance is reported, an airflow volume also needs to be reported. When HEPA or ULPA (Ultra Low Penetration Air) filters are specified with only small reductions in pressure drop, significant energy savings can result from their long-term use. Filter media manufacturers have made great progress in developing low resistance media. Filter manufactures have reduced filter resistance by increasing the total filter media per filter, as accomplished by deeper pack depths and increased number of pleats per inch. Increasing media will increase the filters particulate holding capacity, thus resulting in a longer filter life. See Chapter 10 for additional information.

2.3.4 Slip Flow Condition for Nano-Sized Fibers in Membrane Filters

Nanofibers have a very small diameter and, as a result, only a small fraction of the air molecules paths are redirected by them when compared to larger glass fibers. Since only a small portion of air molecules velocities are impacted by the nanofiber, the air is free to move past the fiber much easier. The movement of the air molecules past the nanofiber without significant interaction is referred to as slip flow.

This slip flow phenomena affects filtration in two important ways. First, because fewer molecules collide with the fiber, there is less air drag on the fiber. This means that the pressure drop through a filter medium of nanofibers will be less than that of a filter medium of microfibers of equal fiber length. The second way that slip flow is important is that it improves the single fiber capture efficiency of small particles on the nanofibers. Because of the slip flow phenomena, the gas flow streamlines pass much closer to the surface of the nanofiber than the microfiber. This means that direct interception of small particles in the gas stream improves because more of these particles pass close enough to collide with the nanofiber than with the microfiber.

2.3.5 Pleated Media

Pleating increases the amount of filtration media that can be inserted into a filter frame; this has a direct impact on the pressure drop, efficiency, and life of a HEPA filter. The additional media and resulting increased surface area provide a higher particle holding capacity as well as added paths for airflow. The additional holding capacity increases the life of the filter and the added paths for airflow decrease the pressure drop across the filter. This explains why a pleated 100 mm filter pack depth can have a lower pressure drop than a 50 mm pack depth, assuming both filters have the same pleat density (pleats per inch). The increased surface area and additional flow paths also decrease a particle's velocity through the filter which improves the overall filtration efficiency. Additional details and information related to the structure and fabrication of pleated media are discussed in Chapter 4.

3 Filter Standards

3.1 GMP Regulatory Requirements

It is the responsibility of the designer and owner/operator of the facility to know the specific GMP requirements of the authorities having jurisdiction in both the location of the facility and the locations in which the products from the facility may be used. In general, the GMP regulations specify what is required and the filter standards and references provide guidance on how those requirements are best achieved. Therefore, there are relatively few specific requirements regarding filters in most global GMP regulatory documents. However, some GMPs do have specific requirements as to the "how", and some GMP regulations even include reference to applicable filter standards for filter construction, performance, and/or testing.

The requirements within GMP regulatory documents vary country by country. However, most country GMP regulations worldwide generally follow either the US, EU, or Japan GMP regulations [4, 5, 6] and may include additional requirements of their own for filters. Therefore, organizations need to be knowledgeable about the specifics of the GMP regulations as they apply to the specific facility. Among the GMP requirements related to filters that are most commonly addressed in the various worldwide regulatory documents are the following examples:

- Definition of the minimum performance of a HEPA/ULPA filter in terms of both efficiency and integrity (leak) testing
- Required use of prefilters and HEPA/ULPA filters in the appropriate areas – specific applications are addressed in some GMP regulatory documents for both rooms (classified areas) and for some process equipment with HEPA/ULPA filters
- Air velocity (and/or volume) and directional flow (airflow patterns) supplied by HEPA/ULPA filters into clean areas
- Velocity uniformity through the HEPA/ULPA filter
- Required testing of filters – in some cases, the parameters, frequency, and method are specified
- HEPA/ULPA filter repairs
- Documented records of HEPA/ULPA filter testing and maintenance need to be kept
- Use of HEPA/ULPA filters in hazardous or toxic containment applications
- Where recirculation through a HEPA/ULPA filter is allowed or prohibited

As with other pharmaceutical technologies, filter technology advancements generally outpace GMP regulatory documents and filter standards and references. Therefore, some requirements in the current GMP regulatory documents may not represent the most current knowledge about filters. In order to implement methods that may differ from current GMP regulations, it is important to develop a strong documented technical and scientific rationale that is based on science and risk-based assessments. For more information regarding science and risk-based approaches, refer to ICH Q8 [12], Q9 [13], and Q10 [14]. See also the *ISPE Guide Series: Product Quality Lifecycle Implementation (PQLI®) from Concept to Continual Improvement* [15].

Chapter 11 (Appendix 1) contains more detailed information about the various global GMP regulatory documents regarding filter requirements.

3.2 Relevant Organizations

There are various technical organizations that have developed additional standards and recommended practices beyond GMP regulations which provide more practical guidance to assist the industry in the best methods to meet the requirements stated in various GMP regulations. Where there are relevant country standards that the authors are aware of, the standards have been included below. It should be further noted that although some of these organizations (CETA (Controlled Environment Testing Association) [16], NSF (National Science Foundation) [17], UL (Underwriters Laboratories) [18], NEBB (National Environmental Balancing Bureau) [19], etc.) do not publish filter standards, per se, as do some others (ISO (International Organization for Standardization) [20], CEN (European Committee for Standardization) [21], IEST (Institute of Environmental Sciences and Technology) [22], etc.), they do publish standards and reference documents as to how to test filters in specific applications (cleanrooms, biosafety cabinets, etc.).

3.2.1 ISO (International Organization for Standardization) [20]

The ISO 14644 series of standards [23] are rapidly becoming the standard governing the pharmaceutical industry; it defines cleanroom standards and the specification and associated testing of the rooms and their filters. Furthermore, both US and EU GMP regulations [4, 5] directly reference ISO 14644-1 [24] and ISO 14644-2 [25], thereby making these ISO standards a part of GMP guidance. The ISO standards are meant to serve several industries with different applications for cleanrooms, whereas the GMP guidance is specific to the pharmaceutical industry. Therefore, GMP guidance on the topics of cleanrooms and HEPA filters may contain different, sometimes more stringent, requirements than those stated in ISO 14644 [23].

3.2.2 CEN (European Committee for Standardization) [21]

CEN is described as follows [21]:

> *"CEN, the European Committee for Standardization, is an association that brings together the National Standardization Bodies of 33 European countries.*
>
> *CEN is one of three European Standardization Organizations (together with CENELEC [European Committee for Electrotechnical Standardization] and ETSI [European Telecommunications Standards Institute]) that have been officially recognized by the European Union and by the European Free Trade Association (EFTA) as being responsible for developing and defining voluntary standards at European level.*
>
> *CEN provides a platform for the development of European Standards and other technical documents in relation to various kinds of products, materials, services and processes."*

3.2.3 ASHRAE (American Society of Heating, Refrigerating and Air-Conditioning Engineers) [26]

ASHRAE is an international organization with the goal to advance the arts and sciences of heating, ventilation, air conditioning, and refrigeration to serve humanity and promote a sustainable world [26]. ASHRAE develops many standards for cleanrooms, including requirements for air filtration. Their primary standard for air filters is ASHRAE 52.2-2017, Method of Testing General Ventilation Air-Cleaning Devices for Removal Efficiency by Particle Size [8].

3.2.4 BSI (British Standards Institution) [27]

BSI is the organization officially chartered as the National Standards Body (NSB) for the UK. BSI is accountable to develop, maintain, and revise consensus standards across a wide variety of industries. International standards (such as ISO 14644-1 [24]) become codified as national standards in the UK when they are adopted as BSI standards.

3.2.5 ANSI (American National Standards Institute) [28]

ANSI is the organization officially chartered as the NSB for the US. ANSI is accountable to develop, maintain, and revise consensus standards across a wide variety of industries. International standards (such as ISO 14644-1 [24]) become codified as national standards in the US when they are adopted as ANSI standards.

3.2.6 IEST (Institute of Environmental Sciences and Technology) [22]

IEST is the US technical organization that is the ANSI-accredited US TAG (Technical Advisory Group) responsible for developing US cleanroom standards and for providing technical advice from the US to the ISO 14644 [23] governing and working groups. IEST has established a filter rating system for the higher-grade filters. IEST Recommended Practices may be used as references in the design, construction, commissioning and qualification, operational, and maintenance phases of a cleanroom's lifecycle.

3.2.7 NEBB (National Environmental Balancing Bureau) [19]

NEBB is an association of certified firms that perform building systems commissioning, building enclosure testing, cleanroom performance testing, fume hood testing, retro-commissioning, sound and/or vibration measurement, and testing, adjusting and balancing of HVAC systems. In addition to certifying firms, NEBB is a major source of industry information, providing technical and procedural standards, publications, study courses, and newsletters.

3.2.8 CETA (Controlled Environment Testing Association) [16]

CETA is an organization of individuals and companies that test cleanrooms and other controlled environments. CETA is heavily involved in the development of standards related to testing requirements for controlled environments as well as the training and practical execution of standards related to the controlled environment industry. CETA has been very active in developing test methods for USP <797> [29] for compounding pharmacy environments and biosafety cabinets.

3.2.9 NSF (National Science Foundation) [17]

NSF is an independent, accredited organization tasked with developing public health standards and certifications that help to protect food, water, consumer products, and the environment. They are responsible for testing, auditing, and certifying products and systems and for providing education and risk management training. Their primary involvement in clean spaces is to own and maintain the standards for Biosafety Cabinet (BSC) certification and to maintain the accreditation of individuals who can certify BSCs.

3.2.10 UL (Underwriters Laboratories) [18]

UL is the largest global organization for product safety testing and certification. UL standards for air filter product safety are generally accepted as requirements for the specification of air filters in the US and many other countries.

Two of the primary UL standards which apply to filters are the following:

- UL 900 (Standard for Air Filter Units) [30] *"requirements cover tests to determine the amount of smoke generated and the combustibility of air filter units of both washable and throwaway types used for removal of dust and other airborne particles from air circulated mechanically in equipment and systems installed in accordance with the Standards for Installation of Air Conditioning and Ventilating Systems, NFPA 90A (Other Than Residence Type), Installation of Warm Air Heating and Air Conditioning Systems, NFPA 90B (Residence Type), the International Mechanical Code, the International Fire Code, and the Uniform Mechanical Code. These requirements also cover media intended for assembly into air filter units."*

- UL 586 (Standard for Safety for High-Efficiency, Particulate, Air Filters Units) [31] *"requirements cover high-efficiency, particulate, air-filter units intended for the removal of very fine particulate matter (not less than 99.97 percent of 0.3 micron diameter particles) from the air of industrial and laboratory exhaust and ventilating systems."*

3.2.11 PHSS (Pharmaceutical & Healthcare Sciences Society) [32]

PHSS is dedicated to sharing knowledge, regulatory guidance, and best practices to those within the pharmaceutical, biotechnology, and related healthcare sectors.

3.3 Filter Classifications/Grades/Performance Criteria

3.3.1 ISO 14644 [23]

The following are the various parts of ISO 14644[1] (Cleanrooms and associated controlled environments) [23] and the topics which are addressed (not all of these parts address filters in cleanrooms):

- ISO 14644-1 (Part 1: Classification of air cleanliness by particle concentration) [24] specifies the classes of air cleanliness in terms of the number of particles expressed as a concentration in air volume and specifies the standard method of testing to determine cleanliness class
- ISO 14644-2 (Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration) [25] addresses the need to consider a monitoring strategy in addition to the initial or periodic execution of the classification of the cleanroom or clean zone
- ISO 14644-3 (Part 3: Test methods) [33] specifies test methods for designated classification of airborne particulate cleanliness for characterizing the performance of cleanrooms and clean zones
- ISO 14644-4 (Part 4: Design, construction and start-up) [34] specifies the requirements for the design and construction of cleanroom facilities as classified by ISO 14644
- ISO 14644-5 (Part 5: Operations) [35] specifies the basic requirements for cleanroom operations as classified by ISO 14644
- ISO 14644-7 (Part 7: Separative devices (clean air hoods, gloveboxes, isolators and mini-environments)) [36] specifies the minimum requirements for the design, testing, and approval of separative devices
- ISO 14644-8 (Part 8: Classification of air cleanliness by air chemical concentration (ACC)) [37] covers the classification of Airborne Molecular Contamination (AMC) in cleanrooms and associated controlled environments
- ISO 14644-9 (Part 9: Classification of surface cleanliness by particle concentration) [38] establishes the classification of cleanliness levels on solid surfaces by particle concentration in cleanrooms and associated controlled environments
- ISO 14644-10 (Part 10: Classification of surface cleanliness by chemical concentration) [39] defines the classification system for cleanliness of surfaces in cleanrooms with regards to the presence of chemical compounds or elements
- ISO 14644-12 (Part 12: Specifications for monitoring air cleanliness by nanoscale particle concentration) [40] specifies the guidelines for monitoring of air cleanliness by particles in terms of concentration of airborne nanoscale particles
- ISO 14644-13 (Part 13: Cleaning of surfaces to achieve defined levels of cleanliness in terms of particle and chemical classifications) [41] provides the guidelines for cleaning to a specified degree on cleanroom surfaces, surfaces of equipment in a cleanroom, and surfaces of materials in a cleanroom

[1] Part 6 and Part 11 of ISO 14644 have been withdrawn.

- ISO 14644-14 (Part 14: Assessment of suitability for use of equipment by airborne particle concentration) [42] specifies the methodology to assess the suitability of equipment (e.g., machinery, measuring equipment, process equipment, components, and tools) for use in cleanrooms and associated controlled environments, with respect to airborne particle cleanliness as specified in ISO 14644-1 [24]

- ISO 14644-15 (Part 15: Assessment of suitability for use of equipment and materials by airborne chemical concentration) [43] specifies the requirements and guidelines for assessing the chemical airborne cleanliness of equipment and materials which are foreseen to be used in cleanrooms and associated controlled environments which are linked to the ISO standard for cleanliness classes by chemical concentration

- ISO 14644-16 (Part 16: Energy efficiency in cleanrooms and clean air devices) [44] covers how to optimize energy usage and maintain energy efficiency in new and existing cleanrooms, clean zones, and separative devices

- ISO 14644-17 (Part 17: Particle deposition rate applications) is undergoing development at the time of writing and intends to provide guidance on the interpretation and application of the results of the measurement of the particle deposition rate

3.3.2 ISO 16890 [11]

ISO 16890 (Air filters for general ventilation) [11] is a global filtration standard which received unanimous approval in 2016. ISO 16890 replaced EN 779 [45] and is being discussed to replace ASHRAE 52.2-2017 [8] in the US. This international filtration standard consists of the following four parts:

- ISO 16890-1 (Part 1: Technical specifications, requirements and classification system based upon particulate matter efficiency (ePM)) [46]

- ISO 16890-2 (Part 2: Measurement of fractional efficiency and air flow resistance) [47]

- ISO 16890-3 (Part 3: Determination of the gravimetric efficiency and the air flow resistance versus the mass of test dust captured) [48]

- ISO 16890-4 (Part 4: Conditioning method to determine the minimum fractional test efficiency) [49]

Table 3.1 provides an overview of the classifications of filters according to ISO 16890-1 [46].

Table 3.1: Filter Groups (from ISO 16890-1 [46])

The initial arrestance and the three efficiency values ePM_1, $ePM_{2.5}$, and ePM_{10} and the minimum efficiency values $ePM_{1,\ min}$ and $ePM_{2.5,\ min}$ shall be used to classify a filter in one of the four groups given below.

Group Designation	Requirement			Class Reporting Value
	$ePM_{1,\ min}$	$ePM_{2.5,\ min}$	ePM_{10}	
ISO Coarse	—	—	< 50%	Initial grav. arrestance
ISO ePM_{10}	—	—	≥ 50%	ePM_{10}
ISO $ePM_{2.5}$	—	≥ 50%	—	$ePM_{2.5}$
ISO ePM_1	≥ 50%	—	—	ePM_1

The filter classes are reported as class reporting value in conjunction with the group designation. For the reporting of the ePM classes, the class reporting values shall be rounded downwards to the nearest multiple of 5% points. Values larger than 95% are reported as "> 95%". Examples of reporting classes are ISO Coarse 60%, ISO ePM_{10} 60%, ISO $ePM_{2.5}$ 80%, ISO ePM_1 85%, or ISO ePM_1 > 95%.

In addition, ISO [20] has an international standard for the field testing of air filtration devices: ISO 29462 (Field testing of general ventilation filtration devices and systems for *in situ* removal efficiency by particle size and resistance to airflow) [50]. This document is a useful reference for enabling owners and operators to provide field verification of the air filtration performance of their HVAC filtration devices.

3.3.3 ISO 29463 [51]

ISO 29463 (High efficiency filters and filter media for removing particles from air) [51] is the ISO standard for specifying the requirements for filter classes beyond those of ISO 16890 [11]. The requirements for the various ISO 29463 filter classes and a relative comparison to those of the EN 1822 standard [52] for higher-grade filters are shown in Table 3.2. (See Section 3.3.6.2 and Table 3.7 for the requirements specific to EN 1822.)

Table 3.2: HEPA Filter Classification Comparison – EN 1822 [52] and ISO 29463 [51]
Used with permission from AAF International, https://www.aafintl.com/.

Group		EN-1822	ISO 29463	Integral Value		Local Value		Leakage Factor
				Efficiency at MPPS	Penetration at MPPS %	Efficiency at MPPS	Penetration at MPPS %	
	EPA	E10		≥ 85	≤ 15			
		E11	ISO 15 E	≥ 95	≤ 5			
			ISO 20 E	≥ 99	≤ 1			
		E12	ISO 25 E	≥ 99.5	≤ 0.5			
			ISO 30 E	≥ 99.9	≤ 0 1			
	HEPA	H13	ISO 35 H	≥ 99.95	≤ 0.05	≥ 99.75	≤ 0.25	5
			ISO 40 H	≥ 99.99	≤ 0.01	≥ 99.95	≤ 0.05	5
		H14	ISO 45 H	≥ 99.995	≤ 0.005	≥ 99.975	≤ 0.025	5
			ISO 50 H	≥ 99.999	≤ 0.001	≥ 99.995	≤ 0.005	5
	ULPA	U15	ISO 55 U	≥ 99.9995	≤ 0.0005	≥ 99.9975	≤ 0.0025	5
			ISO 60 U	≥ 99.9999	≤ 0.0001	≥ 99.9995	≤ 0.0005	5
		U16	ISO 65 U	≥ 99.99995	≤ 0.00005	≥ 99.99975	≤ 0.00025	5
			ISO 70 U	≥ 99.99999	≤ 0.00001	≥ 99.9999	≤ 0.0001	10
		U17	ISO 75 U	≥ 99.999995	≤ 0.000005	≥ 99.9999	≤ 0.0001	20

3.3.4 ISO 16170 [53]

ISO 16170 (*In situ* test methods for high efficiency filter systems in industrial facilities) [53] may be either a requirement or a useful reference in some applications. It specifies *in situ* test methods for HEPA filters used to limit releases towards the environment from nuclear facilities or facilities with aerosol toxic or biological releases. It excludes the applications already covered in ISO 14644-3 [33].

3.3.5 ASHRAE [26]

The ASHRAE 52.2-2017 standard [8] rates prefilters and intermediate filters using a MERV (Minimum Efficiency Reporting Value) rating from 1 through 16. The requirements for the various grades of ASHRAE filters are shown in comparison to their equivalent EU grades in Table 3.3.

Table 3.3: MERV Parameters (from ASHRAE 52.2-2017 [8])
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Minimum Eff. Reporting Value	Composite Average Particle Size Efficiency, % in Size Range, µm			Average Arrestance
	Range E_1	Range E_2	Range E_3	
(MERV)	0.30 – 1.0	1.0 – 3.0	3.0 – 10.0	%
1	N/A	N/A	$E_3 < 20$	$A_{avg} < 65$
2	N/A	N/A	$E_3 < 20$	$65 \leq A_{avg}$
3	N/A	N/A	$E_3 < 20$	$70 \leq A_{avg}$
4	N/A	N/A	$E_3 < 20$	$75 \leq A_{avg}$
5	N/A	N/A	$20 \leq E_3$	N/A
6	N/A	N/A	$35 \leq E_3$	N/A
7	N/A	N/A	$50 \leq E_3$	N/A
8	N/A	$20 \leq E_2$	$70 \leq E_3$	N/A
9	N/A	$35 \leq E_2$	$75 \leq E_3$	N/A
10	N/A	$50 \leq E_2$	$80 \leq E_3$	N/A
11	$20 \leq E_1$	$65 \leq E_2$	$85 \leq E_3$	N/A
12	$35 \leq E_1$	$80 \leq E_2$	$90 \leq E_3$	N/A
13	$50 \leq E_1$	$85 \leq E_2$	$90 \leq E_3$	N/A
14	$75 \leq E_1$	$90 \leq E_2$	$95 \leq E_3$	N/A
15	$85 \leq E_1$	$90 \leq E_2$	$95 \leq E_3$	N/A
16	$95 \leq E_1$	$95 \leq E_2$	$95 \leq E_3$	N/A

3.3.6 EU EN Standards

The EU standards for air filter rating previously consisted of EN 779 [45] and EN 1822 [52]. EN 779 has been superseded by ISO 16890 [11], and EN 1822 in the process of being superseded by ISO 29463 51]. Because ISO 16890 and ISO 29463 are relatively new, many industry documents still reference EN 779 and EN 1822. At the time of this writing, these EU standards are still the governing standards in some countries that have not yet adopted ISO 16890 or ISO 29463.

3.3.6.1 EN 779 [45]

EN 779 [45] addressed the classes of filters usually used for prefiltration and intermediate filtration, up to class F9. Tables 3.4, 3.5, and 3.6 describe the comparison of the classes of the EN 779, ASHRAE 52.2-2017 [8] and ISO 16890 [11] relative to one another.

Table 3.4: Comparison of Standards

Used with permission from AAF International, https://www.aafintl.com/.

		ASHRAE 52.2: 2012	ISO 16890	EN 779: 2012
Standard	Aerosol	KCl	DEHS/KCl	DEHS
	Aerosol Range	0.3 to 10.0 µm	DEHS: 0.3 to 1.0 µm KCl: 1.0 – 10 µm	0.4 µm
	Particle Sizes for Rating	E1: 0.3 – 1.0 µm E2: 1.0 – 3.0 µm E3: 3.0 – 10.0 µm	PM1: 0.3 – 1.0 µm PM2.5: 0.3 – 2.5 µm PM10: 0.3 – 10 µm	0.4 µm
	Loading Dust	ASHRAE 52.2 Dust	ISO Fine	ASHRAE 52.2 Dust
	Conditioning	Optional: Appendix J (whole filter)	Mandatory: IPA Vapor (whole filter)	Mandatory: IPA Liquid (flat sheet)
	Conditioning Substance	0.03 µm KCl	IPA Vapor	IPA Liquid
	Conditioning Time	Efficiency measured after minimum increments of 6.4×10^7 particles/cm^3 min. Conditioning stops after no further significant drop in efficiency.	25 h	2 min soak
	Classification	MERV 4 – MERV 16	ePM1, ePM2.5, ePM10	G1 – G4, M5 – M6, F7 – F9
	Rating	Worst case	Average of initial and discharged condition	Worst case

Table 3.5: HVAC Filter Designations

Used with permission from AAF International, https://www.aafintl.com/.

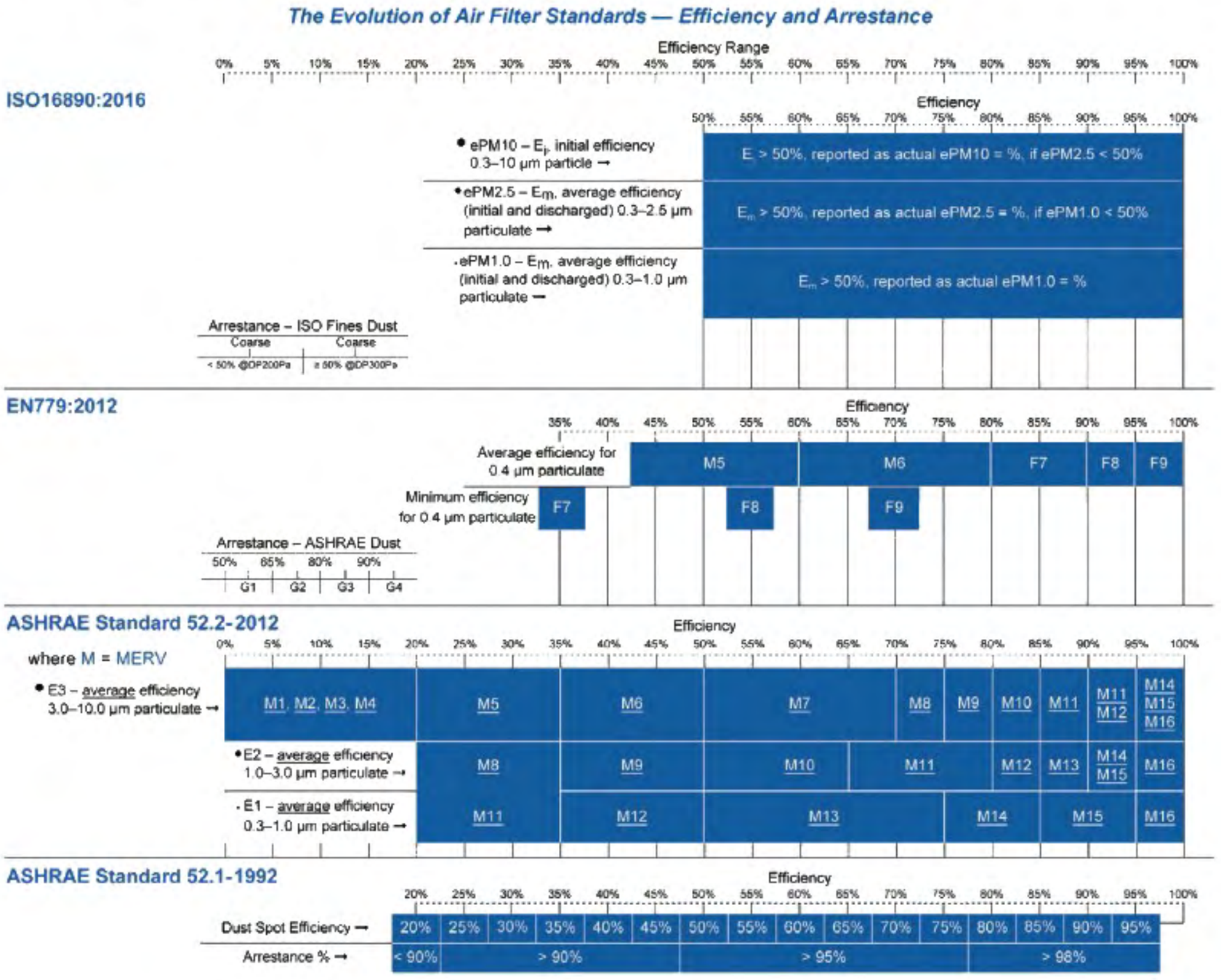


Table 3.6: Comparison of EN 779 [45] and EN ISO 16890 [11] Rated Filter Classes
Used with permission from AAF International, https://www.aafintl.com/.

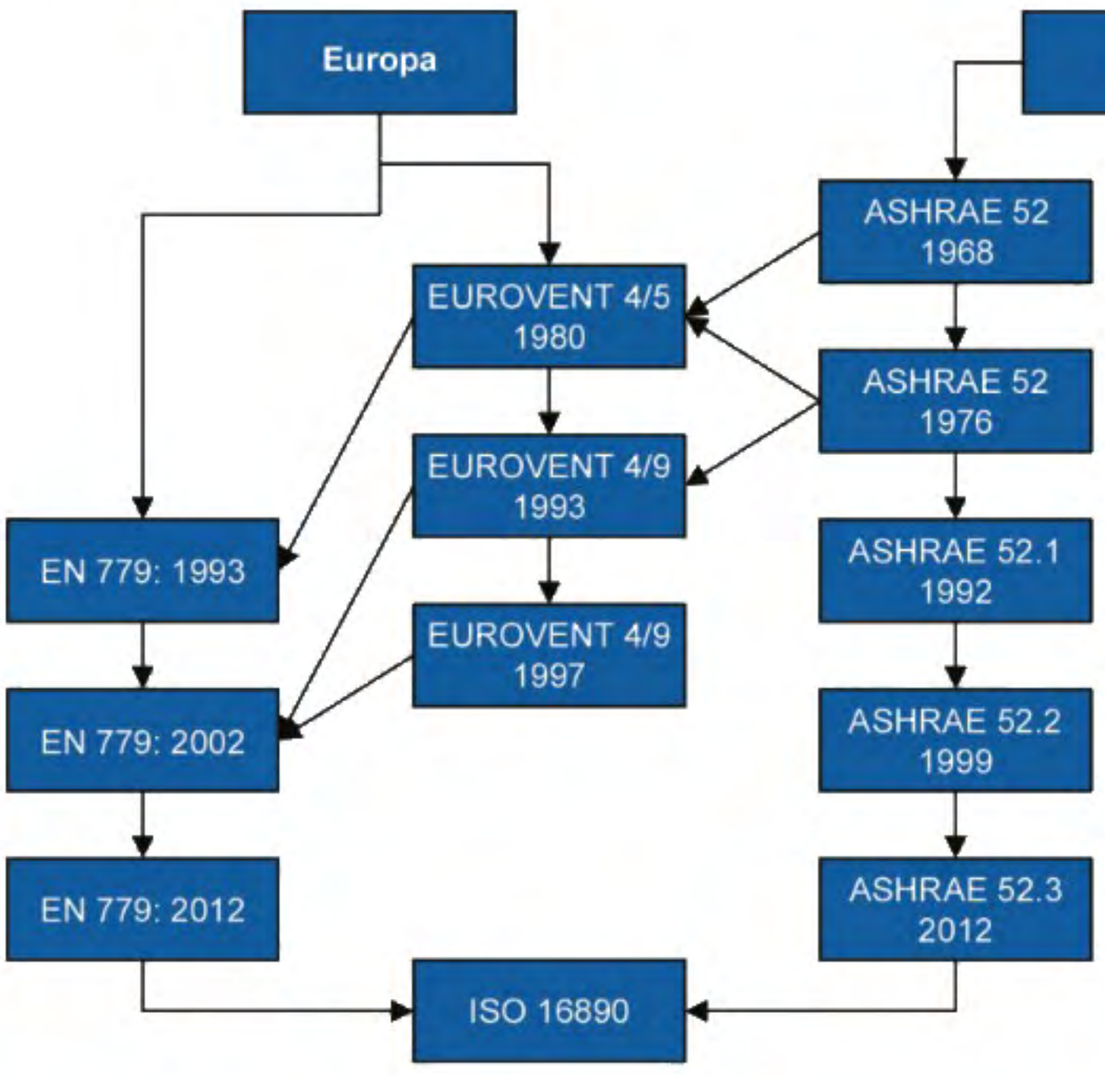
The direct conversion of EN 779 and EN ISO 16890 classes is not possible. To facilitate an indicative comparison, particularly for the purpose of replacing existing filters, the Eurovent Association has developed a table matching both EN 779 and EN ISO 16890 classes tested for the same filters.

The comparison shows the actual overlapping of EN 779 and EN ISO 16890 classes and was developed based on real test data of 91 filters provided by Eurovent Certita Certification.

ASHRAE 52.2	EN 779 2012	EN ISO 16890 – Range of Actual Measured Average Efficiencies		
Filter Class		ePM_1	$ePM_{2.5}$	ePM_{10}
MERV 10	M5	5% – 35%	10% – 45%	40% – 70%
MERV 11	M6	10% – 40%	20% – 50%	60% – 80%
MERV 13	F7	40% – 65%	65% – 75%	80% – 90%
MERV 14	F8	65% – 90%	75% – 95%	90% – 100%
MERV 15	F9	80% – 90%	85% – 95%	90% – 100%

Figure 3.1 summarizes the evolution of filter standards in the US and EU over the years and the harmonization into ISO 16890 [11].

Figure 3.1: History of HVAC Air Filter Standards
Used with permission from AAF International, https://www.aafintl.com/.



- In 1968, ASHRAE published the first unified standard which measured the arrestance, as well as the dust-spot efficiency with article test dust.
- In 1976, ASHRAE 52-76 was published introducing the atmosphere dust-spot efficiency.
  - Dust spot efficiency
  - Arrestance
  - Dust holding capacity
- Initial efficiency as a function of a particle size (MERV: Minimum Efficiency Reporting Value).
- This standard had many improvements over time. Some of the improvements are found in the ANSI/ ASHRAE 52.2 standard. The improvement of the 52.2 standard allowed for the 52.1 standard to be retired.

3.3.6.2 EN 1822 [52]

EN 1822 [52] addresses higher levels of filtration including the EPA (Efficiency Particulate Air), HEPA, and ULPA filter classes from E10 to U17. EN 1822 specifies the requirements of the various EPA/HEPA/ULPA filter classes as shown in Table 3.7.

Table 3.7: EN 1822 [52] Filter Classifications

Permission to reproduce extracts from British Standards is granted by BSI Standards Limited (BSI). No other use of this material is permitted. British Standards can be obtained in PDF or hard copy formats from the BSI online shop: www.bsigroup.com/Shop.

Filter Class	Particle Size for Testing	Global Values	
		Collection Efficiency (%)	Penetration (%)
E10	MPPS	≥ 85	≤ 15
E11	MPPS	≥ 95	≤ 5
E12	MPPS	≥ 99.5	≤ 0.5
H13	MPPS	≥ 99.95	≤ 0.05
H14	MPPS	≥ 99.995	≤ 0.005
U15	MPPS	≥ 99.9995	≤ 0.0005
U16	MPPS	≥ 99.99995	≤ 0.00005
U17	MPPS	≥ 99.999995	≤ 0.000005
Efficiency Particulate Air (EPA) filters = E10, E11, E12 High Efficiency Particulate Air (HEPA) filters = H13, H14 Ultra Low Penetration Air (ULPA) filters = U15, U16, U17			

3.3.6.3 BS EN 12469 [54]

BS EN 12469 [54] specifies the basic requirements for Microbiological Safety Cabinets (MSCs/BSCs) with respect to safety and hygiene. It sets the minimum performance criteria for safety cabinets for work with microorganisms and specifies test procedures for MSCs/BSCs with respect to the protection of the worker and environment, product protection, and cross-contamination.

3.3.7 IEST [22]

IEST [22] has established a filter rating system for the higher-grade filters. IEST Recommended Practices (RP), as listed in Table 3.8, may be used as references in the design, construction, commissioning/qualification, operational, and maintenance phases of a cleanroom's lifecycle.

