Cleanroom Classification

Clean rooms are classified by the cleanliness of their air. The method most easily understood and most universally applied is the one suggested in the earlier versions (A to D) of Federal Standard 209 of the USA. In this old standard the number of particles equal to and greater than 0.5 m m is measured in one cubic foot of air and this count used to classify the room. The most recent 209E version has also accepted a metric nomenclature. In the UK the British Standard 5295, published in 1989, is also used to classify clean rooms. This standard is about to be superseded by BS EN ISO 14644-1.

Federal Standard 209

This standard was first published in 1963 in the US and titled "Clean Room and Work Station Requirements, Controlled Environments". It was revised in 1966 (209A), 1973 (209B), 1987 (C), 1988 (D) and 1992 (E). It is available from:

Institute of Environmental Sciences and Technology
940 East Northwest Highway
Mount Prospect, Illinois, 60056 USA
Tel: 0101 708 255 1561
Fax: 0101 708 255 1699
e-mail: **iest@iest.org**:

The clean room classifications given in the earlier A to D versions are shown in Table 1.
Table 1: Federal Standard 209D Class Limits

	MEASURED PARTICLE SIZE (MICROMETERS)				
CLASS	0.1	0.2	0.3	0.5	5.0
1	35	7.5	3	1	NA
10	350	75	30	10	NA
100	NA	750	300	100	NA
1,000	NA	NA	NA	1,000	7
10,000	NA	NA	NA	10,000	70
100,000	NA	NA	NA	100,000	700

In the new 209E published in 1992 the airborne concentrations in the room are given inmetric units, (i.e. per m3), and the classifications of the room defined as the logarithm of theairborne concentration of particles ³ 0.5 m m e.g. a Class M3 room has a particle limit forparticles ³ 0.5 m m of 1000/m3. This is shown in Table 2.
Table 2: Federal Standard 209E Airborne Particulate Cleanliness Classes

		Class Limits									
Class Name		0.1μ m		0.2μ m		0.3μ m		0.5μ m		5μ m	
		Volume Units		Volume Units		Volume Units		Volume Units		Volume Units	
SI	English	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)
M 1		350	9.91	75.7	2.14	30.9	0.875	10.0	0.283	--	--
M 1.5	1	1 240	35.0	265	7.50	106	3.00	35.3	1.00	--	--
M 2		3 500	99.1	757	21.4	309	8.75	100	2.83	--	--
M 2.5	10	12 400	350	2 650	75.0	1 060	30.0	353	10.0	--	--
M 3		35 000	991	7 570	214	3 090	87.5	1 000	28.3	--	--
M 3.5	100	--	--	26 500	750	10 600	300	3 530	100	--	--
M 4		--	--	75 700	2 140	30 900	875	10 000	283	--	--
M 4.5	1 000	--	--	--	--	--	--	35 300	1 000	247	7.00
M 5		--	--	--	--	--	--	100 000	2 830	618	17.5
M 5.5	10 000	--	--	--	--	--	--	353 000	10 000	2 470	70.0
M 6		--	--	--	--	--	--	1 000 000	28 300	6 180	175
M 6.5	100 000	--	--	--	--	--	--	3 350 000	100 000	24 700	700
M 7		--	--	--	--	--	--	10 000 000	283 000	61 800	1 750

British Standard 5295:1989

This standard is available from:

B S I Standards
389 Chiswick High Road
London W44 AL
Tel 0181 996 9000
Fax 0181 996 7400
e-mail: **info@bsi.org.uk**

Because of the imminent publication of EN ISO 14644-1 parts of this British Standard have a limited life. Parts will be superseded by the ISO standards as they appear as an EN standard.

The British Standard is in five parts. These are:

Part 0 - General introduction and terms and definitions for clean rooms and clean air devices. (4 pages)

Part 1 - Specification for clean rooms and clean air devices. (14 pages)

Part 2 - Method for specifying the design, construction and commissioning of clean room and clean air devices. (14 pages)

Part 3 - Guide to operational procedures and disciplines applicable to clean rooms and clean air devices. (6 pages)

Part 4 - Specification for monitoring clean rooms and clean air devices to prove continued compliance with BS 5295. (10 pages)

Part 1 of the standard contains ten classes of environmental cleanliness. Shown in Table 3 are the classes given in the standard. All classes have particle counts specified for at least two particle size ranges to provide adequate confidence over the range of particle size relevant to each class.

Table 3 BR 525 Environmental Cleanliness Classes

	Maximum permitted number of particles per m3 (equal to, or greater than, stated size)					Maximum floor area	Minimum pressure difference*	
Class of environ-mental cleanliness	0.3 μ m	0.5 μ m	5 μ m	10 μ m	25 μ m	per sampling position for clean rooms (m2)	Between classified areas and unclassified areas (Pa)	Between classified area and adjacent areas of lower classification (Pa)
C	100	35	0	NS	NS	10	15	10
D	1 000	350	0	NS	NS	10	15	10
E	10 000	3 500	0	NS	NS	10	15	10
F	NS	3 500	0	NS	NS	25	15	10
G	100 000	35 000	200	0	NS	25	15	10
H	NS	35 000	200	0	NS	25	15	10
J	NS	350 000	2 000	450	0	25	15	10
K	NS	3 500 000	20 000	4 500	500	50	15	10
L	NS	NS	200 000	45 000	5 000	50	10	10
M	NS	NS	NS	450 000	50 000	50	10	NA

BS EN ISO Standard

Because of the large number of clean room standards produced by individual countries it is very desirable that one worldwide standard of clean room classification is produced. The first ISO standard on clean rooms has been published (June 1999) as 14644-1 ‘Classification of Air Cleanliness’. It is about to be adopted as a European standard and hence a standard for all countries in the EU. This standard is available from standard organizations throughout the world and in the UK is available from the BSI. Shown in Table 4 is the classification that has been adopted.

