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CLEANROOM

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CLEANROOM

DEFINITION

- **Although not determining, I'd like to draw attention to the nuance in writing of "Clean Room" vs. "Cleanroom":**

  Clean Room is what your mother always wants from you...

  whereas;

  Cleanroom is a room in which the air supply, filtration and distribution, design and materials of construction, and operating procedures are regulated to control particle concentrations so that appropriate air cleanliness levels can be met.

CLEANROOM

DEFINITION

- Although the cleanroom applications have started years ago in the fields of nuclear and electronics production, now they are frequently employed in fields of healthcare and pharmaceutical industries.
- The cleanroom applications which had first been regularized by a US FED standard have later been widespread and updated by international standards.
- The Federal Standard FED-STD-209 is no longer valid, nor used outside the US; while, in place, the International Standard ISO-14644 finds worldwide acceptance.

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DEFINITION

- **FED-STD-209**

  … a room in which the concentration of airborne particles is controlled.

- **ISO-14644**

  … a room in which the concentration of airborne particles is controlled and which is constructed and used in a manner to minimize the introduction, generation and retention of particles inside the room, and which the relevant parameters, e.g. temperature, humidity and pressure are controlled as necessary.

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Note: The applications and considerations which are utilized mostly in the design of cleanroom applications in healthcare and pharmaceutical industries are included in the study.

The rules, assessments and applications which are utilized mostly in the design of cleanrooms in healthcare and pharmaceutical industries are considered.

In general, the classification in accord with the EU GMP (Good Manufacturing Practice) have been considered, although the definitions and criteria as set forth in the ISO and FED standards have been made use of.

ISPE (International Society for Pharmaceutical Society) and PDA (Parenteral Drug Association) documentation have been referred for application examples.

As for the applications with in Turkey, it is advised to refer to the requirements as set forth in the GMP guides issued by TR Ministry of Health, or TR Ministry of Food, Agriculture and Livestock.

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- FED-STD-209 takes ft^3 as the basic volume of measurement, and classifies the cleanrooms from Class-1 to Class 100,000 as per the number of particles equal to or greater than 0.5 µm in every ft^3 of volume.
- In addition, it classifies the cleanrooms from Class-M1 to Class M7 as per the number of particles equal to or greater than 0.5 µm in every m^3 of volume.

CLASS-	1	10	100	1000	10,000	100,000
/ft^3	1	10	100	1000	10,000	100,000

SI-	M1	M1.5	M2	M2.5	M3	M3.5	M4	M4.5	M5	M5.5	M6	M6.5	M7
/m^3		10		100		1000		10,000		100,000		1 mil	10 mil
		10^1		10^2		10^3		10^4		10^5		1	10^7

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- **ISO-14644 takes m^3 as the basic volume of measurement, and classifies the cleanrooms from ISO-1 to ISO-9 as per the number of particles equal to or greater than 0.1 µm in every m^3 of volume.**

ISO- CLASS	1	2	3	4	5	6	7	8	9
0,1 µm /m^3	10	100	1000	10,000	100,000	1 milyon	10 million	100 million	1 billion
	10^1	10^2	10^3	10^4	10^5	10^6	10^7	10^8	10^9
0,5 µm /m^3	--	4	35	350	3,500	35,200	352,000	3,520,000	35,200,000
FED- CLASS									
0,5 µm /ft^3			1	10	100	1,000	10,000	100,000	(1,000,000)

For example: at ISO-5, the number of particles ≥ 0.1 µm in every m^3 is 10^5, or the number of particles ≥ 0.5 µm in every m^3 is 100 (for that reason, we can say that ISO-5 ≅ Class 100)

1 m^3 ≅ 35,3 ft^3

For ISO-7 and bigger, the number of particles ≥ 0.5 µm is taken into account, not ≥ 0.1 µm.

- **a normal living room is generally at ISO-9 cleanliness class (not defined in FED-STD-209);**
- **ISO-8 or FED-CLASS 100,000 is considered unclassified area.**

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CLASSIFICATION

- **ISO-14644 is respected in the healthcare and pharmaceutical industries; however, the cleanrooms are usually graded as Grade-A, -B, -C, and -D in the EU GMP Guidelines. In this grading methodology, the volume is measured in m^3 and the number of particles at rest or in-operation equal to or greater than 0.5 µm, as well as 5 µm are taken into account.**

EU GMP CLASS	at rest 0,5 µm /m^3	at rest 5 µm /m^3	in-operation 0,5 µm /m^3	in-operation 5 µm/m^3
A	3,520	20	3,520	20
B	3,520	29	352,000	2,900
C	352,000	2,900	3,520,000	29,000
D	3,520,000	29,000	not defined	not defined

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CLASSIFICATION

EU GMP, PIC/S, TR GMP classification

Grade	Maximum permitted number of particles/m³ equal to or greater than the tabulated size			
	At rest		In operation	
	0.5µm	5.0µm	0.5µm	5.0µm
A	3,520	20	3,520	20
B	3,520	29	352,000	2,900
C	352,000	2,900	3,520,000	29,000
D	3,520,000	29,000	not defined	not defined

GOOD MANUFACTURING PRACTICES (GMP) GUIDE FOR MANUFACTURING PLANTS OF HUMAN MEDICINAL PRODUCTS - ANNEX-1 MANUFACTURE OF STERILE MEDICINAL PRODUCTS
REPUBLIC OF TURKEY MINISTRY OF HEALTH TURKISH MEDICINES AND MEDICAL DEVICES AGENCY
Version: 2017/01 Effective Date: 01/10/2017 (Compatible with PIC/S GMP Guide version: PE 009-13)

GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS - ANNEXES
PHARMACEUTICAL INSPECTION CONVENTION PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME
PE 009-13 (Annexes) 1 January 2017

Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Annex 1 Manufacture of Sterile Medicinal Products (corrected version)
EudraLex The Rules Governing Medicinal Products in the European Union Brussels, 25 November 2008 (rev.)

CLEANROOM

CLASSIFICATION

Cleanroom states:

- **as built: construction completed, ready for operation with all services connected and functional, but without equipment or operating personnel.**
- **at rest: complete, with all services functioning, and with equipment installed and operable or operating as specified, but without operating personnel.**
- **in-operation: in normal operation, with all services functioning, and with equipment installed and functioning, and with personnel -if applicable- present and performing normal operation as defined.**