Table 3.8: Listing of IEST Recommended Practices [22]

IEST Recommended Practice (RP)	Title
IEST-RP-CC001	HEPA and ULPA Filters
IEST-RP-CC002	Unidirectional-Flow, Clean-Air Devices
IEST-RP-CC003	Garment System Considerations for Cleanrooms and Other Controlled Environments
IEST-RP-CC004	Evaluating Wiping Materials Used in Cleanrooms and Other Controlled Environments
IEST-RP-CC005	Gloves and Finger Cots Used in Cleanrooms and Other Controlled Environments
IEST-RP-CC006	Testing Cleanrooms
IEST-RP-CC007	Testing ULPA Filters
IEST-RP-CC008	High-Efficiency Gas-Phase Adsorber Cells
IEST-RP-CC009	Compendium of Standards, Practices, Methods, and Similar Documents Relating to Contamination Control
IEST-RP-CC011	A Glossary of Terms and Definitions Relating to Contamination Control

Table 3.8: Listing of IEST Recommended Practices [22] (continued)

IEST Recommended Practice (RP)	Title
IEST-RP-CC012	Considerations in Cleanroom Design
IEST-RP-CC013	Calibration Procedures and Guidelines for Select Equipment Used in Testing Cleanrooms and Other Controlled Environments
IEST-RP-CC014	Calibration and Characterization of Optical Airborne Particle Counters
IEST-RP-CC016	The Rate of Deposition of Nonvolatile Residue in Cleanrooms
IEST-RP-CC018	Cleanroom Housekeeping: Operating and Monitoring Procedures
IEST-RP-CC019	Qualifications for Organizations Engaged in the Testing and Certification of Cleanrooms and Clean-Air Devices
IEST-RP-CC020	Substrates and Forms for Documentation in Cleanrooms
IEST-RP-CC021	Testing HEPA and ULPA Filter Media
IEST-RP-CC022	Electrostatic Charge in Cleanrooms and Other Controlled Environments
IEST-RP-CC023	Microorganisms in Cleanrooms
IEST-RP-CC024	Measuring and Reporting Vibration in Microelectronics Facilities
IEST-RP-CC025	Evaluation of Swabs Used in Cleanrooms
IEST-RP-CC026	Cleanroom Operations
IEST-RP-CC027	Personnel Practices and Procedures in Cleanrooms and Controlled Environments
IEST-RP-CC028	Minienvironments
IEST-RP-CC029	Contamination Control Considerations for Paint-Spray Applications
IEST-RP-CC031	Method for Characterizing Outgassed Organic Compounds from Cleanroom Materials and Components
IEST-RP-CC032	Flexible Packaging Materials for Use in Cleanrooms and Other Controlled Environments
IEST-RP-CC034	HEPA and ULPA Filter Leak Tests
IEST-RP-CC035	Design Considerations for Airborne Molecular Contamination Filtration Systems in Cleanrooms
IEST-RP-CC036	Testing Fan Filter Units
IEST-RP-CC040	Cleaning of Equipment Surfaces in the Cleanroom and Controlled Environments (under development)
IEST-RP-CC041	Recovery from Disruption to Cleanrooms and Other Controlled Environments (under development)
IEST-RP-CC042	Sizing and Counting of Submicrometer Liquid-Borne Particles Using Optical Discrete-Particle Counters
IEST-RP-CC043	Surface Molecular Contamination (under development)
IEST-RP-CC044	Vacuum Cleaners and Systems for Cleanrooms and Other Controlled Environments
IEST-RP-CC045	Design Considerations for Critical Exhaust Systems (under development)
IEST-RP-CC046	Contamination Control in Controlled Environments
IEST-RP-CC047	Cleanroom Lighting (under development)
IEST-RP-CC048	Guidance of Design, Performance, and Operations for Controlled Environments per USP 797 (under development)
IEST-RP-CC049	Controlled Environments for Regulated Industries

IEST-RP-CC001 [55] specifies the requirements for various HEPA and ULPA filter classes as shown in Table 3.9.

Table 3.9: Recommended Test and Minimum Rating for Filter Types A Through K (from IEST-RP-CC001 [55])

Filter Type	Particle Size for Testing (µm)	Global Values
		Collection Efficiency (%)
A	0.3 [a]	≥ 99.97
B	0.3 [a]	≥ 99.97
E	0.3 [a]	≥ 99.97
H	0.1 – 0.2 or 0.2 – 0.3 [b]	≥ 99.97
I	0.1 – 0.2 or 0.2 – 0.3 [b]	≥ 99.97
C	0.3 [a]	≥ 99.99
J	0.1 – 0.2 or 0.2 – 0.3 [b]	≥ 99.99
K	0.1 – 0.2 or 0.2 – 0.3 [b]	≥ 99.995
D	0.3 [a]	≥ 99.999
F	0.1 – 0.2 or 0.2 – 0.3 [b]	≥ 99.9995
G	0.1 – 0.2	≥ 99.9999

High Efficiency Particulate Air (HEPA) filters = A, B, C, E, H, I, J, K
Ultra Low Penetration Air (ULPA) filters = D, F, G
[a] Mass median diameter particles (or with a count median diameter typically smaller than 0.2 µm as noted).
[b] Use the particle size range that yields the lowest efficiency.

Although a comparison between the three major standards to relate exactly the relevant filter classes for higher grade filters is not possible, Table 3.10 provides a practical comparison of the filter classes for the IEST-RP-CC001 [55], EN 1822 [52] and ISO 29463 [51] filter standards.

Table 3.10: Comparison of Filter Classifications (from IEST-RP-CC001 [55], EN 1822 [52] and ISO 29463 [51])
Used with permission from Norm Goldschmidt, Genesis Engineers, http://www.geieng.com/.

Designation	IEST-RP-CC001 [55] Filter Type	EN 1822 [52] Classification Filter Class	Particle Size for Testing	Global Value	Local Value	ISO 29463 [51] Classification Filter Class (Group)
				Collection Efficiency %	Multiple of Global Efficiency %	
EPA (Efficient Particulate Air Filter)		E10		> 85	-	
		E11	MPPS	≥ 95	-	ISO 15 E
			MPPS	≥ 99	-	ISO 20 E
		E12	MPPS	≥ 99.5	-	ISO 25 E
HEPA (High Efficiency Particulate Air Filter)		MPPS	> 99.9	-	ISO 30 E	
		H13	MPPS	≥ 99.95	5	ISO 35 E
	A		0.3*	≥ 99.97	-	
	B		0.3*	≥ 99.97	-	
	E		0.3*	≥ 99.97	-	
	H		MPPS	≥ 99.97	-	
	I		MPPS	≥ 9.97	5	ISO 40 E
	C		0.3*	≥ 99.99	1	
		H14	MPPS	≥ 99.995	5	ISO 45 E
	K	H14	MPPS	≥ 99.995	1.6	
ULPA (Ultra Low Penetration Air Filter)			MPPS	≥ 99.999	5	ISO 50 E
	D		0.3*	≥ 99.999	5	
	F	U15	MPPS	≥ 99.9995	5	ISO 55 E
			MPPS	≥ 99.9999	5	ISO 60 E
	G	U16	MPPS	≥ 99.99995	5	ISO 65 E
			MPPS	≥ 99.99999	10	ISO 70 E
		U17	MPPS	≥ 99.999995	20	ISO 75 E

Note: The EN 779:2012 differentiates between Medium Filter and Fine Filter. The intent is to have a clear segregation between Medium filter and the Fine Filter with a minimum efficiency. Please refer to the relevant standard for further details and data (i.e. retention, overall and local penetration).

3.3.8 NSF/ANSI 49 [56]

NSF/ANSI 49 (Biosafety Cabinetry: Design, Construction, Performance, and Field Certification) [56] *"applies to Class II (laminar flow) biosafety cabinetry designed to minimize hazards inherent in work with agents assigned to Biosafety Levels 1, 2, 3, or 4. It also defines the tests that shall be passed by such cabinetry to meet this Standard. This Standard includes basic requirements for the design, construction, and performance of biosafety cabinets (BSCs) that are intended to provide personnel, product, and environmental protection; reliable operation; durability and structural stability; cleanability; limitations on noise level; illumination; vibration; and motor/blower performance."*

3.3.9 BS 5295 (Withdrawn) [57] and PD 6609 [58]

British Standard BS 5295 [57] was the BSI guidance document for cleanrooms and HEPA filters. BS 5295 was withdrawn when the BSI formally adopted ISO 14644 [23] as the national standard for cleanrooms. After the BSI adopted ISO 14644, much of the content from BS 5295 related to HEPA filters was preserved in another Published Document (PD) from the BSI, BS PD 6609 (Environmental cleanliness in enclosed spaces – Guide to *in situ* high efficiency filter leak testing) [58]. If working in a locale in which PD 6609 may apply, it is important to be aware of the differences between PD 6609 and the test methods in ISO 14644-3 [33].

3.3.10 China GB and GB/T Standards

In China, the national standards are classified as either GB or GB/T. The GB standards are mandatory in China. The GB/T standards are recommended national standards but are not mandatory. The relevant Chinese national standards are the following:

- GB/T 25915 (Cleanrooms and associated controlled environments) [59] consists of six national standards in this series, with requirements similar to the ISO 14644 series [23]
- GB 50457 (Code for design of pharmaceutical industry clean room) [60]
- GB/T 36066 (Cleanrooms and associated controlled environments – Analysis and application of test technology) [61]
- GB/T 16292 (Test method for airborne particle in clean room (zone) of the pharmaceutical industry) [62]
- GB/T 14295 (Air filters) [63]
- GB/T 13554 (High efficiency particulate air filter) [64]

3.3.11 French NF-C Standards

In France, local authorities may expect local projects to meet the requirements of French Standard NF S90-351 (Clean rooms and related controlled environments in medical establishments) [65], which establishes standards for healthcare facilities such as cleanrooms for hospitals and operating blocks.

3.3.12 Japan JIS Standards

The Japanese Industrial Standards Committee (JISC) [66], Japan's national standardization body, plays a central role in developing standards in Japan covering a wide range of products and technologies from robots to pictograms. The JISC creates Japanese Industrial Standards (JIS) and is also responsible for Japan's growing contribution to setting international standards through its work with ISO [20] and the International Electrotechnical Commission (IEC) [67].

The relevant Japanese standards are the following:

- JIS Z 8122 (Contamination Control – Terminology) [68]
- JIS B 9920 (Classification of air cleanliness for cleanrooms) [69]

4 Filter and Filter Housing Design and Construction

4.1 Filtration Media Structures and Media Manufacturing

4.1.1 Carded Media

The carding process separates and aligns staple fibers using a series of combs to produce a web. The carded web is sent to secondary operations, perhaps to cross-lap the web for transverse directional strength, and then is finished in a bonding process, typically an oven or other thermal method.

4.1.2 Spun Bond Media

Spun bond air filtration media are produced by depositing extruded spun filaments onto a moving belt in a uniform yet random manner, followed by bonding the fibers. The fibers are separated during the web laying process by air jets or electrostatic charges. The collecting surface is usually perforated to prevent the air stream from deflecting and carrying the fibers in an uncontrolled manner. The spun bond media process, since the fabric production is combined with fiber production, is generally more economical than when using staple fiber to make nonwoven fabrics, or instance filtration media made with carded webs.

4.1.3 Melt Blown Media

Melt blown filtration media, produced by melting and extruding polymers directly into a web, can be produced in a wide range of fiber diameters and web basis weights. Melt blown media are recognized for material uniformity, wide range of polymer capability, and ability to consistently meet key performance characteristics. Melt blown webs can be electrostatically charged to increase the attraction of particles.

4.1.4 Wet Laid Media

Wet laid air filtration media are generally produced on a paper machine with short synthetic or glass fibers suspended in a fluid, which are deposited onto a screen or porous surface where the fluid is removed, and the web is formed. The web consolidation bonding can be carried out mechanically, chemically, or thermally.

4.1.5 Air Laid Media

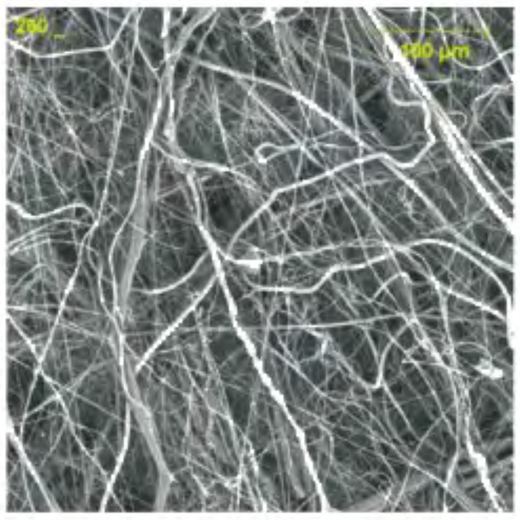
Air laid glass fiber air filter media are made by melting glass pellets and drawing the liquefied glass through a strainer before it is collected at a uniform depth on a belt and dried. Air laid media are characterized as being lofted (i.e., thicker and less dense), resulting in lower resistance to airflow and higher dust holding capacity per unit area. This media is only used in deep-pleated and bag/pocket style air filters.

4.1.6 Nanofiber Media

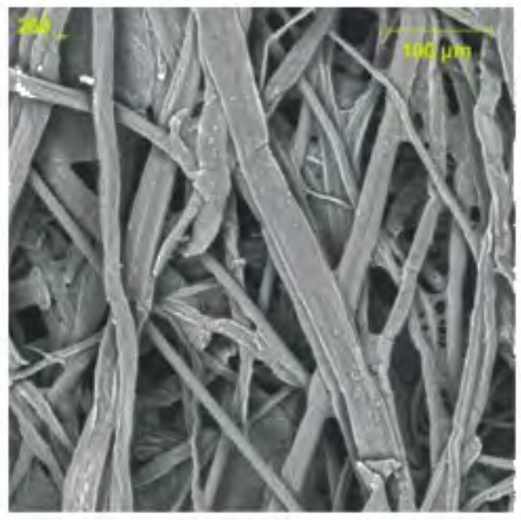
Nanofiber media offer a high fiber surface area without negatively impacting other performance characteristics, such as basis weight or caliper. Nanofiber coatings are formed with fibers typically ranging from 0.3 µm to 0.5 µm in size but can be increased up to 1 µm. The fiber diameter distribution and layer thickness can easily be varied according to the application requirements. This nanofiber layer, which consists of the nanofiber coatings, has a thickness in the range of 15 µm to 30 µm and is applied directly to the macro filtration substrate. The nanofiber web has a thickness of between 100 µm to 200 µm when supplied as a standalone substrate. The nanofiber web can be applied as a coating to any nonwoven base material, such as glass, cellulose, or synthetic fibers.

Figure 4.1 shows examples of nanofiber media applied to substrates.

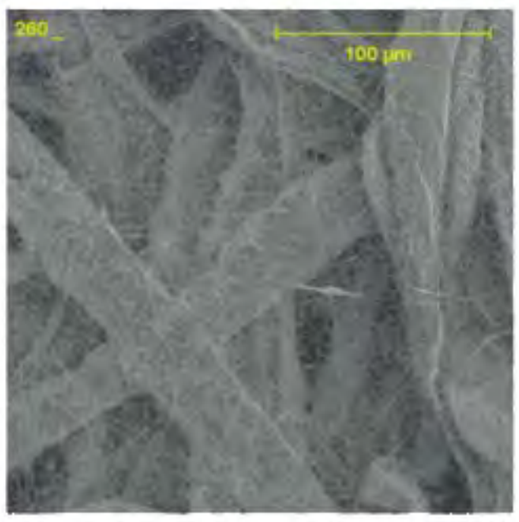
Figure 4.1: Examples of Nanofiber Media Applied to Substrates
Used with permission from Hollingsworth & Vose, http://www.hollingsworth-vose.com/.



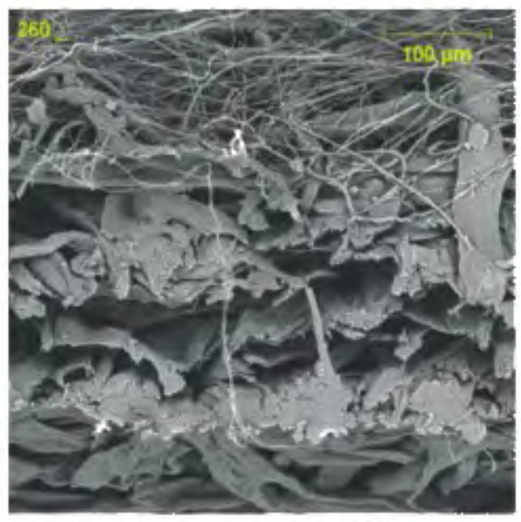
Top view of nanofiber coating, 260X.



Top view of standard cellulose media, 260X



Top view of electrospun nanofiber coating, 260X.



Side view of nanofiber coating, 260X.

4.1.7 *Needle Punched Media*

Needle punched media are produced by using barbed needles to mechanically entangle the nonwoven web. Typically needle punching is used on the nonwoven carded webs to produce very strong yet lofty filtration media.

4.1.8 *Electrostatically Charged Media*

Electrostatically charged media are a high performance electrostatically charged nonwoven media used in air filtration. They have a high efficiency with lower initial resistance and with higher dust loading capacity. They exhibit a unique electrostatic charge that is beneficial for multiple air filtration applications such as HVAC and facemasks.

Electrostatically charged media can be an effective and energy-efficient air filtration media, but caution needs to be taken to evaluate and understand the efficiency of these filters after the electrostatic charge has been dissipated, as required by ASHRAE [26], EN, and ISO [20] standards. The designer needs to be aware of the requirements for rating these filters after the electrostatic charge has been dissipated, as specified in ASHRAE 52.2-2017 Appendix J [8], EN 779 [45] and ISO 16890 [11].

4.1.9 *Membrane Media*

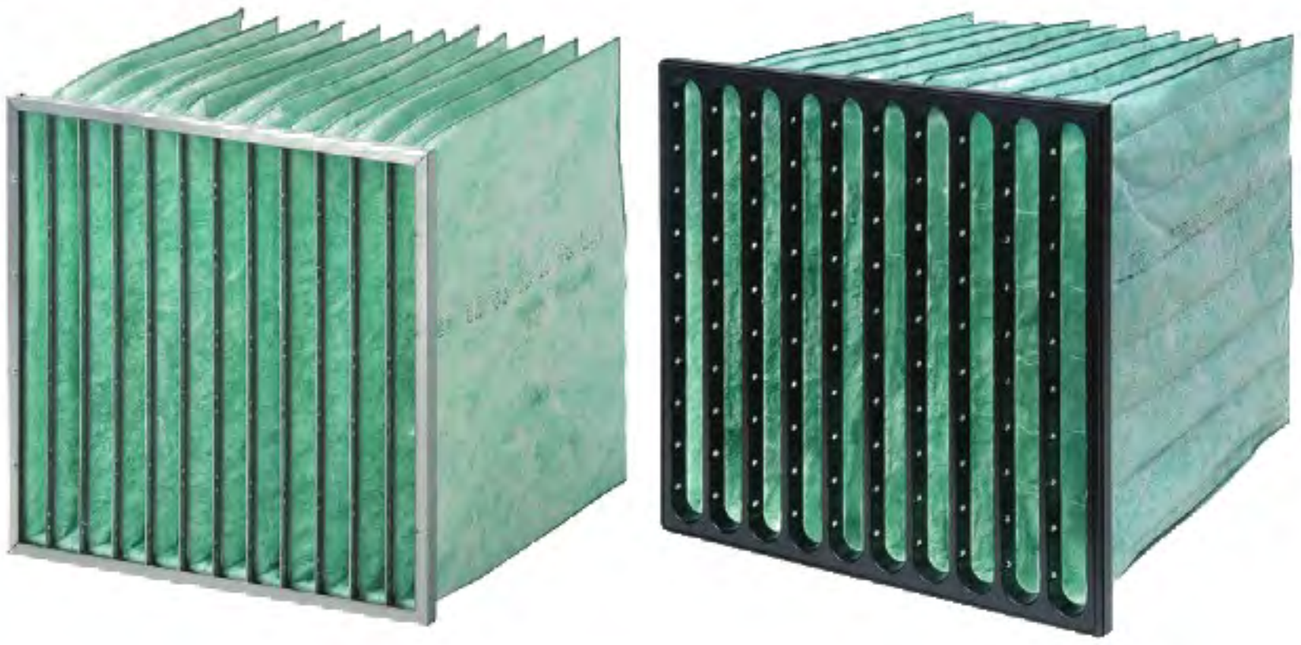
Membrane media for air filtration are essentially limited to expanded polytetrafluoroethylene (ePTFE). ePTFE membranes are typically used as the fine filtration layer bonded within spun bond support layers to make the air filtration media. The ePTFE membrane is made from the compression of PTFE (polytetrafluoroethylene) powder suspended in oil that is then expanded in both the length and width dimensions, with the depth of the membrane being approximately the same thickness as prior to the expansion. ePTFE media are characterized by having approximately half the pressure resistance of glass fiber media and its mechanical strength. Semiconductor grade ePTFE media are susceptible to flooding by oil-based test aerosols, but pharmaceutical grade ePTFE media are available with the same initial tolerance of oil aerosols as micro-glass media.

4.2 Filter and Filter Housing Construction

4.2.1 Bag Filter Prefilters

In pharmaceutical applications, bag filters are most often used as prefilters. A typical bag filter has a nominal dimension of 592 mm (2 ft) × 592 mm (2 ft) and consists of 4 to 12 parallel bags. The nominal length and depth of the bag filter varies from 300 mm (12 in) up to 900 mm (36 in). Bag filter media efficiency varies from very low (coarse fibers) to very high (fine fibers). The bag filter material is made of glass or polymer fibers of different sized fibers and different thickness or number of layers, depending on the required filter performance. Figure 4.2 shows an example of bag filters.

Figure 4.2: Example of Bag Filters
Used with permission from Camfil, https://www.camfil.com/en-us.



Because of the large media area, bag filters are expected to have longer service cycle times as compared to disposable pleated prefilters. The maximum length and depth of a bag filter that can be utilized in an air handling unit is dependent upon the design of the air unit.

Note: Bag filters can become a problem in Variable Air Volume (VAV) systems, especially if they deflate or collapse at low airflow rates. Consideration should be taken to understand how the specific bag filters will perform at minimum airflow and in pulsing and surging airflows before using them in a VAV system.

4.2.2 Pleated Prefilters

Pleated filters are most often used as prefilters in pharmaceutical air handling units. A typical pleated filter has a nominal dimension of 592 mm (2 ft) × 592 mm (2 ft) and consists of zig-zag pleated media. The length and depth of the pleated prefilter varies from 50 mm (2 in) up to 200 mm (8 in). Pleated prefilter media efficiency is low (mostly coarse fibers). The pleated prefilter media material is made of mostly polymer and glass fibers of different thickness or number of layers, and sometimes contains natural fibers, like cotton, depending on the required filter performance. Because of the low stiffness of some prefiltration media, wire reinforcement is needed for pleat formation and to provide filter strength. Prefiltration media can also be formed by heat setting pleats. Figure 4.3 shows an example of a pleated prefilter.

Figure 4.3: Example of a Pleated Prefilter
Used with permission from Camfil, https://www.camfil.com/en-us.

The service cycle of pleated prefilters is dependent upon the quality and amount of filtration media and the pleat design in the filter. Servicing of fully loaded pleated prefilters is easier than servicing fully loaded bag filters whose shape has collapsed with the weight of captured dust.

4.2.3 Rigid Filters

Rigid filters are designed to meet specifications in medium to high efficiency applications. Rigid filters are most often used as either prefilters or secondary filters in pharmaceutical air handling units. They are ideal for VAV systems where changes in airflow rates can have adverse affects on non-rigid (bag type) filters. A typical rigid filter has a nominal dimension of 592 mm (2 ft) × 592 mm (2 ft) and consists of media with controlled spacing through the use of flame retardant, plastic media separators, which are part of the filter framing. The nominal depth of the rigid filter varies from 150 mm (6 in) up to 300 mm (12 in). Rigid filter media efficiency varies from very low (coarse fibers) to very high (fine fibers). The filter media is a high density micro-glass fiber or synthetic fiber. The media is supported by heavy-duty metal backing to aid in maintaining its rigid configuration. Figure 4.4 shows an example of a rigid filter.

Figure 4.4: Example of a Rigid Filter
Used with permission from Camfil, https://www.camfil.com/en-us.

The service cycle of rigid filters is dependent upon the dust capturing capability and the efficiency of the media in the filter. Servicing of fully loaded rigid filters is relatively easy even if fully loaded. The design (with or without header) and depth of a bag filter that can utilized in an air handling unit is dependent upon the design of the air unit filter frames.

4.2.4 Extended Surface Area (Low Pressure Drop)

Most modern air filters are developed with extended surface areas usually composed of pleated micro-glass, synthetic, or natural fiber media inside a frame. Flat panel (non-extended surface area) filters have to be made increasingly thicker to achieve higher efficiencies or with greater fiber densities, which can restrict the airflow. The larger surface area of extended surface area filters reduces the pressure drop and increases the capacity of the filter to remove particles, up to 50% over a standard flat panel filter. It also extends the lifecycle of the filter. While inexpensive flat panel filters need to be changed monthly in high use seasons to maintain optimal performance and efficiency, pleated extended surface area air filters generally have a minimum of three to twelve months, possibly longer, before recommended replacement.

4.2.5 Box Style Filters

Box style air filters have additional filter surface area and can be a direct replacement for older, less efficient rigid cell or bag filters. Box filters are designed for use in air filtration handler systems using filter banks and/or side access housings. These filters are specifically designed to withstand surging and pulsations due to variable airflow situations. Box filters provide a combination of low pressure drop and high efficiency through the use of aluminum separators or a mini-pleat design. This extended surface area design ensures low resistance to airflow and reduces energy cost. Bypass is often eliminated by the use of urethane sealants between the media and the filter housing.

Box filters come in variety of filter pack configurations—from designs similar to the rigid box, but with more media separated by glue beads (mini-pleat, greater area) or separated by narrow aluminum or plastic separators (separator style, greater area), to V-bank designs with even more media separated by solid glue beads with mini-pleat media packs in multiple *V's* within the same dimensions as the rigid box. Box filters are typically in the middle to high (HEPA) efficiency ranges, made with media that ranges from synthetics, micro-glass, and ePTFE membranes. Some box filters in the V-bank style are available with a combined particle and charcoal absorber, allowing the removal of particles and odors with a single filter cell.

Figures 4.5 through 4.8 show examples of box type filters.

Figure 4.5: Example of a Box Type Filter, Aluminum Separator Style for Air Handling Units – Middle to HEPA Efficiency

Used with permission from Camfil, https://www.camfil.com/en-us.

Figure 4.6: Example of a Box Type Filter, V-Bank Style for Air Handling Units – Middle to High Efficiency
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Figure 4.7: Example of a Box Type Filter, V-Bank Style for Air Handling Units – HEPA Efficiency
Used with permission from Camfil, https://www.camfil.com/en-us.

Figure 4.8: Example of a Box Type Filter, Mini-Pleat Style Terminal Cleanroom Filters – HEPA Efficiency
Used with permission from Camfil, https://www.camfil.com/en-us.

4.3 HEPA Filters

HEPA panel filters provide fine airborne particulate control to meet the requirements of high technology cleanrooms, clean benches, and clean air devices. HEPA filters utilize micro-glass fiber or ePTFE media with efficiencies from 99.95% at 0.3 µm to 99.9995% at MPPS (Most Penetrating Particle Size). MPPS is typically between 0.1 µm to 0.2 µm for glass media and 0.05 µm to 0.10 µm for membrane media; It will vary with velocity but at normal design for a terminal filter, this range is accurate 80% of the time with a H14 filter at 90 FPM (0.45 m/sec), MPPS is 0.17 µm to 0.18 µm. The MPPS is typically identified in a factory scan test and noted on the HEPA filter label.

The HEPA filter active face area should be determined exclusive of the filter frame. For example, the gasket seal version of a HEPA filter may have an extruded aluminum frame with an industry standard 3/4 in flange, resulting in active face dimensions that are 1 in to 1-1/2 in smaller than the overall face dimensions. An additional subtraction also needs to be made if a center divider is present. Some manufacturers may base their calculations on overall dimensions which may be misleading. When comparing products, it is important to ensure performance data is provided in a consistent format. Figure 4.9 shows an example calculation of performance data.

Figure 4.9: Example of HEPA Filter Performance Data Calculation
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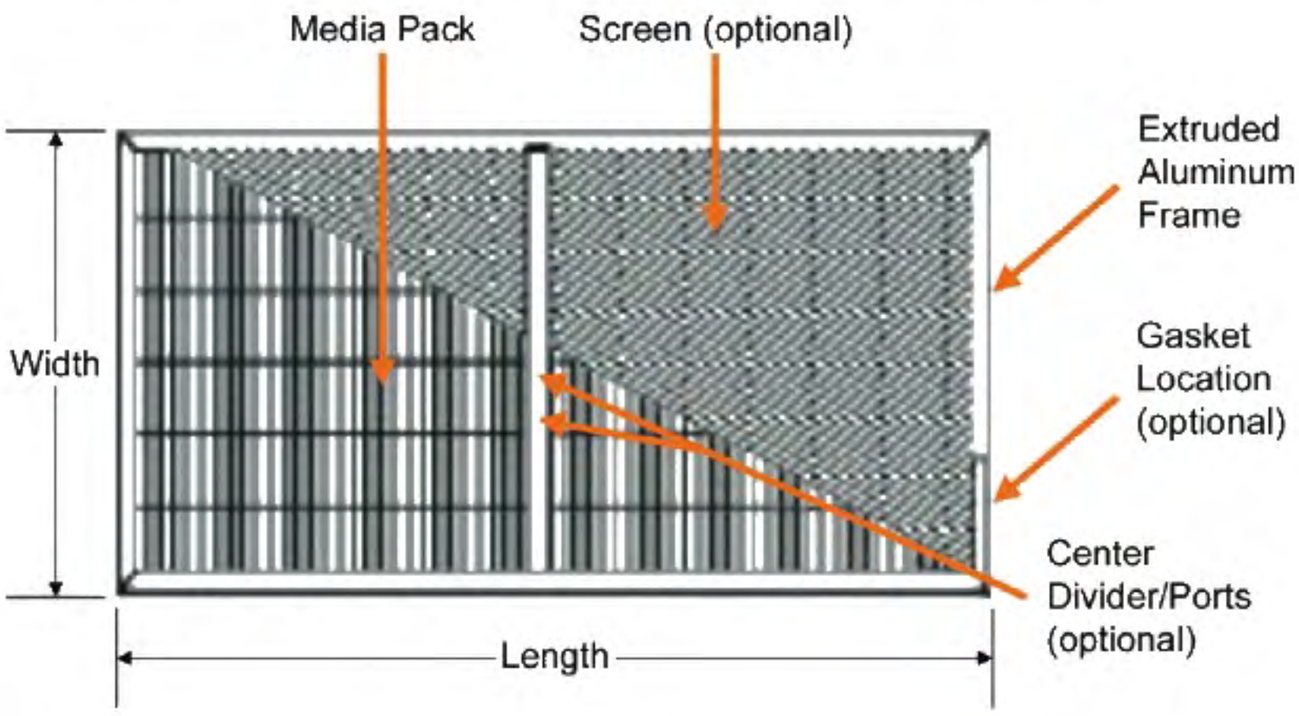

$$Q_{CFM} = V_{FPM} \times A_{ft}^2$$

Where:

Q = volumetric flow rate, CFM (ft^3/min)

V = filter face velocity, FPM (ft/min)

A = active face area, ft^2

$A = \{24 \text{ in} - (2 \times 0.75 \text{ in})\} \times \{48 \text{ in} - (2 \times 0.75 \text{ in})\} = 1046.25 \text{ in}^2$ or 7.27 ft^2

If V = 100 FPM, then Q = 727 CFM

Various framing materials and configurations are used for mounting HEPA filters into a wide variety of ceiling grid, housings, and equipment configurations, including:

- Center dividers and additional access ports
- Gaskets, profile, and materials

- Face screens, various finishes, and materials
- Media choices including micro-glass fiber and PTFE

4.3.1 Sealing Techniques

4.3.1.1 Gel Seal

A common sealing technique is a gel seal. The filter frame is designed with an integral gel channel that is filled with a silicone or low outgassing polyurethane-based gel. The gel interfaces with an opposing knife edge integral to the ceiling grid, housing, or equipment. The gel offers a fluid seal integrity that makes it a good choice for filters that are difficult to install or frequently replaced. This technique is most often seen in bottom loading or room side replaceable applications. Figure 4.10 shows an example of a gel seal.

Figure 4.10: Example of Gel Seal
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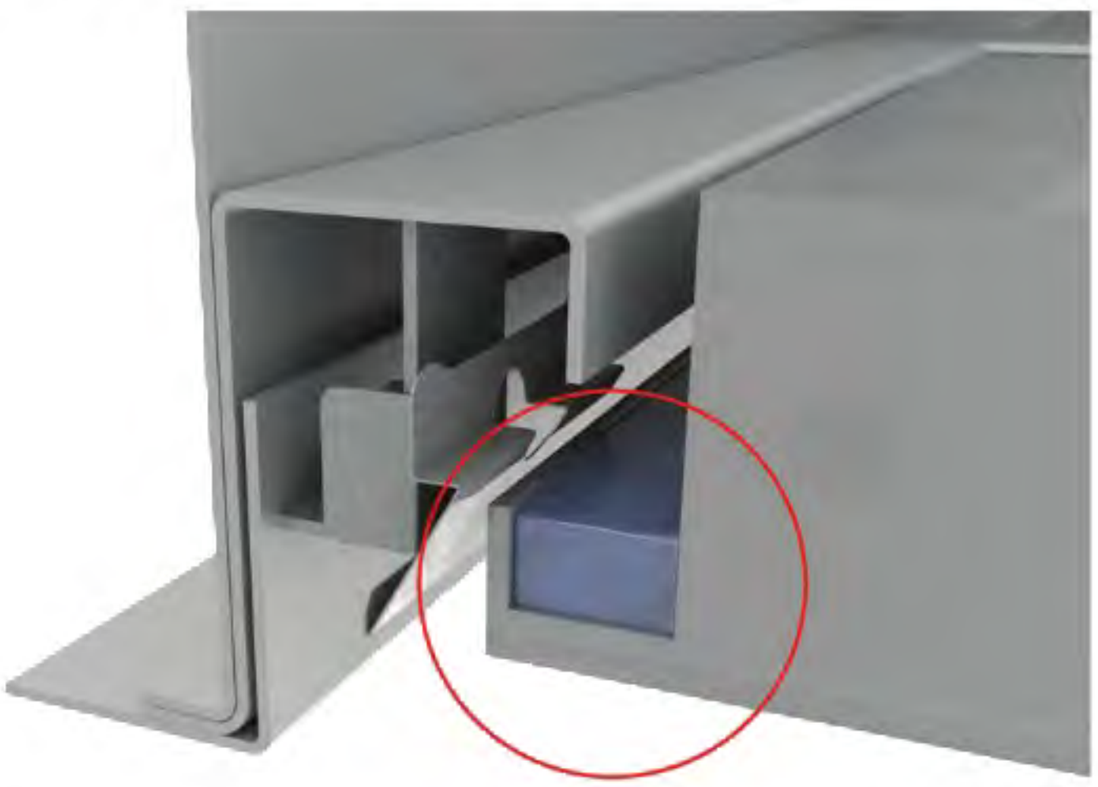

A filter guide within the grid or housing ensures that the HEPA filter fits properly to the gel-sealing knife edge of the housing. The filter should fit into place creating a uniform gel penetration and leak free filter perimeter seal. The filter is then secured into place with filter clamps.