Table 4. Selected ISO 209 airborne particulate cleanliness classes for clean rooms and clean zones.

Classification numbers Numbers (N)	Maximum concentration limits (particles/m^3 of air) for particles equal to and larger than the considered sizes shown below					
	0.1μ m	0.2μ m	0.3μ m	0.5μ m	1μ m	5.0μ m
ISO 1	10	2				
ISO 2	100	24	10	4		
ISO 3	1 000	237	102	35	8	
ISO 4	10 000	2 370	1 020	352	83	
ISO 5	100 000	23 700	10 200	3 520	832	29
ISO 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO 7				352 000	83 200	2 930
ISO 8				3 520 000	832 000	29 300
ISO 9				35 200 000	8 320 000	293 000

The table is derived from the following formula:

$$Cn = 10^N \times \left[\frac{0.1}{D}\right]^{2.08}$$

where:

Cn represents the maximum permitted concentration (in particles/m3 of air) of airborne particles that are equal to or larger than the considered particle size. Cn is rounded to the nearest whole number. N is the ISO classification number, which shall not exceed the value of 9. Intermediate ISO classification numbers may be specified; with 0.1 the smallest permitted increment of N. D is the considered particle size in m m. 0.1 is a constant with a dimension of m m. Table 4 shows a crossover to the old FS 209 classes e.g. ISO 5 is equivalent to the old FS 209 Class 100.

The occupancy state is defined in this standard as follows:

As built: the condition where the installation is complete with all services connected and functioning but with no production equipment, materials, or personnel present.

At-rest: The condition where the installation is complete with equipment installed and operating in a manner agreed between the customer and supplier, but with no personnel present.

Operational: The condition where the installation is functioning in the specified manner, with the specified number of personnel present and working in the manner agreed upon. The standard also gives a method by which the performance of a clean room may be verified i.e. sampling locations, sample volume etc. These are similar to FS 209. It also includes a method for

specifying a room using particles outside the size range given in the table 4. Smaller particles (ultrafine) will be of particular use to the semiconductor industry and the large (³ 5m m macro particles) will be of use in industries such as parts of the medical device industry, where small particles are of no practical importance. Fibers can also be used.

The method employed with macro particles is to use the format:

'M(a; b);c'

where

a is the maximum permitted concentration/m3
b is the equivalent diameter.
c is the specified measurement method.

An example would be:

'M(1 000; 10m m to 20m m); cascade impactor followed by microscopic sizing and counting'.

Pharmaceutical Clean Room Classification
EU GGMP

The most recent set of standards for use in Europe came into operation on the 1st of January 1997. This is contained in a 'Revision of the Annex to the EU Guide to Good Manufacturing Practice-Manufacture of Sterile Medicinal Products'. The following is an extract of the information in the standard that is relevant to the design of clean rooms:

For the manufacture of sterile medicinal products four grades are given. The airborne particulate classification for these grades is given in the following table.

	Maximum permitted number of particles/m3 equal to or above			
Grade	At rest (b)		In operation	
	0,5µ m	5µ m	0,5µ m	5,0µ m
A	3 500	0	3 500	0
B(a)	3 500	0	350 000	2 000
C(a)	350 000	2 000	3 500 000	20000
D(a)	3 500 000	20 000	not defined (c)	not defined (c)

Notes:
(a) In order to reach the B, C and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate filters such as HEPA for grades A, B and C.
(b) The guidance given for the maximum permitted number of particles in the "at rest" condition corresponds approximately to the US Federal Standard 209E and the ISO classifications as

follows: grades A and B correspond with class 100, M 3.5, ISO 5; grade C with class 10 000, M 5.5, ISO 7 and grade D with class 100 000, M 6.5, ISO 8.
(c) The requirement and limit for this area will depend on the nature of the operations carried out. The particulate conditions given in the table for the "at rest" state should be achieved in the unmanned state after a short "clean up" period of 15-20 minutes (guidance value), after completion of operations. The particulate conditions for grade A in operation given in the table should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself. Examples of operations to be carried out in the various grades are given in the table below. (see also par. 11 and 12).

Grade	**Examples of operations for terminally sterilized products. (see par. 11)**
A	Filling of products, when unusually at risk.
C	Preparation of solutions, when unusually at risk. Filling of products.
D	Preparation of solutions and components for subsequent filling.
Grade	**Examples of operations for aseptic preparations. (see par. 12)**
A	Aseptic preparation and filling.
C	Preparation of solutions to be filtered..
D	Handling of components after washing.

Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitization.

	Recommended limits for microbial contamination (a)			
GRADE	air sample cfu/m3	settle plates (diam. 90 mm), cfu/4 hours(b)	contact plates (diam.55 mm), cfu/plate	glove print. 5 fingers.cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Notes:
(a) These are average values.
(b) Individual settle plates may be exposed for less than 4 hours.
(c) Appropriate alert and action limits should be set for the results of particulate and

microbiological monitoring. If these limits are exceeded operating procedures should prescribe corrective action.