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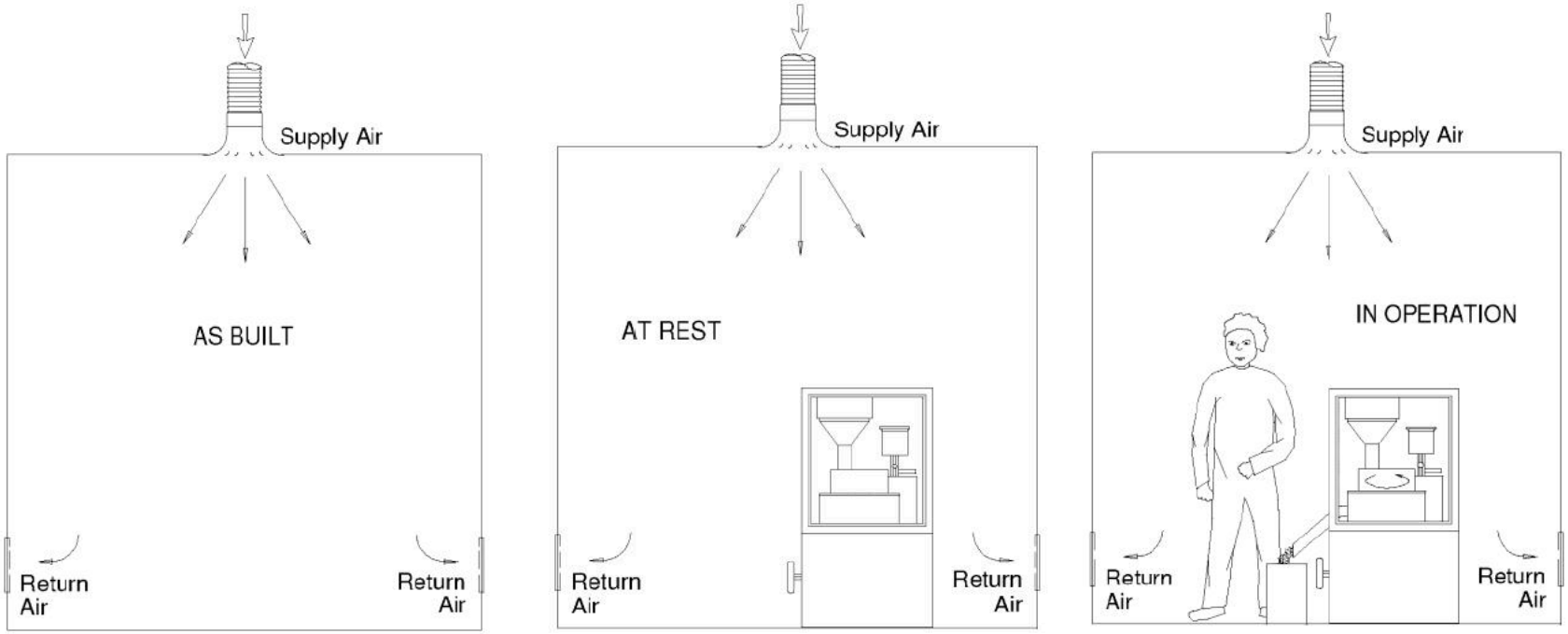
CLEANROOM

CLASSIFICATION



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CLASSIFICATION

- EU GMP cleanroom grading (PIC/S):
- Grade A: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 - 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated.

  A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.
- Grade B: For aseptic preparation and filling, this is the background environment for the Grade A zone.
- Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

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CLASSIFICATION

- **EU GMP cleanroom grading (PIC/S):**

grade	For terminally sterilized products
A	Filling of products, when unusually at risk
C	Filling of products / Preparation of solutions, when unusually at risk
D	Preparation of solutions and components for subsequent filling

grade	For aseptic preparations (not to be sterile filtered or terminally sterilized)
A	Open aseptic preparation and filling
B	Background area for open aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

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CLASSIFICATION

- **FDA**

TABLE 1- Air Classifications[a]

Clean Area Classification (0.5 um particles/ft^3)	ISO Designation[b]	≥ 0.5 µm particles/m^3	Microbiological Active Air Action Levels[c] (cfu/m^3)	Microbiological Settling Plates Action Levels[c,d] (diam. 90mm; cfu/4 hours)
100	5	3,520	1[e]	1[e]
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

a- All classifications based on data measured in the vicinity of exposed materials/articles during periods of activity.
b- ISO 14644-1 designations provide uniform particle concentration values for cleanrooms in multiple industries. An ISO 5 particle concentration is equal to Class 100 and approximately equals EU Grade A.
c- Values represent recommended levels of environmental quality. You may find it appropriate to establish alternate microbiological action levels due to the nature of the operation or method of analysis.
d- The additional use of settling plates is optional.
e- Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants.

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CLASSIFICATION

- **FDA**

  The nature of the activities conducted in a supporting clean area determines its classification.

  It is recommended that the area immediately adjacent to the aseptic processing line meet, at a minimum, Class 10,000 (ISO-7) standards.
  (Manufacturers can also classify this area as Class 1,000 (ISO-6) ,
  or maintain the entire aseptic filling room at Class 100 (ISO-5).

  An area classified as Class 100,000 (ISO-8) is appropriate for less critical activities, such as equipment cleaning, etc.

FDA Guidance for Industry Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice September 2004

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- **ISO-14644**

ISO-5 aseptic processing

ISO-7 other processing zones directly supporting aseptic processing

ISO-8 support zones of aseptic processing, including controlled processing zones

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CLASSIFICATION

- **EU GMP, FED-STD-209 and ISO-14644 compared...**

at rest	in-operation	Clean Area Classification (0.5 um particles/ft^3)	ISO Designation[b]	> 0.5 µm particles/m^3
A, B	A	100	5	3,520
		1000	6	35,200
C	B	10,000	7	352,000
D	C	100,000	8	3,520,000

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CLASSIFICATION

- **EU GMP, FED-STD-209 and ISO-14644 compared...**

Classification System	Classifications					
ISO 14644-1	Class 3	Class 4	Class 5	Class 6	Class 7	Class 8
Federal Standard 209E	1	10	100	1000	10,000	100,000
EU GGMP	-	-	A/B	-	C	D

! Comparison in this table may be misleading. REY

CLEANROOM

CLASSIFICATION

- **Comparison of the number of particles generated in one minute against EU GMP, US FED-STD-209 and ISO-14644 classifications**

Old Fed Std 209E	ISO EN14644	EU GMP Annex 1	Maximum permitted particles per m^3 equal to or greater than tabulated size	
			At rest	In operation
			0.5 µ	0.5 µ
100	ISO 5	Class A & B*	3,520	3,520
1,000	ISO 6	---	35,200	---
10,000	ISO 7	Class C	352,000	3,520,000
100,000	ISO 8	Class D	3,520,000	Not defined

People Activity	Particles/Minute (≥0.3 µ)
Motionless (Standing or Seated)	100,000
Walking about 2 mph	5,000,000
Horseplay	100,000,000

! Comparison in this table may be misleading. REY

Cleanroom Design, Construction and Qualification
Ed White
Journal of Validation Technology Autumn 2009

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- **EU GMP, US FED-STD-209 and ISO-14644 compared...**

	SI	1	10	100	1,000	10,000	100,000
Comparison of Major Cleanroom Standards							
US 209 E 1992	English	M1.5	M2.5	M3.5	M4.5	M5.5	M6.5
ISO Class 14644-1 1999		3	4	5	6	7	8
EEC GGMP 1989		N/A		A & B	N/A	C	D
France AFNOR 1981		N/A		4000	N/A	400,000	4,000,000
Germany VDI 2083 1990		1	2	3	4	5	6
Britain BS 5295 1989		N/A		E or F	G or H	J	K
Japan JACA 1989		3	4	5	6	7	N/A

! Comparison in this table may be misleading. REY

CLEANROOM

CLASSIFICATION

- **EU GMP, US FED-STD-209 and ISO-14644 compared...**

Table 3 Requirements for Air Particles – USA and Europe

Room Class				Maximal Number of Particles / m^3 / ft^3				
US FDA[24] / USP[13] in operation**	**ISO 14644-1[20]**	**ISO 13408[28]**	**EU[11]**	**USP[13]** > 0,5 µm	**ISO 14644-2[30] US FDA Draft[12]** > 0,5 µm	**ISO 14644-2[30]** > 5 µm	**EU guide[11]** in operation** (only EU) > 0.5 /5 µm	**EU guide[11]** at rest *** (only EU) > 0.5 / 5 µm
100 / critical / M 3.5	5	critical	**A**	3530 100	3 520 / 100	29	3 500/1****	3 500 / 1****
1 000*/ M 4.5	6	not defined	not defined	35 300 1 000	35 200 / 1000	293	not defined	not defined
10 000* / M5.5	7	other	**B**	353 000 10 000	352 000 / 10 000	2930	350 000 / 2 000	3 500 / 1****
100 000 / controlled / M6.5	8	support area	**C**	3 530 000 / 100 000	3 520 000 / 100 000	29 300	3 500 000 / 20 000	350 000 / 2 000
not defined	9	support area	**D**		35 200 000	293 000	not defined	3 500 000 / 20 000

* introduced with FDA Draft Guidance[12]

** in operation / dynamic conditions: with personnel present, equipment in place, and operations ongoing
carried out at representative locations normally not more than 1 foot away from the work site, within the airflow, and during filling / closing operations, upstream of the airflow.