The gel-penetrating knife edge affects a positive seal between the housing and the filter. The corner joints of knife edge junctures should be continuously welded to eliminate leak paths. A controlled depth knife edge design ensures that the filter will not bottom out in the track, eliminating metal to metal contact and the most common location for potential air bypass.

4.3.1.2 Gasket Seal

Another optional sealing technique is a gasket seal. Cleanroom seamless foam gaskets can be applied to either the upstream or downstream flange. The gasket is compressed between an opposing flange mating surface on the ceiling grid, housing, or equipment. Proper compression is important; too much can result in the gasket failing.

4.3.1.3 Knife Edge Seal

HEPA filter panels can also be produced in a frame with an integral knife edge. The knife edge interfaces with a gel channel that is integral to the ceiling grid or equipment. This technique is frequently seen in common plenum applications where the weight of the filter and pressure from airflow are all that is needed to affect a positive seal—no mounting hardware should be required. Figure 4.11 shows an example of a knife edge seal.

Figure 4.11: Example of Knife Edge Seal
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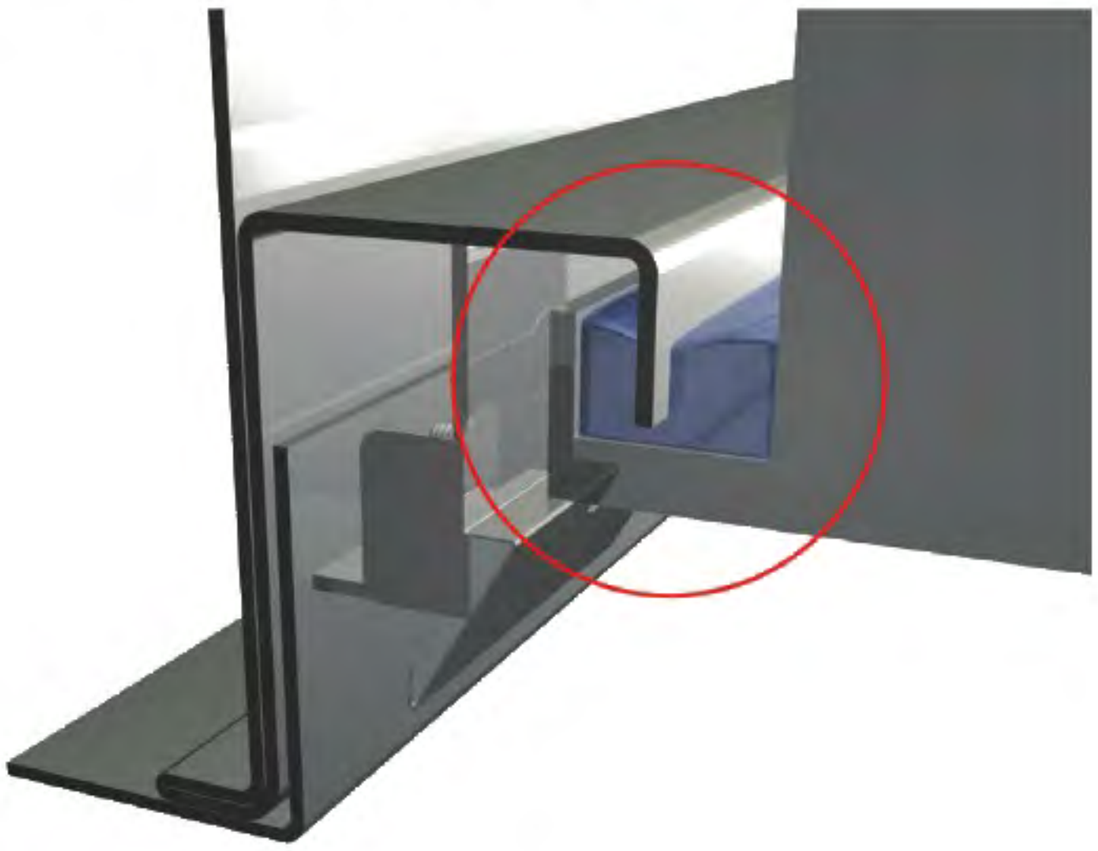

4.3.2 Room Side Testing Capability

HEPA filters and/or HEPA filter housings used in GMP applications require a sample port accessible from the room side. This port is used to sample the upstream side of the installed filter in order to evaluate filter pressure drop across the filter as well as sampling of the upstream aerosol concentration during filter scan testing. This port allows fast easy service from the room side for filter change, airflow adjustment, and filter scan testing.

Ideally, the HEPA filter module or housing has an injection nozzle accessible from the room side to inject an aerosol challenge into the unit's upstream plenum for testing. The injection nozzle typically mates to an aerosol distribution system that is used to radially disperse the aerosol challenge to provide uniform mixing in accordance with IEST-RP-CC034 [70]. It is important that the design of the aerosol distribution system (ring, wand, etc.) provide a uniform challenge to the filter.

4.3.3 Dampers

Dampers serve multiple functions; they are used to adjust and regulate airflow to the room, to close off access to the HVAC duct system from the room during testing or decontamination, and to prevent the chance of contamination from the dirty side of the HVAC system during filter changes. Figure 4.12 shows an example of a damper.

Figure 4.12: Example of a Damper
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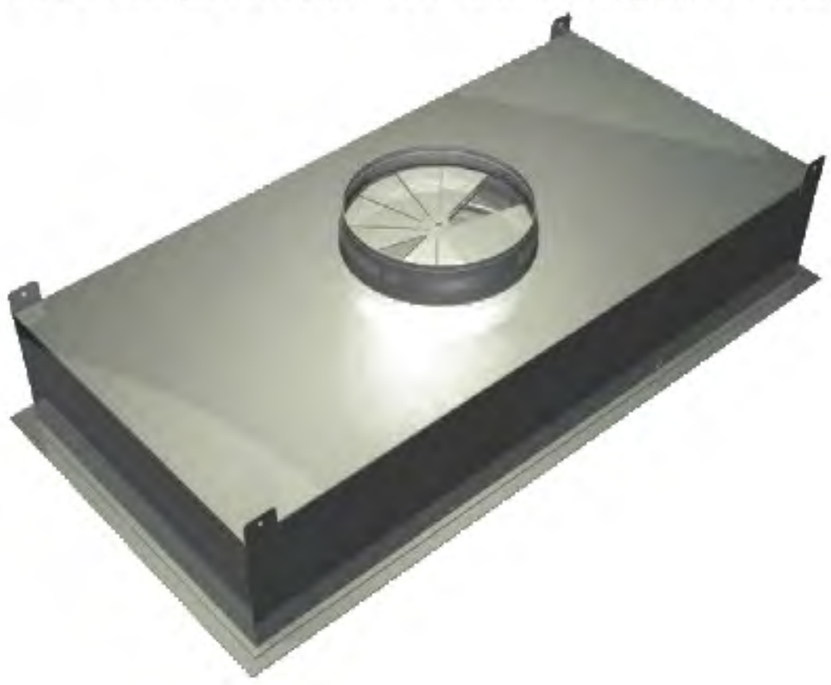

4.3.3.1 Guillotine Damper

A guillotine damper has two blades that slide horizontally from open to close. This damper type facilitates room balancing and airflow control. It is adjusted using a rotary mechanism attached to a mechanical linkage and heavy-duty blades. The damper assembly should be welded to the hood body to increase rigidity and eliminate binding of the damper blades. Damper adjustments should be fully accessible from the room side utilizing a damper control rod which ideally features a positive locking feature and a damper position indicator. Figure 4.13 shows an example of a guillotine damper.

Figure 4.13: Example of Guillotine Damper
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4.3.3.2 Radial Bow Tie Damper

Radial bow tie dampers facilitate accurate airflow modulation and control using a linkage. This damper type typically has a low torque operation through the entire range of adjustment. This damper can be riveted to the filter housing. Figure 4.14 shows an example of a radial bow tie damper.

Figure 4.14: Example of Radial Bow Tie Damper
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4.3.3.3 Butterfly Damper

Butterfly dampers feature split wings that open and close within the inlet collar, adjusted via a rotating shaft and cable configuration, mounted to a gear assembly.

4.3.3.4 Isolation Damper

Isolation dampers facilitate the complete isolation of the housing, allowing for the change-out of HEPA filters without the risk of contamination to the cleanroom. This damper type is designed to reduce production downtime during filter change and room decontamination. The damper should be adjustable from fully open to fully closed in 15 revolutions (approximate). It can eliminate the need for full room decontamination during filter replacement, depending on the application. This damper style has a fluid (gel) seal channel that mates with a knife edge in the hood. Positive stops on the damper adjustment mechanism eliminate twisting of the stainless steel flexible cable, providing high-cycle life. Cable failure is greatly reduced. The damper should include a fully-welded inlet collar. Figure 4.15 shows an example of an isolation damper.

Figure 4.15: Example of Isolation Damper
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4.3.4 Filter Housings

4.3.4.1 Installation

This section addresses room ceiling installations. Unidirectional Airflow (UAF/UDF) hoods are specialty equipment with similar, but different specific instructions. HEPA hoods are generally installed into one of two types of ceiling construction:

- T-Bar/Grid
- Hard/Plaster Ceilings

Grids are typically manufactured from aluminum or painted steel, suspended from structural members and arranged in a grid pattern to provide uniformly spaced holes into which ceiling panels, light fixtures, filtration equipment, etc. may be installed.

Hard ceilings typically consist of structural members, such as metal studs, covered with drywall, plaster, or prefabricated honeycomb panels with aluminum or stainless steel skins.

Permanent Trim for T-Bar Ceiling (Factory Mounted)

In this type of installation, the hood typically installs from the top side of the grid, with the permanent trim resting on the grid. The interface between the trim and the grid should be sealed with Room Temperature Vulcanizing (RTV) sealant.

Figure 4.16 provides further details on T-bar ceiling installation.

Figure 4.16: T-Bar Ceiling Installation
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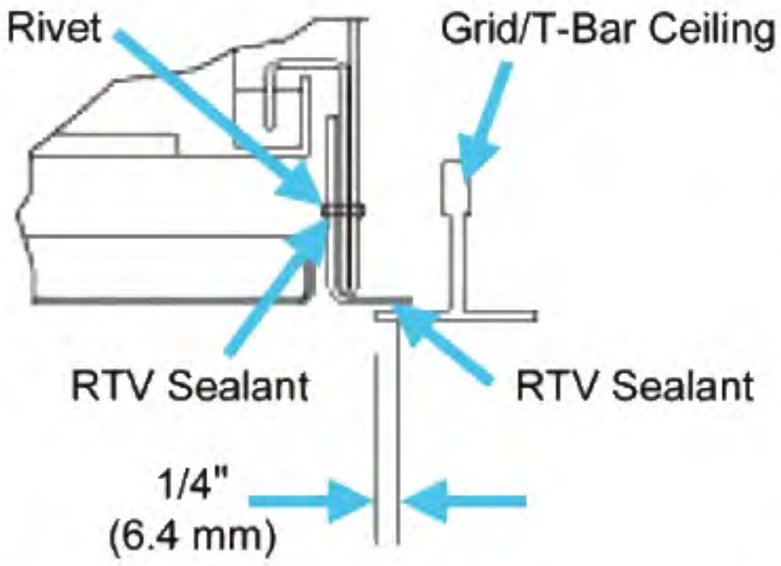

- Prior to installing the hood, thoroughly clean the trim on the hood and the surface of the grid to remove any oil, grease, or residue that would keep the RTV from bonding.
- Apply a 1/4" diameter bead of RTV to the grid.
- Remove the grill from the hood and install the hood into the opening and center in the opening.
- Seat the hood by pushing down with enough pressure to ensure that the permanent trim is bonded in the grid.
- Smooth out any sealant that pushes out around the perimeter of the hood. Remove excess sealant with a clean rag.

Stainless Removable Trim (SRT) for Hard Ceiling

HEPA hoods can be supplied with SRT that is not attached until the hood is installed in the ceiling. The hood may be installed from either the room side or from above the ceiling. Once installed, the perimeter trim is secured and sealed to the ceiling providing a flush finish.

Figure 4.17 provides further details on SRT ceiling installation.

Figure 4.17: Stainless Removable Trim Ceiling Installation
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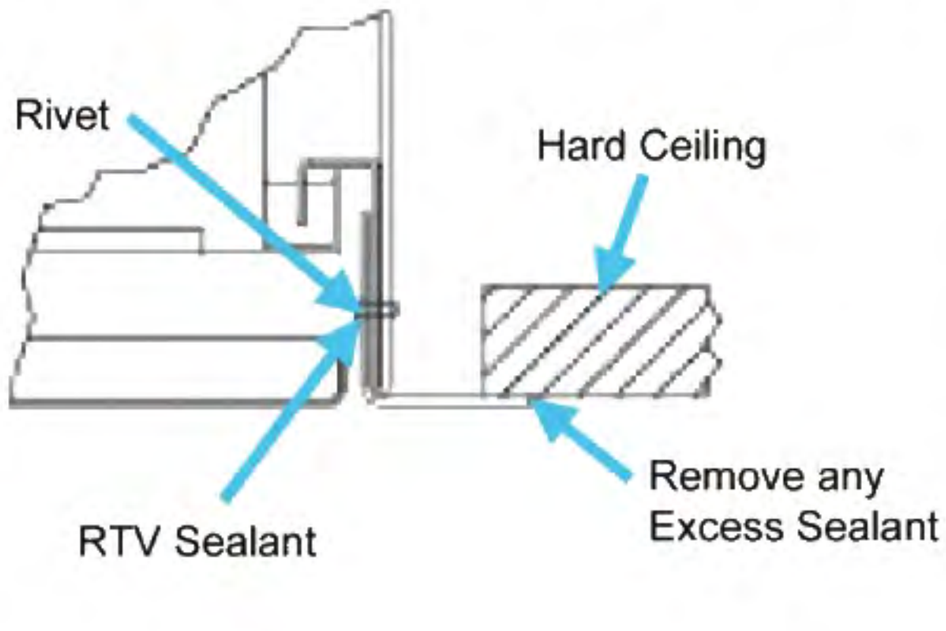

- Suspend the hood using the universal mounting brackets. Adjust the height of the hood until flush with the ceiling.
- Remove the grill and insert the stainless trim to the proper position with trim in the correct orientation and position. Drill a #30 hole (1/8" diameter) through the hood body using the predrilled holes in trim as a template. Remove the trim and apply a 1/4" diameter bead of RTV on the surface of the trim that will be against the ceiling.
- Reinsert the trim lining up the rivet holes. Use closed-end pop rivets to attach the trim to the hood. It is important to use closed-end pop rivets or blind pop rivets to attach the trim. If not, dirty air can pass the shaft of the rivet and result in contamination of the cleanroom.

4.3.4.2 Mounting Options

HEPA housings with brackets can be suspended using wire or rods. The brackets can also be used to clamp the hood to the ceiling substrate. Mounting brackets are located on the body near the four corners of the hood.

Warping of the Hood

If hood becomes out of square, i.e., warped, uneven spacing between the trim and the grille can be noticed. An out of square hood may prevent the filter from properly fitting, which can cause leakage. If out of square, the hood can be realigned by removing the grille and applying a slight pressure across the corners of the hood using a bar clamp. The grille should only be removed when absolutely necessary. The grille acts as a stabilizer during shipping, handling, and installation.

4.3.5 HEPA Filter Handling, Installation, and Removal

Procedures for the handling of HEPA filters should include the following:

- Extreme care needs to be taken with HEPA filters during installation, removal, and handling. HEPA filter micro-glass media is fragile and easily damaged; membrane media is more robust but should still be handled with care. Exercise caution when removing the filters from their packaging. Filters are often inadvertently damaged during handling and installation by contacting belt buckles, pens, pencils, and other items placed in shirt pockets, etc.

- Exercise caution when removing the HEPA filter from the plastic bag. Occasionally the plastic bag will stick to the gel located in the channel of the filter frame. If this happens, slowly pull the bag away from the gel. Quickly pulling it away may damage the gel.

- Never touch the filter media or the gel. Handle filters by firmly grasping the filter frame, using care not to touch the media or gel.

It is strongly recommended that filter handling be carried out by two persons.

Procedures for the installation and removal of HEPA filters should include the following:

- Firmly grasp the filter by the frame using care not to touch the media or the gel.

- Use the filter retainer clips or filter guides to guide and center the filter onto the knife edge. Apply a small amount of force to the filter frame with your fingers.

- If using a flexible gasket seal instead of gel seal, the gasket is attached to the open frame of the filter face and should be compressed against the flat face of the mounting framework using enough pressure to prevent air bypass, but not so much force that the gasket is completely compressed.

- Engage the filter clamps. It is important not to force the clamp closed or to overtighten. Forcing or over tightening will damage or break the clamp and the filter will not be able to seal properly.

- To remove, reverse the process.

4.4 Containment/Biosafety

The purpose of a containment system is to filter dangerous chemical, biological, or carcinogenic contaminants from the air. Containment systems, as their name infers, are also designed to contain the filtered contaminants in a sealed housing until such time as the filter media needs replacement or regeneration. Containment systems can filter out particulates, gases, or both, depending upon the filter used. Refer to the *ISPE D/A/CH Affiliate: Containment Manual (English Translation)* [71] for additional information.

Containment housings are designed for use in critical processes where hazardous airborne materials need to be prevented from escaping to the atmosphere. Air filters may be replaced using a control barrier to protect change-out personnel from contaminants within the housing or contaminants captured by the filters.

Containment housing minimizes exposure to harmful contaminants during filter service through the use of a PVC (Polyvinyl Chloride) bag enclosure system. The entire filter changing process isolates personnel from the hazardous materials.

There are three types of containment technologies for control of potent APIs, liquids, or biological agents:

- Traditional cleanroom

- Restricted Access Barrier System (RABS)
- Full isolated system

All three types of containment technologies have advantages and disadvantages when it comes to operating cost, risk, and capital investment. The common factor that is consistent and necessary in all three types is the use of HEPA filters and containment housings.

Best engineering practice for state-of-the-art bio-containment facilities at CL3 or CL4 facilities should include the following attributes:

- HEPA filter systems configured for manual or automated full face scan of filters to allow routine and/or replacement filter testing.
- The ability to safely and effectively bio-decontaminate filters and housings to a defined level of performance using the reference spore forming indicator organism indicated by the gas or vapor used. To achieve this requires ultra-low leakage housings, tight shut-off dampers, and systems to circulate the fumigant through the filtration network. Airflow controls are essential to maintain negative pressurization of containment areas as filters foul.

Containment systems can include a combination of several components, depending on the nature of the contaminant and application. These components can include prefiltration, test section, high efficiency or final filtration, and adsorber sections mounted in series. There are also systems that include working and safety filters and are equipped with containment systems and explosion protection. The capacity of these systems can be increased by adding multiple sections in parallel. Containment systems can also include an option called bag-in/bag-out to facilitate the safe change-out of air filters.

Figure 4.18 shows an example of a containment system.

Figure 4.18: Example of a Containment System
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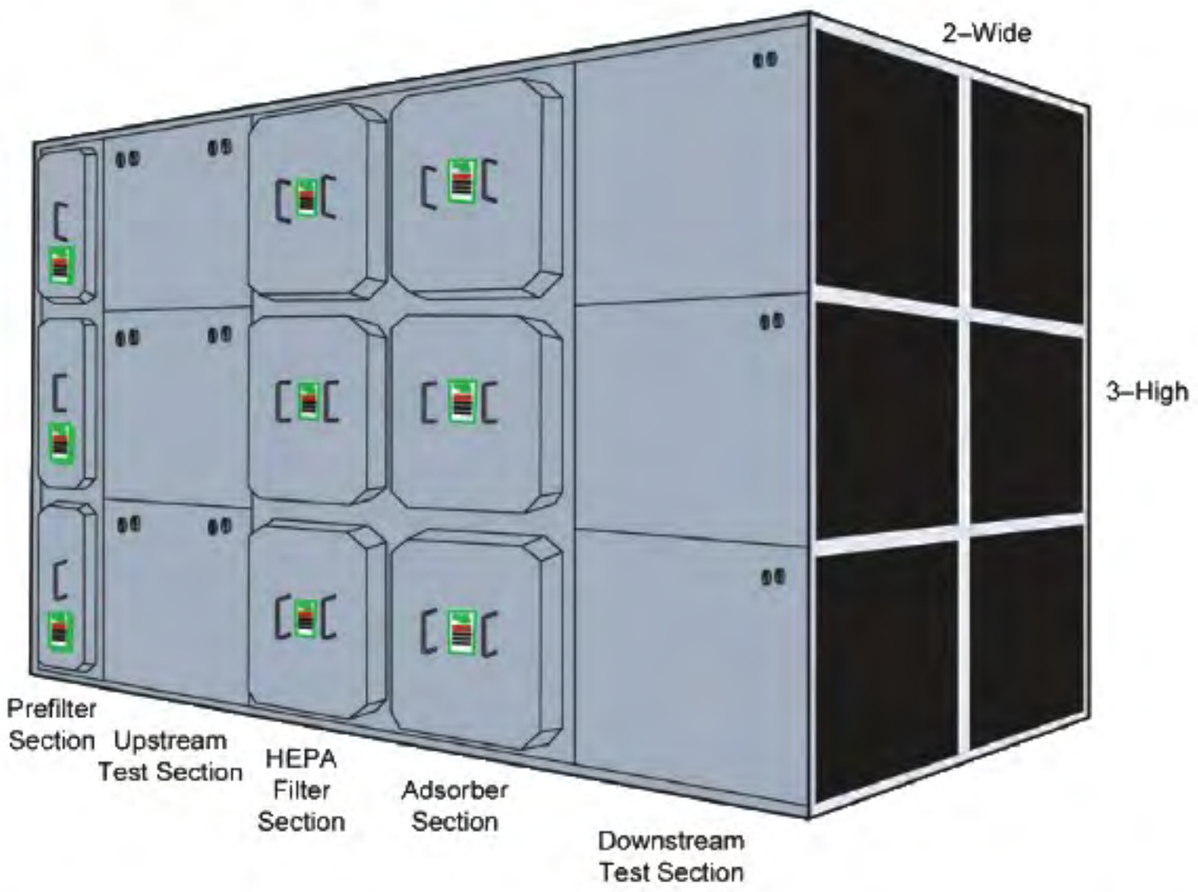


Typically, the primary filter in a containment system is a HEPA filter. Each HEPA filter should be tested to ensure that the particulate efficiency meets or exceeds the requirements of the application. Particulate filters are available from 99.97% for particles 0.3 µm in size to 99.9995% for particles 0.12 µm in size. Gel seal filter housings provide an easier way to achieve a leak free seal between the housing filter mount and the filter, thereby ensuring that all of the air moving through the housing is treated by the air filter for the removal of harmful contaminants.

Another type of safe change filter is the push through or push-push system for cylindrical HEPA cartridge filters that fit containment isolators without the need for unidirectional airflow.

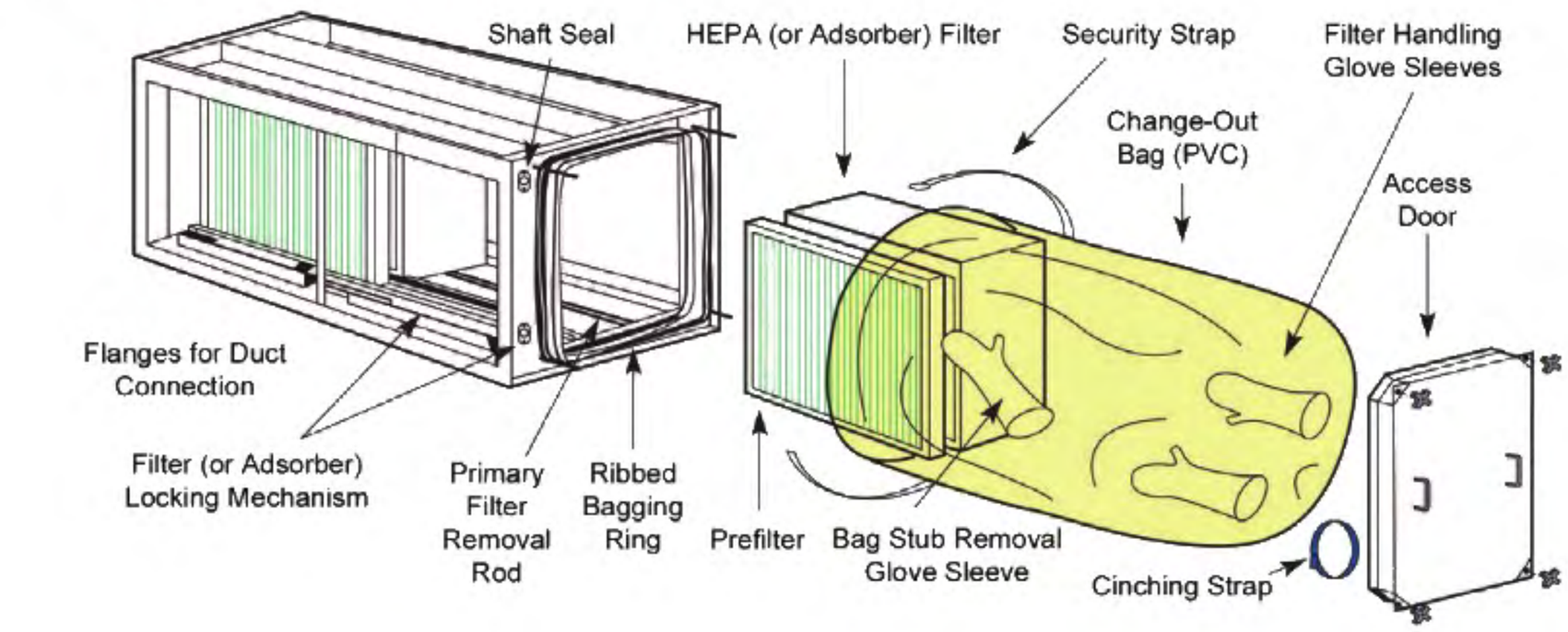
4.4.1 Bag-In/Bag-Out

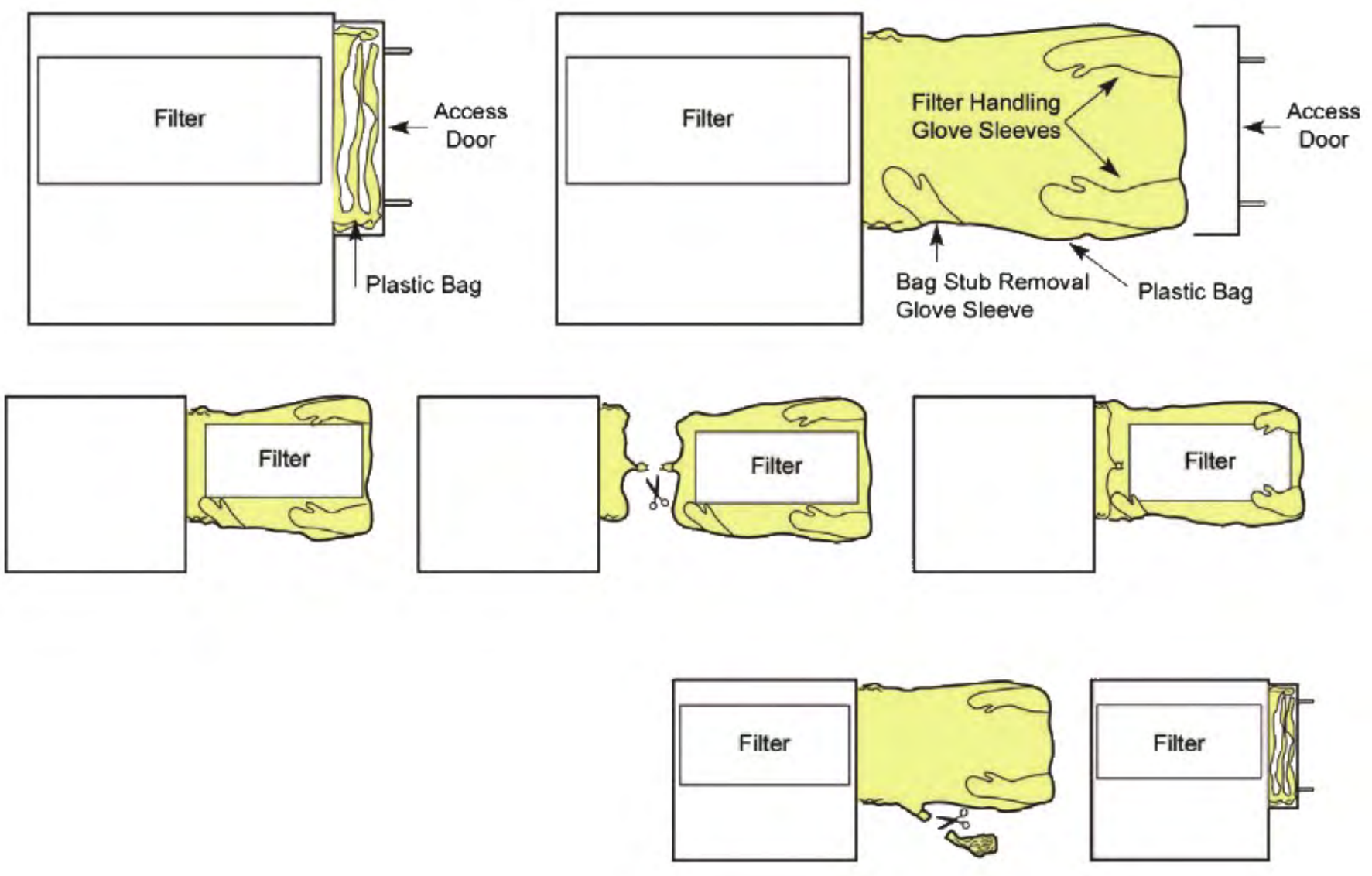
Containment housings are designed with safety in mind. Bag-in/bag-out systems are containment systems with the added option of including a PVC bag that includes integral gloves. The bags are used to seal the containment housing while changing filters that are contaminated with dangerous matter. Utilization of very specific procedures is required for the safe use of bag-in/bag-out systems. The basics of filter change include installing the new filters in the change-out bag, securing the bag over the ribbed openings on the housing door opening, and performing the filter change entirely within the bag.

Figure 4.19 provides additional information on filter change-out in a bag-in/bag-out system.

Figure 4.19: Bag-In/Bag-Out System Filter Change-out

Used with permission from Camfil, https://www.camfil.com/en-us.





4.4.2 Testability and Maintenance

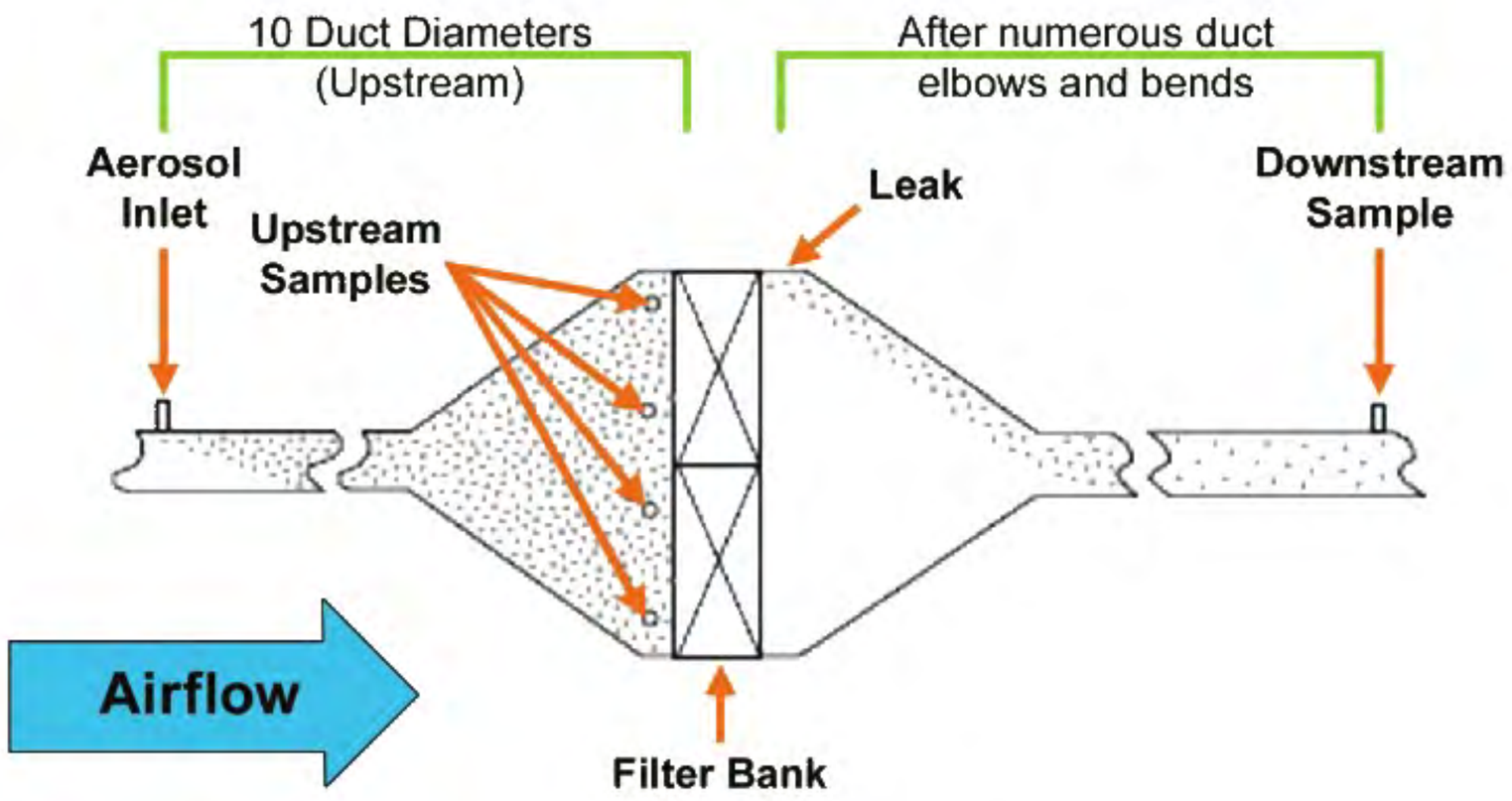
Containment testability is a function of design; containment air filtration systems should be designed and manufactured for in-place testability. Adequate access and space need to be provided for testing and change-out of the filters. Access for two maintenance technicians and the use of a lifting table, if possible, is recommended to ensure the safe change-out of a contaminated filter.