Isolator and Blow Fill Technology (extract only)

The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled and for aseptic processing be at least grade D.

Blow/fill/seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A/B clothing is used. The environment should comply with the viable and non-viable limits at rest and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products for terminal sterilization should be installed in at least a grade D environment.

Guideline on Sterile Drug Products Produced by Aseptic Processing

This document is produced by the FDA in the USA and published in 1987. Two areas are defined. The 'critical area' is where the sterilized dosage form, containers, and closures are exposed to the environment. The 'controlled area' is where unsterilized product, in-process materials, and container/closures are prepared.

The environmental requirements for these two areas given in the Guide are as follows:

Critical areas 'Air in the immediate proximity of exposed sterilized containers/closures and filling/closing operations is of acceptable particulate quality when it has a per-cubic foot particle count of no more than 100 in a size range of 0.5 micron and larger (Class 100) when measured not more than one foot away from the work site, and upstream of the air flow, during filling/closing operations. The agency recognizes that some powder filling operations may generate high levels of powder particulates, which by their nature do not pose a risk of product contamination. It may not, in these cases, be feasible to measure air quality within the one-foot distance and still differentiate "background noise" levels of powder particles from air contaminants, which can impeach product quality. In these instances, it is nonetheless important to sample the air in a manner, which to the extent possible characterizes the true level of extrinsic particulate contamination to which the product is exposed.

Air in critical areas should be supplied at the point of use as HEPA filtered laminar flow air, having a velocity sufficient to sweep particulate matter away from the filling/closing area. Normally, a velocity of 90 feet per minute, plus or minus 20%, is adequate, although higher velocities may be needed where the operations generate high levels of particulates or where equipment configuration disrupts laminar flow.

Air should also be of a high microbial quality. An incidence of no more than one colonyforming unit per 10 cubic feet is considered as attainable and desirable.

Critical areas should have a positive pressure differential relative to adjacent less clean areas; a pressure differential of 0.05 inch of water is acceptable'.

Controlled areas 'Air in controlled areas is generally of acceptable particulate quality if it has a per-cubic-foot particle count of not more than 100,000 in a size range of 0.5 micron and larger (Class 100,000) when measured in the vicinity of the exposed articles during periods of activity. With regard to microbial quality, an incidence of no more than 25 colony forming units per 10 cubic feet is acceptable.

In order to maintain air quality in controlled areas, it is important to achieve a sufficient airflow and a positive pressure differential relative to adjacent uncontrolled areas. In this regard, airflow sufficient to achieve at least 20 air changes per hour and, in general, a pressure differential of at least 0.05 inch of water (with all doors closed), are acceptable. When doors are open, outward airflow should be sufficient to minimize ingress of contamination'.

Country and standard	U.S.A. 209D	U.S.A. 209E	Britain BS 5295	Australia AS 1386	France AFNOR X44101	Germany VD I.2083	ISO standard
Date of current issue	1988	1992	1989	1989	1972	1990 onwards	1997
					-	0	
	1	M1.5	C	0.035	-	1	3
	10	M2.5	D	0.35	-	2	4
	100	M3.5	E or F	3.5	4 000	3	5
	1 000	M4.5	G or H	35	-	4	6
	10 000	M5.5	J	350	400 000	5	7
	100 000	M6.5	K	3500	4 000 000	6	8

This information was compiled from various sources including the listed agencies and the handbook 'Clean Room Technology' as written by Bill Whyte.

Air Filter Selection

Preface

The following guidelines on selecting high efficiency air filters for the pharmaceutical industry mainly deals with filters in the HVAC system (i.e. make up air and terminal and exhaust filtration). The guide, while general, is a Camfil Farr recommendation based on our experience supplying filtration systems to the industry.

There are many different types of processes in pharmaceutical manufacturing, with different demands and concerns placed on the filtration systems. In contrast, a semiconductor fab has a standard design, while in pharma there are probably no two cleannroom facilities the same, unless its for the same owner and process.

We are concerned with many issues when we talk about filtration in the pharmaceutical industry as follows:

- global & local standards
- filter economy
- filter efficiency
- location of filters
- environmental effects of used filters
- classification of the room
- testing of filters

This article will focus on testing and standards.

Testing of filters (both in house & in situ tests)

Camfil Farr's Pharmaseal

There are many reason why filters ‘fail’ on site. These include bad packing, transport damage, inexperienced personnel handling filters, and finally, and probably most common, wrong selection or specification of filters. This is understandable due to the many different standards and client demands.

Example’s of filter testing protocols:

1. EN 1822 High efficiency air filters (HEPA & ULPA) classification and test of filters.

Eurovent 4/4 (replaced by EN 1822, however still used and misunderstood especially when specifying efficiency, Eurovent uses NaCl (0.65 micron diameter) whereas EN1822 uses the most penetrating particle size (typically 0.15-0.2 micron diameter). The resulting efficiency can be in the range of 99.997 for 0.65 micron particles and 99.95 for MPPS for the same filter.

Eurovent 4/4 is a volumetric test and may not detect pinhole leaks within the filter, whereas EN1822 involves a full media scan test, on the higher grades of HEPA filters they would be the natural choice for pharmaceutical use.

Care, however, should be used when selecting HEPA filters for areas that are required to be in-situ tested. (i.e. factory scan test and meeting requirements of the in-situ scan test, for instance the 0.01% penetration requirement).

