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A FILTER GUIDE FOR CLEANROOMS IN THE PHARMACEUTICAL INDUSTRY

RAMBØLL

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The filter guide was completed by Benedikte Rosling Winter and Camilla Saabøll.

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1. PREFACE

This filter guide only deals with filters in air conditioning systems for Cleanrooms.

A filter guide for Cleanrooms can deal with many different aspects.

- International and national standards.
- Cleanroom classification (cleanliness classes)
- Filter performance classes (efficiency)
- Testing filters – manufactures test – test at site
- Pre-filters
- Design of air conditioning systems for Cleanrooms: where is the filter placed?
- Environment : disposal of used filters – Safe-X-Change
- Microbiological growth in filters
- Types of filters: fibers – pleated filter – etc.
- Pleated filters: EPA - HEPA – ULPA - VESPA

We have chosen to concentrate on a few of the above topics, which are of immediately relevance to the projects that we deal with in the pharmaceutical industry. This guide concerns primarily on HEPA and ULPA filters.

- Cleanroom classifications and number of air changes
- Filter performance classes
- Filter materials
- Filter efficiency and particle size
- Testing filters and the pressure difference across filters
- Which filters are used where and when?

2. CLASSIFICATIONS AND AIR CHANGES

This filter guide is based on the different guidelines and standards listed below. These standards cover the areas in which we design air conditioning systems.

- ISO 14644-1:1999, Cleanrooms and associated controlled environments, Part 1: Classification of air cleanliness
- ISO 14644-2:2000, Cleanrooms and associated controlled environments, Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1
- ISO 14644-4:2001, Cleanrooms and associated controlled environments, Part 4: Design, construction and start-up
- US FED STD-209D, 1988 – FDA's Cleanroom classifications (this issue D was replaced by issue E in 1992)
- US FED STD-209E, 1992 – FDA's Cleanroom classifications (this issue E was replaced by ISO 14644-2 in 2001)
- GMP Volume 4: Medicinal Products for Human and Veterinary Use
  Annex 1: Manufacture of Sterile Medicinal Products. Feb. 2008.

2.1 Cleanroom classifications

- ISO 14644-1:1999 describes the 9 ISO classes that cleanrooms have been divided into. For each ISO class there are requirements to the maximum number of particles per m^3 air, for different particle sizes. Requirements to the number of particles for the different particle sizes are also stated in other guidelines/standards cf. table 2.1-1. The listed maximum numbers of particles are for the cleanroom "at rest". The European guideline GMP Volume 4 also sets requirements to the maximum number of particles for the cleanroom "in operation". ISO14644-

1 and US FED STD-209E have no specific demands to the cleanroom specifications according to whether the room is tested "at rest" or "in operation" – one must determine for themselves the conditions under which the cleanroom should be tested.

	Maximum number of particles per m³ air for the different particle sizes					
	≥0,1 µm	≥0,2 µm	≥0,3 µm	≥0,5 µm	≥1 µm	≥5 µm
ISO 14644-1: 1999						
Class 1	10	2	0	0	0	0
Class 2	100	24	10	4	0	0
Class 3	1.000	237	102	35	8	0
Class 4	10.000	2.370	1.020	352	83	0
Class 5	100.000	23.700	10.200	3.520	832	29
Class 6	1.000.000	237.000	102.000	35.200	8.320	293
Class 7	-	-	-	352.000	83.200	2.930
Class 8	-	-	-	3.520.000	832.000	29.300
Class 9	-	-	-	35.200.000	8.320.000	293.000
FED STD-209E						
M 1	350	75,7	30,9	10	-	0
M 1.5	1.240	265	106	35,3	-	0
M 2	3.500	757	309	100	-	0
M 2.5	12.400	2.650	1.060	353	-	0
M 3	35.000	7.570	3.090	1.000	-	0
M 3.5	-	26.500	10.600	3.530	-	0
M 4	-	75.700	30.900	10.000	-	0
M 4.5	-	-	-	35.300	-	247
M 5	-	-	-	100.000	-	618
M 5.5	-	-	-	353.000	-	2.470
M 6	-	-	-	1.000.000	-	6.180
M 6.5	-	-	-	3.530.000	-	24.700
M 7	-	-	-	10.000.000	-	61.800
FED STD-209D *						
1	1.236	265	106	35	-	0
10	12.359	2.648	1.059	353	-	0
100	-	26.483	10.593	3.531	-	0
1.000	-	-	-	35.310	-	247
10.000	-	-	-	353.100	-	2.472
100.000	-	-	-	3.531.000	-	24.717
GMP Volume 4: Annex 1 **"at rest"**						
A	-	-	-	3.520	-	20
B	-	-	-	3.520	-	29
C	-	-	-	352.000	-	2.900
D	-	-	-	3.520.000	-	29.000