When designing a system to provide a method for *in situ* testing, the methods used include overall efficiency testing, efficiency testing for each filter by test section, and scan testing. Issues to consider are where the test air will come from and whether the system needs to operate during maintenance.

Figure 4.20 provides additional information on the testing of HEPA filters.

Figure 4.20: Testing of HEPA Filters

Used with permission (and modifed) from Camfil, https://www.camfil.com/en-us.



There should be a well-designed transition piece on the inlet and outlet of the housing and no obstructions, such as other filters, adsorbers, etc., in the system. Figure 4.20 illustrates a bank of filters in such a system. Uniform mixing of the challenge aerosol is essential for an accurate test. This is achieved by bends and elbows in the ductwork or the addition of a Stairmand disk. Multiple sample ports upstream of the filters under test are required to measure the challenge concentration and uniformity. Distance ensures mixing on both sides of the filter bank, whereas it is the system design (e.g., the transition) that aids in balancing the flow through the bank and results in a uniform challenge to the bank.

Figure 4.21 shows examples of aerosol mix test sections.

Figure 4.21: Examples of Aerosol Mix Test Sections
Used with permission from Camfil, https://www.camfil.com/en-us.

Manufacturers of filter housings have developed test sections designed and qualified to adequately mix an aerosol challenge aerosol and sample the penetration downstream in a very short airway length (less than the 10 duct diameters that is normally accepted).

HEPA filter efficiency is tested using scan probes to find pin hole leaks. The scan probes cross the face of the filter measuring particle counts across the entire face area, including filter seals. Any leaks in the filter will be identified, quantified, and recorded in a database for further action. Scanning can be done manually or automatically.

Figure 4.22 shows an example of an automated filter scanning.

Figure 4.22: Example of Automated Filter Scanning
Used with permission from Camfil, https://www.camfil.com/en-us.

4.4.3 Manual Filter Scanning

This method can have highly variable results and is subject to human error. Manual scanning requires laboratory shutdown and system decontamination, and is a slow process with results that are not always consistent and repeatable. It can be difficult for the operator to see inside while scanning and difficult to scan through glove ports. There is also the possibility of a filter rupture.

Figure 4.23 shows an example of the manual HEPA scan procedure.

Figure 4.23: Example of Manual HEPA Scan Procedure
Used with permission from Camfil, https://www.camfil.com/en-us.

4.4.4 Automated or Non-Intrusive Filter Certification Scan

A non-intrusive filter scan automates the most important and challenging part of *in situ* filter validation, the scanning process. Automation minimizes the risk of inadvertent containment system damage that might be caused by puncturing the HEPA filter with a manual scan probe or damaging the access door gaskets during removal.

4.4.5 Push/Push Filters

Another type of safe change filter is the push through system for cylindrical HEPA cartridge filters that can fit containment isolators without the need for unidirectional airflow.

4.4.6 Decontamination

Vaporized Hydrogen Peroxide (VHP) is commonly used to decontaminate a variety of enclosures, including BSCs and laboratories, filling and sterility test isolators, animal holding and cleanrooms, decontamination chambers, and pass-throughs.

In some cases, the VHP is introduced via a HEPA filter and in others, the HEPA filters are part of systems used to recirculate and distribute the vapor.

In some instances, the aeration phase of a decontamination cycle is the longest. Initially a rapid decline in concentration can be observed that directly correlates with the rate of peroxide-free air introduced. This is followed by a much more gradual decline following the first few air exchanges where eliminating peroxide from an enclosure becomes a function of desorption.

5 Process Equipment Air Filters

Air filters are used in a number of process applications; selection, installation, and testing will vary depending on the use. Note that dust control systems and the associated specialist filters are not included in the scope of this Guide – although the final discharge air will typically go through a HEPA grade filter.

For filters used in process gases, refer to the *ISPE Good Practice Guide: Process Gases* [72].

5.1 Tablet Processing Equipment

Although tablet manufacturing does not require a classified environment in most jurisdictions, it is considered a good practice to provide high quality filtration to processing equipment that passes a large quantity of air over product during processing, such as coaters and granulators. Typically H13/14 filters are used, fitted with a gasket type seal and with the filters leak tested (total penetration) on installation and annually thereafter. Specialized filters are often used for system containment, or dedusting, with a final HEPA grade filter on the discharge that may be tested to a recognized standard (refer to Chapter 3).

Where there is the potential for dust explosion (e.g., coaters, granulators, dedusting units), HEPA filters are used with the addition of explosion protection (suppression or explosion vents). Note that some filter manufacturers deliver particle filter with, for example, ATEX certification for use in potentially explosive environments.

5.2 Depyrogenation Tunnels/Ovens

The filters fitted to a depyrogenation tunnel are subject to prolonged periods of high temperature operation, so standard filters are not suitable. Special filters rated to 350°C are available with a manufacturer guaranteed efficiency of 99.99% for 0.3 µm particles (note that the FDA definition of a HEPA is > 99.97% at 0.3 µm) at a temperature of 350°C) with a ceramic material used for the media to frame seal. Recently there have been advances in the materials available and flexible sealants are being introduced that can reduce the heat up time and reduce the risk of sealant cracking. Traditional filters need to have a controlled heat up and cool down time (typically not to exceed 1°C per minute; the rate should be confirmed with the filter supplier) to prevent heat stress damage to the seals. Often the systems are maintained hot during periods of non-use to reduce the heat cycling on the filter.

Filters used for this application are generally H14. These filters can be full face scan leak tested on installation, but after the initial heating cycle (burning in the filter, which usually results in the filter grade becoming equivalent to H13) traditional testing is not recommended. The oil aerosol (if it is Polyalphaolefin (PAO)) will load onto the filter and burn off, giving off unhealthy fumes, and may load the filter media; this is usually more fragile after burn in as the binder holding the media together has off-gassed. DEHS (Diethylhexyl Sebacate) is an alternative oil that may evaporate faster.

The ongoing monitoring is typically done by a particle counter to ensure all zones meet ISO 5/Grade A[2]; monitoring at locations across the width of the belt on the in-feed with the unit operational is suggested as an initial assessment. This test covers all of the air supplied to the system due to the differential pressure across the tunnel sweeping air from the higher pressure fill room to the lower pressure washing area. This test is generally followed by testing in the three zones: heating, hot, and cooling zones. Such tests are typically carried out with the units cool or at a temperature below the maximum temperature that the particle counter can handle.

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[2] For additional information regarding area classification, refer to the *ISPE Baseline® Guide: Volume 3 – Sterile Product Manufacturing Facilities (Third Edition)* [73] which takes the following into account: ISO 14644-1 Classification of Air Cleanliness [24], the FDA September 2004 Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice [74], and Annex 1 of the EU GMPs [75].

5.3 Unidirectional Airflow Applications

Unidirectional Airflow (UAF) applications are one of the most common applications of filters in the industry. The application needs to be well defined in order to apply the appropriate requirements; for example, laboratories often have both personnel and external environmental requirements as well as requirements for product and/or process protection.

Use of UAF is also common in dispensaries, process areas such as critical areas in aseptic operations (e.g., preparation, filling), handling of sterile components, or transfer of partially closed containers prior to completion of stoppering. These areas are classified as ISO 5 (particulate limits only) or Grade A (EU terminology, incorporating the specific requirement for particles equal to or greater than 5 µm and the associated suggested microbiological limits). Airflow must be demonstrated to sweep particles away from the critical area during operations. Regulatory guidance [74] suggests an *"[air] velocity of 0.45 meters/second (90 feet per minute) … with a range of plus or minus 20 percent around the set point"* to achieve this. Experience has shown that this value may be too high for some applications, creating undesirable turbulence (Brande et al., 2017 [76]).

Note: Organizations should verify the requirements with local regulations. Laboratory equipment that meets Health, Safety, and Environment (HSE) requirements may be subject to other regulations with their own requirements.

HEPA is the minimum filtration level for this application, and ULPA may be desirable. Higher airflow velocities in UAF applications may exceed HEPA filter ratings for efficiency which may cause lower efficiency performance. Higher efficiency ULPA filtration offers more protection against bleed through at higher airflow velocities.

Commissioning verifies that the correct grade of filter has been installed, with the appropriate certification. Either a total penetration test or full face scan, depending on the application and local regulations, is carried out on installation and periodically thereafter. For applications related to aseptic processing, leak testing is required on a 6-month basis, whereas other applications (such as oral solid dose) may be tested less frequently, e.g., annually.

Weighing and dispensing (downflow) booths are a specific application that provides ISO 5/Grade A air supply with directional control to protect the material being dispensed, and protect the operator from exposure to the product to a degree.

5.4 Washing Machines

Washing machines and bin wash systems often incorporate HEPA grade filters to manage the quality of the air used for drying components. The management of these is usually based on risk with testing not exceeding a 24-month period.

6 Filter Testing (HVAC Related Only)

6.1 Introduction

HEPA and ULPA filters are characterized by a minimum efficiency rating accompanied by flow and resistance values. These values are measured at the factory before filter installation and are typically identified on the label affixed to the filter frame. After the factory testing is completed, the filter will be exposed to many activities that may pose risks to the operational performance of the filter when installed and put into use. Activities such as packaging, transit to the customer, storage, handling during installation, testing, and use throughout the filter's life are risks that can result in damage to the filter.

In addition to the factory efficiency testing, filter integrity testing (also referred to as leak testing in this chapter, see Section 6.4) is commonly periodically performed after filter installation at the customer's location to ensure the filters are continuously performing to the criteria identified for their end use. When put in operation, it is important that the filter's operating flow rate is as close as possible to, or lower than, the nominal flow rate specified by the manufacturer in order to ensure the filter performs as classified.

Although incorrect and commonly used interchangeably with integrity testing, efficiency testing is not a test end-users would commonly carry out *in situ* or in the field. The differences between efficiency testing and filter integrity testing (leak testing) are discussed in the following sections.

6.2 Relevant Test Standards and Recommended Practices

Information from relevant HEPA filter related test standards typically covers one or more of the following categories:

- Classification system that defines the filter performance based on measured global efficiency and local leakage criteria
- Filter media test methodology
- Global filter efficiency (factory test) and global integrity (field test) test methodology
- Local filter leakage test methodology (factory and field tests)

The following test standards and recommended practices relate to filter testing:

- IEST-RP-CC001 (HEPA and ULPA Filters) [55]
- IEST-RP-CC007 (Testing ULPA Filters) [77]
- IEST-RP-CC021 (Testing HEPA and ULPA Filter Media) [78]
- IEST-RP-CC034 (HEPA and ULPA Filter Leak Tests) [70]
- EN 1822 High efficiency particulate air filter (HEPA & ULPA) [52]
  - EN 1822-1 (Part 1: Classification, performance testing, marking) [79]
  - EN 1822-2 (Part 2: Aerosol production, measuring equipment, particle counter statistics) [80]
  - EN 1822-3 (Part 3: Testing flat sheet filter media) [81]

- EN 1822-4 (Part 4: Determining leakage of filter elements (scan method)) [82]
- EN 1822-5 (Part 5: Determining the efficiency of filter elements) [83]

- MIL-STD-282 (Filter Units, Protective Clothing, Gas-Mask Components and Related Products: Performance Test Methods) [84]
- ISO 29463 (High efficiency filers and filter media for removing particles from air) [51]
  - ISO 29463-1 (Part 1: Classification, performance, testing and marking) [85]
  - ISO 29463-2 (Part 2: Aerosol production, measuring equipment and particle-counting statistics) [86]
  - ISO 29463-3 (Part 3: Testing flat sheet filter media) [84]
  - ISO 29463-4 (Part 4: Test method for determining leakage of filter elements–Scan method) [88]
  - ISO 29463-5 (Part 5: Test method for filter elements) [89]
- ISO 14644 (Cleanrooms and associated controlled environments) [23]
  - ISO 14644-3 (Part 3: Test methods) [33]
- NEBB Procedural Standard for Certified Testing of Cleanrooms [90]
- ISO 16170 (*In situ* test methods for high efficiency filter systems in industrial facilities) [53]
- NSF/ANSI 49 (Biosafety Cabinetry: Design, Construction, Performance, and Field Certification) [56]
- BS EN 12469 (Biotechnology – Performance criteria for microbiological safety cabinets) [54]

Caution should be exercised when considering the test methods identified in the standards and recommended practices. It is important to make a distinction between the factory and field tests to ensure that they are applied appropriately.

6.3 Factory Tests

Filters are factory tested to verify a specific classification level is met. This test is typically composed of two parts (overall filter efficiency and local efficiency) that are simultaneously performed at a known volumetric flow rate and corresponding differential pressure.

In order to establish highly repeatable test methods and procedures, many factory test setups have converted to automated scan test systems that significantly reduce factors related to human error. In certain instances, batch sample testing of lower-rated HEPA filters may be applied at the factory. It is important to note in purchase contracts with filter manufacturers that 100% of HEPA filters purchased shall be factory tested.

During either the factory scan test or factory efficiency test, the filters pressure drop should also be measured and recorded when operating at the filter's designed airflow volume.

6.3.1 *Factory Efficiency Test*

Due to the cost, size, and complexity of the equipment required to perform the testing, efficiency tests are limited to a factory or R&D setting. A filter's efficiency is determined at the filter's defined MPPS or otherwise stated particle size or range. As discussed in Section 2.2, a filter has a defined MPPS for a specified flow. For detailed information regarding efficiency and penetration, see also Section 2.2.

Factory efficiency testing is carried out using a Discrete Particle Counter(s) (DPC), dilution system, and aerosol generator. The filter efficiency, as determined as the lower efficiency, when tested for particle size ranges of 0.1 µm to 0.2 µm and 0.2 µm to 0.3 µm, is calculated from automated scan data collected by the methods outlined in EN 1822-4 [82] or ISO 29463-4 [88]. Acceptable alternatives are efficiency tests utilizing a thermal aerosol generator and photometer (which measures total downstream penetration as compared to the upstream concentration) or tested in accordance with IEST-RP-CC007 [77], EN 1822-5 [83] or ISO 29463-5 [89].

6.3.2 *Factory Scan Test*

Each filter is subjected to an automated scan test for the detection of leaks in the media and the perimeter seal. Small filters (filters less than 18 inches wide) or small lot sizes (less than five pieces of a given size) may be manually scan tested. The scanning is accomplished by passing a scan probe over the filter face with overlapping strokes to ensure the entire filter face area is sampled. Factory scanning is performed in accordance with IEST-RP-CC034 [70] or in accordance with EN 1822-4 [82] or ISO 29463-4 [88]. The following specifications and criteria relate to the factory scan test:

- The particle counting equipment used should have a detection limit of 0.10 µm or smaller at a sample flow rate of 1 ft^3/min (28.3 LPM) and should be calibrated and within its recommended calibration cycle.

- The common challenge aerosols for factory scan testing are PAO, DEHS, or microspheres. The maximum leakage is in accordance with a Type K filter as specified in IEST-RP-CC034 [70]; the specified leakage threshold for this filter type is defined as 0.008% of the upstream concentration. If testing is performed in accordance with EN 1822-4 [82] or ISO 29463-4 [88], a filter classification of H14 or ISO 45 H respectively, should be utilized with a modified local efficiency value of 99.992% (0.008% penetration).

- An acceptable alternative to the above method is a manual scan in accordance with IEST-RP-CC034 [70] with the exception that a thermal aerosol generator be utilized and the penetration limit is set to 0.008% when scanning with a photometer. In this case the minimum aerosol concentration should be 10 µg/L.

6.4 *In Situ*/Field Testing of HEPA Filters: Filter Integrity Leak Testing

Filter integrity testing, also referred to as leak testing, is carried out to identify gross defects within the filter media and filter support framework of installed filters. For simplification, filter integrity testing will be referred to as leak testing throughout this chapter.

In the pharmaceutical industry, HEPA filter leak testing is commonly conducted on an annual or semi-annual basis over the operational life of the filters to ensure that they are performing within specifications.

Leaks in the HEPA filter or housing might be found in the following typical locations:

- Physical damage to filter media that can occur on the upstream side, downstream side, and within the depths of the pleated media

- Fabrication defects in media that were missed in factory tests

- Defects or voids where the filter media is bound to the filter frame

- Filter framing defects along joints and/or other structures
- Bypass of unfiltered air around gaskets or gel seals

The two tests that relate to *in situ* leak testing are the scan test and overall leak test. It is important to note that a scan test is a localized test only considering the filter area covered by the scan probe, while an overall leak test measures the filter's performance overall (as a whole). In both tests, common factors are required to carry out adequate test conditions to produce valid measurements.

The majority of international and industrial test standards have identified two main test instruments used to perform a leak test: the aerosol photometer and the DPC. The differences in the equipment and methodology for each test type is described below.

6.4.1 Filter Leak Testing: Scan Test

In the scan test, the total face of the filter is scanned using a photometer or particle counter while an artificial particle challenge is introduced upstream of the filter. A rectangular isokinetic scan probe is passed over the entire filter face with overlapping strokes. The probe is held approximately 1 in (2.54 cm) off the filter face and is also passed around the perimeter of the filter media to identify any potential bypass of air around the filter frame. Unlike in an automated factory scan test, the filter scan probe is almost always handheld at an installation site. This allows for a less controlled test and a recommended scan rate of 2 in/sec (5 cm/sec) or less is commonly reported and practiced in the field. Exceeding the scan rate of 2 in/sec (5 cm/sec) can result in leaks near the acceptance limit being missed therefore it is important to adhere to the scan rate recommendations.

In order to identify and size a leak, the downstream penetration of the filter area covered by the probe is compared to the upstream concentration to determine the leakage percent. Filter leak testing in less clean areas can result in false leak indications especially around filter edges due to the introduction of particles from surrounding areas in the room. Under these conditions, it may be useful to utilize a physical barrier or shield around the filter or frame edge to isolate the filter under test from particle contributions from the room.

6.4.2 Filter Leak Testing: Overall Leak Test

In certain scenarios, it may not be possible to access the downstream side of the filter face in order to scan it for leaks. As an alternative under these circumstances and other instances, an overall leak test is often carried out. This is a much less stringent test compared to the scan test because larger localized defect(s) can be masked in the overall leakage. The overall leak test determines the amount of penetration through a filter as a whole (or globally) versus locally with a scan probe, therefore a single leak is diluted into a much larger volume of clean air. In the scan test, the leak is diluted into 1 CFM (28.3 LPM) of air (the flow rate of the test instrument) while in the overall leak test, the leak is diluted into the total volumetric airflow of the filter. As an example, for a filter with a volumetric airflow of 500 cfm (850 m^3/hr), a single 0.25% leak in a scan test will show up as 1/500th of 0.25% or 0.0005% in an overall leak test. This is assuming there are no other defects in the filter.

In comparison to the filter scan test, the overall leak measurement should be taken much farther downstream of a filter; this enables sampling at a location where the downstream air has had the ability to mix, resulting in evenly distributed particles at the sample location. This prevents a leak from streamlining past the sample location which would result in a missed or undersized leak measurement. If uniform mixing cannot be achieved downstream of the filters, then multiple downstream samples are taken either in the duct as a duct traverse or at the room registers. The average of the readings is then reported. The leakage percent in an overall leak test is determined by taking the downstream aerosol concentration over the upstream aerosol concentration multiplied by 100.

6.5 Background on Leaks and Sizing

There are a number of standard factors that play into the historic definition of a leak and how it is understood today. In general, a leak is defined as any bypass of unfiltered air that is not expected for the filter under consideration. It should be noted that filters are not 100% efficient for all particle sizes; therefore, penetration of particles, especially near the MPPS, is expected through undamaged filter media. Similar to the penetration of a filter measured from factory efficiency testing, a leak is the proportion of particles passing through the filter to the number of particles in the air flowing to the filter. In the case of leak testing, it is assumed that the intact filter media is performing to specification and the bypass of particles is occurring through larger defects in the filter media, filter construction materials, or gaskets sealing the filter to the supporting structure. Because these defects or leaks are considered large in comparison to the particles used in a factory efficiency test, it is not critical to test at the MPPS in the field. Although large in physical size compared to the particle sizes used in the leak test, filter media defects near the common failure limits are often not easily visible to the naked eye, even at close distances. The defects are also large compared to the particles used in the field. Defects large enough to easily see are almost always guaranteed to fail any test acceptance limits.

In an overall leak test, the leak size is determined by taking the ratio of the downstream particle concentration to the upstream concentration. In this type of test, a single leak is diluted in the total volumetric airflow of the filter. In a scan test, the leak is only diluted into the volumetric flow rate of the sampling instrument because the isokinetic probe is positioned in close proximity to the downstream side of the filter face. Historically, a scan test leak size was defined using a 1 CFM (28.3 LPM) sampling instrument. In the case of a 0.01% leak, the amount of unfiltered air passing through a defect of this size would be 0.01% of 28.3 LPM, or 2.83 cm^3/min (CCM). It is because of the defined 1 CFM (28.3 LPM) sampling conditions that leaks measured in a scan test are also referred to as standard leak penetration or standard local penetration.

6.6 Challenge Aerosols

In order to perform a reliable, repeatable filter leak test, an artificial particle challenge needs to be generated upstream of the filter under test. It is necessary to know the concentration of the aerosol challenge in order to determine the leak size of a defect. The most common challenge aerosols for the testing of HEPA and ULPA filters used in pharmaceutical manufacturing are liquids such as PAO-4, Dioctyl Sebecate (DOS or DEHS), and Ondina EL. Ambient challenges are not recommended as they are typically too low in concentration or too unstable to provide an adequate challenge for a leak test.

6.6.1 Challenge Aerosol Concentration

The artificial particle challenge used in filter leak testing is typically significantly higher than what would be expected under normal operation, especially in cases where the outside air being delivered to the HEPA filter is treated with adequate prefiltration. The common minimum upstream concentration values reported in IEST-RP-CC034 [70] for field leak tests are 10 µg/l for a photometer and 12 million particles/ft^3 (4.2×10^8 particles/m^3) for a particle counter. These minimum upstream challenge concentration limits exist, because when considering a leak of approximately 0.01%, the recommended minimum upstream concentration values would be reduced to concentrations approaching instrument stability and detection limits when scanning or leak sizing. In addition to the lower concentration limits, upper concentration limits should also be taken into account. The performance of the test equipment can be compromised by exposure to excessive aerosol challenges which can lead to contamination or fouling of sample chamber optics, saturation of dilution devices, or collection of oil within the sampling path due to coalescence. Additionally, excess aerosol challenges can lead to premature or unnecessary loading of the filters under test. Recommended upstream concentrations per IEST-RP-CC034 [70] are approximately 10 µg/l to 90 µg/l for photometer tests and 12 to 50 million particles/ft^3 (4.2×10^8 to 1.8×10^9 particles/m^3) for particle counters.

6.6.2 Particle Challenge Uniformity

Particle challenge uniformity, both temporal (over time) and spatial (across the filter face), is critical for all filter tests and its importance is commonly overlooked. A leak is measured by taking the ratio of particles penetrating the filter to the number of particles flowing to the filter. When performing a filter leak test, it is necessary that the particle distribution upstream of the filter is uniform so that each area of the filter is exposed or challenged with the same number of particles during a test. As an example, if section A of a filter was challenged by twice the number of particles as section B during the test, a leak in section A would show up twice the size as one from an identical defect in section B. As a general rule, it is best to introduce a particle challenge as far away from a filter as possible, since bends in the duct work and other objects contributing to air turbulence will aid in aerosol mixing and challenge uniformity.

The use of room side injectable filter housings with aerosol distribution ports can provide options when considering an approach to testing. Limiting the filter leak test to a single terminal filter enables a user to utilize a lower output aerosol generator in comparison to one that would be required to challenge multiple filters simultaneously. An additional advantage is that when testing a single filter, other filters being supplied on the same air handler or plenum are not exposed to the artificial challenge aerosol used during the test. Various room side injectable housing designs exist and the aerosol distribution components of these housings should be carefully evaluated prior to their installation or prior to carrying out any HEPA filter testing. It is difficult to achieve adequate distribution of test aerosols within such a short distance to the upstream side of the filter, and many designs may not provide the proper conditions to carry out a valid filter integrity leak test. IEST-RP-CC034 [70] gives guidance on evaluating the spatial and temporal uniformity of an aerosol challenge upstream of a filter under test.

6.6.3 Use of Particle Counter Test Method

Traditionally in the pharmaceutical industry, an oil-based aerosol has been used as the challenge agent while using an aerosol photometer to detect defects. The microelectronics industry on the other hand has progressed to using particle counter based test methods with an upstream aerosol composed of microspheres which are typically made of polystyrene. This material selection was chosen due to the fact that oils have the potential to outgas over time and are considered airborne molecular contaminants. Some pharmaceutical applications have adopted the particle counter based testing as a means to reduce the amount of oil used in a filter leak test or to eliminate the oil completely. The aerosol challenge requirements for the particle counter based tests can be in the order of 100 to 1000 times less than that used for a photometer. Applications that have been noted to transition to the particle counter test methods either due to direct observations, hypothesis, or as a means to eliminate potential issues related to oil-based challenges include the following:

- High temperature filtration equipment: Systems such as depyrogenation tunnels can have issues with oil retention in the filters when the systems are brought back up to elevated temperatures, resulting in burn off and the generation of smoke. Additional information relating to high temperature testing can be found in Section 8.5.4.

- Isolators: In some cases, oil retention in HEPA filters has been reported to impact the effectiveness of the VHP sterilization processes. More frequent filter change-outs have been a means to overcome the noted decrease in VHP concentrations with each sequential sterilization cycle performed after filter testing.

- ePTFE filter media: Certain forms of ePTFE filter media, especially earlier generations, are intolerant to high concentrations of oil which will cause a rapid increase in pressure drop across the media. [7] It should be noted that pharmaceutical grade ePTFE filters are available that can tolerate the levels of oil-based challenges used in photometer-based testing.

- Gel seals and gaskets: PAO and other oil-based aerosols have been reported to have an effect on the quality of some HEPA filter gel seals and/or gaskets. [118]

6.7 Equipment Used for Filter Integrity Leak Testing

6.7.1 Aerosol Photometer

An aerosol photometer uses forward light scattering to measure the mass concentration of particles in an aerosol. Figure 6.1 provides an example of an aerosol photometer.

Figure 6.1: Example of an Aerosol Photometer
Used with permission from Air Techniques International, https://www.atitest.com/.

As part of the leak test, the mass concentration of particles upstream of a filter under test is measured and the downstream mass concentration is compared to this value in order to determine the leakage percentage. The recommended upstream concentration for a photometer leak test per IEST-RP-CC034 [70] is 10 µg/l to 90 µg/l. In a scan test, a photometer's rectangular scan probe is passed, typically at 2 in/sec (5 cm/sec) or less, over the entire face of the filter with overlapping strokes and also around the perimeter of the filter to detect leakage.

The two most common aerosol generators for a photometer leak test are the Laskin nozzle and the thermal generator.

6.7.1.1 Aerosol Generator: Laskin Nozzle

The Laskin nozzle aerosol generator system uses a submerged nozzle to generate a polydispersed aerosol from a liquid, such as PAO-4 or DOS/DEHS. Compressed air is delivered to the nozzle, and the high velocity jet of the air exiting the holes in the nozzle atomizes the surrounding liquid producing an aerosol with a particle size distribution ideal for performing a leak test.

The Laskin nozzle generator is sufficient to test smaller systems of approximately 1350 CFM (2,300 m^3/hr) where the reported PAO output of a Laskin nozzle at 23 psi (1.6 bars) is 10 µg/l in 1350 CFM (2,300 m^3/hr). Additional nozzles can be run simultaneously to increase the output of the Laskin nozzle generator. The output of the Laskin nozzle has been well studied, therefore it is possible to calculate the output of the nozzle under known conditions. This can be useful in situations where a plenum upstream of a filter may be contaminated and a user may not be capable of taking a direct measurement. It should be noted that output calculations may not hold with the operation of multiple nozzles simultaneously. Although output calculations can be used in certain instances, it is always best to take a direct reading, when possible, since instruments may not always perform to specifications.

Figure 6.2 provides an example of a Laskin nozzle generator.

Figure 6.2: Example of a Laskin Nozzle Generator
Used with permission from Air Techniques International, https://www.atitest.com/.

6.7.1.2 Aerosol Generator: Thermal Generator

As an alternative to the Laskin nozzle generator, a thermal generator can be utilized in order to achieve much higher output concentrations that can exceed 10 µg/l in 50,000 CFM (85,000 m^3/hr). A thermal generator uses a heated assembly to vaporize an aerosol reagent such as PAO. This process is carried out in the presence of an inert gas supplied by a compressed gas cylinder, and as the vapor exits the generator, it condenses forming an aerosol. While Laskin nozzles are typically utilized for injection ports or in duct work close to the filter under test, the thermal generator output is high enough to introduce at the air handling unit supplying multiple filters. The advantage of this is that introduction at the air handling unit provides a more turbulent airflow path that contributes to aerosol mixing and challenge uniformity when the aerosol reaches the filter under test. This level of uniformity is often difficult to achieve when injected locally with a Laskin nozzle. If injecting aerosol from a thermal generator into a positive pressure duct or plenum, a blower or injection pump is typically required.

Figure 6.3 provides an example of a thermal aerosol generator.

Figure 6.3: Example of a Thermal Aerosol Generator
Used with permission from Air Techniques International, https://www.atitest.com/.

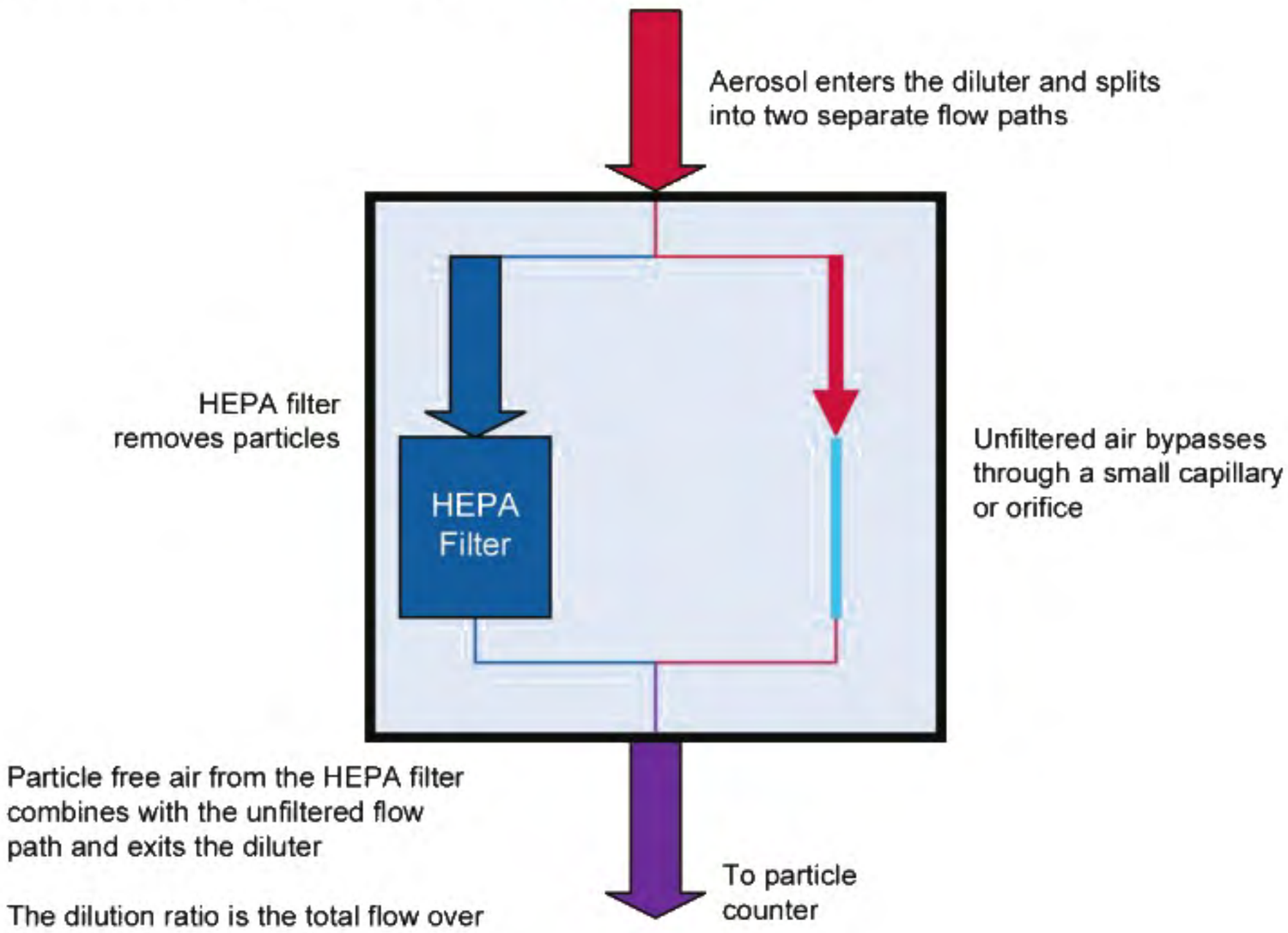
6.7.2 Particle Counter

Similar to a photometer, a particle counter uses light scattering to detect the concentration of particles passing through a sample chamber. Rather than a mass concentration of particles, a particle counter can detect and size the individual particles. Figure 6.4 provides an example of a particle counter.

Figure 6.4: Example of a Particle Counter
Used with permission from Lighthouse Worldwide Solutions, https://www.golighthouse.com/en.

In addition to the particle counter, an aerosol diluter is required to measure the upstream particle concentration in a HEPA filter leak test. The function of the aerosol diluter is to reduce the aerosol concentration to a level within the particle counter's measurement capabilities. A generalized schematic of the airflow path through a diluter is shown in Figure 6.5.

Figure 6.5: Airflow Path through an Aerosol Diluter



Exceeding the upper concentration limit of the particle counter can result in what is referred to as a coincidence counting error. This occurs when two or more particles entering the sample chamber simultaneously are counted as one larger particle. Based on the minimum upper concentration limit for leak testing, a diluter with a minimum dilution ratio of 100:1 is recommended. Dilution ratios greater than 100:1 will allow for a wider range of upstream challenge conditions.

As part of the particle counter based leak test, the concentration of particles upstream of a filter under test is measured and the downstream particle concentration is compared to this value in order to determine the leakage percentage. The recommended upstream concentration range for a particle counter based leak test per IEST-RP-CC034 [70] is 12 to 50 million particles/ft^3 (4.2 × 10^8 to 1.8 × 10^9 particles/m^3). In a scan test, a particle counter's rectangular scan probe is passed, typically at 2 in/sec (5 cm/sec) or less, over the entire face of the filter with overlapping strokes and also around the perimeter of the filter to detect leakage.