Other testing protocols include:

2. IEST-RP-CC001.3 HEPA & ULPA Filters (1993)
3. IEST-RP-CC006.2 Testing Cleanrooms (1997)

4. IEST-RP-CC021.1 Testing HEPA & ULPA filter media (1993)
5. IEST-RP-CC034.1 HEPA & ULPA filter leak test (1999)

It is not the purpose of this article to discuss each individual recommendation. However, discussing each project on a 'case by case' basis with the owner, designer, contractor and supplier and 'pooling' the collective knowledge before a detailed specification is written can eliminate costly mistakes.

Table 1: Standards applicable to the American & European markets

	Classification & Particle Counting in The Room	**Filter Classes**	**Testing Filters**
FDA/USA	US FED STD-209 E	IEST-RP-CC001.3	IEST-RP-CC006.2 IEST-RP-CC021.1 IEST-RP-CC034.1
GMP/Europe	ISO-14644	EN-1822	EN-1822

Standards International & National:

Today we are getting closer and closer to having one standard for cleanroom classification meeting the requirements of GMP for Europe, the US and Asia. They generally follow the aforementioned standards. Many countries in Asia will use their own national standards. For example, in Japan the JACA and in Australia AS1386. These standards are generally applied to manufacturers located within the borders of the region. However, if an American or European manufacturer invests in Asia and intends to ship product to their home country/continent, they will generally follow their standards (i.e. GMP, or FDA).

Examples of cleanroom classification standards:

1. ISO 14644 (1-9), introduced in 2000
2. US FED STD 209D 1998 - FDA's Cleanroom classification (edition D was replaced by Edition E in 1992)
3. US FED STD-209E, 1992 - FDA's Cleanroom classification
4. GGMP PIC/EEC Annex 1 (January 1997) Cleanroom classifications

Below is a general comparison of these standards

FED STD-209D	**FED STD-209E**	**ISO 14644-1**	**GGMP PIC/EEC**
1	M 1.5	Class 3	
10	M 2.5	Class 4	
100	M 3.5	Class 5	A & B
1000	M 4.5	Class 6	
10,000	M 5.5	Class 7	C
100,000	M 6l5	Class 8	D

Summary

Selecting, high efficiency filters and accessories (housings, mounting frames etc) is not easy. One must consider many parameters including filter efficiency, application, lifetime, running costs, equipment costs, accessibility, etc. Camfil Farr has developed many software programs for optimizing filter selection. The programs include of hepa/ulpa selection, cleanroom design, chemical/carbon selection, and LCC (life cycle cost, make up air). Most of this software is available upon request.

With their enormous R&D budgets, pharmaceutical and biotechnology companies play an extremely important role in the future of health care. Filters are and will remain a critical part of the production of their products. Camfil Farr is proud to be the leading supplier of 'clean air solutions' to the pharmaceutical and biotechnology industries. For further information, contact your nearest Camfil Farr sales office and or visit our web site at **www.camfilfarr.com**.

Sean O' Reilly
Bio-Pharma Segment Manager
Camfil Farr Group

Filter Bleed-Through, the Myth, the Reality and the Solution

Preface:

Filter "Bleed-Through" is a condition existing primarily in the Bio-Pharm marketplace within Class A areas (fully filtered ceilings). Although a Band-Aid is not required, the outcome of such encounters, when dealing with end users that have a clean room off-line, can literally be "bloody" (possibly the real history for the term "Bleed-Through"). Filter "Bleed-Through" can be defined as the measurement of background filter penetration exceeding the leakage specification during field certification.

For example, if the percentage (%) penetration over the entire face of a filter measures 0.02% and the maximum percentage (%) penetration leakage specification is 0.01% , you are experiencing Bleed-Through. This is extremely troublesome to end users where downtime can very quickly become extremely costly in terms of lost production.

Several key factors can have an effect on and/or result in filter Bleed-Through:

- Inappropriate Filter Specifications
- Filter Face Velocity
- Test Particle Size

There are misconceptions in the industry concerning the true cause of filter Bleed-Through. This article reviews these misconceptions (myths), provides insight on the true mechanisms resulting in Bleed-Through, and recommends solutions.

Bleed-Through, the Myth:

It is generally thought within the industry that filter or media manufacturers have made a substantive change that has caused Bleed-Through. In most cases, the blame is directed at the media. The claims being made are:

- The filter manufacturers are using cheap media

- New medias are thinner than MIL-SPEC media, resulting in higher penetration.

Certainly, the newer standard media are less expensive and thinner than MIL-SPEC media. The standard media grades utilized by Camfil Farr typically have the same percentage (%) penetration specification as the MIL-SPEC media grades *(Remember: percentage (%) penetration is percentage (%) penetration regardless of how you measure it). In identical configurations, these different media grades would perform the same, with respect to percentage (%) penetration. Therefore, media thickness, in this case, has no impact on penetration performance. It does, however, have an impact on pressure drop and its capability to stand up to very harsh conditions.

As a consequence of higher tensile strength, MIL-SPEC grade media has a pressure drop penalty of nearly 20%.

