CLASSIFICATION OF CLEANROOMS

Cleanrooms 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 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 cleanrooms. This standard is about to be superseded by BS EN ISO 14644-1.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 USA and titled "Cleanroom 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 cleanroom classifications given in the earlier 209 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 in metric units, i.e per m^3 and the classifications of the room defined as the logarithm of the airborne concentration of particles ? 0.5 ?m e.g. a Class M3 room has a particle limit for particles ?0.5 ?m of $1000/m^3$. This is shown in Table 2.

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Table 2: Federal Standard 209E Airborne Particulate Cleanliness Classes

Class Name		Class Limits									
		0.1? m		0.2? m		0.3? m		0.5? m		5? 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

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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 cleanrooms and clean air devices. (4 pages)
Part 1 - Specification for cleanrooms and clean air devices. (14 pages)
Part 2 - Method for specifying the design, construction and commissioning of cleanroom and clean air devices. (14 pages)
Part 3 - Guide to operational procedures and disciplines applicable to cleanrooms and clean air devices. (6 pages)
Part 4 - Specification for monitoring cleanrooms 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 BS 5295 Environmental cleanliness classes

Class of environmental cleanliness	Maximum permitted number of particles per m^3 (equal to, or greater than, stated size)					Maximum floor area per sampling position for cleanrooms (m^2)	Minimum pressure difference*	
	0.3 ?m	0.5 ?m	5 ?m	10 ?m	25 ?m		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

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BS EN ISO Standard

Because of the large number of cleanroom standards produced by individual countries it is very desirable that one world-wide standard of cleanroom classification is produced. The first ISO standard on cleanrooms 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 organisations 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 cleanrooms 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					
	0.1? m	0.2? m	0.3? m	0.5? m	1? m	5.0? 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/m^3 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.

0.1 is a constant with a dimension of ? 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.

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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 cleanroom 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 (?5?m macroparticles) will be of use in industries such as parts of the medical device industry, where small particles are of no practical importance. Fibres can also be used. The method employed with macroparticles is to use the format:

'M(a; b);c'

where

a is the maximum permitted concentration/m^3
b is the equivalent diameter.
c is the specified measurement method.

An example would be:

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

Pharmaceutical Cleanroom 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 Annexe 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 cleanrooms:

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	
	0,5?m	5?m	0,5?m	5,0?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.

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(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 sterilised 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 sanitisation.

	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.

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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 sterilisation 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 colony forming 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 air flow and a positive pressure differential relative to adjacent uncontrolled areas. In this regard, an air flow 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'.

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Comparison of Various Standards

Shown in Table 5 is a comparison of the classes given in the standards discussed above.

Table 5: A comparison of international standards.

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

The above information has been extracted from the handbook 'Cleanroom Technology' written by Bill Whyte.

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