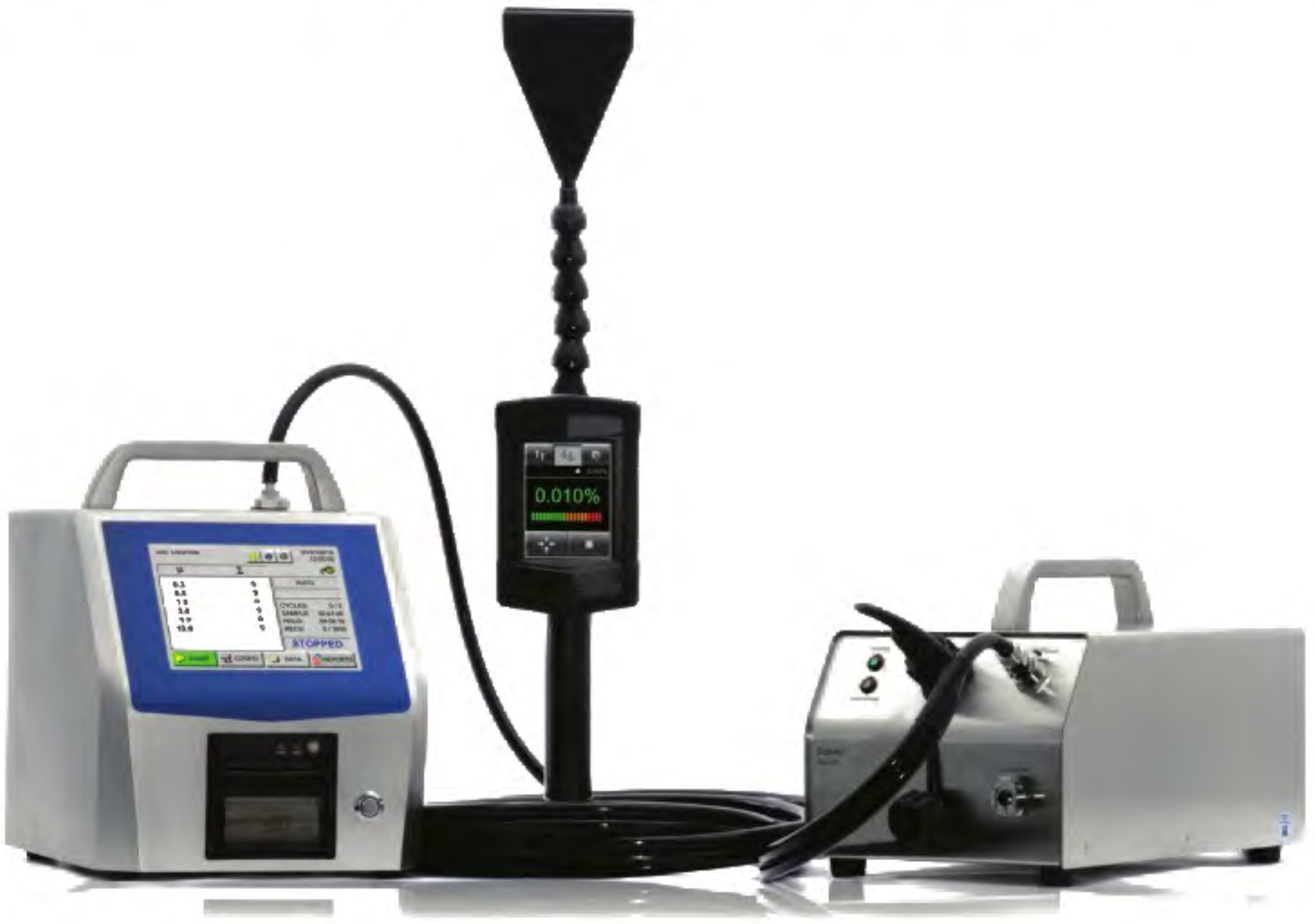
The aerosol challenge requirements for a particle counter based test are quite different than that of a photometer test since the particle counter is measuring individual particles in the sample stream. When comparing the minimum challenge requirements, a particle counter leak test would require in the order of 100 to 1000 times less challenge than that required for a photometer. Lower output aerosol generators or fractional Laskin nozzle generators are typically required because the output from a full Laskin nozzle or thermal generator would very likely oversaturate the aerosol diluter and the detection system of the particle counter when testing a smaller system. The lower output requirement offers advantages in reducing the equipment weight and size.

Figure 6.6 provides an example of a low output aerosol generator.

Figure 6.6: Low Output Aerosol Generator Designed for Particle Counter Based Filter Leak Testing
Used with permission from Milholland & Associates, https://www.dmilholland.com/.

Compared to the photometer test method, the particle counter test method is slightly more complex to implement as many particle counters were not designed as leak test instruments. Particle counter leak test methods have additional factors to consider which can open up the potential for errors or poor practice techniques due to the lack of proper training and experience. A rise in the popularity of particle counter leak testing has led to the development of new integrated particle counter based leak test instruments. These instruments behave very similarly to an aerosol photometer and eliminate many of the variables found in traditional or historic particle counter test methods. Figure 6.7 provides an example of an integrated particle counter based leak instrument.

Figure 6.7: Integrated Particle Counter Based Filter Leak Instrument
Used with permission from Lighthouse Worldwide Solutions, https://www.golighthouse.com/en.



6.8 Acceptance Criteria

The approach most test standards take regarding acceptance criteria is that the acceptable leak size limits are ultimately determined by the customer and supplier. However, a scan test leak size limit of greater than or equal to 0.01% has generally been adopted for many applications utilizing HEPA filters or clean areas of varying classifications. Although the 0.01% leak size has been used historically and has its origins linked to early generation analog photometer test equipment, establishing a leak size limit of 0.01% as an acceptance criteria without performing a science and risk-based assessment can result in issues relating to leak testing and can contribute to significant operational costs if an out of tolerance or failed condition is identified in a low risk area. As previously noted in Section 6.5, filters are not 100% efficient and are expected to have some natural or integral penetration of particles near the MPPS. Test acceptance limits become more controversial or problematic when utilizing lower-rated HEPA filters where the acceptable factory penetration at or near MPPS can be comparable to or larger than the field test leak size acceptance criteria. This is especially true where the bleed through effect can occur (see Section 6.9). When purchasing a filter, it is therefore important to consider a filter's rating as well as how it will be tested after installation in order to avoid unnecessary field test failures.

ISO 14644-3 [33] gives guidance on how alternative leak acceptance criteria can be implemented. In a risk-based approach, it may be ideal to have acceptance criteria that trends with the efficiency of the filters being used or the cleanliness of the room being tested. ISO 14644-3 uses the factory filter efficiency rating as the basis of acceptance criteria negotiation. The leak acceptance criteria for a photometer leak test and a particle counter based leak test should be the same, as the theory and methodology behind leak sizing is identical for both methods. If performed properly, a leak test with a photometer and a particle counter will result in the same leak size (Meek, et al., 2011 [121]).

6.9 Bleed Through or Excessive Widespread Non-Site Specific Penetration

Under certain field test conditions, HEPA filters can experience excessive widespread non-site specific penetration or leakage which is referred to as bleed through in the HEPA filter industry. This excessive leakage can occur anywhere across the filter's face. Lower levels of bleed through can cause smaller defects below the acceptance limits to be measured higher than the established leak acceptance criteria. This behavior has been attributed to the type or classification of the filter under test, the particle size or size range used to test the filter, and the operational airflow of the installed filter. The bleed through issue becomes much more pronounced for lower-rated HEPA filters, and especially those field tested using a thermal aerosol generator where the test aerosol produced can have a size distribution close to the MPPS of the filter. The bleed through issue is reduced when using a Laskin nozzle generator as the particle size distribution from these generators is farther away from the MPPS of a filter when compared to a thermal generator. Exceeding the intended airflow rates of a filter can also contribute to bleed through as the velocity of air through the media has an impact on a filter's efficiency.

It is because of these reasons that when ordering a filter, a good understanding of operational conditions and field tests that will be carried out in the future is necessary. An industry trend has been to recommend a type K filter as defined by IEST-RP-CC001 [55] over a type C filter performance specification in order to mitigate issues related to bleed through that may occur during the periodic leak testing of HEPA filters after installation.

6.10 Filter Repairs

A leak found in the field, or in the factory, can often be repaired using approved materials evaluated for compatibility with the filter media and end use processes. Filter repair criteria can vary based on standards or agencies applicable to end use applications, customer specifications, or a variety of other factors. It is important that the exact location of a defect is isolated and repaired as a large patch covering an underlying defect may cause a leak to migrate and become diluted as it moves around the patch to an alternate location or locations. In conditions where a defect is covered versus repaired, new leak size readings below the leak acceptance limit may be achieved when in fact the defect is still present and unchanged. Additionally, very large filter patches can impact airflow patterns as well as airflow volumes through the filter. These are some of the reasons many standards or guidance documents have implemented size restrictions on repairs.

When repairing filters in the field, it is important to evaluate the effect on the functionality of the filter. When field repairs are allowed, IEST-RP-CC034 [70] states that a field repair should not block or restrict more than an additional 3.0% of the filters face area with the additional criteria that the lesser dimension of the repair may not exceed 3.8 cm (1.5 in).

Filter manufacturer factory repair specifications can differ significantly from field repair criteria in regards to materials used as well as size restrictions; therefore it is important to understand and communicate this information in purchasing agreements.

6.11 Additional *In Situ* Filter Measurements

In addition to the integrity or leak testing of HEPA filters, additional *in situ* measurements, which are often required, can be carried out to evaluate if the filters are operating within certain design specifications. Airflow volume or velocity measurements as well as filter pressure drop readings can provide useful information regarding the amount of clean air being supplied to a controlled area, changes in parameters that can impact room pressurizations, and overall HVAC performance.

6.11.1 Airflow

The volume of HEPA filter supplied air and airflow patterns are critical parameters in controlling particles in cleanrooms. The facility HVAC system is designed on the premise of a specified range of airflow (typically minimum airflow volume, but may also include a maximum volume). The cleanroom facility is initially balanced by a Testing,

Adjusting, and Balancing (TAB) contractor. A facility monitoring system is typically used to monitor the cleanroom HVAC system once the TAB contractor is finished. Critical room pressure relationships and room air exchange rates rely on maintaining the designed airflow volume.

Capture flow hoods have become a popular instrument choice as they can easily provide an accurate and repeatable measurement of airflow volume for many filter designs and configurations. The manufacturer provided accuracies are typically around ± 3%, but the measurement accuracy of the instruments can be impacted by erratic airflow patterns that may be introduced by certain diffusers or other devices. Figure 6.8 provides an example of a capture flow hood.

Figure 6.8: Example of a Capture Flow Hood
Used with permission from Evergreen Telemetry, https://evergreentelemetry.com/.

It is imperative to get a good airtight seal around the top of the hood for accurate readings. Most manufacturers can provide a custom sized hood to meet the customer's specification. This allows for a good fit for non-standard filter sizes or where teardrop lighting and filter frames may limit the use of standard hood sizes. As detailed in Section 4.3, the average exit air velocity of a filter can be determined by dividing the measured volumetric flow by the active area of the filter being measured.

Some hood manufacturers provide a backpressure compensation method for greater accuracy. This procedure is not typically required in the routine periodic testing of cleanrooms. Single non-corrected airflow readings can be done in less than a third of the time of the corrected reading. Trends and changes in the cleanroom airflow can be observed using non-corrected values. As filters load with debris, their resistance to airflow (pressure drop) increases. The HVAC fan should have the capacity to maintain the minimum required airflow while overcoming a gradual increase in resistance.

6.11.2 Air Velocity

Air velocity measurements can be taken in close proximity to the face of a terminal filter or diffuser, at work surface heights, and other areas in a clean environment. These measurements can be useful to identify changes in operational conditions over time or provide insight on the volume of air delivered to a location. It was noted earlier that the volume of air delivered as well as the airflow patterns play a critical role in maintaining clean spaces. Air velocity measurements with instruments such as anemometers or multipoint arrays are commonly utilized in unidirectional airflow environments. Measurements from these devices can be heavily impacted by the angle at which the airflow enters the device or variations over small distances. The directional dependence and localized sensitivity of these devices can lead to poor measurement repeatability when the airflow is non-unidirectional. This is especially true for work surface height measurements taken using a thermal anemometer in a non-unidirectional cleanroom [122]. The practice of measuring air velocity 6 in (15 cm) below a filter's face or certain airflow diffuser screens can improve the

repeatability of measurements. However current trends are moving towards recommending direct airflow volume measurements for filters when possible for filters supplying non-directional airflow environments.

6.11.3 Pressure Drop

It is typical for both airflow and filter resistance (filter pressure drop) to be recorded at the time the HEPA filters are tested. This may not be necessary if the cleanroom has a building monitoring system. It should be noted that filter resistance measurements are of no value without supporting airflow volume. The resistance of a HEPA filter is nearly linear to the airflow; therefore, if the airflow volume increases by 10%, the resistance will increase by approximately 10%. This is true for the initial and earlier loading stages of a filter. In the later stages of a filter's life, the pressure drop can begin to increase exponentially with time, providing a good indicator that the filter is near the end of its operational life. With periodic testing and monitoring of the filters performance for leakage and pressure drop, a standardized change-out period and/or expiration date can become controversial. This is especially true since HEPA filters are subjected to a wide variety of conditions based on the end use application.

The primary function of the HVAC design is to provide a sufficient volume of clean, HEPA filtered air to the process area. As long as this volume of air is being delivered, there is no set maximum filter resistance value. However, it is common practice to replace a filter when the operational pressure drop of a filter reaches twice its initial pressure drop under the same flow conditions. Well-designed prefiltration can significantly extend the lifecycle of a HEPA filter by reducing the rate of increase in pressure drop with time.

As the filters load, the resistance to airflow increases. The added resistance requires additional demand from the fan in order to maintain expected flow rates. This results in an increase in energy cost associated with the operation of the cleanroom or HEPA filtered equipment. A HEPA filter cost of ownership program may be used to determine when the energy cost outweighs the filter replacement cost. Most major HEPA filter manufactures have a program available for their customers to evaluate the cost of ownership. In addition, manufacturers may be able to provide filter loading specification sheets or other useful supporting data. Chapter 10 provides further information on how a filter's pressure drop can impact lifecycle costs.

6.11.4 Example of an In Situ HEPA Filter Test Form

Reporting of test data is typically mandatory and a valuable means of obtaining trending information over the operational lifetime of a HEPA filter. This data can be useful in identifying potential issues or risks before they occur. Additionally, current and historic information can be critical in the event a failure is noted and corrective active action is required based on risk analysis. At a minimum the test report should contain the following information:

- Test date
- Filter ID
- Certifier name or ID of the individual(s) performing the tests
- Identification (serial number and calibration date) of test instruments
- Test methods used (airflow volume, airflow velocity, photometer, particle counter)
- Identification (size and location) of any leaks that exceed the acceptance criteria
- Identification (size and location) of any repairs that were performed
- Any out of tolerance or non-compliant conditions

Refer to Chapter 12 (Appendix 2) for an example form to document the installation of the correct filter and example forms to document leak testing of a HEPA filter (for Imperial and metric units).

7 Verification (Commissioning and Qualification)

7.1 Introduction

This chapter covers commissioning and qualification with a focus on filters; it is aligned with the *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (Second Edition)* [120] which describes a science and risk-based approach to verifying that a system is fit for the intended purpose.

Example forms are provided in Chapter 12 (Appendix 2) for documenting the installation of the correct filter and to document leak testing of a HEPA/ULPA filter.

Filters are a component in a system that will be commissioned and may also be qualified. Commissioning is used to confirm that a system is installed and operates to meet the specifications and design based on the user requirements. As a good engineering practice, documented evidence should be generated to confirm that this has been completed.

The approach described in the Baseline® Guide [120] confirms that Critical Aspects (CAs) and Critical Design Elements (CDEs) are installed and tested. In terms of the filters, this approach typically applies to any HEPA/ULPA filters installed, because prefilters are generally installed to prolong the life of the more expensive HEPA/ULPA filters. The prefilters would be commissioned and not qualified.

7.1.1 Good Engineering Practice

Good Engineering Practice (GEP) is a set of established engineering methods and standards that are applied throughout the facility lifecycle to deliver appropriate and effective solutions.

GEP covers all engineering activities and documentation, and encompasses the following:

- Design and installation that takes into account GMP, safety, health, environmental, ergonomic, operational, maintenance, recognized industry guidance, and statutory requirements
- Professional and competent project management, engineering design, procurement, construction, installation, and commissioning that demonstrates functionality in accordance with design specifications
- Appropriate documentation, including design concepts, design schematic drawings, as-installed drawings, test records, maintenance and operations manuals, statutory inspection certificates, etc.

7.1.2 Subject Matter Experts

Subject Matter Experts (SMEs) have specific expertise and responsibility in a particular area or field. For HVAC systems, SMEs include the system designer and could include the HVAC engineer, metrology, quality unit, automation experts, or operations.

7.1.3 Use of Vendor Documentation

Vendor documentation is required to support the commissioning documentation for a HEPA/ULPA filter, providing a record that the filter is compliant with the relevant specifications, meets the efficiency requirements, and has passed the factory tests.

7.2 Design, Specification, Verification, and Acceptance Process

This section addresses the overall specification, design, and verification process as it relates to the associated manufacturing or HVAC system.

7.2.1 User Requirements Definition

Product knowledge, process knowledge, regulatory requirements, and company quality requirements should be considered when determining the requirements for the system. These are generally documented in a User Requirement Specification document.

7.2.2 Design Review/Qualification

The system design is reviewed to:

- Ensure that the product and process requirements, user requirements, design criteria, and design standards and specifications are understood and incorporated into the design documents
- Incorporate lessons learned from previous projects into the design through SME input
- Ensure that quality critical aspects are met where applicable
- Ensure all stakeholders are given the opportunity to review the design
- Provide a forum for review of the design against quality, business, HSE, code, operations, maintenance, project, and technical requirements
- Confirm that the method of testing has been defined, and that the system design incorporates the means and methods to allow for testing
- Confirm that the type and efficiency of the filter specified is adequate for the intended use
- Define precautions that should be taken during filter installation to promote successful initial testing
- Define acceptance criteria in the event a leak is encountered and repaired
- Define stock requirements for spare and replacement filters

This process should include the assessment of the filter specifications as they relate to the location and associated area classification.

7.2.3 Commissioning and Qualification

The commissioning process should include the generation of documented evidence that the specified filter has been installed in the specified location. This documentation is typically provided using the filter installation data sheet. Often there is a detachable sticker on the filter that is a duplicate of the manufacturer's product and test data adhered to the filter frame. This sticker should be retained and attached to the filter installation data sheet.

For HEPA/ULPA filters, this process should also include confirmation that the manufacturer's documentation has been received. The documentation is compiled and provided as part of a turnover package or commissioning report.

For HEPA/ULPA filters, commissioning generally includes installed leak testing to confirm that the filter and housing meet the specifications. Where this testing is carried out later in a project (after commissioning), the contract should ensure the responsibility for the supply and installation of a suitable filter and housing remains the responsibility of the contractor until the testing is completed.

Qualification verifies that CDEs are correctly installed and tested. In terms of filters, qualification would typically only apply to the HEPA/ULPA filters installed, as explained previously in Section 7.1. Verification that the correct prefilters are installed is usually part of system commissioning.

Thus, qualification documentation should confirm that the specified HEPA/ULPA filters have been installed in the appropriate locations and have been tested to meet the specifications.

The Qualification Summary Report should also address:

- **System Operational Requirements**: Confirming the Standard Operating Procedures (SOPs) required to operate the system have been identified

- **System Maintenance and Calibration**: Confirming the SOPs required to maintain the system have been identified (routine testing of filters, replacement intervals, differential pressures, etc.)

8 Operations and Maintenance

8.1 Filter Storage

8.1.1 Limited Access to Storage Area

Filters should be stored in an indoor location with controlled access to limit who can enter the filter storage space. Vermin and pest control measures should be in place.

8.1.2 Oldest Filters Used First

It is recommended that filters be stacked such that the filter label is clearly readable from the storage aisle to minimize handling by personnel when searching for a specific filter. When pulling a filter from stock, select the oldest filter to rotate stock.

8.1.3 Safe Handling

Warehouse and receiving personnel need documented training in the proper handling and transport of HEPA/ULPA filters as they are fragile and can be damaged by rough handling.

Upon delivery of filters from the freight company, visual inspection of the filter skids should be performed for apparent exterior damage and should be documented with the freight company prior to accepting delivery.

8.1.4 Filter Storage Position (Pleats)

Filters should be stored in their original cartons and stacked no more than three cartons high.

HEPA/ULPA filters should be stored in a vertical upright position. Arrows on the carton indicate which direction should be up, so that pleats are in a vertical position.

If the outer wrapping or carton is opened for inspection, they should be replaced and positively sealed upon completion of the inspection to maintain the integrity of the enclosure.

Filter cartons should be stored elevated, i.e., not stored flush onto a warehouse floor, as a precaution against the unlikely event of a water leak that could damage the filter media and storage carton. Typically a pallet is sufficient to elevate filters above floor level to prevent such occurrences.

Filter cartons should be protected from direct sunlight and ultraviolet rays.

8.1.5 Storage Conditions (Temperature/Humidity)

The storage space should have environmental controls to limit temperatures between 38°F (3.3°C) and 100°F (37.7°C), and should be ventilated using forced ventilation with air filtration of not less than MERV 8 (EU 5 / F 5).

Room temperature and humidity levels should be measured at regular intervals. Additional precautions may be required when the filters are stored in a very dry environment; the storage conditions given by the manufacturer should be followed.

Some equipment, such as biological safety cabinets, use filter frames manufactured from wood and/or particle board and may expand or warp when subjected to high level humidity conditions for extended periods of time. It is recommendation that these filters constructed of wood-based materials are stored in a controlled temperature/humidity environment.

Filter frames constructed out of aluminum or stainless steel are not subject to change by humidity and do not require these more stringent storage conditions.

8.2 Filter Inventory

8.2.1 5% Spares in Stock

The manufacturing time of a HEPA/ULPA filter can range from days to months depending on numerous variables such as production queue, time of year, material availability, weather conditions, and holiday schedules. It is advisable to maintain a minimum of one and no less than 5% of each unique size/type of filter that may be considered critical spares.

8.2.2 Standardize Filter Sizes and Models

Standardizing filter sizes can reduce stocking levels and require less storage space for critical spares. Additionally, standardizing on a specific manufacture, size, or filter attributes can provide improved availability and/or reliability. Initial filter costs are not the primary consideration when selecting a filter vendor/supplier. There are hidden costs such as time spent qualifying a new manufacture of filters, inspecting their manufacturing facility for compliance with standard practices, and adding new vendors in to an established spare parts management system.

Before changing filter suppliers, interview and partner with stakeholders to take into account the capabilities of filter manufacturers. During the design of large ceiling grid systems, it is beneficial to standardize on filter sizes to reduce the need to stock multiple unique filter sizes.

8.3 Filter Bank Frames

8.3.1 Support of the Filter Frame

Filter frames should be supported by vertical supports (stiffener bars) specified by the manufacturer. The thickness and width of the vertical supports depends on the filter wall height, the strength of the filter frame, and the weight of the filters being used. If vertical supports are not used or designed correctly, significant flexing of the filter wall may occur during operation. This flexing could cause air bypass or damage to ventilation systems if a mechanical failure occurs. Vertical supports should also be fastened to fixed rough opening supports (studs, supported walls, concrete floors, ceilings, etc.).

8.3.2 Leaks Around Frames and Bypass

Leaks around the filter frames can often result from improper sealing between the frames during installation and/or not following the manufacturer's specifications for supporting the frames. If the filter walls flex enough during operation, the flexing or movement of the frames could break the seals between the frames and/or create leak paths for air.

8.3.3 Frame Gaskets

The typical gasket materials are neoprene, PVC, polyethylene, urethane, and EPDM rubber (Ethylene Propylene Diene Monomer). Gaskets also vary between closed cell and open cell. Closed cell gaskets are recommended as they provide the best design for sealing.

Rather than locating the gaskets in the frame, specify the gasket to be part of the replacement filter so that as the filter is replaced, there is a new gasketing surface to make the seal.

8.3.4 Filter Hardware

Filter hardware is made from various materials and finishes such as galvanized steel, galvannealed steel, painted steel, powder coated steel, anodized steel, stainless steel, mill finished aluminum, and polymer based such as polyethylene or ABS (Acrylonitrile Butadiene Styrene). Some materials are more desirable for corrosion resistance such as stainless steel, polymer, or aluminum, while others are more suitable for typical HVAC applications such as galvanized steel. Different supporting structures for filter walls may be needed for different materials of construction.

8.3.5 Separation Distance Between Filters

Depending on the design of the second stage of filtration, placing a prefilter directly up against the second stage filter may block airflow through the prefilter, thus not allowing full use of the media area of the prefilter. This blockage greatly increases static pressure across the system if filter configurations do not harmonize together.

Some manufacturers have designed plenum spaces on their second stage filters to create a space between the two stages of filtration in a side by side configuration. This plenum space allows for air to flow between the two filters, reducing static pressure and energy consumption.

8.4 Filter Life

8.4.1 Pressure Drop

As particles collect on the surfaces of filter media fibers, these particles form a dust layer referred to as a filter cake. After the formation of the filter cake, the resistance of the filter to airflow increases as the particles accumulate. The high concentration of particles will increase filter loading and increase its operating differential pressure drop.

A typical HEPA panel filter can have a clean initial pressure drop of 0.40 in wg (100 Pa) at 90 FPM (0.46 m/sec) face velocity. A general practice is to establish a trigger point for scheduling filter replacement when the pressure drop reaches double the clean initial pressure drop, in this example 0.80 in wg (200 Pa).

HEPA/ULPA filters operating in an ISO 5/Grade A clean space, or those protected upstream by a high level of filtration and high recirculation of room air, can take fifteen years or more to load before the pressure drop drives replacement. In an application using 100% outside air without adequate upstream filtration, loading can increase such that the filters require replacement in one year.

8.4.2 Monitoring of Filter Pressure Drop

Maintenance activities for the filter, including replacement, is defined according to Preventive Maintenance (PM) and/or Predictive Maintenance plans (PdM). Periodic requalification may be required for all filters that are identified as quality critical to ensure that the initial qualified status is maintained appropriately.

It is recommended to implement a monitoring program with an annual evaluation of the filter pressure drop over the useful life of the filter to identify trends in filter loading as a predictive measure. This historical data can be used to adjust routine maintenance, testing frequency, predict filter replacement, and avoid repairs and failures.

8.4.3 Time Based System

There is no reliable evidence that HEPA filters have a defined life; for traditional filters, the efficiency improves with use. An estimated duration of the useful lifecycle can be established to determine a replacement schedule for HEPA/ULPA and ASHRAE [26] rated filters. The frequency of replacement is related to the volume of outside air utilized for pressurization, particle load and moisture content in the outside air, and volume of air recirculated from the cleanroom. Other minor contributors may include the frequency and amount of challenge medium injected into the filtration system, type of aerosol injected to challenge the filters, total media area of HEPA filter, media depth, and pleats per inch.

Modeling software products are available from filter manufacturers, which use these variables to predict useful service life and optimize energy consumption.

8.4.4 Filter Maximum Air Velocity

Typical panel type HEPA/ULPA filters are designed and tested to 100 FPM (0.51 m/sec) filter face velocity. A rigid box style ASHRAE [26] filter operates at 500 FPM (2.54 m/sec). If the installed application operates significantly above this range, the filter efficiency will be reduced. The filter will load faster and will have a shorter service life.

8.4.5 Prefiltration (Powders)

The service life of primary filters can be prolonged by the frequent replacement of prefilters in an environment with significant particulates in the air stream, such as a process using powders.

8.4.6 Outside Air Pretreatment (100% Outside Air/Fog)

Applications requiring large quantities of outside air, such as laboratory or isolation processes, may require the added protection of multi-step air filtration banks and moisture eliminators. Outside air can be saturated with moisture and/or impacted by conditions of wind driven rain. Seasonal atmospheric conditions such as fog can saturate particulates (filter cake) accumulated on filters located in filtration banks or terminal filtration (HEPA/ULPA), resulting in increased filter resistance and reduced integrity of the filter due to moisture saturation.

The addition of a moisture extraction system at the entry point of outside air intake can assist in limiting air saturated with moisture during these seasonal times when fog is present in outdoor air.

Special consideration needs to be given when designing outside air intake for air handling systems located in areas that may have continuous or seasonal periods of high particulate load. Sources of particulates may include, for example, processes from nearby industrial and manufacturing facilities, farm land seasonal release of pollen or seeds into local air, or freeway and local train activity (additional emission exhaust levels).

8.5 Filter Repair Techniques

8.5.1 Repair Material and Methods

When the filter leak is pinpointed to a specific location and the filter is removed from its housing, the leak can be repaired on the air upstream side of the filter using a syringe and self-leveling silicone. By applying it on the upstream side, the silicone will travel by gravity down into the pleat and provide a repair with the least amount of silicone and minimal size patch.

When a tear or hole is visible on the tip of a pleat, a small section of spare filter media matching the efficiency and specifications of the filter can be used to repair the filter by forming it into a V-shape, sliding it down over the defect, and tucking it in place by sliding a credit card down between the fold and the next separator/pleat. This method requires great skill and experience; if done incorrectly, it will make other defects in the filter media.

When filters need to be repaired in their installed state, silicone sealant is applied over the affected area.

The repair material needs to seal the defect at the source. A surface only application will only divert unfiltered air under the patch.

8.5.2 Sealant Types

Generally, in most countries and in most applications, it is acceptable to repair HEPA filters within certain restrictions. HEPA filters are usually field repaired with clear silicone caulking materials that have been proven effective at repairing imperfections and tears in filter media. When filters can be removed and the leak pinpointed on the upstream side of filter, self-leveling caulking has an advantage as its lower viscosity is able to fill more crevices and voids and go deeper into the pleat, minimizing the area of repair.

Note: It is the experience of the authors that although the US FDA [4] generally has not made an issue of HEPA filter repairs (within IEST [22] limits), EU inspectors can often be less accepting of HEPA filter repairs (refer to the "no HEPA repair" guidance in legacy document BS 5295 cleanroom standard [57] and the current BS PD 6609 [58] whose stated purpose is to provide additional guidance on meeting the requirements of ISO 14644 [23]). As a result, many pharmaceutical end-users that are inspected by both the US and EU will concede to a 'replace, not repair' policy in more critical applications (such as ISO 5/Grade A) but will allow repair within the acceptable guidelines in other areas.

8.5.3 Retesting After Earthquake

In locations that are subject to moderate seismic activity, it is recommended that a value be agreed to, such as the magnitude of the earthquake, that would trigger filter integrity testing. If the value of an earthquake is below the agreed value, no action is taken.

8.5.4 High Temperature Filter Applications

Depyrogenation tunnels are used in the pharmaceutical industry to void glass vials of pyrogens or fever causing proteins. The typical tunnel has three zones: 1) pre-heat, 2) hot, and 3) cool down. All zones are supplied with HEPA filtered air.

A conveyer moves the glassware from the glass washer into the in-feed of the tunnel. The glassware needs to be exposed to only ISO 5/Grade A conditions from the washer to the capper. Midway through the tunnel, the hot zone is typically maintained above 572°F (300°C). Special high temperature filters are used in these areas. Conventional glass media are not used in this application; the glass binder burns off, leaving a very fragile mantle similar to the mantles in gas camping lanterns.

The FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing [74] states the following:

> *"Among the filters that should be leak tested are those installed in dry heat depyrogenation tunnels and ovens commonly used to depyrogenate glass vials. Where justified, alternate methods can be used to test HEPA filters in the hot zones of these tunnels and ovens".*

Any oil challenge that has been introduced to a high temperature filter will burn off as the tunnel ramps up to temperature. Thus the photometer test method should not be used due to the mass of the aerosol required for the test. If an integrity test is to be performed, a DPC and very low aerosol challenge should be used.

Scan testing the filters will most likely reveal perimeter leakage. As the temperature in the tunnel ramps up, the metal in the filter frames and in the housing undergo thermal expansion which can result in perimeter leakage. They will expand at different rates due to the differences in mass. Performing a scan test requires testing at ambient temperature. The conditions that the glass vials experience may be different at operating temperatures.

In high temperature applications, greater than 212°F (100°C), and if repairs are permitted in the application, silicone caulking materials that are appropriately rated are recommended. Repairs cannot be made in depyrogenation tunnel hot zones.

8.6 Filter Replacement

8.6.1 Informed Decision (Data)

The pressure drop of HEPA/ULPA filters should be monitored annually and compared to the initial clean filter pressure drop, as discussed in Section 8.4.2. Total cost of ownership evaluation should be performed taking into account the rate of filter loading, cost of electrical energy, and labor replacement costs. Filter manufacturers commonly offer services that use software to perform these calculations and offer optimized replacement frequencies based on end-user environmental conditions and use. If filter repairs within each certification period become frequent, early replacement of the filter element should be scheduled.

8.6.2 Reasons for Replacement

Generally HEPA/ULPA filters are replaced in the following scenarios:

- Result of a cost of ownership evaluation
- Patch area exceeds limit for patch area
- Minimum airflow can no longer be maintained
- Manufacturer's differential pressure limit of filter is reached
- Leak cannot be patched or repaired
- Filters become wet (i.e., very humid conditions caused by a humidification failure, infiltration of water, etc.)
- Noticeable damage, discoloration to filter media, and visible water dripping off the element
- Extreme filter conditions such as high temperature ovens (may require replacement after a predetermined amount of operating hours)
- Extremely critical application such as potent compounds, hazardous area with compounds and for safety
- After a history of problems, repeat failures, or a high fail rate

8.6.3 Document Filter Data

It is essential to record the replacement filter make, model, serial number, and efficiency rating upon replacement since this information is typically located on a tag that will not be visible or accessible unless the filter is removed for inspection.

It is also helpful to document the filter housing make and model for future reference. Keeping records of the filter replacement date and characteristics of the filter installed can be helpful should this information be requested by an auditor.

Information and test results for each filter may include the following:

- Filter model number
- Filter serial number
- Penetration (efficiency) test data and results

- Resistance to airflow (expressed in inches of water column)
- Challenge method (including a statement of aerosol type and challenge particle size used)
- CFM values at 100 FPM
- Media lot number of filter paper
- Leak information
- Filter rating (i.e., IEST [22] Type C or EN1822 [52] H14)

8.7 Filter Failure Modes

8.7.1 Potting Material Failure

Potting material is the urethane component that is poured into the filter frame during filter assembly; the filter media is then placed into the potting material to create a leak free bond between the paper element and the filter frame.

A case study involved occasions when leaks were found at this bond only a few months after new filters were installed and initially passed a leakage test. It was determined the manufacture of the potting material supplied to the filter assembler/manufacture had changed their formulation. The new formulation had insufficient quality control before it was released for use. The inferior potting material over time would shrink, eventually pulling on the filter element and breaking the bond and seal.