Bleed-Through, the Reality:

What is the reality or true cause of filter Bleed-Through? As mentioned earlier, the primary causes are related to Inappropriate Filter Specifications, Filter Face Velocity and/or Test Particle Size. Let's explore each of these possibilities to understand how they impact on filter Bleed-Through:

Inappropriate Specifications: This is the start or origin of most filter Bleed-Through problems. The typical Face Velocity specified to filter manufacturers for HEPA filters used in Class A application areas is 90 or 100 FPM. These specifications do not usually set the maximum utilization velocity that the filters will be subjected to in their actual application (in situ). Since velocity has a significant impact on penetration, the maximum utilization velocity should be the actual test velocity used by the filter manufacturer to guarantee compliance with field testing conditions. Another specification issue is attributed to the efficiency and leakage specification. Most specifications are written referring to industry-recommended practices such as IEST (Institute of Environmental Science and Technology) or utilizing the verbiage contained within such a document. Most, if not all bio-pharm facilities specify a "type C" or performance indicative of a "type C" filter. The performance level specified here is a minimum global efficiency of 99.99% on 0.3 micron particles and a fully leak-tested (scanned) filter with a maximum leakage rate of 0.01% (which is identical to the global efficiency minimum penetration). The recommended practice of IEST recommends laskin nozzle generated aerosols for leak testing due to this issue of the maximum leakage penetration value being identical to the minimum efficiency value. This helps because the mass mean particle size diameter of a laskin nozzle generated oil aerosol is in the order of 0.7 microns in diameter. This eliminates problems with background penetration and allows you to look only for leakage *(Note: a leak is not particle size selective). If thermal aerosols are utilized, the mass mean particle size becomes much smaller, resulting in potential filter Bleed-Through problems by design. Since more of these smaller challenge aerosol particles will penetrate, the filter will have a lower filter efficiency versus these smaller particles when tested in situ.

Specifications do not address this issue, and leave the field testing requirements up to the certifier. In fact, in many cases, field testing requires the use of thermally generated aerosol (which generate smaller challenge aerosol particles by design) to achieve sufficient concentrations, which in turn will lead to a higher penetration/lower efficiency filter when tested in the field.

Filter Face Velocity: As stated above, Filter Face Velocities are typically specified at 90-100 FPM in bio-pharm applications. However, the actual velocities in situ are usually significantly

higher. It is not unheard of to see Filter Face Velocities of 120, 140, 150 or even up to 180 FPM in the field. This upward shift in velocity rather dramatically impairs filter efficiency.

As an example, on the following chart:

	Efficiency @ 0.3 Micron			
Filter Type	100 FPM	120 FPM	140 FPM	150 FPM
2" Media Pack - 99.99%	99.9945%	99.992%	99.989%	99.987%

As shown in the table, if the in situ application subjects the filter to a higher than specified velocity, the filter efficiency drops below the 99.99% level, resulting in Bleed-Through in the field. Keep in mind that if a laskin nozzle generated challenge aerosol is utilized, the possibility of Bleed-Through due to a high application velocity is greatly diminished.

Test Particle Size: As stated previously, most, if not all bio-pharm facilities specify a “type C” or performance indicative of a “type C” filter. The performance level specified here is a minimum global efficiency of 99.99% on 0.3 micron particles and fully leak tested filter with a maximum leakage rate of 0.01% (which is identical to the global efficiency minimum penetration). The “type C” requirements specify efficiency testing with 0.3 micron diameter thermal DOP. In Class A areas (fully filtered ceilings), field certifiers utilize portable thermal generators to achieve sufficient upstream concentrations. The problem with these generators is that they generate a particle size equivalent or very close to a typical filter’s MPPS (Most Penetrating Particle Size). If a factory-tested filter just meeting the 99.99% @ 0.3 micron efficiency specification is then tested with thermal aerosol in the field, it is likely to exhibit Bleed-Through since the efficiency in the field tested MPPS range will always be lower than at the 0.3 micron factory efficiency testing *(likely in the range of 99.996% -99.98%). This is typically not a problem for Bio-Safety Cabinets or Terminal Housings since a laskin nozzle generator is utilized.

*NOTE: you significantly compound the Bleed-Through issue when testing in situ at higher face velocities utilizing smaller sized (MPPS range) particles.

Filter Bleed-Through, the Solution:

The solution is quite simple. The filter specified/purchased by end users should be rated at an efficiency/particle size and maximum velocity to guarantee acceptance when tested with a thermal generator in the field. Simply speaking, Camfil Farr would recommend a filter efficiency purchasing specification of H14 per EN1822 (a minimum efficiency of 99.995% @ MPPS). This performance level would be specified at the maximum velocity to be encountered in situ. The leakage threshold would be set at a maximum of 0.008% at the factory to guarantee 0.01% scanning results in the field.

Summary:

Although filter Bleed-Through has been thought of as a mystery caused by media and/or filter manufacturers, the root of the problem clearly stems from many possibilities. It is evident that a key factor for filter Bleed-Through is related to particle size. The particle size issue stems from the use of portable thermal generators. The use of these generators is typically restricted to Class A areas to achieve sufficient concentrations. Bleed-Through, therefore, generally occurs in these applications and not in applications such as Terminal Housings or Bio-Safety Cabinets. It is vitally important that both end users and filter manufacturers develop an appropriate filter specification, as proposed in the solution section, to guarantee that all filters purchased meet the

field testing requirements.

CEN Classification: HEPA/ULPA Filters EN 1822-1:1998

Filter Class	Overall Value (%)		Local Value (%)	
	Efficiency	Penetration	Efficiency	Penetration
H 10	85	15	---	---
H 11	95	5	---	---
H 12	99.5	0.5	---	---
H 13	99.95	0.05	99.75	0.25
H 14	99.995	0.005	99.975	0.025
U 15	99.9995	0.0005	99.9975	0.0025
U 16	99.99995	0.00005	99.99975	0.00025
U 17	99.999995	0.000005	99.999975	0.000025

Filters are and will remain a critical part of the installation to maintain the cleanliness required in bio-pharm manufacturing and packaging facilities. Camfil Farr is proud to be the leading manufacturer supplying clean air solutions to this industry.