*** at rest: equipment in place, personnel absent

**** the areas are expected to be completely free from particles of size greater than 5 µm; for statistical reasons the value is set to 1 particle / m^3.

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CLASSIFICATION

- **EU GMP, US FED-STD-209 and ISO-14644 compared...**

Table 4 Requirements for Viable Organisms (Air, Surfaces and Personnel) – USA and Europe

class	a. air active CFU / 10 ft³ b. settling plates (diameter 90 mm / CFU / 4 hours) c. US FDA 1987[24]			air passive CFU / plate		surfaces CFU / contact plate		glove CFU / 5 finger		gowning CFU / contact plate	
ISO / US / EU	USP[13] CFU / m³ air (CFU / ft³ air)	a. / b. US FDA 2003[12]	EU[11] CFU / m³	US[12]	EU[11]	US[12] (USP[13])	EU[11]	US[12] (USP[13])	EU[11]	US[12] (USP[13])	EU[11]
5 / 100 / A	< 3 / (< 0.1)	a. < 1 b. < 1 c. < 1	< 1	-	< 1	3 (3 including floor)	< 1	3	< 1	5	
6 / 1000 / n.d.	n.d.	a. 7 b. 3 c. n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
7 / 10 000 / B	< 20 / (< 0.5)	a. 10 b. 5 c. n.d.	10	n.d.	5	5 10 (floor)	5	10	5	20	n.d.
8 / 100 000 / C	< 100 / (< 2.5)	a. 100 b. 50 c. 25	100	n.d.	50	n.d.	25	n.d.	n.d.	n.d.	n.d.
9 / n.d. / **D**	n.d.	n.d.	200	n.d.	100	n.d.	50	n.d.	n.d.	n.d.	n.d.

n.d. = not defined

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CLASSIFICATION

- **EU GMP AND ISO-14644 compared...**

Table: EU grades and equivalent ISO classes.

Activities	EU grade	ISO Class	Non-viable particulate (particles/m³)			
			At rest		In operation	
			0.5 µm	5.0 µm	0.5 µm	5.0 µm
The local zone for high-risk operations (e.g., filling zone), stopper bowls, open ampoules and vials, making aseptic connections.	A	4.8	3520	20	3520	20
For aseptic preparation and filling, this is the background environment for the grade A zone.	B	5 at rest, 7 in operation	3520	29	352,000	2900
Clean areas for carrying out less critical stages in the manufacture of sterile products.	C	7 at rest, 8 in operation	352,000	2900	3,520,000	29,000
Clean areas for carrying out less critical stages in the manufacture of sterile products.	D	8 at rest, not defined in operation	3,520,000	29,000	Not defined	Not defined

Cleanroom Design, Construction and Qualification
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Journal of Validation Technology Autumn 2009

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Cleanroom criteria compared...

EU GGMP grade rest	EU GGMP grade oper.	SI class	FS 209 class	ISO 14644-1 class	≥ 0,1 µm m³	≥ 0,1 µm ft³	≥ 0,2 µm m³	≥ 0,2 µm ft³	≥ 0,3 µm m³	≥ 0,3 µm ft³	≥ 0,5 µm m³	≥ 0,5 µm ft³	≥ 1 µm m³	≥ 1 µm ft³	≥ 5 µm m³	≥ 5 µm ft³	≥ 10 µm m³	≥ 10 µm ft³	≥ 25 µm m³	≥ 25 µm ft³	British BS 5295 class
				ISO-1 10^1	**10**		2		--		--		--		--						
				ISO-2 10^2	**100**		24		10		4		--		--						
		M 1			350	9,91	75,7	2,1	30,9	0,88	**10**	0,283	--	--	--	--					
				ISO-3 10^3	**1.000**		237		102		35		8								
		M 1.5	1		1.240	35	265	7,5	106	3	35,3	1	--	--	--	--					
		M 2			3.500	99,1	757	21,4	309	8,75	**100**	2,83	--	--	--	--					
				ISO-4 10^4	**10.000**		2.370		1.020		352		83								
		M 2.5	10		12.400	350	2.650	75	1.060	30	353	10	--	--	--	--					
		M 3			35.000	991	7.570	214	3.090	87,50	**1.000**	28,3	--	--	--	--					
											3.000				0		0		0		BS class 1
A	A										3.520				20 , 29						
				ISO-5 10^5	**100.000**		23.700		10.200		3.520		832		29						
		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	--	--	--	--					
				ISO-6 10^6	**1.000.000**		237.000		102.000		35.200		8.320		293						
		M 4.5	1.000		--	--	--	--	--	--	35.300	1.000	--	--	247	7					
		M 5			--	--	--	--	--	--	**100.000**	2.830	--	--	618	17,5					
											300.000				2.000		30				BS class 2
C	B										352.000				2.900						
				ISO-7							352.000		83.200		2.930						
		M 5.5	10.000		--	--	--	--	--	--	353.000	10.000	--	--	2.470	70					
		M 6			--	--	--	--	--	--	**1.000.000**	28.300	--	--	6.180	175					
D	C										3.520.000				29.000						
				ISO-8							3.520.000		832.000		29.300						
		M 6.5	100.000		--	--	--	--	--	--	3.530.000	100.000	--	--	24.700	700					
													1.000.000		20.000		4.000		300		BS class 3
		M 7			--	--	--	--	--	--	**10.000.000**	283.000	--	--	61.800	1.750					
				ISO-9							35.200.000		8.320.000		293.000						

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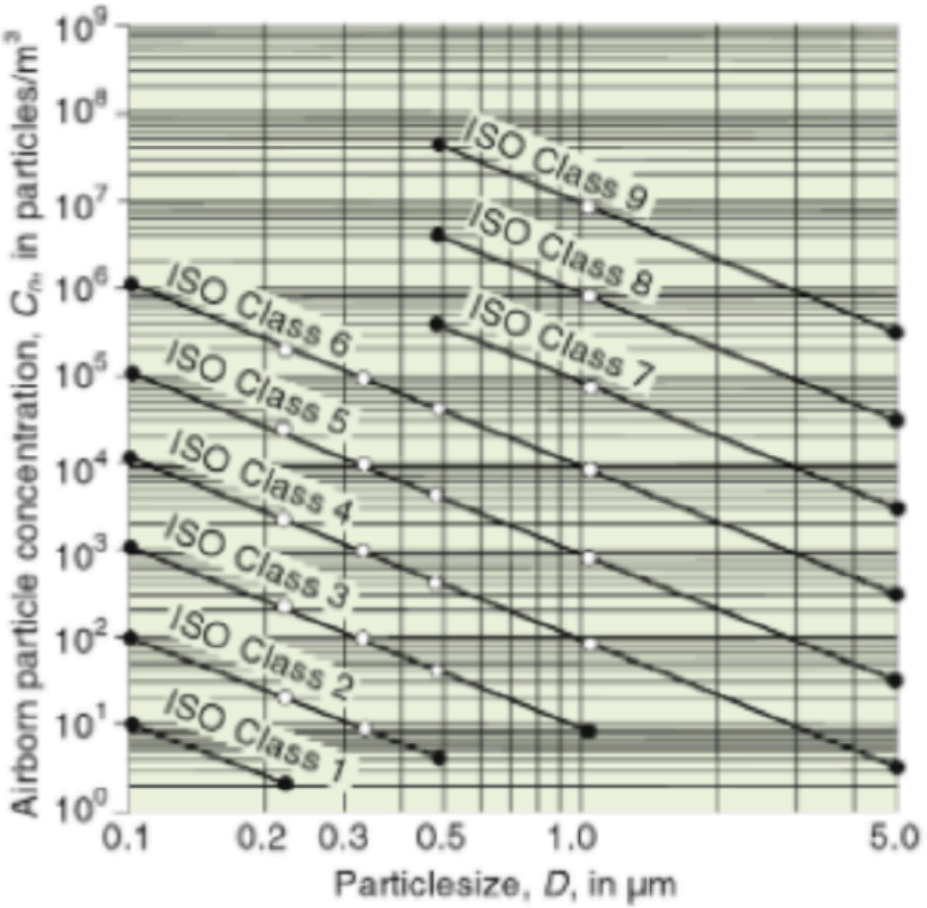
CLASSIFICATION