When selecting a filter manufacturer, it is prudent to inquire about their quality control measures and those applied to their material suppliers. It is also imperative that the purchase agreement includes a requirement that if at any time the filter manufacturer suspects a possible universal problem, all end-users of the impacted filters be notified.

8.7.2 Insufficient Amount of Gel in the Filter Track

There have been some cases observed in which the HEPA/ULPA filters are delivered from the factory with an insufficient amount of gel in the track such that the knife edge does not penetrate the gel sufficiently, resulting in air bypass leakage.

8.7.3 Loss of Gel Adhesion

Loss of gel adhesion is not a common failure mode. Adhesion between the gel and other surfaces may be compromised if the surface in contact with the gel is contaminated with foreign substances or oils. Off-ratio mixing of the gel, or other manufacturing errors or defects with the gel itself, can lead to surface blooming and exudation of unbound components that can interfere with the surface tack (stickiness) of the gel.

8.7.4 Knife Edge Alignment

The ideal position for the installed filter is with the knife edge at the center of the gel track. In some cases, the knife edge contacts the metal edge of the gel track; this may result in air bypass (a seal leak) in the immediate area. Spacers or guides may be used to position the filter properly.

8.7.5 Degradation of Filter Gel Performance

There have been observations in pharmaceutical applications in which the filter gel materials appeared to have degraded into a flowable, viscous material rather than a firm gel. This behavior has been studied extensively in the industry and is the result of several factors that contribute to this failure mode. This failure is primarily due to the

diffusion of unbounded gel components migrating to the surface of the gel. Therefore this migration is a degradation of gel performance; technically it is not a degradation of the bonded gel polymer since the polymer bonds are not broken. The filter manufacturers have each developed their own gel systems to reduce the risk of this mode of gel performance degradation, and it is advised to work with the filter vendor to understand the appropriate gel system and filter design for the specific application.

It should also be noted that when gel materials in pharmaceutical applications are observed to lose or change color, this does not necessarily equate to degradation in gel performance. Cleaning and sanitizing chemicals often used in pharmaceutical cleanrooms can discolor the gel by bleaching the coloring agent in the gel, but do not usually break the bonded silicone polymers.

Even though gel systems might appear on first observation to be similar to one another, they can have other properties which make them very different when subjected to operating conditions in the pharmaceutical industry. However, all gel systems need to meet the required physical properties to perform the task of sealing the filter frame to the filter housing, such as adhesion and stiffness to allow the correct knife edge penetration and sealing.

Identified factors that contribute to this mode of degradation of gel performance include the following:

- The **amount of cross-linked (bonded) gel material** should be optimized since it is desirable to minimize the amount of polymer that is unbounded. This needs to be balanced with the mechanical properties required for the gel to properly seal the filter. Controlling the ratio of the components and the mixing operation during manufacturing is critical to a properly cross-linked gel.

- The **molecular weight** of the gel system is important. A higher molecular weight gel system component reduces the diffusion of unbounded polymer. A narrow distribution of molecular weight is most desired. This needs to also be balanced with properties such as viscosity of starting components and final surface tack of cured gel.

- As much as possible, **minimize exposure of the gel to PAO and other nonvolatile oil-based test aerosols** as excessive PAO may accelerate the rate of unbounded polymer diffusion by swelling the gel and increasing free volume. Although the liquid test aerosol will not break apart bonded polymer material, it does act as a solvent to increase the migration of unbounded polymer components. Testing at low aerosol concentrations, good aerosol distribution, minimizing the amount of time that the filter is subjected to the aerosol challenge, and alternative test methods are steps that can be taken.

- The gel components need to be manufactured and mixed under a **rigid quality control system**. This needs to include strict control of the manufacturing and mixing environments, testing of all relevant chemical and physical properties of every batch of gel material including limiting any impurities.

- **Miter joint integrity** of the frame is critical for filter performance. It needs to contain any gel failure from leaking into the cleanroom. Use the correct sealing compounds at the miter joints to prevent leakage at the joints.

- **Silicone gels** are more resistant than urethane gels to oxidizing chemicals normally seen in the cleaning and sanitizing of pharmaceutical cleanrooms, and thus are generally the preferred gel system. Oxidizing chemicals can attack the urethane gel and create a hardened surface. Semiconductor cleanrooms generally do not use these oxidizing chemicals routinely and urethane gels are common in those rooms. Silicone gels will generally not degrade in the presence of these oxidizing chemicals. However, there may be some specific applications, such as when acid or caustic chemicals are present, that the silicone gels may be subject to hydrolysis (rather than oxidation) and it may be possible that a urethane gel system might be a preferred system.

8.7.6 Gaskets

Filters may be mated to installation structures using gaskets to form a reliable pressure boundary seal and to avoid air bypass of the filter element. A variety of gasket materials is available including neoprene, polyurethane, silicone sponge, etc. Gaskets may be applied manually with brushed-on adhesive or pressure sensitive adhesive. Gasket

sections should be joined by a flexible adhesive. Alternatively, liquid gasket material can be directly applied in a continuous length along the filter perimeter and allowed to expand into foam and cure in place forming a one-piece, continuous gasket.

8.7.7 Silicone Gel

Silicone gel has been used to seal filters successfully for many years. It exhibits good qualities, service life, and resistance to oxidation. Care needs to be taken when selecting silicone gels to anticipate the environment to which they will be exposed. Silicone gel should not be used where frequent or prolonged exposure to acids or bases is reasonably anticipated. Silicone gels are generally more resistant to oxidizing chemicals used for cleaning and sanitizing pharmaceutical cleanrooms (such as bleach, sterilant, phenolic cleaner/disinfectant) than are urethane gels.

8.7.8 Urethane Gel

Polyurethane gel materials are commercially available and often used when low outgassing properties are required (such as in semiconductor cleanrooms), where silicone cannot be tolerated, or where the use of silicone gel is known to be a problem. Polyurethane gel has proven to be a good alternative to silicone gel in some applications. Polyurethane gel does exhibit the formation of a thin surface skin over time and may undergo surface oxidation or limited shallow stress crack formation (as it is exposed to PAO); however, these aging effects have been shown to not compromise sealing of the filter over time. Aging of the gel may be accelerated if the gel is exposed to high doses of vapors from oxidative cleaning agents. Urethane gels in general tend to be more resistant to degradation in applications in which acid or bases are present than are silicone gels. Filters with gel older than about five years, or that show signs of gel aging, should be replaced and not reinstalled if removed from the system.

In summary, in order to minimize the risk of gel degradation in pharmaceutical applications, it is generally advised to select a silicone gel system with the following characteristics:

- High molecular weight
- Lower percentage of unbounded gel components
- Manufactured and mixed under a rigid quality control system, with properly designed miter joints in the frame
- Exposure to a minimum amount of PAO during filter testing

There may be specific applications in which urethane gels might be appropriate. It is advised to work with the filter vendor to select the most appropriate gel for the specific application.

Figure 8.1 illustrates the superior adhesion properties of a silicone gel.

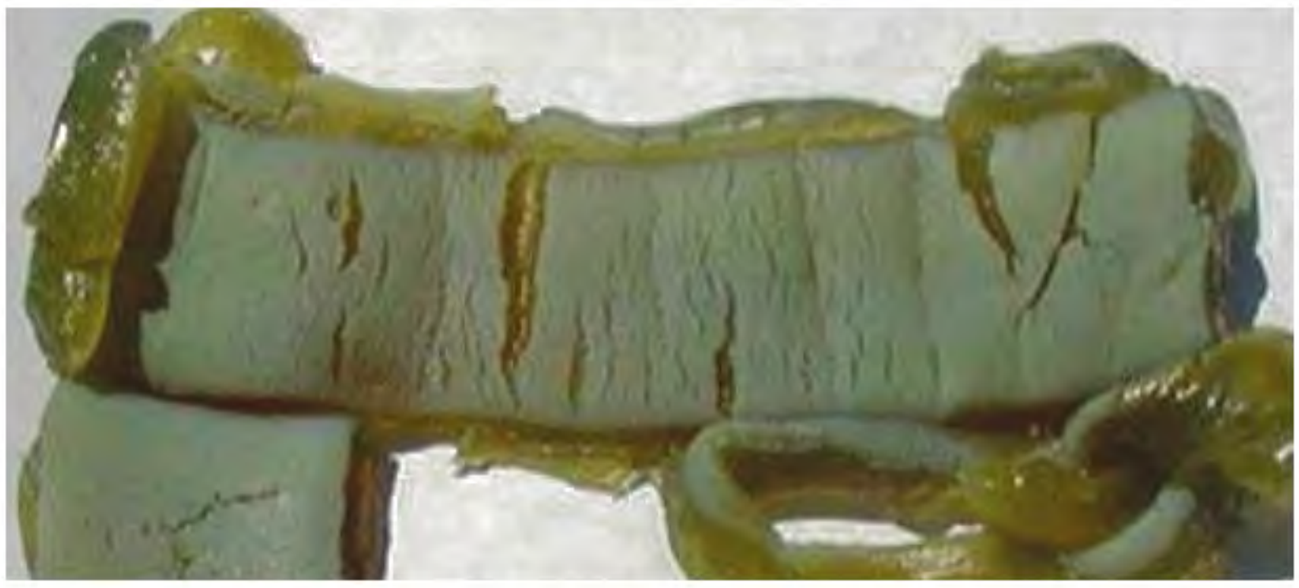
Figure 8.1: Example of the Superior Adhesion Properties of a Silicone Gel
Photo credit: Ronald Roberts, Bayer U.S.

Figure 8.2 shows an example of the liquification of filter gel.

Figure 8.2: Example of the Liquification of Filter Gel

Figure 8.3 illustrates urethane gel developing toughening and cracking on the surface.

Figure 8.3: Example of Urethane Gel Developing Toughening and Cracking on the Surface
Photo credit: Ronald Roberts, Bayer U.S.



8.8 Filter Serviceability

8.8.1 Placement for Access

Containment housings such as bag-in/bag-out require a pull distance to be kept free and clear in order to remove and replace filters. Access paths need to be sufficient in size to transport replacement filters to the filter housing. Bag-in/bag-out housings should not be installed suspended close to the ceiling. The filter change process requires a flat firm surface (table) with free personnel access. The filter installers will likely be wearing personal protective equipment that is not conducive to man lifts.

8.8.2 Layout Considerations

Depending on the grade of the cleanroom space, annual or semi-annual inspection and certification of the filter will be required. Certification requires accessibility under the filter housing to perform scanning and testing methods. High ceiling heights may require scaffolding, ladders, or lifts to access the filter housing so it is important that floor space below is free and clear to allow for the access to perform routine servicing of the filter.

8.8.3 Face Clearance to Remove Filter

Consideration needs to be given when placing and anchoring tall equipment under terminal ceiling housings to provide sufficient clearance for removing and replacing the filter. Depending on the shape of equipment and proximity to the filter housing, 12 in to 18 in (31 cm to 46 cm) may be required to ensure adequate space to drop and replace the filter and for even air distribution out of the face of the filter housing.

8.9 Specifying and Ordering HEPA/ULPA Filters

8.9.1 Certificate of Conformance

At the request of the customer, prior to placing the filter order, individual results of filter tests can be documented and a Certificate of Conformance (C of C) can be supplied for review and acceptance prior to the shipment of the filters. This additional documentation provides additional and specific information for the filter that may assist in answering questions in an audit or event investigation.

8.9.2 Specify MPPS

The MPPS of a filter is the most penetrating particle size at which the filter has its highest penetration or lowest efficiency. When specifying and ordering HEPA/ULPA filters, evaluate filter pack depth, filter efficiency, and media surface area that can offer a robust service life.

8.9.3 Specify Filter Face Velocity

When ordering filters, it is important to specify the anticipated filter face velocity of the HEPA/ULPA filter.

8.9.4 Factory Repaired Filters

HEPA/ULPA filter media are manufactured in controlled environments, with procedures and methods that yield high quality media paper. There are instances when imperfections in paper media or when making a roll of media, a splice is made to complete the roll. When the assembled filter is tested as a unit, these imperfections can be detected and repaired by the filter manufacturer prior to shipment using industry approved recommended practices. In ISO 5/Grade A spaces, some end-users may prefer to install only HEPA/ULPA filters that are patch free or free of factory repairs. There is an additional premium cost to order a patch free filter.

8.9.5 Shipping Protection of Pallet

It is recommended when ordering filters to instruct the filter manufacturer to palletize filters for shipment with cartoned filters stacked side by side and stretch-wrapped to the pallet with vertical corner protection to protect box edges. Additional cladding can be placed around filter boxes before shrink wrapping to provide an additional layer of protection from impact to the side of boxes.

8.9.6 Packing Carton

Each filter should be bagged and placed in a box with a protective cardboard insert on the two sides to protect the media face.

Note: It is important to position the cartons on the pallets to ensure the media faces and pleats remain vertical at all times during shipping and transfer.

Cartons should be stacked no higher than 6.5 ft (2.0 m).

The boxed filters should be stretch-wrapped on the pallet. All filters should be shipped on a pallet with full height wafer board panels on all four sides and vertical corner braces.

At least two sides of the palletized load should be prominently labeled with **"Do not double stack pallets"**.

8.9.7 Double Poly Bag Packing

Due to the various steps involved in bringing new filters into a clean space, it may be advantageous to request at the time of ordering, that the filter manufacturer double bag the filter media elements. Filters should always be transported in their cardboard box to ensure protection. At some point in the facility material flow, cardboard is no longer allowed into the space. When the filter is shipped in a double bag, the outer bag provides an initial layer of protection; then as the filter is moved into a cleaner environment, the primary bag is removed and the secondary bag is in place to protect the filter until final installation.

8.9.8 Media Screens Face Guards

Upon specifying the filters, consideration can be made to include perforated protective screens, to be installed on both the air entering and leaving side of the filter media. This feature is a low-cost way to reduce the risk of damage during transportation and installation of the filter.

8.9.9 Double Label on Filter Carton

Filter manufacturers may offer, at extra cost, an additional filter label placed on the filter or on the exterior of shipping carton that can be removed and saved with documentation. Information contained on the label attached to the filter will not be accessible after the filter is installed and may prove valuable in the future should questions arise about specifications of the filter.

8.9.10 Direct Point to Point Shipments (No Pallet Breakdown at Hubs)

When ordering HEPA/ULPA filters, it is recommended that precautions be taken to ensure filters arrive at the end-user facility with minimal handling. It may be necessary to communicate to filter manufacturers that filters are to be transported on a dedicated truck. Freight companies, unless directed otherwise, may disassemble pallets at their hubs and place them on different trucks several times. This handling can lead to filter damage.

8.9.11 Documentation

A request should be made that the filter manufacturer provide with filter shipment a packing slip that lists the filter model numbers, the total number of filters ordered, identification or any back ordered filters, and the quantity in the shipment.

8.9.12 Minimize Handling

Upon receiving delivery of the filters, it is important to minimize the physical handling and transportation of the filters as they are very fragile and require extreme care during handling and storage. It is recommended to wear protective gloves (i.e., nitrile, latex, etc.) to protect the filters and minimize contamination from hands. While transporting with a forklift, pallet jack, and/or hand truck, minimize speed to reduce jarring such as traveling over an uneven surface or speed bump. Secure filter boxes to the pallet with banding material, not cinch straps, chains, slings, or hooks.

Key steps to follow when working with HEPA/ULPA filters include the following:

- Do not touch the filter media as it is very delicate
- Do not slide, drop, bump or rough handle filters
- If the filter width is greater than 36 in (0.9 m) or height is greater than 30 in (0.8 m), use two people to handle the filter
- Do not transport filters on a damaged pallet
- Do not stack such that the filters overhang from the pallet
- Do not transport the filters with other materials/items
- Keep the directional arrow on the filter element, or the filter in the shipping carton pointing up, to ensure pleats are transported and stored in a vertical direction
- Do not lift the filter out of the box as it is possible to puncture the filter media while pulling the filter directly out the box; open one end, turn the box upside down, and lift the box off the filter
- Grasp the filter only on outside surface of the frame assembly

8.10 HEPA/ULPA Filter Installation

8.10.1 Sequence of Work

There is a specific sequence of events and coordination of personnel that needs to be followed to ensure the successful installation, balancing, and certification of terminal HEPA/ULPA filters.

The following approach incorporates best practices and lessons learned from past projects that involved the installation of new HEPA/ULPA filters into filter housings (including balancing and certification).

8.10.2 Contractor Training

All contractors who perform any function of data recording, such as filling out performance or operating data on a GMP system, need to have current training in site data recording rules. See Chapter 9 for more information on contractor training requirements.

8.10.3 Ductwork Blow Down

It is highly recommended that an appropriate duct cleaning protocol be followed during the fabrication and installation of ductwork, with compliance verified and documented as part of the commissioning process.

The purpose of a ductwork blow down is to purge the ductwork system of any debris that may remain from construction activity. During this phase, all ductwork is connected, dampers are fully open, and construction filters are in place at return air intake locations.

The air handler should be operated at maximum delivery/volumetric flow rate (CFM) for a period of not less than four hours during this blow down process.

8.10.4 Branch Duct and Filter Housing Volume Damper Verification

Before installing the filters, each individual volume damper quadrant (in branch supply ductwork and filter housing) should be checked to ensure it is functional and does not bind. Move each manual or automatic volume damper device from its fully open to closed travel position. This work can be performed during blow down of ductwork.

Verify the damper position indicator (usually an etched mark or line on damper shaft) matches the position of the damper blade(s). It is easy to incorrectly install the handle such that it is installed opposite the position of damper blades; this can mislead those trying to balance air system.

Verify the damper handle is identified with a bright contrast color flag, the damper quadrant is in a fully open position, and the quadrant is secured to prevent movement.

It is beneficial also at this time to verify the duct drawings accurately depict what is installed.

8.10.5 Room Cleaning

At this time, all equipment, walls, and floors should be wiped down. The floors should be swept and vacuumed. It is beneficial at this stage to require shoe covers for personnel who reenter cleaned areas to prevent the accumulation of dirt.

8.10.6 Filter Staging

Filter staging involves locating the space under the terminal filter ceiling housing and staging the filters in their protective cardboard sleeves/boxes in that space.

8.10.7 Data Collection

The individual data for each housing and filter element should be recorded at this point, as follows:

- Filter housing: Record the unique HEPA/ULPA filter ID and manufacturer and model number of the filter housing onto a data sheet

- Filter element: Record the filter manufacturer, model number, serial number, lot number (if applicable), rated efficiency, rated pressure drop, and rated volumetric flow rate (CFM)

Once the filters are seated into the filter housing, this information is no longer accessible.

In addition, it is essential to create a terminal air filter locations facility flow diagram that identifies each filter housing location in the room. Unique identifiers, for example, 57TAF26-8 for Building 57, Terminal Air Filter, Room 26, position 8 on the filter location map.

8.10.8 Terminal Housing Preparation and Filter Installation

The following are the specific tasks and sequence to ensure the filter housings that are room side replaceable with a gel seal are prepared to receive new HEPA/ULPA filters:

1. Remove the perforated diffuser screen.

2. Open the volume damper in the terminal filter housing to 100% fully open.

3. Clean the blast plate under the air entry point into the housing making sure no foreign matter is left on top of the plate using 70% Isopropyl Alcohol (IPA) and lint free wipes.

4. Clean the entire interior of the filter housing, the ledge above the knife edge, and both sides of the knife edge using 70% IPA solution and lint free wipes.

5. Inspect the interior of housing for any areas of air leakage such as holes in the housing, rivets, mounting tabs, gaps, welds, etc. If any leaks are observed, apply silicone sealant to all suspected areas on non-filtered air side of the housing only.

6. Turn off the air supply prior to installing filters into the housing.

7. Using two people, carefully remove the filter from its box. Visually inspect both sides of the filter for any physical damage. Carefully remove the filter from the plastic bag, avoiding any contact with the filter media at all times.

8. Using two people, carefully raise the filter into position, centering the filter into the housing. Center left to right and front to back. After positioning, with one deliberate movement, push the filter into the filter gel and seat it into the gel. Swing the retainer clips around to secure the filter.

9. Snug up the filter retaining clips, using a socket or hand tight, as per the manufacturer's recommendations.

10. Replace the diffuser screen and secure the screen retention fasteners.

11. Reestablish the air supply to the filters after filter installation for each air handler is complete.

8.10.9 Pleat Orientation is Vertical When Filter is Installed in a Vertical Position

For applications when the HEPA/ULPA filter is mounted and operated in a vertical position, ensure the filter is installed with the pleats in a vertical position to prevent damage to the filter as it loads. Because filter accumulates and builds a filter cake when pleats are installed in a horizontal plane, the possibility exists for media to sag and tear.

8.10.10 Pre-Air Balance Prior to Certification

The purpose of the prebalance is to bring the terminal HEPA/ULPA filters near to their operational state, similar to their final balanced state.

Balance each terminal supply HEPA/ULPA filter to plus or minus 20% of the design/target supply volumetric flow rate (CFM) value.

8.10.11 Witness Testing

Certification tests may be subject to observation by the owner to ensure that the practices and methods being used are appropriate. The company should define witness requirements in any contract with a testing company. See Chapter 6 for more information on HEPA/ULPA filter testing requirements.

8.10.12 Documenting Filter Certification

The air system should be prebalanced before filter certification may begin. Certification results should be documented onto test forms. Perform filter integrity testing per user requirements, recording results of filter integrity, filter pressure drop, and delivery/volumetric flow rate (CFM) and/or face velocity.

9 Training

9.1 Vendor/Contractor Training and Qualification versus In-House Training and Qualification

Filter testing may be performed by either an outside contracted testing firm or by trained in-house personnel. Whether the testing is performed internally or contracted out to a testing firm, the training requirements and qualifications should be the same. It is critical that all personnel who are involved with the testing of filters are qualified, competent, and have been appropriately trained on the operation of filter testing equipment and the testing methodologies.

9.2 Responsibility

The owner organization is responsible for ensuring that all personnel, whether internal or externally contracted, are adequately qualified to perform filter testing.

Testing personnel should also be trained on any facility specific SOPs related to filter testing. The owner organization should assume responsibility to ensure all personnel have been trained accordingly.

Testing personnel should be responsible for following all applicable SOPs and policies. In addition, testing personnel should identify any deficiencies in the SOPs where discrepancies in the actual testing processes and written procedure are found.

A robust, documented training program should exist for both in-house and contracted testing firms. The owner organization should verify that testing personnel have completed the appropriate training and are competent in their ability to perform filter testing. For contracted testing firms, verification of training can be performed by reviewing the training program through an on-site quality audit or through supplier/vendor qualification questionnaires. The contracted testing firm is responsible for ensuring that a formal training program is in place and is periodically reviewed for effectiveness. The firm should maintain training records and provide written documentation and verification as required or requested.

9.3 Training Program, Policies, and Procedures

Training programs need to be formally documented and comprehensive. An outline of the training requirements and qualifications should be detailed in a written procedure. Training programs should clearly define the roles and responsibilities of the technicians performing filter leak testing. In addition, the training program should also include a competency evaluation of the personnel involved in testing.

Policies should be in place to ensure that there is oversight of the training program and that the effectiveness of the training program is maintained. Routine evaluations and retrainings should be performed. If the training program is found to be ineffective, corrective actions should be taken to improve upon the deficiencies.

The training programs should be maintained, and training should be conducted on a routine basis by SMEs or by persons of a qualified designee. The subject matter expert or designee should have a system in place to monitor changes to industry guidance documents and update the training program and SOPs as required. Retraining should also occur when there are changes to the testing SOPs and industry guidance documents on testing methodologies.

Since in-house technicians may not perform testing as frequently as contracted firms, or it may not be their primary responsibility, more frequent retrainings may be required to ensure continued proficiency.

9.4 Accreditation/Certification

Accreditation and certification programs exist internationally for both testing firms and individuals who perform testing and certification. Using an accredited firm and/or technician can provide confidence that the contracted firm/personnel are knowledgeable and have the appropriate equipment, technician training programs, and quality systems in place.

The NEBB [19] Cleanroom Performance Testing (CPT) program provides accreditation to firms. The firm is required to comply with specific requirements defined by the NEBB in order to maintain the accreditation. The program has two levels of accreditation, certified professional and certified technician. The accredited firm needs to have a certified professional to achieve the firm accreditation. The certified professional is required to attend mandatory annual training and supply NEBB equipment records and certificates of calibration. In addition, NEBB backs up the facility if the contracted testing firm does not comply with the requirements or contract agreements if the contract states that certification will be performed in accordance with NEBB CPT guidelines.

The NSF International NSF/ANSI 49 [56] accreditation program provides certification for individuals in the testing of Class II BSCs. While the testing of BSCs may not apply to HVAC systems, understanding the general concepts of airflow, HEPA filters, and HVAC systems is required to achieve the accreditation. The individuals are required to pass a written multiple choice examination and a hands-on practical examination to obtain their NSF Class II Biosafety Cabinet Field Certifier accreditation.

The CETA National Board of Testing (CNBT) [16] currently has two accreditation programs, the Registered Certification Professional – Sterile Compounding Facilities (RCP-SCF) and Registered Certification Professional – Fume Hoods (RCP-FH). Both programs require the successful completion of passing a multiple choice and written practical exam. While the RCP-SCF and RCP-FH programs are not specific to the pharmaceutical industry cleanrooms, the knowledge and general concepts can be applied and are required to achieve the individual accreditations.

9.5 Education and Training

Educational programs are available through the following non-profit organizations:

- CETA (Controlled Environment Testing Association) [16]
- NEBB (National Environmental Balancing Bureau) [19]
- Eagleson Institute, Sanford, ME [91]

10 Lifecycle Costs

10.1 Introduction

The most significant cost affecting filter lifecycle costs is energy. However, other costs should be considered in any total cost analysis; examples include filter cost, installation, disposal, freight, procurement overhead, storage, and filter effectiveness in maintaining clean coils and ductwork and in protecting terminal HEPA filters to prevent ancillary maintenance costs. A Total Cost of Ownership (TCO) analysis can be performed on a single filter or on all filters in the air handling units along with the cleanroom HEPA filters. A comprehensive TCO on all air handling units and cleanroom filters in a complete facility is helpful in assessing alternative filter configurations.

10.2 Annual Filter Energy Cost Factors

The Annual Filter Energy Cost factors are shown in the following equations:

Annual Filter Energy Cost ($/year) = Price of Energy ($/kWh) × Filtration Energy (kWh/year)

Where Filtration Energy is defined as:

$$\text{Filtration Energy (kWh)} = \frac{\text{Average System Airflow} \times \text{Average Filter Pressure Drop} \times \text{Annual Cycle Time}}{\text{Fan System Fractional Efficiency} \times \text{Conversion Constant}}$$

Where the units for the parameters are:

Parameter	SI Units	Imperial Units
Average System Airflow	m^3/sec	ft^3/min (CFM)
Average Filter Pressure Drop	Pascals (Pa)	Inches of water gauge (in wg)
Annual Cycle Time	Operational hours per year	Operational hours per year
Fan System Fractional Efficiency	Between 0 and 1	Between 0 and 1
Conversion Constant	1,000	8,520

Note: This equation is valid for fan/motor systems with a constant air volume being delivered to the space. This is typically achieved by using a Variable Frequency Drive (VFD) set to an airflow rate and with a feedback control signal to monitor the airflow rate being delivered. This equation will not give accurate results if applied to a system where the air volume is changing over time, e.g., a fan/motor operating at a set constant speed.

Table 10.1 shows the key relationship between the annual energy costs and different variables in the filter energy equation.

Table 10.1: Annual Filter Energy Cost Factors
Used with permission from AAF International, https://www.aafintl.com/.

Annual Filter Energy Cost ($/yr)		Cycle Time (years)		Price of Energy ($/kWh)		System Airflow (m^3/sec or CFM)		Average Filter Pressure Drop (Pa or in wg)		Fan System Efficien cy (0.00)
Goes Down	with	Same	as	Goes Down	and/as	Goes Down	because	Goes Down	or as	Goes Up
Goes Up	with	Same	as	Goes Up	and/as	Goes Up	because	Goes Up	or as	Goes Down

10.3 Additional Factors Impacting Total Cost of Ownership

10.3.1 Filter Physics: System Airflow and Average Filter Pressure Drop

The system airflow and the average filter pressure drop are interrelated through filter physics. As previously shown in Table 10.1, when system airflow increases, average filter pressure drop increases; conversely, as system airflow decreases, average filter pressure drop decreases.

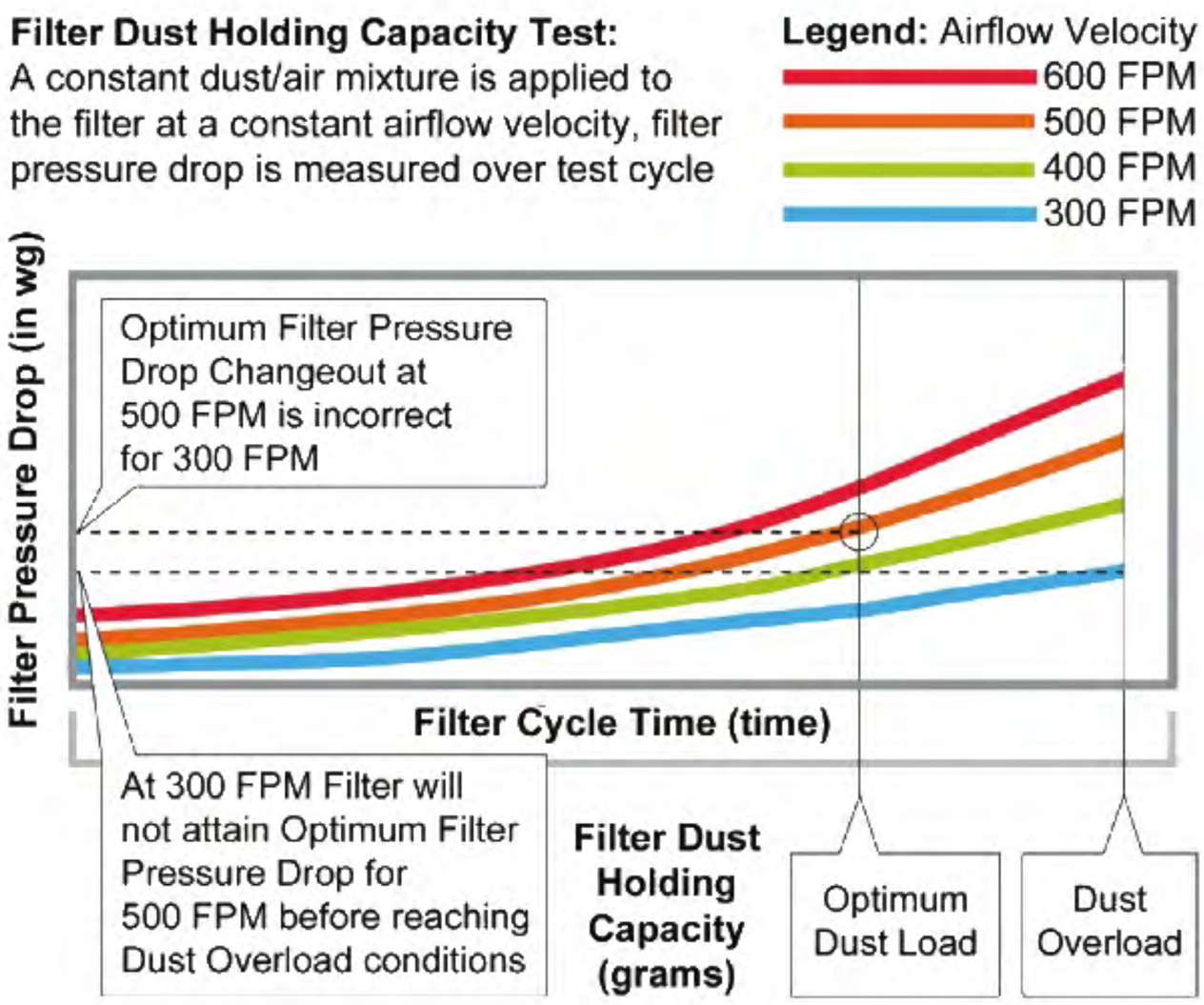
Figure 10.1 shows the relationship between system airflow (as velocity) and filter pressure drop, where a filter was tested at 600 FPM, 500 FPM, 400 FPM, and 300 FPM (3.05 m/sec, 2.54 m/sec, 2.03 m/sec, and 1.52 m/sec) velocities. The filter pressure drop at 500 FPM is often cited as the manufacturer's recommended pressure drop for changing out the filter. However, if the filter is operating at 300 FPM, then operating the system to achieve the filter change-out resistance based on 500 FPM will result in the filter being maintained in the system for a much longer time than had the system operated at 500 FPM. This additional operating time may have a negative effect on both energy cost and can potentially allow sufficient time for microorganism growth on the filter.

These filter physics are the reason why the fan law equation below is not applicable for the real life of an air handling system. Calculations and measures have shown that the exponential value for a system with three filter sections, based on the values of the individual filters, would be approximately 1.6 for a supply system and approximately 1.8 for an exhaust system.