CEN EN 1822-1:1998				
High efficiency air filters (HEPA & ULPA). Classification, performance testing, mar				
Filter	Efficiency % @ MPPS		Penetration % @ MPPS	
Classification	Overall Value	Local Value	Overall Penetration	Local Pe
H10	= > 85	-	15	-
H11	= > 95	-	5	-
H12	= > 99.5	-	0.5	-
H13	= > 99.95	99.75	0.05	0.2
H14	= > 99.995	99.975	0.005	0.0
U15	= > 99.9995	99.9975	0.0005	0.0
U16	= > 99.99995	99.99975	0.00005	0.00
U17	= > 99.999995	99.9999	0.000005	0.0

Notes:

1) Filters in the class H10, H11 & H12 do not require verification of local penetration.
2) Filters in the class H13 & H14 may, as an alternative, be verified with the visual oil-smok viously known as DIN 24.184).
3) U17 is an exception to the rule. IN this case local penetration may NOT exceed 20 times all penetration value.

HEPA/ULPA Cleanroom Filter Testing

Filter Classifications

Quite a few inaccuracies and erroneous "jargon" are commonplace in the high efficiency filtration industry. One of the key issues pertains to nomenclature (i.e., HEPA, ULPA, VLSI, SULPA, etc.). This issue involves misconceptions regarding a filters efficiency and the relationship to particle size.

CEN, the Comite European de Normalization, has developed a Standard, EN 1822-1:1998, based on particle counting at the Most Penetrating Particle Size (MPPS). This European Standard applies to High Efficiency Particulate Air (HEPA) and Ultra Low Penetration Air (ULPA) filters used in the field of ventilation and for technical processes (e.g., for clean room technology or applications in the nuclear and pharmaceutical industries).

Key definitions from this Standard include:

- Penetration — The ratio of the particle count downstream of the filter to the particle count upstream.

- Efficiency — The ratio of the number of particles captured by the filter to the number of the particles challenging the filter.
- Overall Efficiency/Penetration — The efficiency/penetration averaged over the "superficial/useable" face area of a filter element under given operating conditions of the filter.
- Superficial/Useable Face Area — The cross-sectional area of the filter element, through which the air passes.
- Local Efficiency/Penetration — The efficiency/penetration at a specific point on the superficial/useable face area of the filter element under given operating conditions of the filter.
- Leak Threshold — Local penetration greater than or equal to five (5) times the filters overall penetration.

This Standard allows a classification of filters in terms of efficiency and is, therefore, useful for both buyer and seller.

Basic Test Protocols

Leak Scanning

Camfil Farr leak tests each Megalam Panel and Ducted Ceiling Module HEPA/ULPA filter. Testing is performed in Class 100 (M3.5) clean zones within a Class 10,000 (M5.5) cleanroom. All testing is conducted per the controlled and documented procedures of Camfil Farr's ISO 9001 certified quality system.

To enhance upstream sampling capability, leak-scanning systems are equipped with dilution equipment for measuring high particle concentrations. Probe geometry has been optimized to maximize traverse rate and eliminate undetected leaks while maintaining isokinetic sampling. The entire face of the filter is scanned with overlapping strokes including the media to frame interface. Per customer requirements, Polystyrene Latex Spheres (PSL) is Camfil Farr's standard challenge aerosol.

Any leak with a penetration exceeding five (5) times the filters average rated penetration, is repaired with an alcohol based silicone sealant per industry standards or customer specifications. Polyurethane and other repair materials are available upon request.

Menu-driven, computer controlled auto-scanning is utilized for standard filter configurations. Manual scanning is performed for small quantity, custom filter designs/sizes and leak repair.

Filter Media Efficiency Testing

Per Camfil Farr raw goods supplier specifications, suppliers are required to test each master roll of Camfil Farr filtration media for efficiency utilizing Condensation Nuclei Counters (CNC) & Q127 Penetrometers. Test results are submitted to Camfil Farr for review & material acceptance prior to release authorization.

Filter Efficiency Testing

Manual Scan: Camfil Farr's computer integrated system gathers efficiency information from a fully encapsulated filter. The system features simultaneous upstream and downstream data collection. If the efficiency is lower than specified, the filter is rejected.

Auto-Scan: The discrete data points generated during the scan test are integrated to calculate the test filters global efficiency. If the efficiency is lower than specified, the filter is rejected.

Filter Media Pressure Drop Testing

Per Camfil Farr specifications, approved suppliers test each lot of media for pressure drop. Test results are submitted to Camfil Farr for review & material acceptance prior to release authorization.

Filter Pressure Drop Testing

Manual Scan: During the test, the system continuously monitors and collects filter pressure drop data. If the pressure drop is higher than specified, the filter is rejected.

Auto-Scan: During the scan test, the system continuously measures the filters pressure drop. If the pressure drop is higher than specified, the filter is rejected.

Manual Scanning Protocol

Depending on customer requirements, either Photometer or Particle Counter manual scanning techniques are utilized. Typically, depending upon the detection equipment selected, a solid aerosol (i.e., PSL - Polystyrene Latex spheres) is used. Probe geometry has been optimized to maximize traverse rate and eliminate undetected leaks while maintaining isokinetic sampling.