- ISO-14644

There may be fewer number of larger particles, or greater number of smaller particles.

e.g. for ISO-5:

100,000	0,1 µm
23,700	0,2 µm
10,200	0,3 µm
3,520	0,5 µm
832	1 µm
29	5 µm



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CLASSIFICATION

- FED-STD-209 and ISO-14644 standards may be considered being equivalent to each other, when compared; like Class 100 ≅ ISO-5 or Class 10,000 ≅ ISO-7. However, it wouldn't be appropriate to match an EU GMP grade one to one with FED or ISO class; because an EU GMP grade would correspond to a different FED or ISO class, depending on being at <u>at rest</u> state or <u>in-operation</u> state.
  - Grade A at rest and/or in-operation may be considered ≅ ISO-4.8 (when the number of ≥ 5 µm particles in 1 m^3 is taken into account)
  - Grade B at rest ≅ ISO-5
    in-operation ≅ ISO-7
  - Grade C at rest ≅ ISO-7
    in-operation ≅ ISO-8
  - Grade D at rest ≅ ISO-8
    in-operation ≅ not defined

CLEANROOM

CLASSIFICATION

- **ISPE classification**

The International Society for Pharmaceutical Engineering (ISPE) that holds many experts on design, construction, validation and operation of cleanrooms, recommends the following classification:

ISPE		EU GMP
Grade 5	≅	Grade A
Grade 7	≅	Grade B
Grade 8	≅	Grade C
CNC+	≅	Grade D
CNC	≅	not defined

CNC+ : monitored CNC
CNC : Controlled but Not Classified
NC : Not Classified

Table 2.2: Suggested ISPE Environmental Classifications for Aseptic Filling and Terminal Sterilization, including a Comparison of US and EU Regulatory Requirements

Reference	Description			Classification				
ISPE Sterile Product Baseline® Guide (Second Edition)	Environmental Classification			Grade 5	Grade 7	Grade 8	Controlled Not Classified (with local monitoring)	Controlled Not Classified (CNC)
European Commission EU GMP, Annex 1, Vol. IV, Manufacture of Sterile Medicinal Products (effective 1 March 2009) (similar to PIC/S GMP Annex 1 2007)	Descriptive Grade			A	B	C	D	Not defined
	At Rest	Maximum no. particles permitted per m³ ≥ the stated size	0.5 µm	3,520	3,520	352,000	3,520,000	-
			5 µm	20 ("ISO 4.8")	29	2,900	29,000	-
	In Operation	Maximum no. particles permitted per m³ ≥ the stated size	0.5 µm	3,520	352,000	3,520,000	Not stated	-
			5 µm	20	2,900	29,000	Not stated	-
		Maximum permitted number of viable organisms cfu/m³		< 1	< 10	< 100	< 200	-
FDA, October 2004, Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing	In Operation	Maximum no. particles permitted ≥ the stated size	0.5 µm	ISO 5 (Class 100)	ISO 7 (Class 10,000)	ISO 8 (Class 100,000)	Not defined	See ISPE Biopharm Baseline® Guide
		Action level number of viable airborne organisms cfu/m³		1	10	100	Not defined	-

CLEANROOM

CLASSIFICATION

- **ISPE classification**

ISPE		EU GMP
Grade 5	≅	Grade A
Grade 7	≅	Grade B
Grade 8	≅	Grade C
CNC+	≅	Grade D
CNC	≅	not defined

CNC+ : monitored CNC
CNC : Controlled but Not Classified
NC : Not Classified

Table 5.1: Airborne Environmental Requirements

ISPE Classification Grade	FDA, CDER September 2004 Guideline on Sterile Drug Products by Aseptic Processing			European Commission Annex 1, 2008 – Manufacture of Sterile Medicinal Products					
	In Operation[Note 1]		Descriptive	Descriptive/ Grade	At Rest[Note 4]		In Operation		
	Particulate limits per m³ ISO class (part/ft³)	Action Levels			Maximum permitted number of particles per m³ equal to or greater than 0.5 µm and 5.0 µm, respectively		Maximum permitted number of particles per m³ equal to or greater than 0.5 µm and 5.0 µm, respectively		Maximum permitted number of viable micro-organisms (CFU) per m³
	0.5 µm and larger	CFU/m³ (CFU/ 90 mm plate)[Note 7]			0.5 µm	5.0 µm	0.5 µm	5.0 µm	CFU/m³
Grade 5	3,520[Notes 2, 8] ISO 5 (100)	1 (1)[Note 1a]	Critical Areas	Grade A[Note 5]	3,520[Note 6] ISO 5	20 ISO 4.8	3,520 ISO 5	20 ISO 4.8	< 1
Grade 6	35,200[Note 3] ISO 6 (1,000)	7 (3)	Supporting Clean Area						
Grade 7	352,000[Note 3] ISO 7 (10,000)	10 (5)	-	Grade B	3,520 ISO 5	29 ISO 5	352,000 ISO 7	2,900 ISO 7	10
Grade 8	3,520,000[Note 3] ISO 8 (100,000)	100 (50)	Controlled Areas	Grade C	352,000 ISO 7	2,900 ISO 7	3,520,000 ISO 8	29,000 ISO 8	100
Monitored CNC	-	-	-	Grade D	3,520,000 ISO 8	29,000 ISO 8	Not defined	Not defined	200
CNC[Note 9]	-	-	-		-	-	-	-	-
Unclassified	-	-	-		-	-	-	-	-