Table 2.1-1: Requirement to the maximum number of particles for different standards.
**Values for FED STD-209D are converted to per m³, cf. appendix 1.*

In the pharmaceutical industry in Denmark one primarily uses the cleanroom classifications defined in the American US FED STD-209D 1988, and in the European guideline GMP Volume 4 - all though new standards have taken effect.

Table 2.1-2 compares the different cleanroom classifications defined in the different standards.

FED STD-209D (1988)	**FED STD-209E (1992)**	**ISO 14644-1 (1999)**	GMP Annex 1 **(2008)**
1	M 1.5	~ Class 3	
10	M 2.5	~ Class 4	
100	M 3.5	~ Class 5	~ A og B
1.000	M 4.5	~ Class 6	
10.000	M 5.5	~ Class 7	~ C
100.000	M 6.5	~ Class 8	~ D

Table 2.1-2: Room classifications compared across the various norms /standards.

The requirements set in the different standards are not completely comparable. Generally if the requirements set in US FED STD-209D are met, then the requirements set in US FED STD-209E are also met.

Comparing US FED STD-209 and ISO 14644-1, and saying that the cleanroom classes are the same is approximately correct. Generally the requirements set in ISO 14644-1 are more stringent than those set in the US FED STD-209E.

Among other things, FDA (FED STD-209) only require tests to be performed by a particle size larger than 0.5 μm, where the European GMP require tests done by two particle sizes 0.5 μm and 5.0 μm respectively. ISO 14644 does not set requirements on how many and what particle sizes need to be tested. This must be indicated in the design phase of the room in question.

2.2 Number of air change

None of the standards listed in section 2 sets requirements for the number of air changes in cleanrooms. The European Union has in the "Rules governing medical products in EU. Volume IV – GMP" specified guidelines for the number of air changes necessary to obtain class B, C and D according to GMP Volume 4 . If the number of air change is minimum 20 h^{-1} in a cleanroom with good mixing throughout the room and appropriate HEPA-filters, it is possible to obtain class B, C and D.

In the pharmaceutical industry today the number of air change set to minimum 20 h^{-1} is almost regarded as a requirement. Experience shows that it is possible to maintain for example class 100.000 (referring to US FED STD-209D) with only 10 h^{-1} in cleanrooms where no particles are generated in connection with the pharmaceutical production. To obtain cleanliness class 10.000 or cleaner, the number of air changes has to be at least 20 h^{-1}, to be sure that the requirements to the maximum number of particles are met. The final air change must be determined on the basis of particle entry into the cleanroom.

To obtain class 100 UDF-modules are typically used. Class 100 is only obtained under the UDF-module, the surrounding room will be class 1.000 with a minimum number of air changes set to 20 h^{-1}.

3. FILTERS

This guide primarily regards HEPA- and ULPA-filters.

- HEPA-filter: High Efficiency Particulate Air filter
- ULPA-filter: Ultra Low Penetration Air filter

It should be mentioned that the newest edition of EN 1822 (2009) has adopted the term Efficiency Particulate Air Filter (EPA) for the filter classes 10-12. The designation is therefore E10-E12 instead of the previous H10-12.

The starting point is based on below standards and guide lines (Recommended Practice (RP)) which classifies filters and establishes test methods for filters on the markets in Europe and USA that follows cGMP.