A summary of Camfil Farr's manual scanning protocol follows:

1) Typical test aerosol concentration is: PSL (Polystyrene Latex) > 5 x 107 N/ft3

2) Typical scan speed is 1.5 – 2.0 inches/second.

3) Testing: The entire face of the filter is scanned with overlapping strokes with particular attention given to the media pack to frame seal.

A. Particle Counter Scanning: If a particle count is detected, the operator checks the area for continuous counts. If continuous counts in excess of the specified leakage threshold are detected, the leak is repaired.

B. Photometer Scanning: If a discernable displacement of the % Penetration indicator occurs, or the alarm sounds, the operator re-checks the area of concern. If the % Penetration indicator displacement exceeds the specified leakage threshold, the leak is repaired.

4) Leak Repairs: If a leak exceeds the specification, it is repaired with a silicone sealant. Alcohol-based silicones and polyurethane are also available for use as leak repair materials. After a repair has been made, the entire filter face is re-scanned.

Note: Photometer Scanning is generally reserved for HEPA filters, while Particle Counter Scanning is used for ULPA filters and/or for customers with stringent outgassing requirements.

Auto-Scanning Protocol

Camfil Farr Auto-Scanners have been designed to detect pinhole leaks in HEPA/ULPA filters. The test apparatus is an automated, computer-controlled system, utilizing multiple particle counters for accuracy. Polystyrene Latex (PSL) is the standard challenge aerosol. To further enhance system sensitivity, Camfil Farr uses advanced dilution equipment for measuring high upstream particle concentrations. The automated system eliminates the possibility of incorrect test results that can result from human error. The computer interface controls filter airflow rate, test aerosol injection, particle counting upstream and downstream of the test filter, probe traverse rate, data reduction and data storage.

A description of system parameters follows:

1) System protocol includes:

a) Aerosol Concentration: PSL concentration = 3 x 108 N/ft3 (typical)
b) Particle Counter Flow = 1 CFM (cubic foot per minute)
c) Sampling = Isokinetic d) Sample Time = Continuous e) Size Range = 0.1 – 0.5 m (0.1 m band widths)

2) Required operator input:

a) Min./Max. and Rated Efficiency
b) Leakage factor (per customer specification
c) Dilution ratio
d) Min./Max. and Rated Pressure Drop
e) continuous upstream sampling during the scan process
f) Programmed to automatically traverse the filter with overlapping strokes. Proximity sensors (mounted in the probe) monitor the probes location with regard to the clamping frame, ensuring that the probe overlaps the media to frame interface along the filters perimeter.
g) The system utilizes the Rated Efficiency, Leakage Factor and Dilution Ratio inputs comparing downstream samples, from the entire scan, with the average upstream sample to determine if a leak exists.
h) If a leak is detected, a reject report is generated that indicates the magnitude and location of the leak.
i) Measuring pressure drop continuously across the filter. If the pressure drop is higher than specified, the filter is rejected.
j) Calculating global efficiency by integrating the discrete data points collected during the scan test. If the efficiency is less than specified, the filter is rejected.

The scan rate is calculated per IEST-RP-00001.3 Section 9.2.2:

$Sr = CcLsFsDp/(60NI)$

Where:

Cc is the challenge concentration in particles/ft3
Ls is a significant leak in terms of standard penetration
Fs is the sample flow rate in CFM
Dp is the probe dimension expressed in inches parallel to the scan direction
NI is the number of particle counts that define the maximum leak
60 is the conversion factor from seconds to minutes.

Camfil Farr specifies that the variable NI is to be set to twice the particle counter background level or a minimum of 25.

Camfil Farr's Cam Count Efficiency Testing Protocol

Camfil Farr's Cam Count efficiency test system is designed to test HEPA/ULPA filters per IEST-RP-CC007.1 and EN1822. All testing is performed per the controlled & documented procedures of Camfil Farr's ISO 9001 certified quality system.

Camfil Farr's Cam Count efficiency test system has been designed to measure the overall efficiency and pressure drop of HEPA/ULPA filters. The test apparatus is an automated, computer controlled system, utilizing a single laser particle counter for accuracy. Poly Alpha Olefin (PAO) is the standard challenge aerosol.
A Poly Styrene Latex Sphere (PSL) test aerosol is also available upon request and is utilized on all high temperature filters. To further enhance system sensitivity, Camfil Farr uses advanced dilution equipment for measuring high upstream particle concentrations. The automated system eliminates the possibility of incorrect data that can result from human error. The computer interface controls the flow rate, the test aerosol injection, particle counting upstream and downstream, and data collection, reduction and storage.

A description of system parameters follows:

1) System protocol includes:

a) Aerosol Concentration: PAO concentration = 3 x 108 N/ft3 (typical) PSL concentration = 1-3 x108 N/ft3
b) Particle Counter Flow = 1 CFM (cubic foot per minute)
c) Sample Time = 20 second upstream & downstream sequentially (typical)
d) Size Range = 0.1 – 0.5 mm, 0.1 – 0.2 mm, 0.2 – 0.3 mm, 0.3 – 0.5 mm, and > 0.5mm.