Notes:
1. US requirements are given only for the dynamic (in-operation) situation. Although no at-rest values are specified, such values should be periodically monitored for trending purposes.
1a. Normally, zero microbial counts are expected in critical zones.
2. When measured not more than one foot from the work site, and upstream of the airflow, during filling/closing operations. Product powder particulates, which, by their nature, do not pose a risk of product contamination, can be ignored. Background operational conditions without product should be qualified so that the true particulate contamination level is understood. Air should be supplied to the point of use by HEPA-filtered Unidirectional Airflow (UAF). Historically, a velocity of 0.45 m/s (90 ft/min), ±20% was considered adequate, although other velocities may create better airflow patterns. Rooms enclosing these areas should have a positive pressure differential, relative to adjacent, less clean areas.
3. Conditions should be measured in the vicinity of exposed articles during periods of activity. The 2004 Aseptic Guideline suggests a minimum of 20 air changes per hour in "classified" areas, and, in general, a pressure differential of 10 to 15 Pa wg (with all doors closed) between air classifications. When doors are opened outwards, airflow or airlocks should minimize ingress of contamination.
4. Particulate conditions given in Table 5.1 for the "at rest" state should be achieved throughout the environment where unmanned, and recovered after a short "clean up" period (usually between 15 to 20 minutes). Note that in the pharmaceutical industry, "at-rest" implies no people or product are present, and the process is not operating.
5. Particulate condition given for grade A "in-operation" should be maintained in the zone immediately surrounding the product, whenever the product or an 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.
6. Such conditions normally are provided by a Unidirectional Airflow (UAF) work station, which operates at a homogeneous air speed of 0.45 m/ sec (90 ft/min) ±20%.
7. 90 mm settling plate for 4 hours. The use of settling plates is optional.
8. Velocity appropriate to maintain UAF patterns at the critical area
9. CNC (Controlled Not Classified as defined in the ISPE Baseline® Guide for Biopharmaceutical Manufacturing Facilities (Reference 12, Appendix 3)) requires HVAC airflow filtration, controlled access by personnel, and cleanability of the area. Although periodic air particle monitoring is not required, CNC should meet EU grade D if manufacturing for both US and EU markets.

Sterile Product Manufacturing Facilities
ISPE Baseline Pharmaceutical Engineering Guide Volume 3
Second Edition / September 2011

CLEANROOM

CLASSIFICATION

- **ISPE classification**

ISPE		EU GMP	ISO at rest	ISO in-operation
Grade 5	≅	Grade A	5	5
Grade 7	≅	Grade B	5	7
Grade 8	≅	Grade C	7	8
CNC+	≅	Grade D	8	not defined

CNC+: monitored CNC
CNC : Controlled but Not Classified
NC : Not Classified

ISPE Classification Grade	FDA, CDER September 2004 Guideline on Sterile Drug Products by Aseptic Processing			European Commission Annex 1, 2008 – Manufacture of Sterile Medicinal Products					
	In Operation(Note 1)		Descriptive	Descriptive/ Grade	At Rest(Note 4)		In Operation		
	Particulate limits per m³ ISO class (part/ft³)	Action Levels			Maximum permitted number of particles per m³ equal to or greater than 0.5 µm and 5.0 µm, respectively		Maximum permitted number of particles per m³ equal to or greater than 0.5 µm and 5.0 µm, respectively		Maximum permitted number of viable micro-organisms (CFU) per m³
	0.5 µm and larger	CFU/m³ (CFU/ 90 mm plate)(Note 7)			0.5 µm	5.0 µm	0.5 µm	5.0 µm	CFU/m³
Grade 5	3,520(Notes 2, 8) ISO 5 (100)	1 (1)(Note 1a)	Critical Areas	Grade A(Note 5)	3,520(Note 6) ISO 5	20 ISO 4.8	3,520 ISO 5	20 ISO 4.8	< 1
Grade 6	35,200(Note 3) ISO 6 (1,000)	7 (3)	Supporting Clean Area						
Grade 7	352,000(Note 3) ISO 7 (10,000)	10 (5)	-	Grade B	3,520 ISO 5	29 ISO 5	352,000 ISO 7	2,900 ISO 7	10
Grade 8	3,520,000(Note 3) ISO 8 (100,000)	100 (50)	Controlled Areas	Grade C	352,000 ISO 7	2,900 ISO 7	3,520,000 ISO 8	29,000 ISO 8	100
Monitored CNC	-	-	-	Grade D	3,520,000 ISO 8	29,000 ISO 8	Not defined	Not defined	200
CNC(Note 9)	-	-	-		-	-	-	-	-
Unclassified	-	-	-		-	-	-	-	-

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CLASSIFICATION

- **ISPE classification**

ISPE		EU GMP	ISO at rest	ISO in-operation
Grade 5	≅	Grade A	5	5
Grade 7	≅	Grade B	5	7
Grade 8	≅	Grade C	7	8
CNC+	≅	Grade D	8	not defined

CNC+: monitored CNC
CNC : Controlled but Not Classified
NC : Not Classified

Table 2.4: Baseline Airborne Environmental Classification for Different Process Steps
(Note: All air classifications refer to the "in operation" condition.)

	Aseptically Processed Products		Terminally Sterilized Products	
Typical Process Step	Background Environment	Product/Container/ Closure Exposure	Background Environment	Product/Container/ Closure Exposure
Raw Material Dispensing	"Grade 8"(Note 1)	Local Protection(Note 2)	"Grade 8"	"Grade 8"
Compounding and (Sterile) Filtration Feed	"Grade 8"(Note 1)	"Grade 7"(Notes 2 and 3)	"Grade 8"	"Grade 8"
(Sterile) Filtration	"Grade 7"	"Grade 5"(Note 7)	"Grade 8"	"Grade 5, 7, or 8"(Note 5)
Initial Prep/Washing Components	"Controlled Not Classified with local monitoring"(Note 6)	"Controlled Not Classified with local monitoring"(Note 6)	"Controlled Not Classified with local monitoring"(Note 6)	"Controlled Not Classified with local monitoring"(Note 6)
Final Rinse of Components	"Grade 8"	"Grade 8"(Note 2)	"Controlled Not Classified with local monitoring"(Note 6)	"Grade 8"(Note 2)
Sterilization/Depyrogenation of Components – Loading	"Grade 8"	"Grade 8"(Note 2)	"Controlled Not Classified with local monitoring"(Note 6)	"Grade 8"(Note 2)
Sterilization/Depyrogenation of Components – Unloading	"Grade 7"	"Grade 5" (or wrapped/sealed)	"Grade 8"	See Note 5
Aseptic Compounding and Formulation of Sterile Materials	"Grade 7"	"Grade 5"(Note 7)	N/A	N/A
Filling and Stoppering (for Open Aseptic Processing)	"Grade 7"	"Grade 5"(Note 7)	"Grade 8"	See Note 5
Filling and Stoppering (for Closed Aseptic Processing)	"Grade 8" (or in EU, may be Monitored CNC)	"Grade 5"(Note 7)	N/A	N/A
Lyophilization – Operation	-	Closed System	N/A	N/A

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CLASSIFICATION

- **ISPE classification**

ISPE		EU GMP	ISO at rest	ISO in-operation
Grade 5	≅	Grade A	5	5
Grade 7	≅	Grade B	5	7
Grade 8	≅	Grade C	7	8
CNC+	≅	Grade D	8	not defined

CNC+: monitored CNC
CNC : Controlled but Not Classified
NC : Not Classified

Table 2.4: Baseline Airborne Environmental Classification for Different Process Steps (continued)
(Note: All air classifications refer to the "in operation" condition.)

	Aseptically Processed Products		Terminally Sterilized Products	
Typical Process Step	Background Environment	Product/Container/ Closure Exposure	Background Environment	Product/Container/ Closure Exposure
Transfer into and out of Lyophilizers (for Open Aseptic Processing)	"Grade 7"	"Grade 5"	N/A	N/A
Transfer into and out of Lyophilizers (for Closed Aseptic Processing)	"Grade 8" (or in EU, may be Monitored CNC)	"Grade 5"	N/A	N/A
Capping and Crimping (of Product Containers)	"Controlled Not Classified with local monitoring"(Notes 4, 6)	Local Protection (Notes 2, 4, and Figure 2.4)	"Controlled Not Classified"	Local Protection (Notes 2, 4 and Figure 2.4)
Terminal Sterilization	N/A	N/A	"Controlled Not Classified"	N/A
Inspection	"Controlled Not Classified"	N/A	"Controlled Not Classified"	N/A
Labeling and Packing	"Controlled Not Classified"	N/A	"Controlled Not Classified"	N/A

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- **Notes on classification recommendations by ISPE (which do not take place in EU GMP):**

- CNC (Controlled Not Classified): controlled area that is cleanable, access controlled, served with filtered ventilation air.