- EN 1822-1:2009 High efficiency air filters (EPA, HEPA and ULPA), - Part 1: Classification, performance testing, marking
- ISO 14644-2:2000, Cleanrooms and associated controlled environments, Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1
- Eurovent 4/4 standart – now replaced by EN 1822.
- IEST-RP-CC001: HEPA and ULPA Filters. (2009)
- IEST-RP-CC006: Testing Cleanrooms. (2004)
- IEST-RP-CC021: Testing HEPA and ULPA Filter Media. (2009)
- IEST-RP-CC034: HEPA and ULPA Filter Leak Tests. (2009)

3.1 Filter materials

The semiconductor industry sets the requirements at the moment, as this industry is far more vulnerable than the pharmaceutical industry.

HEPA and ULPA filters are made of glass fiber material. It is possible to manufacture ULPA filters made from Teflon (PTFE), because glass fiber material contains approximately 10% boron that in the presence of moisture or hydrogen fluoride (HF) can be released. Boron is of great concern for the semiconductor industry and its advanced production. Boron in filter material is of no concern for the pharmaceutical industry.

3.2 Classification of filters

The Eurovent 4/4 standard has classified HEPA and ULPA filters in five different classes EU 10 – EU 14 based on the efficiency determined by using the Sodium Flame test (0,65 μm particles). The Eurovent 4/4 standard has been replaced by the European standard EN 1822.

The European standard EN 1822 classifies EPA, HEPA and ULPA filters in the classes shown in table 3.2-1 (E ~ EPA, H ~ HEPA and U ~ ULPA).

The requirements set to the filter efficiency for a given filter class according to EN 1822 is intimately connected with the test method, which is used. Therefore it is not possible to compare filter efficiencies when the same test method is not used.

	Total value		Local value	
Filter classes	**Efficiency (%)**	**Penetration (%)**	**Efficiency (%)**	**Penetration (%)**
E 10	≧ 85	≦ 15	-	-
E 11	≧ 95	≦ 5	-	-
E 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	≧ 99,999 5	≦ 0,000 5	≧ 99,997 5	≦ 0,002 5
U 16	≧ 99,999 95	≦ 0,000 05	≧ 99,999 75	≦ 0,000 25
U 17	≧ 99,999 995	≦ 0,000 005	≧ 99,999 9	≦ 0,000 1

Table 3.2-1 Classification and requirements to HEPA and ULPA filters according to EN 1822.

As EN 1822 is a rather new standard the classifications in the old Eurovent 4/4 is still used by many persons. A rough comparison of filter classes for the two standards is shown in table 3.2-2. Note that EN 1822 has replaced Eurovent 4/4, - test methods and classifications defined in Eurovent 4/4 do not meet the requirements of today. The test methods and particle size for which the filter efficiency is specified in the two standards is not the same, therefore table 3.2-2 is only a guideline.

Eurovent 4/4		**EN 1822**	
Filter class	**Efficiency %**	**Filter class**	**Efficiency %**
		E 10	85
		E 11	95
EU 10	95 – 99,9		
		E 12	99,5
EU 11	99,9 – 99,97		
EU 12	99,97 – 99,99	H 13	99,95
EU13	99,99 – 99,999		
		H 14	99,995
EU 14	>99,999		
		U 15	99,9995
		U 16	99,99995
		U 17	99,999995

Table 3.2-2 Comparison of filter classes defined by Eurovent 4/4 and EN 1822.

The above mentioned filter classifications are all based on European standards. For Cleanrooms that are subject to the American Food and Drugs Associations (FDA) requirements filters should probably be classified according to IEST-RP-CC001 (shown in table 3.2-3).

IEST-RP-CC001	
Filter class	**Efficiency %**
Type A	99,97 ved ”rated air flow”
Type B	99,97 ved hhv. 20% og 100% af ”rated air flow”
Type C	99,99
Type D	99,999
Type E	tested according to MIL-F-51477 or MIL-F-51068.
Type F	99,999 (0,1 – 0,2 μm particles)

Table 3.2-3 Classification of filters according to IEST-RP-CC001. Note that the background for the efficiency is different for the individual filter classes.

3.3 Testing filters

Notice that in general it is not immediately possible to compare results of filter tests, unless all the test parameters are identical. Among other things shall the test aerosol and the concentration of the aerosol be the same.