2) Required operator input:

a) Minimum, maximum, & target efficiency
b) Minimum, maximum, & target pressure Drop
c) Test flow rate

3) System Operation:

The system sequentially measures the upstream & downstream particle concentration. After applying the dilution ratio to the upstream concentration, it calculates the filter efficiency, while simultaneously measuring the filter pressure drop using a calibrated pressure transducer. These values are automatically compared to the input minimum & maximum values. A filter with values outside the specified range is rejected. The system automatically generates a test label that includes the test results for each passing filter.

UL 900

Camfil Farr Megalam Panel and Ducted Ceiling Module type HEPA/ULPA filters are listed with Underwriters Laboratories per UL 900, "Standard for Test Performance of Air Filter Units" as either of the following:

Class 1: "those that, when clean, do not contribute fuel when attacked by flame and emit only negligible amounts of smoke".

Class 2: "those that, when clean, burn moderately when attacked by flame or emit moderate amounts of smoke, or both".

Please call factory for the specific rating of your product (s).

Factory Mutual

Camfil Farr's Megalam Panel and Ducted Ceiling Module type HEPA/ULPA filters meet the approval requirements of Factory Mutual Research Corporation (FM) for product construction of limited combustibility, when installed in an approved ceiling grid. For this approval, FM tests the filter as a component in a complete ceiling grid system.

During the ten (10) minute fire exposure test for Factory Mutual Standard FM-4920 ceiling system approval, there was no visible ignition of the Camfil Farr filter and no flame spread. For this test, the ceiling system tested was composed of a third party ceiling grid, third party gel sealant, and Camfil Farr filter. The complete system passed all technical requirements of the standard.

References:

Printed copies of referenced documents may be purchased from the following entities:

CEN

European Committee for Standardization
36 rue de Stassart, B - 1050 Brussels
Tel: + 32 2 550 08 11
Fax: + 32 2 550 08 19

IEST

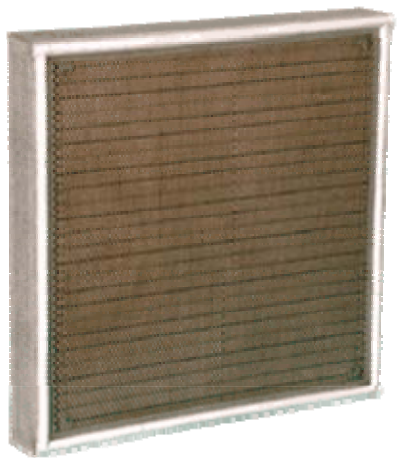
Institute of Environmental Sciences and Technology
5005 Newport Drive, Suite 506
Rolling Meadows, IL 60008
Phone: (847) 255-1561
Fax: (847) 255-1699

Factory Mutual

Factory Mutual
1301 Atwood Avenue
P.O. Box 7500
Johnston, R.I. 02919
Phone: (401) 275 3000
Fax: (401) 275 3029

High temperature filtration for depyrogenation sterilization ovens and tunnels

Endotoxins are poisonous substances that are produced in bacteria, and continue to exist after the bacteria has been destroyed. Therefore, a sterile surface may still retain dangerous endotoxins.



21CFR Part 211.94 states: “Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.”

Depyrogenation and sterilization processes are used to eliminate viable matter and reduce the amount of endotoxin on vials or other containers used in pharmaceutical processing and distribution. These processes utilize dry heat at a prescribed temperature and duration. It is up to the pharmaceutical manufacturer to decide what cleaning, sterilization, and depyrogenation is appropriate for their given process.

The air used in the depyrogenation process must be filtered by leak free HEPA grade air filters.

Depyrogenation tunnels and continuous ovens are continuous systems that are used to reduce the amount of endotoxin to an acceptable level on glass or metal vials or other process containers and accessories.

Depyrogenation ovens are batch systems used to reduce the amount of endotoxin to an acceptable level on glass or metal vials or other process containers and accessories.

The items being subjected to the depyrogenation process must remain at the specified temperature for the specified time period for the process to be successful. Reduced heat-up and cool down periods as well as increased maximum temperature can increase the total throughput of the equipment.

In the past, the duration of batch depyrogenation processes has been determined by the ability of the HEPA filters to maintain the cleanliness class required (normally Class 100). Failure of the HEPA filters was a likely event during the heat-up and cool-down cycles. More recently, advances in HEPA filter technology have helped to reduce the negative impact HEPA filters have on the duration of the process.

Camfil Farr's Termikfil is an example of a new high-temperature HEPA filtration technology. Specifically designed for use in depyrogenation ovens and tunnels for sterilization purposes, Camfil Farr’s Termikfil is the only HEPA filter guaranteed to operate for a minimum of one year at a temperature of 350°C (662°F) while maintaining the leak-free integrity required to pass FDA validations.

The Termikfil frame is manufactured from ceramic based materials. The frame sealing method, using an element constructed of an exclusive polymineral material, provides leak-free performance when properly mounted to filter sealing surfaces. A unique, high-temperature, microfine glass media ensures consistent filter performance throughout the life of the filter. A stainless steel face grid is installed on both the air entering and air exiting sides of the filter to ensure protection of the media pack and add to the filter pack’s structural integrity. The Termikfil is pretreated, and pre-qualified, during the manufacturing process, with an exclusive heat preparation cycle (572º F, 300º C).

New high-temperature air filtration technologies have allowed equipment manufacturers to focus on other process related issues, maximize equipment performance, and reduce the cost of equipment operation.

Visit the **High Temperature Filters** section for more information about Camfil Farr high temperature products.