- Procedural controls and personnel garment upgrades may be applied at the owner's discretion.

- CNC+: CNC area which particulate and microbiological monitoring is applied.
CNC+ (monitored CNC) , meets (at rest) ISO-8 (at rest) with occasional testing to determine the particulate and microbiological characterization of the room.

- CNC+ corresponds to GMP Grade D.

- For aseptically produced products, with sterile raw materials, (e.g., powders), where sterile filtration is not carried out (or terminally sterilized), dispensing and compounding are aseptic processes performed in a Grade 5 (Grade A) environment with Grade 7 (Grade B) background.

- In some cases, where there may be a higher risk of microbial growth when the product is in solution (e.g., protein products), more stringent air classification than local Grade 7 (Grade B) is required.

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- Preparation of components and container closure and formulation of products for terminal sterilization should be performed in a CNC+ (Grade D) environment in order to ensure low risk of chemical or biological contamination prior to sterilization step.
[According to EU GMP, this operation should be performed in Grade D (CNC+) area;
if there is exceptional risk, it should be performed in Grade C (Grade 8) area.]

- Filling terminally sterilized products is carried out under Grade 5 (Grade A) local protection within a Grade 7(Grade B) or Grade 8 (Grade C) surrounding environment. However, there are views that Grade 8 (Grade C) should rarely be used for such products, and that Grade 7 (Grade B) would be a more acceptable classification.
[EU GMP allows filling at Grade 8 (Grade C) for terminally sterilized products, provided that the product is not at risk (e.g., supports microbial growth, or must be held for a long time before sterilization, or are processed in open vessels), in which case higher standards are required, like Grade 5 (Grade A) environment with Grade 7 (Grade B) background.]

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- As the equipment and process associated with handling and crimping of the vial caps may generate large quantities of particles, this operation should not be performed in the same area where the vials are open. When aseptic operations. For aseptic processing, it may be considered advantageous to locate the capping/over-sealing outside the aseptic processing zone or room. Aseptic filling should be performed under Grade 5 (Grade A) protection in Grade 7 (Grade B) background environment. If stoppered vials exit the aseptic processing zone or room prior to capping, the product should be protected under Grade 5 (Grade A) until completion of the crimping step. The transfer and capping/sealing station should be protected with Grade 5 (Grade A) air supply, and be located in a surrounding environment of at least CNC+. The conveyor transferring the vials from the aseptic filling station should not breach the boundary of the aseptic filling room.
[EU GMP imposes that, as the equipment used to crimp the vial caps can generate large quantities of non-viable particulates, the equipment should be located at a separate station equipped with adequate air extraction.]

- [EU GMP: Vial capping can be done as an aseptic process using sterilized caps, or as a clean process outside the aseptic core. Where the latter approach is adopted, the vials should be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter the stoppered vials should be protected with Grade A air supply until the caps are crimped.]

- Manipulations, such as assembly of sterilized equipment should be performed under Grade 5 (Grade A) environment conditions.

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- **ISPE classification**

ISPE		EU GMP	ISO at rest	ISO in-operation
Grade 5	≅	Grade A	5	5
Grade 7	≅	Grade B	5	7
Grade 8	≅	Grade C	7	8
CNC+	≅	Grade D	8	not defined

CNC+: monitored CNC
CNC : Controlled but Not Classified
NC : Not Classified

Table 4.1:

ISPE Environmental Grade/Architectural Element	Controlled Not Classified (CNC)	Controlled Not Classified (with Local Monitoring) CNC+	Grade 8	Grade 7 and Grade 5
Nearest Equivalent in US FDA 2004 Aseptic Processing Guidance	Not Defined	Not Defined	ISO 8 (in operation) [Class 100,000]	(Grade 7) ISO 7 (in operation) [Class 10,000] (Grade 5) ISO 5 (in operation) [Class 100]
Nearest Equivalent in EU, PIC/S, and WHO GMPS	Not Defined	Grade D	Grade C	(Grade 7) Grade B (Grade 5) Grade A

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CLASSIFICATION

Question

Cleanroom design criteria are to be considered as guidelines to the designer, rather than absolute rules to be followed and valid under all circumstances. These criteria have received wide acceptance since they have led to many successful designs. The way that these criteria are defined, however, lead to some questions in defining the classification of cleanrooms.

For example, the number of particles “at rest” and “in-operation” conditions are defined for the cleanliness grades (A, B, C, D) in the GMP, but there’s no mention in the GMPs of the technical requirements* in order to attain those conditions. (* except for the requirement that the air speed should be 0.36 - 0.54 m/s for Grade A, there is no other technical requirement specified; as for the ventilating, it is generally referred to ISO-14644 classification.)

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Question

Different ISO classes correspond to "at rest" and "in-operation" states of the Grades defined in the GMP.

	0.5 µm	0.5 µm	0.5 µm	0.5 µm
	at rest		in-operation	
Grade A	3,520	20	3,520	20
	ISO-5		ISO-5	
Grade B	3,520	29	352,000	2,900
	ISO-5		ISO-7	
Grade C	352,000	2,900	3,520,000	29,000
	ISO-7		ISO-8	
Grade D	3,520,000	29,000	not defined	not defined
	ISO-8		not defined, CNC+, ISO-9 ?..	

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Question

- As it is seen in above tables, for instance, when designing or building a Grade B cleanroom, which criteria should be taken into consideration: ISO-7 or ISO-5?..

  [In those tables referred to in this presentation, some indicate ISO-7, while some do ISO-5 for Grade B. There is not a consensus amongst the practitioners.]

  Since implementing both ISO-7 and ISO-5 criteria* in the same room would not be an appropriate engineering practice**, the decision must be made beforehand, and the cleanroom be defined accordingly.

*, ** ➔

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CLASSIFICATION

Question

* While it is sufficient to cover only 15-25% of the ceiling area with HEPA filters, and change the air in the room 60 times per hour, and have an air flow not necessarily unidirectional with airspeed greater than 0.1 m/s in order to maintain ISO-7 cleanroom criteria; a 40-80% of the coverage of ceiling area with HEPA filters, an air change rate of at least 300 per hour, an airspeed of 0.45±%20 m/s and most importantly, a unidirectional airflow are required to maintain the ISO-5 criteria.

** One may claim that, for a Grade B cleanroom, while the `in-operation´ technical requirements for ISO-7 are attained, it may be possible to attain the technical requirements for ISO-5 when the room switches to the `at rest´ state.
Or, conversely, a Grade B cleanroom designed and built as per ISO-5 technical requirements in order to achieve the cleanliness level `at rest´ state can be operated in ISO-7 conditions during `in-operation´ state of Grade B.
- However, this would not be a favorable (or proper) engineering solution. If the air handling unit was designed and built to change the air in the room 300 times in an hour, at 0.45 m/s airspeed, and if 40% of the ceiling area was covered with HEPA filters, then that cost had been paid already. It is not good engineering practice to operate an installation at one third or fourth of its capacity; nor it is cost effective.