Fan low equation:

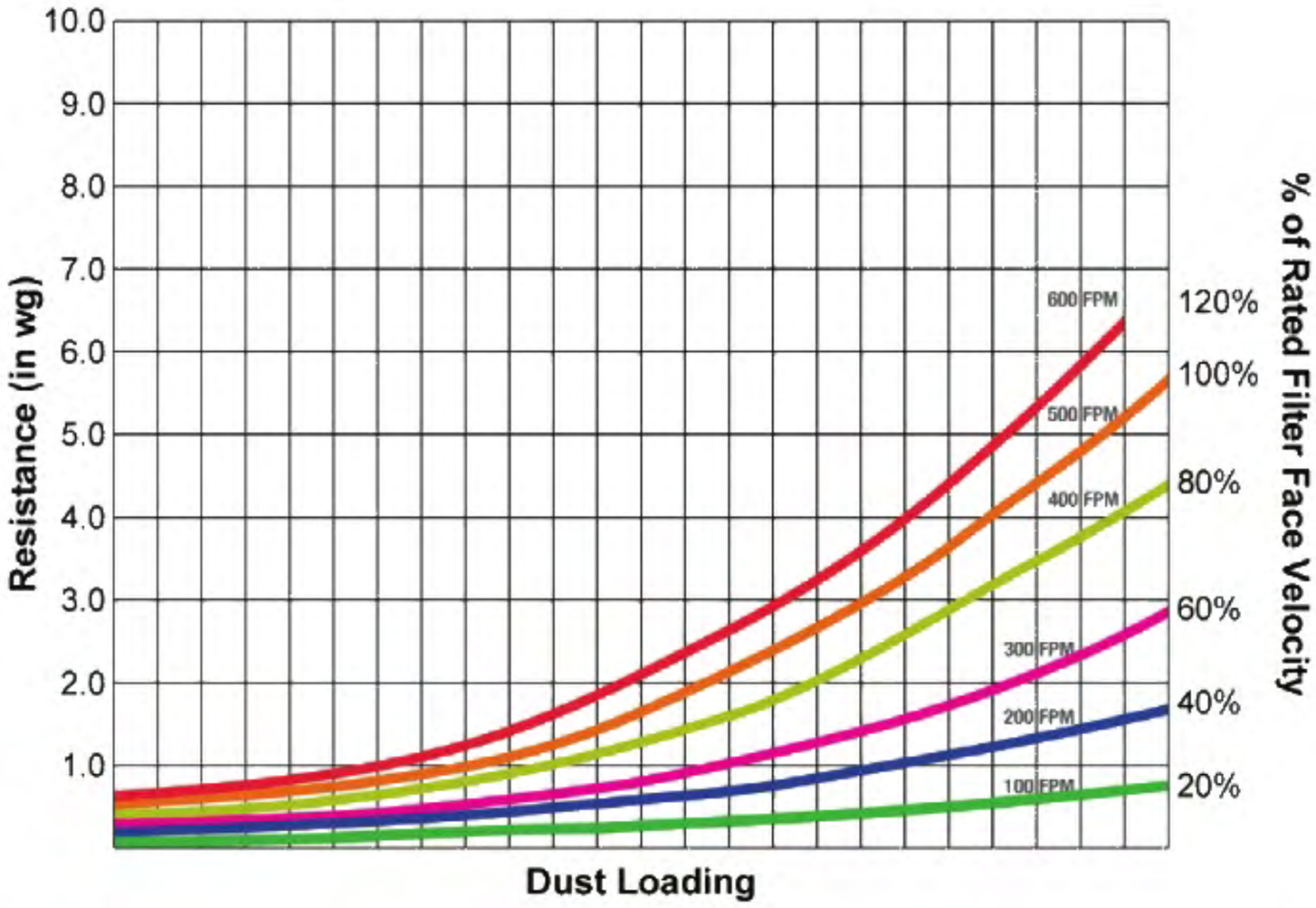
$$\frac{\text{fan1 rotational speed}}{\text{fan2 rotational speed}} = \left[\frac{\text{pressure drop 1}}{\text{pressure drop 2}}\right]^2$$

Figure 10.1: Filter Dust Holding Capacity
Used with permission from AAF International, https://www.aafintl.com/.



The above curves in Figure 10.1 are derived from multiple tests of dust holding of a filter at different air velocities, as shown in Figure 10.2. Note that as the system velocity changes, so does the initial resistance change. From the span of initial resistances, the dust loading curves also form a series of curves.

Figure 10.2: Resistance versus Dust Loading at Various Velocities
Used with permission from AAF International, https://www.aafintl.com/.



In practice, many filtration units are operating at velocities in the 300 FPM to 400 FPM range. At these velocities, the filters will likely not attain the manufacturer's recommended change-out pressure, based on 500 FPM. This could result in the filter being left in the filtration unit for an excessive period of time, likely wasting energy.

As a reference, Figure 10.3 is an example of how the manufacturer's recommended final pressure change-out point of 1.0 in wg at 500 FPM changes with airflow velocity.

Figure 10.3: Recommended Final Resistance at Various Velocities for a Specific Dust Load
Used with permission from AAF International, https://www.aafintl.com/.

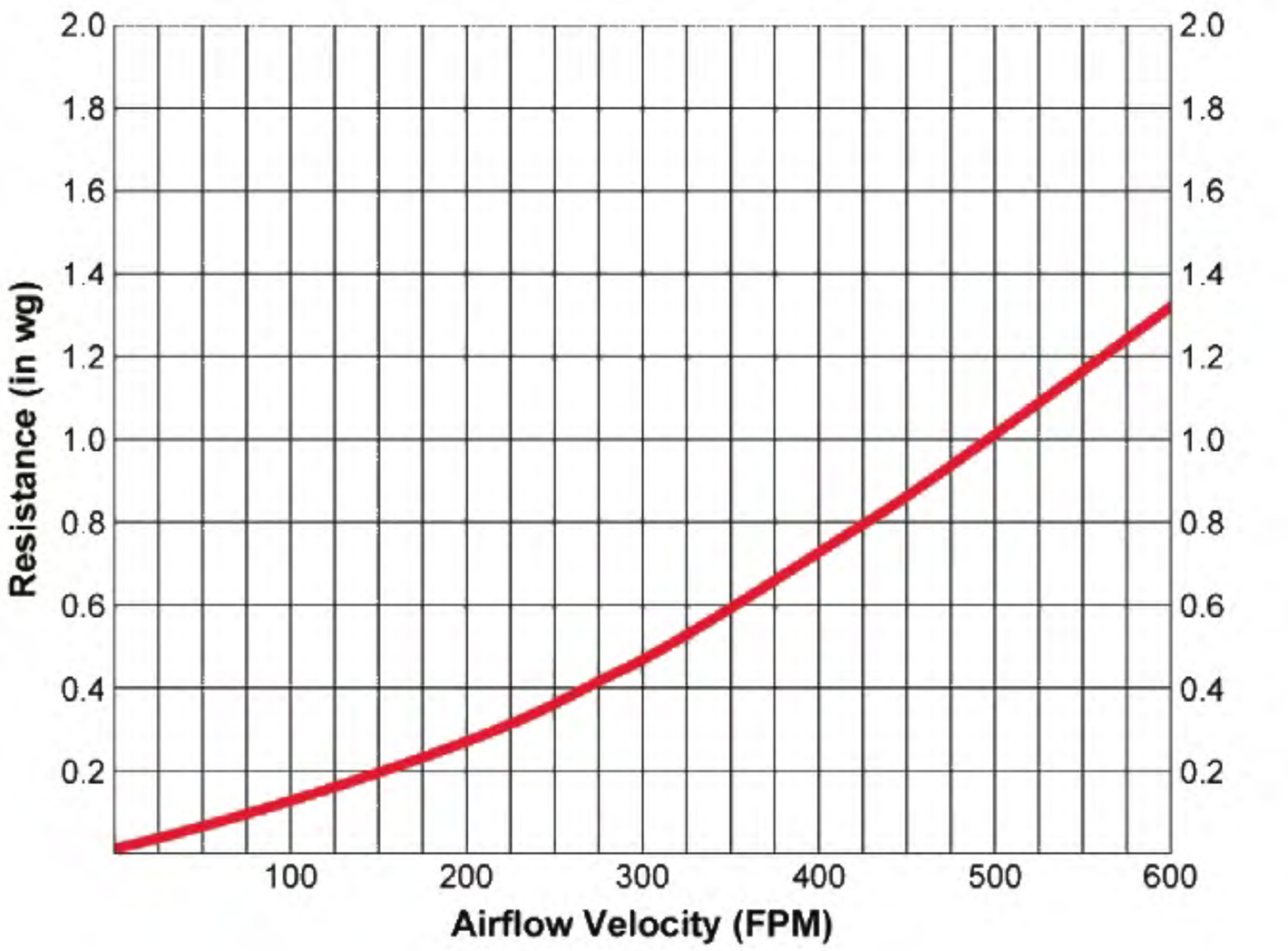


Figure 10.3 illustrates how the change-out resistance for a filter with a 1.0 in wg at 500 FPM with a specific dust load would register a resistance of 0.4 in wg if the airflow velocity was approximately 270 FPM.

10.3.2 Fan System Efficiency

The fan system efficiency is a difficult value to determine because of the many variables in a fan system design and operation and their losses with the system. The overall efficiency, which is calculated from the electrical power input and the power output from the impeller, will include the losses from the various elements of the fan system.

An equation for fan system efficiency is as follows [92]:

$$\eta_e = \frac{P_u}{P_e}$$

Where:

η_e = is the overall fan efficiency

P_u = is the power output from the fan calculated from volume flow (m^3/s) and pressure development (Pa). Note the pressure could be total or static pressure and there can be a significant difference. It is normal to use total pressure, and this should be confirmed with the fan supplier.

P_e = is the electrical power input to the motor (W) (or VSD drive if included in the fan system)

Energy losses in a fan system are manifested as heat losses in the electronic and mechanical components. An example of heat losses for belt driven fan system is shown in Figure 10.4 and an example for a direct driven fan system is shown in Figure 10.5.

Figure 10.4: Energy Losses in Belt Driven Fan System [92]
Used with permission from the Fan Manufacturers Association, http://www.fanassociation.co.uk/.

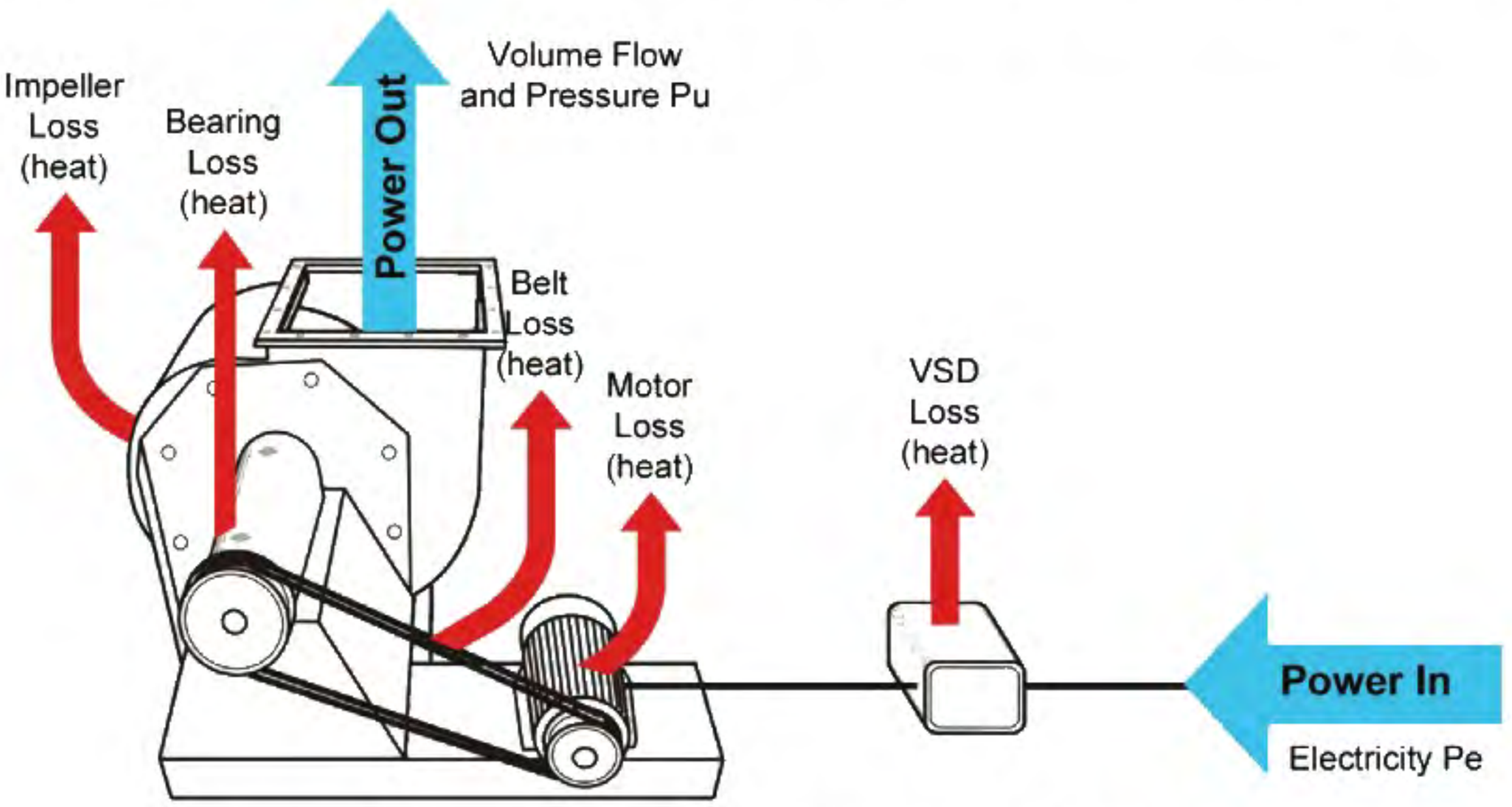


Diagram showing the losses from a fan system including VSD, motor, and belt drive.

Figure 10.5: Energy Losses in Direct Drive Fan System [92]
Used with permission from the Fan Manufacturers Association, http://www.fanassociation.co.uk/.

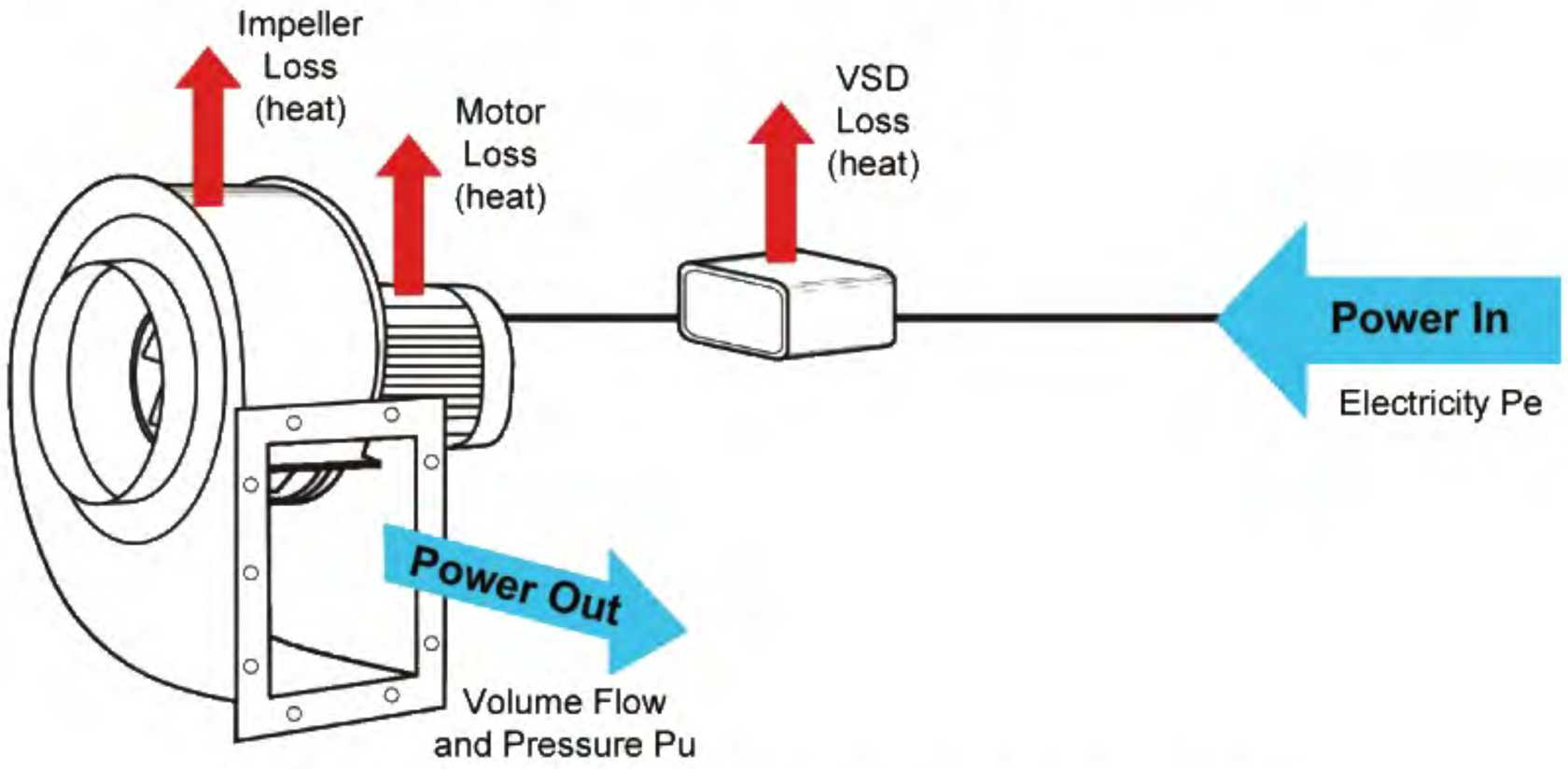
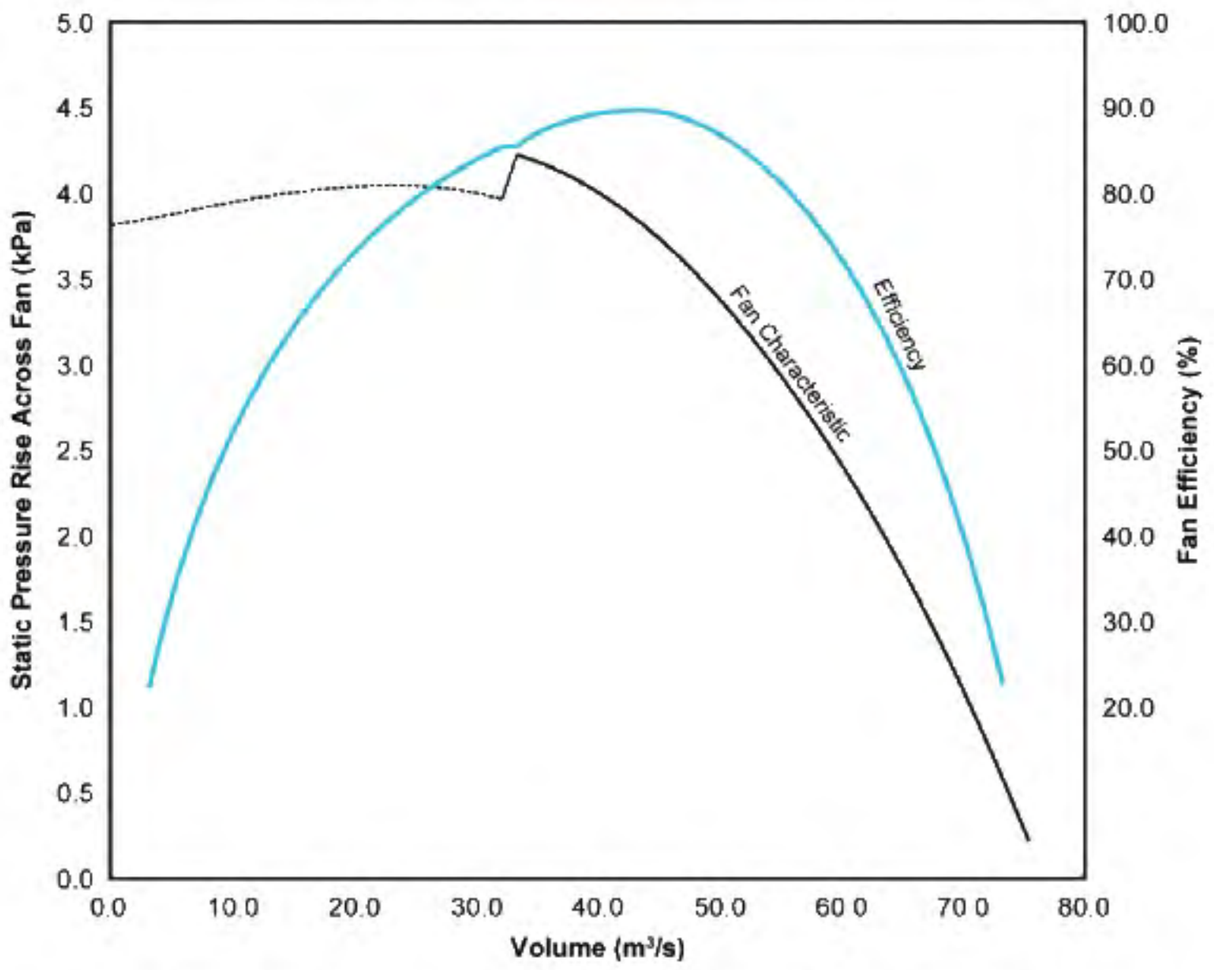


Diagram showing losses from a fan system witha direct drive electric motor and VSD.

Fan system fractional efficiency values used in TCO and energy calculations have been found to range from about 0.25 to 0.85, dependent upon the design of the fan system and the operating fan speed. Fan systems that are overdesigned, resulting in excess airflow (CFM) capacity, are operating its fans at less than optimum RPM. As the fan speed varies, then so does the efficiency of the fan, as shown below in Figure 10.6.

Figure 10.6: Fan Efficiency Curve [92]
Used with permission from the Fan Manufacturers Association, http://www.fanassociation.co.uk/.



Graph showing characteristics of a backward inclined aerofoil section fan (impeller and housing only)

Typically, a fan system is designed to operate at approximately 500 FPM through the heating and cooling coils. Coincidently this is the air velocity through the system air filters. As the fan is operated at reduced air volumes, then the efficiency of the fan alone will decrease, from 90% at 43 m^3/sec to 73% at 20 m^3/sec. The other elements of the fan system will also vary in their efficiency as their operational conditions change.

The impact of an improper assumption of the fractional fan system efficiency is shown in Table 10.2.

Table 10.2: Annual Filter Cost Based on Fan System Efficiency

Annual Filter Energy Cost ($/year)		Annual Cycle Time (operational hours/years)		Price of Energy ($/kWh)	Fan System Efficiency	Annual Filter Cost ($/year) based on Fan System Efficiency
Assume $1,000/year	with	Same	and	Same	Assume Correct Efficiency of 0.60	$1,000
Assume $1,000/year	with	Same	and	Same	Assume Low Efficiency of 0.40	$1,500 (50% error)

Table 10.2 shows the effect on annual filter energy costs of an error in assumption of the fractional fan efficiency. With annual cycle time and energy costs constant, if the true fan system efficiency is 0.60, then the annual energy cost is $1,000; but if an incorrect fan system efficiency of 0.40 is assumed, then the calculated annual energy cost is $1,500, which would result in a 50% error ($500).

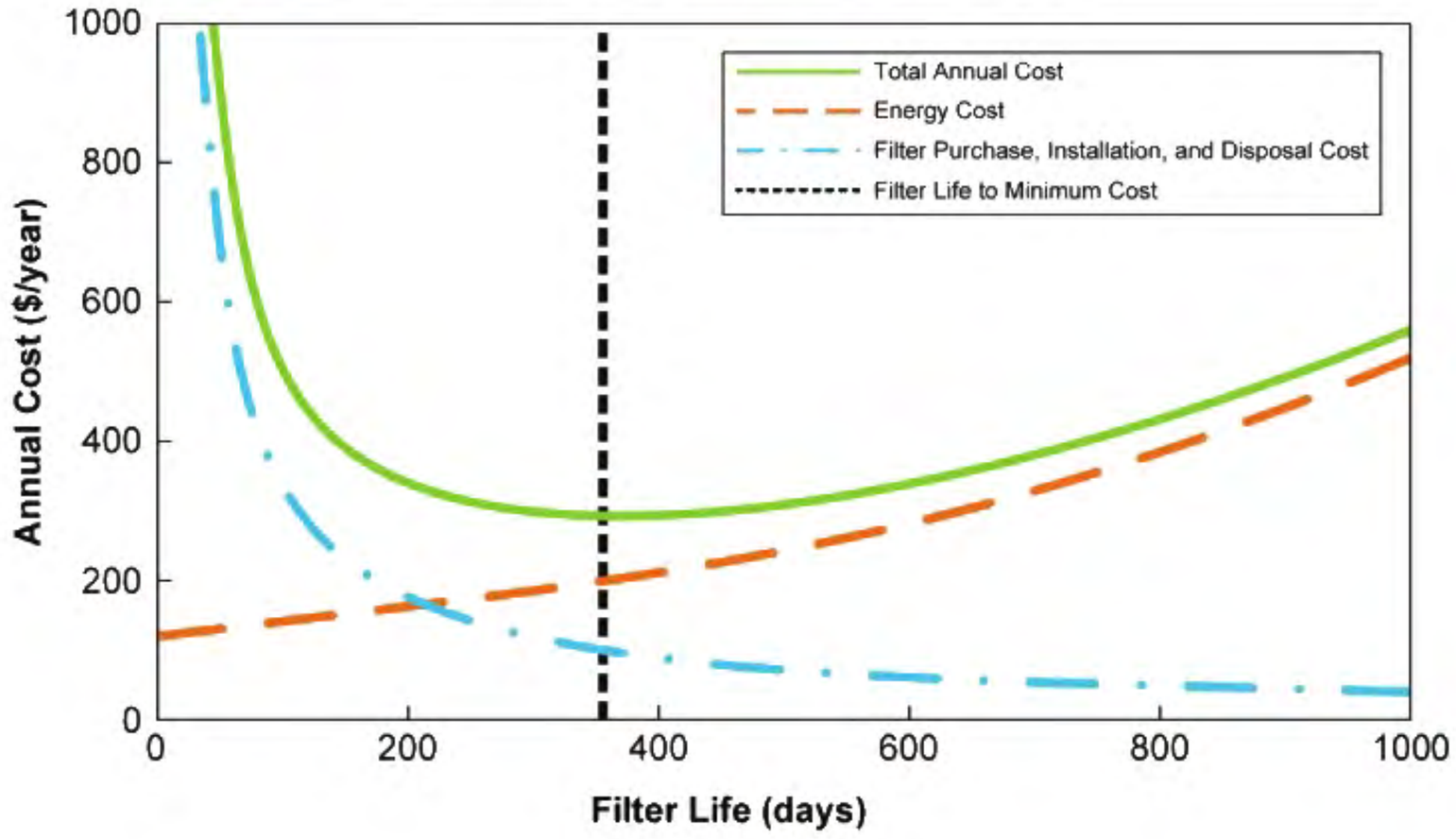
10.4 Total Cost of Ownership (TCO)

For individual filter banks, TCO quantifies the cost of a replacement filter across the filter's entire lifecycle. TCO offers a more accurate basis for determining the value – cost versus Return on Investment (ROI) – of an investment in air filters and their installation and disposal, rather than just considering the purchase price alone.

The overall TCO includes direct and indirect expenses as well as some intangible expenses that can have monetary values assigned to them. Among the intangible expenses are the budget cycles and PM schedules for procurement and replacement. This point might be the operational optimum, which will be a higher cost than the true optimum point.

The method of illustrating the operational optimum is to graphically depict the total annual cost along with the energy cost and filter purchase, installation, and disposal cost versus the operational time, as shown below in Figure 10.7. The true optimum point is at the minimum point in the total annual cost curve, but an operational optimum point can be chosen at the appropriate point in time. Values for all annual costs (total, energy and inclusive of filter) can easily be noted from the graph. The annual TCO for multi-stage filtration systems can be determined by summing the TCO for the individual filter banks.

Figure 10.7: Total Annual Cost of Ownership for Each Filter Bank



11 Appendix 1 – Regulatory and Other Guidance

11.1 Introduction

In general, the various global GMP regulations specify the environmental requirements rather than how to achieve them—though they do mention HEPA filters in a few places.

Some of the GMP expectations come from the associated guidance documents; these are summarized below based on the regulations/regulatory guidance that are current at the time of publication. Note that these regulations were chosen based on the area they cover, or a specific requirement that the authors felt was worthy of note. It is also noted that these regulations are based on known technologies as they existed at the time they were written. In some cases, technology has advanced and published regulations/regulatory guidance may not reflect the new technologies.

11.2 US GMPs

11.2.1 Code of Federal Regulations (CFRs)

The facility requirements are contained in 21 CFR Part 211, Current Good Manufacturing Practice for Finished Pharmaceuticals [93].

21 CFR 211.42 (c) states, in part, that:

> *"Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups during the course of the following procedures: * * * (10) Aseptic processing, which includes as appropriate:*
>
> *(i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;*
>
> *(ii) Temperature and humidity controls;*
>
> *(iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;*
>
> *(iv) A system for monitoring environmental conditions;*
>
> *(v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions;*
>
> *(vi) A system for maintaining any equipment used to control the aseptic conditions."*

21 CFR 211.46 (c) states, in part, that:

> *"Air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production."*

11.2.2 FDA Guidance Documents

More specific information in provided in the FDA guidance documents. The US FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing (September 2004) [74] states the following:

"HEPA-filtered air should be supplied in critical areas at a velocity sufficient to sweep particles away from the filling/closing area and maintain unidirectional airflow during operations. The velocity parameters established for each processing line should be justified and appropriate to maintain unidirectional airflow and air quality under dynamic conditions within the critical area."

"High Efficiency Particulate Air (HEPA)

HEPA filter integrity should be maintained to ensure aseptic conditions. Leak testing should be performed at installation to detect integrity breaches around the sealing gaskets, through the frames, or through various points on the filter media. Thereafter, leak tests should be performed at suitable time intervals for HEPA filters in the aseptic processing facility. For example, such testing should be performed twice a year for the aseptic processing room. Additional testing may be appropriate when air quality is found to be unacceptable, facility renovations might be the cause of disturbances to ceiling or wall structures, or as part of an investigation into a media fill or drug product sterility failure. Among the filters that should be leak tested are those installed in dry heat depyrogenation tunnels and ovens commonly used to depyrogenate glass vials. Where justified, alternate methods can be used to test HEPA filters in the hot zones of these tunnels and ovens.

Any aerosol used for challenging a HEPA filter should meet specifications for critical physicochemical attributes such as viscosity. Dioctylphthalate (DOP) and poly-alpha-olefin (PAO) are examples of appropriate leak testing aerosols. Some aerosols are problematic because they pose the risk of microbial contamination of the environment being tested. Accordingly, the evaluation of any alternative aerosol involves ensuring it does not promote microbial growth.

There is a major difference between filter leak testing and efficiency testing. An efficiency test is a general test used to determine the rating of the filter. An intact HEPA filter should be capable of retaining at least 99.97 percent of particulates greater than 0.3 µm in diameter.

The purpose of performing regularly scheduled leak tests, on the other hand, is to detect leaks from the filter media, filter frame, or seal. The challenge involves use of a polydispersed aerosol usually composed of particles with a light scattering mean droplet diameter in the submicron size range, including a sufficient number of particles at approximately 0.3 µm. Performing a leak test without introducing a sufficient upstream challenge of particles of known size upstream of the filter is ineffective for detecting leaks. It is important to introduce an aerosol upstream of the filter in a concentration that is appropriate for the accuracy of the aerosol photometer. The leak test should be done in place, and the filter face scanned on the downstream side with an appropriate photometer probe, at a sampling rate of at least one cubic foot per minute. The downstream leakage measured by the probe should then be calculated as a percent of the upstream challenge. An appropriate scan should be conducted on the entire filter face and frame, at a position about one to two inches from the face of the filter. This comprehensive scanning of HEPA filters should be fully documented.

A single probe reading equivalent to 0.01 percent of the upstream challenge would be considered as indicative of a significant leak and calls for replacement of the HEPA filter or, when appropriate, repair in a limited area. A subsequent confirmatory retest should be performed in the area of any repair.

HEPA filter leak testing alone is insufficient to monitor filter performance. It is important to conduct periodic monitoring of filter attributes such as uniformity of velocity across the filter (and relative to adjacent filters). Variations in velocity can cause turbulence that increases the possibility of contamination. Velocities of unidirectional air should be measured 6 inches from the filter face and at a defined distance proximal to the work surface for HEPA filters in the critical area. Velocity monitoring at suitable intervals can provide useful data on the critical area in which aseptic processing is performed. The measurements should correlate to the velocity range

established at the time of in situ air pattern analysis studies. HEPA filters should be replaced when nonuniformity of air velocity across an area of the filter is detected or airflow patterns may be adversely affected.

Although contractors often provide these services, drug manufacturers are responsible for ensuring that equipment specifications, test methods, and acceptance criteria are defined, and that these essential certification activities are conducted satisfactorily."

"Cleanrooms are normally designed as functional units with specific purposes. The materials of construction of cleanrooms ensure ease of cleaning and sanitizing. Examples of adequate design features include seamless and rounded floor to wall junctions as well as readily accessible corners. Floors, walls, and ceilings should be constructed of smooth, hard surfaces that can be easily cleaned. Ceilings and associated HEPA filter banks should be designed to protect sterile materials from contamination. Cleanrooms also should not contain unnecessary equipment, fixtures, or materials."

"Manufacturers should build process and environmental control activities into their aseptic processing operation. It is critical that these activities be maintained and strictly implemented on a daily basis. The requirement for review of all batch records and data for conformance with written procedures, operating parameters, and product specifications prior to arriving at the final release decision for an aseptically processed product calls for an overall review of process and system performance for that given cycle of manufacture. All in-process and laboratory control results must be included with the batch record documentation in accordance with section 211.188. Review of environmental and personnel monitoring data, as well as other data relating to acceptability of output from support systems (e.g., HEPA / HVAC, WFI, steam generator) and proper functioning of equipment (e.g., batch alarms report; integrity of various filters) are considered essential elements of the batch release decision."

"Multiple material transfers are generally made during the processing of a batch. Frequently, transfers are performed via direct interface with manufacturing equipment. Properly maintained and operated rapid transfer ports (RTPs) are an effective transfer mechanism for aseptic transfer of materials into and out of isolators. Some transfer ports might have significant limitations, including marginal decontaminating capability (e.g., ultraviolet) or a design that has the potential to compromise isolation by allowing ingress of air from the surrounding room. In the latter case, localized HEPA filtered unidirectional airflow cover in the area of such a port should be implemented. Isolators often include a mouse-hole or other exit port through which product is discharged, opening the isolator to the outside environment. Sufficient overpressure should be supplied and monitored on a continuous basis at this location to ensure that isolation is maintained."

"Blow-fill-seal (BFS) technology is an automated process by which containers are formed, filled, and sealed in a continuous operation. This manufacturing technology includes economies in container closure processing and reduced human intervention and is often used for filling and packaging ophthalmics, respiratory care products, and, less frequently, injectables. This appendix discusses some of the critical control points of this technology. Except where otherwise noted below, the aseptic processing standards discussed elsewhere in this document should apply to BFS technology."

"The classified environment surrounding BFS machinery should generally meet Class 100,000 (ISO 8), or better, standards, depending on the design of the BFS machinery and the surrounding room. HEPA filtered or sterile air provided by membrane filters should be used during the steps when sterile products or materials are exposed (e.g., parison formation, container molding or filling steps). Air in the critical area should meet Class 100 (ISO 5) microbiological standards during operations. A well-designed BFS system should also normally achieve Class 100 (ISO 5) airborne particle levels. Only personnel who have been qualified and appropriately gowned should enter the classified environment surrounding the BFS machinery. Refer to Section V of this document for guidance on personnel training, qualification, and monitoring."

It is important to note that the **ISO 14644 [23] area classifications only speak of total particle concentration and do not differentiate between viable and non-viable particulates.** Therefore, further specification of viable particulate concentration is required for each ISO classification to complete the total requirements for each area classification.

11.3 EU GMPs

The European Commission [94] website states the following:

"The body of European Union legislation in the pharmaceutical sector is compiled in Volume 1 and 5 of the publication 'The rules governing medicinal products in the European Union':

- *Volume 1 – EU pharmaceutical legislation for medicinal products for human use*
- *Volume 5 – EU pharmaceutical legislation for medicinal products for veterinary use*

This basic legislation is supported by a series of guidelines that are also published in [Volumes 2–4 and Volumes 6–10] of 'The rules governing medicinal products in the European Union'."