In this filter guide we have chosen only to describe testing methods according to EN 1822. Testing filters in cleanrooms subject to FDA's requirements then be aware that there can be differences in the following paragraph compared to US FED STD-209E, ISO 14644-3, IES-RP-CC001 and IES-RP-CC006.

In general testing filters can be divided as follows:

- Manufactures test
  - determining MPPS (Most Penetrating Particle size)
  - leak test
  - testing the overall efficiency of the filter
- Testing at site (installation test and maintenance test of the filters)
  - leak test
  - testing the overall efficiency of the filter

The "new thing" concerning testing filters according to EN 1822 is that MPPS (Most Penetrating Particle Size) shall be determined for each filter.

Here follows a short description of how to test filters according to EN 1822:

1. First the efficiency of the test samples of the filter medium shall be determined for a range of particle sizes at the nominal filter medium velocity. From the efficiency vs. particle size curve the MPPS shall be determined, for which the filtration efficiency of the filter medium is at a minimum. MPPS is typically around 0,13 μm.
2. The filter element is tested at nominal flow rate for freedom from leaks using a test aerosol with a mean particle size, which corresponds to the MPPS.
3. Using the same test aerosol, again at the nominal flow rate, the overall efficiency is determined.

Testing filters according to EN 1822 means that the demands to the manufactures documentation for each filter element has intensified.

For description of test aerosols we refer to EN 1822.

HEPA and ULPA filters must be tested continuously over the year. Tests are performed according to the standard specified for the given cleanroom. Often the owners of the filters (the producer / seller in the pharmaceutical industry) have their own GMP manuals or SOP's, regarding cleanrooms and testing filters. Most filters are tested minimum 2 times per year, according to FDA requirements.

ISO 14644-2 discloses the following interval for filter test, see table 3.2-4.

Classification	Maximum time interval	Test method
≦ ISO Class 5	6 months	Annex B in ISO 14644-1
> ISO Class 5	12 months	Annex B in ISO 14644-1

Table 3.2-4 Intervals for filter test according to ISO 14644-2.

3.4 Pressure difference across filters

Generally there is a relation between filter size, air flow and the pressure drop over the filter. Usually the pressure drop for HEPA filters start at approximately 250 Pa and ends (the filter is changed) at 450 Pa. These values can be confirmed by several filter manufactures. You can start with a lower pressure drop than 250 Pa, but 250 Pa is the pressure drop at which the filter is tested, therefore this is often chosen at the start pressure drop for the filter.

When the air handling unit is in use, the pressure drop over filters is typically monitored, and an alarm is given if the pressure drop rises to more than 450 Pa. A HEPA filter can handle pressure drops up to approximately 1000 Pa, before it is so dirty that the efficiency is reduced considerably. At this point one can not only look at the filter, one has to take for instant the ventilator performance, the expenses for electricity etc. into account. Therefore it is custom not to go beyond a pressure drop of 450 Pa.

To prolong the life span of filters, you ought to consider reducing the airflow. It is a question of comparing the initial costs and the operating costs for the air conditioning system to see when it pays to increase the number of filter modules and thereby prolong the life span for each filter module.

4. WHICH FILTERS ARE USED WHERE AND WHEN?

Regarding cleanroom classification, plus classification and test of filters it differs which standards are valid where. In table 4.1-1 below the standards are listed according to their geographical areas.

	Cleanroom classifications and particle counting in the room	Filter classes	Testing filters
FDA	US FED STD-209E	IEST-RP-CC001	IEST-RP-CC006 IEST-RP-CC021 IEST-RP-CC034
EU	ISO 14644	EN 1822	EN 1822

Table 4.1-1 Reference to standards for the American (FDA) and European (EU) market.

Contrary to earlier the requirements set by ISO 14644 are more strict than the requirements at the American (FDA) market. In principle ISO 14644 also sets the requirements for the American market regarding cleanroom classifications and particle tests.

How FDA regards filter classifications and tests of filters according to EN 1822 is not known. Therefore it is important at the beginning of a project to define which standards are used to set the requirements for the cleanroom(s).

4.1 Choosing filters

This section only deals with cleanrooms in the pharmaceutical industry and the food industry.

Table 4.2-1 needs a couple of general remarks to be understood correctly.