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Question

- **Then, the question is:**
  When it comes to a cleanroom in accordance with GMP grading (Grade A, B, C, D), which technical specifications in accordance with which standard should be defined and implemented in the design and construction?
  ... ISO-9, -8, -7, -6, -5, -4 ... which one?..

  [e.g., in the previous example of a Grade B cleanroom, should it be ISO-7 or ISO-5?]

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Towards resolution...

- **For a fair answer to this question, it is necessary to review several documents and reach a resolution that is widely accepted in applications.**

1. FDA Guidance for Industry Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice (September 2004) Table-1. note b.

   ISO 14644-1 designations provide uniform particle concentration values for cleanrooms in multiple industries. ISO-5 particle concentration is equal to Class 100, and approximately equals EU Grade A.

   Here, GMP Grade A (at rest) is approximated to ISO-5.

2. EU GMP Good Manufacturing Practice Medicinal Products for Human and Veterinary Use (November 2008) Annex 1. paragraph 4.

   Clean rooms and clean air devices should be classified in accordance with EN ISO 14644-1.

   paragraph 5.

   For Grade A the airborne particle classification is ISO-4.8 dictated by the limit for particles ≥5.0 µm.
   For Grade B (at rest) the airborne particle classification is ISO-5 for both considered particle sizes.
   For Grade C (at rest & in operation) the airborne particle classification is ISO-7 and ISO-8 respectively.
   For Grade D (at rest) the airborne particle classification is ISO-8.

   Here, ISO-14644 standard is referred to for the technical specifications, and GMP Grade A is equated to ISO-4.8 for particles ≥ 5 µm, and distinction is made between "at rest" state and "in-operation" state.

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CLASSIFICATION

Towards resolution...

3. **The FDA Guide (2004), defining the support areas, states that:**
   ***such areas immediately adjacent to the aseptic processing line should meet at least Class 10,000 (ISO-7) standard under dynamic conditions*.**

   The definition of GMP Grade B resembles the support area mentioned here, as:
   ***the background environment for Grade A zone (which is the aseptic processing zone)*.**
   Hence, Grade B matches with ISO-7 (Class 10,000).

4. ISO-14644-4 Table B.1 - Cleanroom examples for aseptic processing of healthcare products
   ISO-5 (>5 µm) aseptic processing
   ISO-7 (>5 µm) other processing zones directly supporting aseptic processing
   ISO-8 (>5 µm) support zones for aseptic processing, including controlled preparation zones

   Here again, the definitions of ISO-7 and GMP Grade B resemble each other.

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Towards resolution...

5. ISO-14644-4 Table B.1 – Cleanroom examples for aseptic processing of healthcare products
note a: **the occupancy states associated with the ISO Class should be defined and agreed in advance of establishing the optimum design conditions.**

The key point is that it has to be "agreed" upon the ISO Class.

6. **International Society for Pharmaceutical Engineering - ISPE has attempted to find a solution to this problem, hence, created a new ISPE grading compatible with the ISO classification: Grade -5, -7, -8, CNC+ and CNC.**

CNC+ : monitored CNC
CNC : Controlled but Not Classified

In this grading system; **GMP Grade A ≅ ISPE Grade 5 ≅ (in-operation) ISO-5**
(since the number of particles ≥ 5µm is 20, not 29, it is classified as ISO-4.8)
GMP Grade B ≅ ISPE Grade 7 ≅ (in-operation) ISO-7
GMP Grade C ≅ ISPE Grade 8 ≅ (in-operation) ISO-8
GMP Grade D ≅ ISPE CNC+ ≅ not defined

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Towards resolution...

- When designing and building a cleanroom, it is not adequate to define it in accordance with the GMP grading scheme (e.g., Grade B or Grade C, etc.).
- Agreement must be established between the owner of the job and the contractor (designer, constructor) about the technical criteria (defined by the standards) which the cleanroom should maintain.

  For example, it's not good enough to quote a Grade B or ISPE Grade 7 cleanroom... or quote the number of particles as 3,520 at rest and 352,000 in-operation; or class ISO-5 `at rest´ and ISO-7 `in-operation´.
- Since it is not a favorable or proper or -in many cases- possible engineering practice to maintain the technical requirements to achieve both ISO-5 and ISO-7 (or likewise both ISO-7 and ISO-8) criteria in the same room, the decision must be be made beforehand, and the cleanroom must be defined accordingly.

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Towards resolution...

- **For the `at rest´ state**

	0,5 µm /m^3	5 µm/m^3	
	EU GMP	EU GMP	ISO
- for Grade A (at rest) -> ISO-5	3,520	20	29
- for Grade B (at rest) -> ISO-5	3,520	20	29
- for Grade C (at rest) -> ISO-7	352,000	2,900	2,930
- for Grade D (at rest) -> ISO-8	3,520,000	29,000	29,300

criteria would be considered.

Then:

	GMP	ISPE	ISO
Open aseptic filling area	**Grade A**	**≅ Grade 5 ≅**	**ISO-5**
Background for aseptic filling	**Grade B**	**≅ Grade 5 ≅**	**ISO-5**
Background for terminally sterilized filling	**Grade C**	**≅ Grade 7 ≅**	**ISO-7**
Monitored, controlled but not classified area	**Grade D**	**≅ Grade 8 ≅**	**ISO-8**

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Towards resolution...

- For the `in-operation´ state

	0,5 µm /m³	5 µm/m³	
	EU GMP	EU GMP	ISO
- for Grade A (in-operation) -> ISO-5	3,520	20	29
- for Grade B (in-operation) -> ISO-7	352,000	2,900	2,930
- for Grade C (in-operation) -> ISO-8	3,520,000	29,000	29,300

criteria are considered.

-for Grade D (in-operation) -> criteria are not defined.

Then:

GMP		ISPE		ISO
Open aseptic filling area	Grade A	≅ Grade 5	≅	ISO-5
Background for aseptic filling	Grade B	≅ Grade 7	≅	ISO-7
Background for terminally sterilized filling	Grade C	≅ Grade 8	≅	ISO-8
Monitored, controlled but not classified area	Grade D	≅ CNC+	≅	not defined

CNC+: monitored CNC

CNC : Controlled but Not Classified

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Examples

Typical pharmaceutical application	ISPE	ISO	FED-209	GMP
Open area, office, cafeteria, etc.	general area			
Laboratory, corridor, general packaging, warehousing	CNC			
Packaging and storage where non-sterile products and material may be present	CNC+			**Grade D** in-operation
Background for material preparation for aseptic processing	Grade 8	ISO-8	Class 100,000	**Grade C** in-operation
Background for terminally sterilized open filling	Grade 7	ISO-7	Class 10,000	**Grade B** in-operation
Open aseptic processing area	Grade 5	ISO-5	Class 100	**Grade A**