Primary guidance for sterile manufacturing GMPs is provided in Volume 4 (EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use), Annex 1 (Manufacture of Sterile Medicinal Products) [75].

11.3.1 EU GMP Annex 1 [75]

Note: This Guide reflects an understanding of industry standards as of the publication date. It is recognized that a draft revision of Annex 1 of the EU GMPs [75] was issued on 20 December 2017.

EU GMP Annex 1 [75] states the following:

"(1) The manufacture of sterile products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency."

"(51) Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand washing facilities should be provided only in the first stage of the changing rooms."

"(53) A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10 – 15 pascals (guidance values). Particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations."

"(60) All equipment such as sterilizers, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems should be subject to validation and planned maintenance; their return to use should be approved."

Regarding Dry heat, "(97) The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation."

Table 11.1 shows harmonized designations.

Table 11.1: Harmonized Designations for Airborne Particulate and Microbial Monitoring Requirements in an Aseptic and/or Terminal Sterilized Processing Facility, including a Correlation of US and EU Regulatory Requirements [73]

Reference	Description			Classification					
ISPE Sterile Product Baseline® Guide (Third Edition)	Harmonized Designations			ISO 5/ Grade A	ISO 6	ISO 7/ Grade B	ISO 8/ Grade C	Grade D	CNC (Note 1)
US FDA [3]	ISO Designation			ISO 5	ISO 6	ISO 7	ISO 8	N/A (Note 2)	N/A
	In Operation	Maximum no. particles permitted ≥ the stated size	0.5 µm particle/ft³	100	1,000	10,000	100,000	Not defined	Not defined
			0.5 µm particle/m³	3,520	35,200	352,000	3,520,000	Not defined	Not defined
EU [1] and PIC/S [9]	Descriptive Grade			Grade A	N/A (Note 4)	Grade B	Grade C	Grade D	Grade D
	In Operation	Maximum no. particles permitted ≥ the stated size	0.5 µm particle/m³	3,520	35,200	352,000	3,520,000	Not defined	Not defined
			5.0 µm particle/m³	20 (Note 3)	Not defined	2,900	29,000	Not defined	Not defined
	At Rest	Maximum no. particles permitted ≥ the stated size	0.5 µm particle/m³	3,520	Not defined	3,520	352,000	3,520,000	Not defined
			5.0 µm particle/m³	20 (Note 3)	Not defined	29	2,900	29,000	N/A
US FDA [3], EU [1], and PIC/S [9]	In Operation	Microbiological Active Air Action Limits, CFU/m³ (Note 5)		< 1	7	10	100	200	Not defined
ISPE Sterile Product Baseline® Guide (Second Edition)	Legacy ISPE Suggested Classifications			Grade 5	Grade 6	Grade 7	Grade 8	CNC (with local monitoring) or CNC+	CNC

Notes:

1. The "Controlled Not Classified" (CNC) designation is becoming increasingly popular for sterile product facilities. This designation appears to have originated in biologics facilities as a designation for spaces which are access controlled and cleaner than areas with general purpose HVAC, but for which either no claim of cleanliness classification is made or in which an owner may designate the cleanliness classification deemed appropriate (e.g., ISO 9). In some facilities, this designation is used as an equivalent to the EU and PIC/S Grade D (see Note 2).
2. The US FDA does not have an area classification equivalent to Grade D (Grade D is ISO 8 "at rest" only and the US FDA area classifications are based on conditions "in operation"). The lack of a fixed requirement for Grade D "in operation" does not suggest that there is no expectation for "in operation" airborne particulate qualification; rather, Grade D leaves it to the company to define the "in operation" particulate qualification and monitoring limits. When presenting a facility to the US FDA, Grade D manufacturing areas may be presented and qualified as ISO 8 "in operation", as appropriate and when required. Grade D and FDA expectations for ISO 8 "in operation" also have different recommendations for microbiological requirements and, therefore, consideration should be given to use the more stringent requirement (ISO 8). It is important that a facility designed to meet US FDA requirements minimizes performing unit operations in Grade D that are otherwise required to be in an US FDA ISO 8 environment, designated as "Supporting Clean Areas" in the Aseptic Processing Guideline. Consideration should be given to move such functions to ISO 8/Grade C environments or to define Grade D "in operation" as ISO 8, as appropriate or required.
3. For Grade A, there is no airborne particle classification in ISO 14644-1 [4] for particles ≥5.0 µm at or below ISO 5. Classification at this particle size and low count is not recommended by ISO; however, these particle counts may be monitored and reported in conjunction with classification at another particle size and when marked with the Macro-particle designator "M". EU Annex 1 [1] limit of 20 particles/m³ has no ISO equivalent.
4. Although ISO 6 is not included in EU Annex 1 [1] or PIC/S [9], it is referenced as an alternative and is occasionally used as the background for ISO 5 or where companies determine ISO 6 is required for their specific processes.
5. Companies may also elect to use a Compendial Standard (e.g., USP <1116>) for establishing microbial limits, as quantified in terms of Colony Forming Units (CFU).

11.4 Japan GMPs

The Japan Pharmaceuticals and Medical Devices Agency (PMDA) [6] Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing (November 2012) [95] states the following:

Definitions

- *"(2.26) High efficiency particulate air (HEPA) filter: Air filters designed to retain particulates of larger than a certain size with defined efficiency. The filter retains particles of ≥ 0.3 µm size with a minimum efficiency of 99.97%."*

- *"(2.30) Integrity test for filter: A non-destructive test which is used to predict the functional performance of a filter."*

- *"(2.31) Isolator: A sealed and sterilized enclosure capable of preventing ingress of contaminants by means of total physical separation of enclosure to the surrounding exterior environment, An isolator's air supply is filtered using HEPA or ULPA grade filters."*

- *"(2.43) Restricted Access Barrier System (RABS): An integrated system that possesses aseptic processing areas (critical areas) and is composed of some critical elements such as rigid wall enclosure (often equipped with gloves), unidirectional airflow least- to through HEPA filters and appropriate operation procedures."*

(6.1) Key Features of Facility Design

- *"19. Clean areas should be supplied with air filtered through an appropriate filter, e.g. a high-efficiency particulate air (HEPA) filter, to maintain an acceptable level of air quality and pressure difference between areas. The pressure difference should be monitored to maintain as specified."*

(7.2) Heating, Ventilating and Air Conditioning System

- *"Air in clean areas needs to be maintained at appropriate levels by designing, instituting, and managing a suitable heating, ventilation, and air conditioning (HVAC) system. The integrity of the system should be ensured with respect to not only temporal variations due to operational activities, such as door opening and closing and facility equipment operation, but also sustained variations due to non-operational activities, such as seasonal changes in outdoor conditions or deterioration of equipment and apparatuses over time."*

- *"The HVAC system and its management program are comprised of the following basic elements: temperature, relative humidity, air flow volume, air exchange rate, unidirection of air flow, pressure difference relative to adjacent rooms, integrity of HEPA filter, airborne particle count, and microbacterial count."*

(7.2.2) Air

- *"(6) Changes in flow velocity can alter flow direction when airflow is specified to be unidirectional. The velocity should be confirmed to be constant at a predetermined level by monitoring the velocity of airflow from HEPA filters at time intervals specified in the program."*

(7.3.1) Certification of Quality

- *"HEPA filters should be accompanied by vendor's certificate of quality verifying that the filter is capable of eliminating at least 99.97% of particles ≥ 0.3 µm in diameter."*

- *"Leak test of HEPA filters to be used in critical areas (Grade A) and direct supporting areas (Grade B) should be performed by using appropriate leak testing aerosols, e.g. poly-alpha-olefin (PAO). When alternate aerosols are used, such aerosols should be used after confirming that they do not promote microbial growth."*

(7.3.2) Testing of HEPA Filters at Installation and at Regular Intervals

- *"1. HEPA filters should be tested for leaks at installation and thereafter at suitable time intervals. The procedure and frequency of testing should be tailored to the environment, where the filters are installed, and their intended purpose of use. The integrity of HEPA filters in the critical area and direct support area should be confirmed at least once a year. The integrity check is recommended to be twice or more in the case that conditions of use in the critical area are severe or special considerations are required for the prevention of microbial product contamination."*

- *"2. HEPA filters installed in the critical area (Grade A) should be tested for uniformity of air velocity across the filter at installation and thereafter at suitable time intervals. The frequency of integrity check should be determined as stipulated in the preceding Item 1)."*

- *"3. Pressure difference between the HEPA filter's initial and final pressure loss should be tested at installation and thereafter at suitable time intervals. If filter clogging is severe, it is recommended to include pressure difference monitoring in routine control procedures."*

- *"4. When airflow patterns in the [Aseptic Processing Area] are altered or suspected of being altered, the patterns should be evaluated to assess the acceptability of the altered patterns."*

- *"5. HEPA filters should be tested by leak test as directed in relevant SOPs when any events or circumstances that may damage filter integrity occur or when air quality is judged to have deteriorated."*

(13.3) Dry Heat Sterilization

- *"(3) HEPA filters mounted on sterilization equipment should be periodically tested for leaks to check the capacity of the filters. The test should ideally be performed once every 6 months or at least once a year."*

(19.1) Isolator System

- *"A properly designed isolator system provides an extremely aseptic environment but does not provide a hermetically sealed enclosure. Although highly potent pharmaceutical products with high pharmacological activities are occasionally manufactured in an isolator system with a cabinet maintained under negative pressure, sterile pharmaceutical products are usually manufactured using an isolator system operated under positive pressure. In addition, ensuring product sterility requires the establishment and the implementation of a comprehensive preventive maintenance program including maintenance and control procedures for HEPA filters, gloves, half suits, and any other design features that are intended to provide enclosure integrity."*

(19.1.3) HVAC System

- *"(4) Air in the isolator system should be circulated through a HEPA or higher-grade filter. The supply of outside air to the HVAC inlet and the isolator exhaust should also take place through a HEPA or higher-grade filter."*

(19.2) Restricted Access Barrier System (RABS)

- *"A restricted access barrier system (RABS) is a means to produce sterile pharmaceutical products by separating personnel from critical areas and minimizing direct human intervention in critical areas during aseptic processing."*

- *"The RABS is an integrated aseptic processing system to be implemented in aseptic processing areas (critical areas) comprising both hardware and software components, such as physical partitions, air supplied through HEPA filters, and appropriate operational procedures."*

(A4.5) General Requirements for BSL2

- *"(1) Any operations that may generate aerosolized microorganisms should be conducted using closed-system equipment provided with HEPA filters, safety cabinets (Class IIA or higher), or other equipment having a similar capacity for microorganism containment. In addition, air exhausted from such equipment or systems should be cleaned so as to completely eliminate aerosolized microorganisms"*

(A4.6) General Requirements for BSL3

- *"(9) Any operation which may carry a risk of generating aerosolized microorganisms should be conducted in a safety cabinet (Class II or III) equipped with HEPA filters or other closed and contained systems of an equivalent or higher safety level. Additionally, air from such a work environment should be evacuated outside the facility after passing through HEPA filters."*

- *"(10) Air in controlled areas should be filtered and evacuated through an independent HVAC system equipped with HEPA filters."*

11.5 Canada GMPs

The Health Canada [96] Good Manufacturing Practices (GMP) Guidelines 2009 Edition, Version 2 [97] stated the following:

"(3) In all areas where raw materials, primary packaging materials, in-process drugs, or drugs are exposed, the following considerations apply to the extent necessary to prevent contamination."

"(3.6) Air quality is maintained through dust control, monitoring of pressure differentials between production areas and periodic verification and replacement of air filters. The air handling system is well defined, taking into consideration airflow volume, direction, and velocity. Air handling systems are subject to periodic verification to ensure compliance with their design specifications. Records are kept."

"(5) Dusty operations are contained. The use of unit or portable dust collectors is avoided in fabrication areas especially in dispensing, unless the effectiveness of their exhaust filtration is demonstrated and the units are regularly maintained in accordance with written approved procedures."

"(19) The air for clean and aseptic areas is supplied through filters of suitable efficiency. Unidirectional air flow systems are of appropriate design."

"(20) The filtered air supply for clean and aseptic areas is designed to provide a fabrication environment that meets the required grade classifications. Under all operational conditions, a positive pressure of filtered airflow is maintained in relation to surrounding areas of a lower grade. Particular attention is paid to protecting critical areas, that is, the immediate environment in which the sterilized drug product, containers, and closures are exposed."

"(20.1) The air system should be provided with appropriate terminal filters such as high-efficiency particulate air (HEPA) for Grades A, B and C. An intact HEPA filter should be capable of retaining at least 99.97% of particulates greater than 0.3 µm in diameter."

"(20.2) In Grade A areas the air velocity should be sufficient to protect exposed product, product contact components and product contact surfaces from environmental contamination, by sweeping particles away from the filling/closing area and maintain a unidirectional airflow during operations. Air velocity measurements should be taken at locations where meaningful and reproducible results can be obtained. Such locations should normally be not more than 30 cm away from the work site, within the air flow."

"(20.3) In "critical areas" HEPA filters should be leak tested at least twice a year. The purpose of performing regularly scheduled leak tests is to detect leaks from the filter media, filter frame or seal. The aerosol selected for HEPA leak testing should not support microbial growth and should be composed of a sufficient number of particles at approximately 0.3 µm."

"(20.4) HEPA filtered air should be supplied in critical areas at a velocity sufficient to sweep particles away from the filling/closing area and maintaining a unidirectional airflow. In situ air pattern analysis should be conducted at the critical area to demonstrate unidirectional air flow, sweeping action over and away from the product, and the absence of turbulence or eddy currents."

"(27) All equipment, including sterilizers, air-filtration systems, and water-treatment systems, are subject to planned maintenance, validation, and monitoring. Following maintenance/validation, the approval for use of the equipment is documented."

"(79.3.1) The process used includes air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted passes through a HEPA filter."

"Definitions: Grade A Air Supply (flux d'air d'une pureté de classe A): A supply of air which is HEPA filtered, and at the point of supply meets when tested, the non-viable particulate requirements of a Grade A area."

11.6 Mexico GMPs

The COFEPRIS (Comisión Federal para la Protección contra Riesgos Sanitarios/Federal Commission for Protection against Sanitary Risks) [98] provides information regarding Mexico GMPs in the Official Mexican Standard NOM-059-SSA1-2015 (Good manufacturing practices of drug products) [99]. Refer to the table in Section 21 of NOM-056-SSA1-2015 for details regarding area classification requirements.

11.7 China GMPs

The current guidance for China GMPs is found in the document, "Good Manufacturing Practice for Drugs (2010 Revision)" [100]. The categories of medicines covered include:

- Annex 1: Sterile Medicinal Products
- Annex 2: Active Pharmaceutical Ingredients
- Annex 3: Biological Medicinal Products
- Annex 4: Blood Products
- Annex 5: Preparations of Traditional Chinese Medicine

The requirements of the China GMPs closely follow the EU GMPs, and the EU system of cleanliness classification is followed (i.e., Grade A, B, C, and D). Annex 1 of the Chinese GMPs for Sterile Medicinal Products very closely follows the GMP requirements found in EU Annex 1 [75].

11.8 Brazil GMPs

The ANVISA (Agência Nacional de Vigilância Sanitária/Brazilian Health Regulatory Agency) [101] provides the following text in the Brazil GMP regulations [102] that has sometimes been interpreted as prohibiting the repair of HEPA filters used in a Grade A or B area: *"Art. 107. The premises must be kept in good state of conservation, cleaning and hygiene. Sole paragraph. It must be ensured that the maintenance and repair does not represent any risk to product quality."*

The ANVISA's Guide (Guia da Qualidade para sistemas de Tratamento de Ar e Monitoramento Ambiental na Indústria Farmacêutica, 2013) [103] states in item 3.2.3.4 that the repairs of HEPA filters should be done following the methods of EN 1822-4 [82]. Therefore, the most common approach to address a failed HEPA filter is to repair it and retest it according to EN 1822-4, rather than to remove and replace any failed HEPA filter.

11.9 Other Guidance

11.9.1 ICH (International Council for Harmonisation) [104]

ICH Q7 (Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients) [105] states the following:

> *"4.21 Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimise risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture."*

11.9.2 WHO (World Health Organization) [106]

Note: This Guide reflects an understanding of industry standards as of the publication date. It is recognized that the WHO Annex 5 [107] was undergoing revision at the time of this writing.

The WHO Annex 5 (Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms, 2011) [107] generally follows the EU GMPs [5] and the *ISPE Baseline® Guide: Volume 2 – Oral Solid Dosage Forms (Third Edition)* [108], but provides additional advice beyond the regulatory requirements as to how HVAC systems for non-sterile dosage forms (primarily OSD facilities) should be designed. These are recommendations for achieving the requirements of the GMP regulations, but are not the GMP regulations in themselves. There may be other methods to meet the GMP requirements that differ from those in this guidance.

This document provides practical advice on the use and application of air filters to achieve the GMP requirements in an OSD facility during the design, construction, commissioning/qualification, operational, and maintenance phases of a facility's lifecycle.

11.9.3 Pharmaceutical Inspection Co-operation Scheme (PIC/S) [123]

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) are two international instruments between countries and pharmaceutical inspection authorities, which provide together an active and constructive cooperation in the field of GMP.

PIC/S mission is to *"lead the international development, implementation and maintenance of harmonized GMP standards and quality systems of inspectorates in the field of medicinal products."* [123]

This is to be achieved by developing and promoting harmonized GMP standards and guidance documents; training competent authorities, in particular inspectors; assessing (and reassessing) inspectorates; and facilitating the cooperation and networking for competent authorities and international organizations.

The need to form the PIC Scheme became necessary when it was realized that an incompatibility between PIC and European law did not permit individual EU countries that were members of PIC to sign agreements with other countries seeking to join PIC. Only the European Commission was permitted to sign agreements with countries outside Europe, and the Commission itself was not a member of PIC.

Therefore, a less formal and more flexible cooperation scheme was developed to continue and enhance the work of PIC. Instead of being a legal treaty between countries (such as PIC), the PIC Scheme is a cooperative arrangement between Health authorities.

PIC and the PIC Scheme, operating together as PIC/S, provide an active and constructive cooperation in the field of GMP (Good Manufacturing Practice). The purpose of PIC/S is to facilitate the networking between participating authorities and the maintenance of mutual confidence, the exchange of information and experience in the field of GMP and related areas, and the mutual training of GMP inspectors.

The main differences between the PIC Scheme and PIC are listed in Table 11.2.

Table 11.2: Differences between the PIC Scheme and PIC Convention [123]

PIC Scheme	PIC Convention
An informal agreement	A formal treaty
Has no legal status	Has legal status
Between health authorities	Between countries
Exchange of information	Mutual recognition of inspections

11.9.4 USP (United States Pharmacopeia) [109]

The following UPS [109] General Chapters mention HEPA filters, but there is no technical information:

- USP <797> (Pharmaceutical Compounding – Sterile Preparations) [29]: mentions testing
- USP <823> (Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses) [110]: mentions integrity testing
- USP <1046> (Cellular and Tissue-Based Products) [111]
- USP <1116> (Microbiological Control and Monitoring of Aseptic Processing Environments) [112]
- USP <1208> (Sterility Testing – Validation of Isolator System) [113]: mentions initial certification
- USP <1211> (Sterility Assurance) [114]: mentions routine testing
- USP <1788> (Methods for the Determination of Particulate Matter in Injections and Ophthalmic Solutions) [115]

11.9.5 PDA (Parenteral Drug Association) [116]

The PDA Technical Report No. 13 (Fundamentals of an Environmental Monitoring Program) [117] mentions HEPA filters but does not provide specific advice.

11.9.6 PHSS (Pharmaceutical & Healthcare Sciences Society) [32]

The PHSS Monograph No. 2 (Environmental Contamination Control Practices) [119] includes a table with recommended EN 1822 [52] filter classes for the different GMP cleanliness grades.

12 Appendix 2 – Example Forms

12.1 Example Form to Document the Installation of the Correct Filter

HEPA Filter Installation Datasheet	
Project:	Project No.

Shipping Information		
Received By:	☐ No apparent damage to packaging	☐ Damage reported to shipping company and factory

Factory Test Data	
Manufacturer	
Model	
Serial No.	
Factory Test Airflow	
Factory Test DP	
Factory Scan Test Penetration	
Filter Media Area	
Filter Nominal Size	
Order Number	
Media Lot Number	

Filter Configuration		
☐ Gel Seal	☐ Gasket Upstream	☐ Aluminum Frame
☐ Room Side Replaceable	☐ Gasket Downstream	☐ Stainless Steel Frame

Filter Installation Information (location installed)	
Room Number:	Outlet Location ID:

Acceptance	
Data Gathered By (Name):	Date:
Data Gathered By (Name):	Date:

12.2 Example Form to Document Leak Testing of a HEPA Filter (Imperial Units)

HEPA Filter Integrity Test Results

Company/Site	XXXXXX
Testing Firm	ZZZZZZ
Test Date	DD-MMM-YYYY
Filter ID	4321L23

Filter Information	
Location	Room 132
Mfg.	N/A
Model	N/A
Serial #	N/A
Installation Date	DD-MMM-YYYY

Filter Media Dimensions	
Media Length (in)	22
Media Width (in)	46
Media Area (in²)	1012

Airflow Measurements			
Measurement Method: ☐ Velocity (ft/min) ☐ Volume (CFM)			
Velocity (ft/min)		**Volume (CFM)**	
Velocity 1	N/A	Volume 1	538
Velocity 2	N/A	Volume 2	N/A
Velocity 3	N/A	Volume 3	N/A
Average Velocity	N/A	Average Volume	538
Volume CFM	N/A	**Average Velocity**	77

Velocity Setpoint Limit:	≥ 70 ft/min
Meets Acceptance?	Yes

Filter Differential Pressure					
DP at Install	0.62 in wg	at 526 CFM	As Found DP	0.68 in wg	at 538 CFM

Integrity Leak Test	
Aerosol Material	PAO
☐ Scan Test	☐ Overal Leakage Test

Upstream Concentration		
☐ Photometer	22	µg/l
☐ Particle Counter	N/A	#/ft³
Leak(s) detected?	Yes	
Leak(s) repaired?	Yes	
Total in² of repairs	2.3	
Total % repair area (past + current)	0.23%	
Final penetration after repair	< 0.01%	

Filter Drawing

X 0.16%

Leaks (indicated by X)

☐ None (< 0.01%)
☐ Media 0.16%
☐ Gasket _____%
☐ Structural _____%

As-found
☐ In Compliance (< 0.01%)
☐ Out of Compliance (≥ 0.01%)

As-left
☐ In Compliance (< 0.01%)
☐ Out of Compliance (≥ 0.01%)

Additional Notes:

Limits and Acceptance Criteria	**Limits**
The smaller dimension of any repair is limited to	1.5 in
The maximum repair to the total media area is limited to	3% (30.4 in²)
Maximum leak size – scan leak test	≥ 0.01%
Maximum leak size – overall leakage test	≥ 0.01%

This test report represents the actual results of the tests performed on the date performed. The following representative states that the HEPA filter is in compliance with XXXXXX SOP 10.6.2.

Instruments	**Model**	**Serial #**	**Cal. Date**	**Cal. Due**
Aerosol Photometer	AABBCC	1234	DD-MMM-YYYY	DD-MMM-YYYY
Laskin Nozzle	DDEEFF	4321	N/A	N/A
Electric Manometer	GGHHII	4444	DD-MMM-YYYY	DD-MMM-YYYY

Notes:	**Recertification Due:**	MMM-YYYY
	Testing performed by:	**Date:**
		DD-MMM-YYYY
	Reviewed and approved by:	**Date:**
		DD-MMM-YYYY

12.3 Example Form to Document Leak Testing of a HEPA Filter (Metric Units)

HEPA Filter Integrity Test Results

Company/Site	XXXXXX
Testing Firm	ZZZZZZ
Test Date	DD-MMM-YYYY
Filter ID	4321L23

Filter Information	
Location	Room 132
Mfg.	N/A
Model	N/A
Serial #	N/A
Installation Date	DD-MMM-YYYY

Filter Media Dimensions	
Media Length (mm)	560
Media Width (mm)	1170
Media Area (m²)	0.6552

Airflow Measurements			
Measurement Method: ☐ Velocity (m/s) ☐ Volume (m³/s)			
Velocity (m/s)		**Volume (m³/s)**	
Velocity 1	N/A	Volume 1	0.254
Velocity 2	N/A	Volume 2	N/A
Velocity 3	N/A	Volume 3	N/A
Average Velocity	N/A	Average Volume	0.254
Volume m³/s	N/A	**Average Velocity**	0.39

Velocity Setpoint Limit:	≥ 0.36 m/s
Meets Acceptance?	Yes

Filter Differential Pressure					
DP at Install	154 Pa	at 0.248 m³/s	As Found DP	169 Pa	at 0.254 m³/s

Integrity Leak Test	
Aerosol Material	PAO
☐ Scan Test	☐ Overal Leakage Test

Upstream Concentration		
☐ Photometer	22	µg/l
☐ Particle Counter	N/A	#/m³
Leak(s) detected?	Yes	
Leak(s) repaired?	Yes	
Total cm² of repairs	2.3	
Total % repair area (past + current)	0.23%	
Final penetration after repair	< 0.01%	

Filter Drawing

X 0.16%

Leaks (indicated by X)

As-found
☐ In Compliance (< 0.01%)
☐ Out of Compliance (≥ 0.01%)

As-left
☐ In Compliance (< 0.01%)
☐ Out of Compliance (≥ 0.01%)

☐ None (< 0.01%)
☐ Media 0.16%
☐ Gasket _____%
☐ Structural _____%

Additional Notes:

Limits and Acceptance Criteria	**Limits**
The smaller dimension of any repair is limited to	3.8 cm
The maximum repair to the total media area is limited to	3% (197 cm²)
Maximum leak size – scan leak test	≥ 0.01%
Maximum leak size – overall leakage test	≥ 0.01%

This test report represents the actual results of the tests performed on the date performed. The following representative states that the HEPA filter is in compliance with XXXXXX SOP 10.6.2.

Instruments	**Model**	**Serial #**	**Cal. Date**	**Cal. Due**
Aerosol Photometer	AABBCC	1234	DD-MMM-YYYY	DD-MMM-YYYY
Laskin Nozzle	DDEEFF	4321	N/A	N/A
Electric Manometer	GGHHII	4444	DD-MMM-YYYY	DD-MMM-YYYY

Notes:	**Recertification Due:**	MMM-YYYY
	Testing performed by:	**Date:**
		DD-MMM-YYYY
	Reviewed and approved by:	**Date:**
		DD-MMM-YYYY

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14 Appendix 4 – Glossary

14.1 Acronyms and Abbreviations

ABS	Acrylonitrile Butadiene Styrene
ANSI	American National Standards Institute
ANVISA	Agência Nacional de Vigilância Sanitária/Brazilian Health Regulatory Agency (Brazil)
API	Active Pharmaceutical Ingredient
ASHRAE	American Society of Heating, Refrigerating and Air-Conditioning Engineers
BS	British Standard (UK)
BSC	Biosafety Cabinet
BSI	British Standards Institute (UK)
C of C	Certificate of Conformance
CA	Critical Aspect
CCM	Cubic Centimeters per Minute
CDE	Critical Design Element
CEN	European Committee for Standardization
CETA	Controlled Environment Testing Association
CFM	Cubic Feet per Minute
CFR	Code of Federal Regulation
CNBT	CETA National Board of Testing
COFEPRIS	Comisión Federal para la Protección contra Riesgos Sanitarios/Federal Commission for Protection against Sanitary Risks (Mexico)
CPT	Cleanroom Performance Testing
DEHS	Diethylhexyl Sebacate
DOS	Dioctyl Sebecate
DPC	Discrete Particle Counter
EN	European Standard
EPA	Efficiency Particulate Air
EPDM	Ethylene Propylene Diene Monomer
ePTFE	expanded Polytetrafluoroethylene
FDA	Food and Drug Administration (US)

GB and GB/T	Mandatory National Standards and Recommended National Standards (China)
GEP	Good Engineering Practice
GMP	Good Manufacturing Practice
HEPA	High Efficiency Particulate Air
HSE	Health, Safety, and Environment
HVAC	Heating, Ventilation, and Air Conditioning
ICH	International Council for Harmonisation
IEC	International Electrotechnical Commission
IEST	Institute of Environmental Sciences and Technology
IPA	Isopropyl Alcohol
ISO	International Organization for Standardization
JIS	Japanese Industrial Standard (Japan)
JISC	Japanese Industrial Standards Committee (Japan)
MERV	Minimum Efficiency Reporting Value
MPPS	Most Penetrating Particle Size
MSC	Microbiological Safety Cabinet
NEBB	National Environmental Balancing Bureau
NF	Normes Françaises/French Standard (France)
NSB	National Standards Body
NSF	National Science Foundation
OSD	Oral Solid Dosage
PAO	Polyalphaolefin
PD	Published Document (UK)
PDA	Parenteral Drug Association
PdM	Predictive Maintenance
PHSS	Pharmaceutical & Healthcare Sciences Society
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PM	Preventive Maintenance
PTFE	Polytetrafluoroethylene
PVC	Polyvinyl Chloride
R&D	Research & Development

RABS	Restricted Access Barrier System
RCP-FH	Registered Certification Professional – Fume Hoods
RCP-SCF	Registered Certification Professional – Sterile Compounding Facilities
ROI	Return on Investment
RP	Recommended Practice
RPM	Revolutions per Minute
RTV	Room Temperature Vulcanizing
SME	Subject Matter Expert
SOP	Standard Operating Procedure
SRT	Stainless Removable Trim
TAB	Testing, Adjusting, and Balancing
TAG	Technical Advisory Group
TCO	Total Cost of Ownership
UAF	Unidirectional Airflow
UDF	Unidirectional Displacement Airflow
UL	Underwriters Laboratories
ULPA	Ultra Low Penetration Air
USP	United States Pharmacopeia
VAV	Variable Air Volume
VFD	Variable Frequency Drive
VHP	Vaporized Hydrogen Peroxide
WHO	World Health Organization

14.2 Definitions

Acceptance Criteria (WHO Annex 5 [107])

Measurable terms under which a test result may be considered acceptable.

Aerosol Challenge (ISO 14644-3 [33])

Challenging of a filter or an installed filter system by test aerosol.

Aerosol Generator (ISO 14644-3 [33])

Apparatus capable of generating particulate matter having approximate size range (e.g., 0.05 µm to 2 µm) at a constant concentration, which can be produced by thermal, hydraulic, pneumatic, acoustic or electrostatic means.

Aerosol Photometer (ISO 14644-3 [33])

Light-scattering airborne particle mass concentration measuring apparatus, which uses a forward-scattered-light optical chamber to make measurements.

Air Exchange Rate (ISO 14644-3 [33])

Rate expressing number of air changes per unit of time and calculated by dividing the volume of air delivered in the unit of time by the volume of the cleanroom or clean zone.

Classification (ISO 14644-1 [24])

Method of assessing level of cleanliness against a specification for a cleanroom or clean zone.

Cleanroom (ISO 14644-1 [24])

Room within which the number concentration of airborne particles is controlled and classified, and which is designed, constructed and operated in a manner to control the introduction, generation and retention of particles inside the room.

Commissioning (ISPE [120])

A well-planed, documented, and managed engineering approach to the start-up and turnover of facilities, systems, utilities, and equipment to the end-user that results in a safe and functional environment that meets established design requirements and stakeholder expectations.

Dilution System (ISO 14644-3 [33])

System wherein aerosol is mixed with particle-free dilution air in a known volumetric ratio to reduce concentration.

Efficiency (ISO 29463-1 [85])

Ratio of the number of particles retaind by the filter to the number of the particles entering it.

Efficiency, local (ISO 29463-1 [85])

Efficiency at a specific point of the filter element under given operating conditions of the filter.

Efficiency, overall (ISO 29463-1 [85])

Efficiency, averaged over the whole superficial face area of a filter element under given operating conditions of the filter.

Filter Face Area (ISO 29463-1 [85])

Cross-sectional area of the filter element including the frame.

Filter Integrity Test (or Leak Test)

(see: Installed Filter System Leakage Test)

Filter Medium (ISO 29463-1 [85])

Material used for filtering.

Filter System (ISO 14644-3 [33])

Assembly composed of filter, frame and other support mechanism or other housing.

Good Enginering Practice (GEP) (ISPE [120])

Established engineering methods and standards that are applied throughout a project lifecycle to deliver appropriate, cost-effective solutions.

High Efficiency Particulate Air (HEPA) Filter

A filter with an efficiency in excess of 99.97% for 0.3 µm particles.

Installed Filter System Leakage Test (ISO 14644-3 [33])

Test performed to confirm that the filters are properly installed by verifying that there is absence of bypass leakage of the filter installation, and that the filters and the grid system are free of defects and leaks.

Leak (of air filter system) (ISO 14644-3 [33])

Penetration of contaminants that exceed an expected value of downstream concentration through lack of integrity or defects.

Particle (ISO 14644-1 [24])

Minute piece of matter with defined physical boundaries.

Particle Concentration (ISO 14644-1 [24])

Number of individual particles per unit volume of air.

Particle Size (ISO 14644-1 [24])

Diameter of a sphere that produces a response, by a given particle-sizing instrument, that is equivalent to the response produced by the particle being measured.

Particle Size Distribution (ISO 14644-1 [24])

Cumulative distribution of particle concentration as a function of particle size.

Particulate (ISPE [73])

Usually a solid particle large enough to be removed by filtration.

Penetration

Ratio of the number of particles that pass through the filter to the number of particles entering the filter.

Prefilter (HVAC) (ISPE [73])

Air filter placed ahead of a more efficient air filter to reduce the loading and extend the life of the higher efficiency filter.

Restricted Access Barrier System (RABS) (ISPE [73])

An aseptic processing system that provides an enclosed, but not closed, environment meeting ISO 5/Grade A conditions utilizing a rigid wall enclosure and air overspill to separate its interior from the surrounding environment.

Scanning (ISO 14644-3 [33])

Method for disclosing leaks in filters and parts of units, whereby the probe inlet of an aerosol photometer or a light-scattering airborne-particle counter is moved in overlapping strokes across the defined test area.

Test Aerosol (ISO 14644-3 [33])

Gaseous suspension of solid and/or liquid particles with known and controlled size distribution and concentration.

Ultra Low Penetration Air (ULPA) Filter (ISPE [1])

Extended media dry filters in a rigid frame that have a minimum particle-collection efficiency of 99.999% for particles greater than or equal to 0.12 µm in size.

Unidirectional Airflow (UAF) (ISO 14644-1 [24])

Controlled airflow through the entire cross-section of a cleanroom or a clean zone with a steady velocity and airstreams that are considered to be parallel.

Verification (ISPE [120])

An activity that is performed within the C&Q process to document that the manufacturing facilities, systems, utilities, and equipment are suitable for the intended purpose.

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