The filter classes specified are chosen with a certain marginally safety, as this guide is meant as a tool that shows the level at which filters in air conditioning systems for cleanrooms could be chosen. Based on our experience cleanrooms designed for class 100.000 (according to US FED STD-209D) often meets the requirements for class 10.000. The pharmaceutical industry and the inspectors are very critical when it comes to observing cleanroom classifications. Therefore it has never been part of project for cleanrooms to optimize the filter classes used in the air conditioning systems. Today's computer technology gives you the possibility to optimize which filter classes are used. There exists computer programs, where you can set requirements to the cleanroom classification, and then experiment using different filter classes, different loads of particles produced in the room, and then get a calculation showing whether the cleanroom classification can be obtained or not. Such calculations must be used carefully, as it is almost impossible to specify the work procedures in the different industries.

Composing this filter guide has drawn our attention to the complexity in choosing filters for air conditioning systems for cleanrooms. When designing and describing filters you must be very careful to specify the filter class and the standard setting the requirements for the specific filter classes. Alternatively you can specify the filters efficiency at a specific particle size, and then leave it to the supplier / contractor to choose the correct filters. To avoid getting lost in the world of standards we recommend defining the filter class according to a specific standard, thereby it is also specified how the filter must be tested.

In table 4.2-1 the filter classes are given and also the standard specifying the requirements. The table is primarily based on ISO 14644 and EN 1822 for the European marked. Not every cleanroom classes are mentioned, we have chosen to focus on the cleanroom classes that we normally deal with in the pharmaceutical industry.

Cleanroom classification (US FED STD-209D)	Filter 1 (pre-filter for the supply air system)	Filter 2	Filter 3	Filter 4 pre-filter for the final-filter	Filter 5 final-filter	Final-filter material	Final-filter placement
ISO Class 5 (~100)	F7 (EN 779) in supply air system before heat exch., fan etc.	F9 (EN 779) or E11 (EN 1822) in supply air system/main duct	E12 (EN 1822) in supply air system / main duct	H14 (EN 1822) in ceiling diffusers in the cleanroom	H14 (EN 1822)	Glass fiber	UDF-module
ISO Class 6 (~1.000)	F7 (EN 779) in supply air system before heat exch., fan etc.	F9 (EN 779) or E11 (EN 1822) in supply air system/main duct	-	E12 (EN 1822) in supply air system / main duct	H14 (EN 1822)	Glass fiber	In ceiling diffusers in the cleanroom
ISO Class 7 (~10.000)	F7 (EN 779) in supply air system before heat exch., fan etc.	-	-	F9 (EN 779) or E11 (EN 1822) in supply air system/main duct	H14 (EN 1822)	Glass fiber	In ceiling diffusers in the cleanroom
ISO Class 8 (~100.000)	F7 (EN 779) in supply air system before heat exch., fan etc.	-	-	-	F9 (EN 779) or E11 (EN 1822)	Glass fiber	In supply air system / main duct

Table 4.2-1 Choosing filters and placing them in supply air systems for different cleanroom classes.

APPENDIX 1

US FED STD-209D, 1988 set requirements for the maximum number of particles per ft³, as listed in table 1.

Table 2 shows the maximum number of particles converted to particles per m³, making it possible to compare the cleanroom classifications according to US FED STD-209D 1988 with other standards.

Class / particle size (µm)	0,1	0,2	0,3	0,5	5
1	35	7,5	3	1	
10	350	75	30	10	
100		750	300	100	
1000				1000	7
10000				10.000	70
100000				100.000	700

Table 1. Maximum number of particles per ft³.

Conversion from number of particles per ft³ to number of particles per m³ :

$$number\_of\_particles\_per\_m^3 = 35{,}31\frac{ft^3}{m^3} \times number\_of\_particles\_per\_ft^3$$

Class / particle size (µm)	0,1	0,2	0,3	0,5	5
1	1236	265	106	35	0
10	12.359	2648	1059	353	0
100	0	26.483	10.593	3531	0
1000	0	0	0	35.310	247
10000	0	0	0	353.100	2472
100000	0	0	0	3.531.000	24.717

Table 2. Maximum number of particles per m³.