* Grade 5, 7, 8 , CNC+ are ISPE Grades per ISPE grading system

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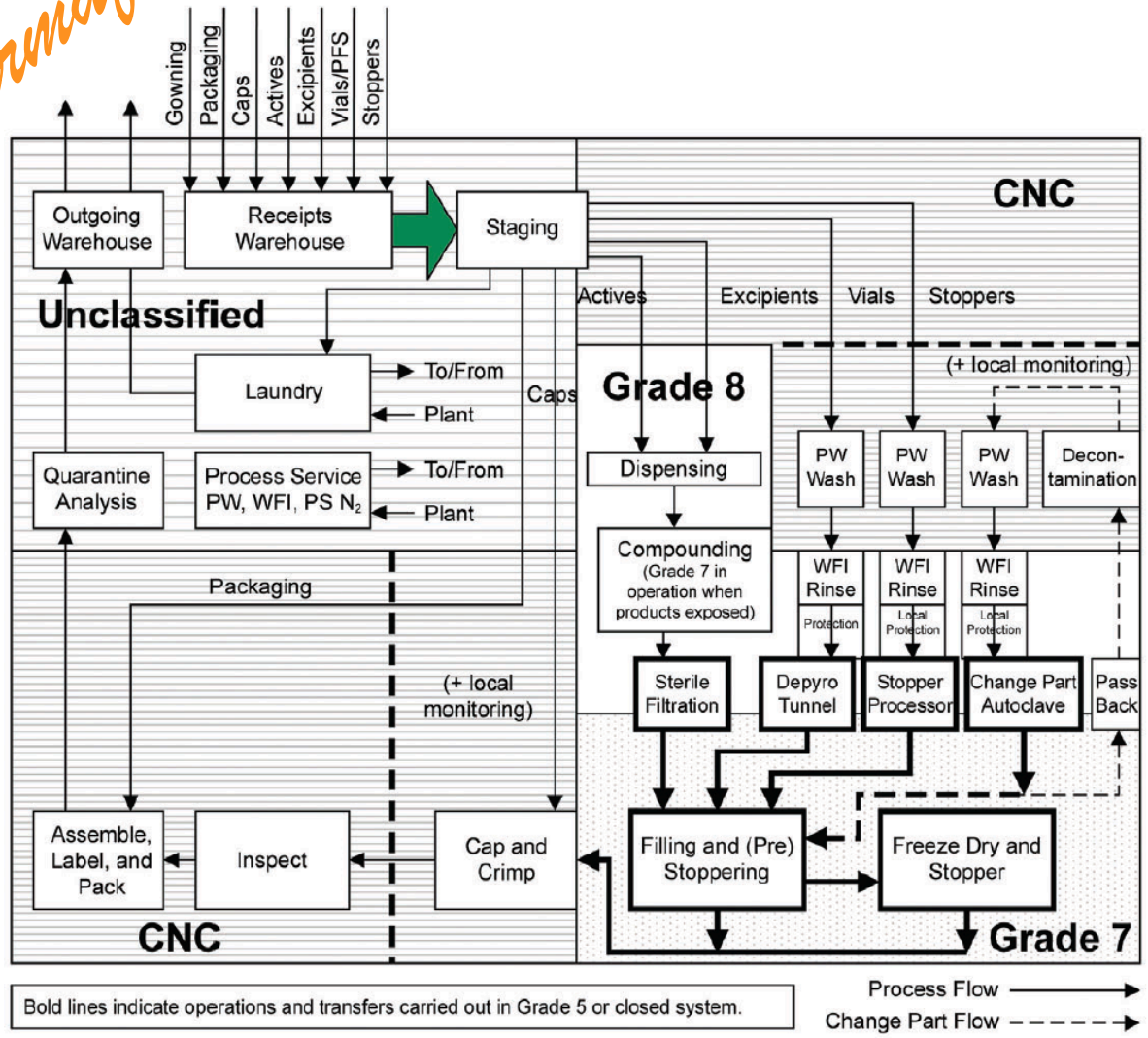

CLASSIFICATION

Examples

- Background for aseptic filling, which is supposed to be GMP Grade B, is shown as ISPE Grade 7 (i.e., ISO-7).
- Washing and depyrogenation stations for aseptic filling, which are supposed to be GMP Grade C, are shown as ISPE Grade 8 (i.e., ISO-8).

* Grade 5, 7, 8 , CNC+ are ISPE Grades per ISPE grading system

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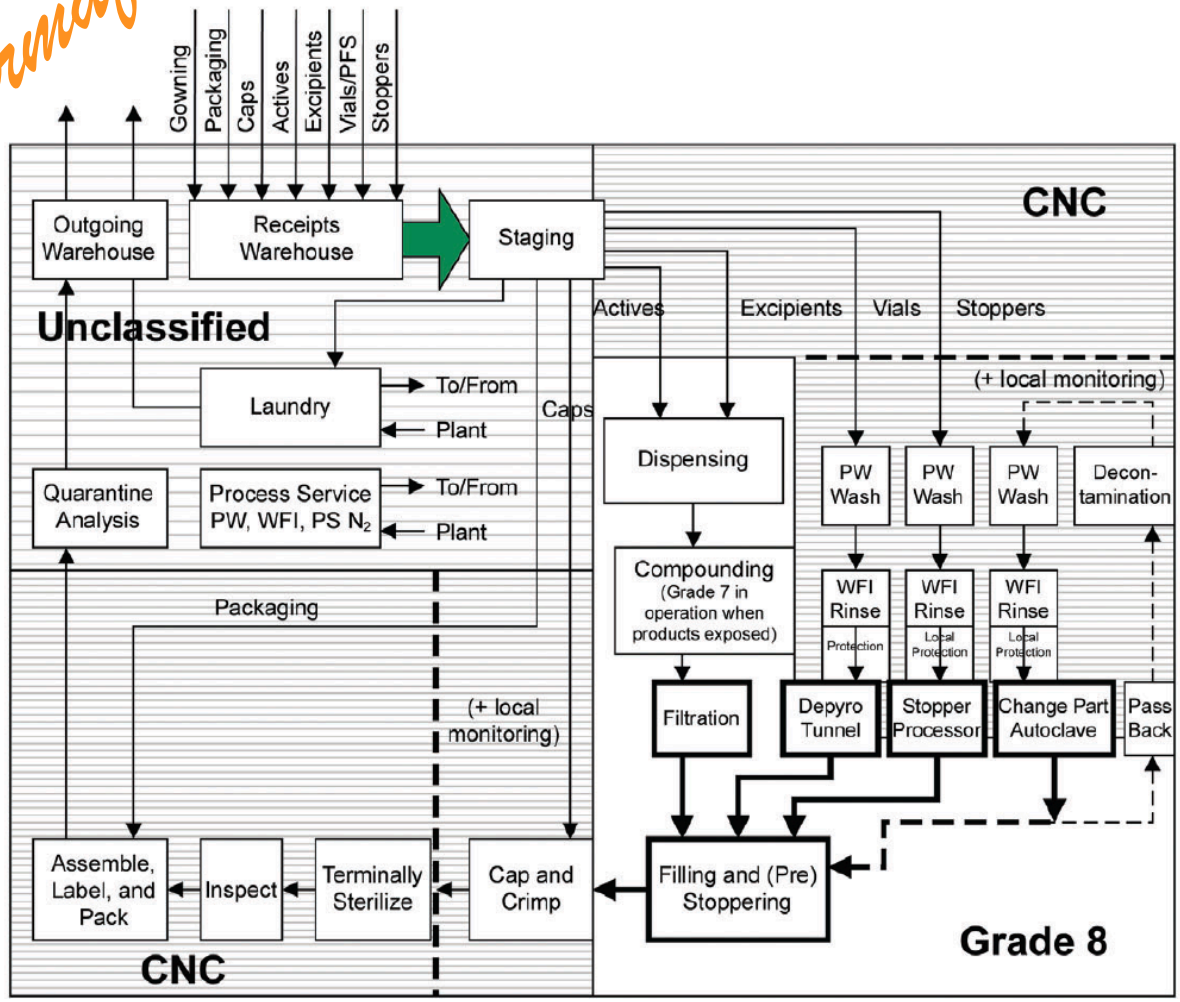

CLASSIFICATION

Examples

- Background for terminally sterilized filling, which is supposed to be GMP Grade C, is shown as ISPE Grade 8 (i.e., ISO-8).
- Washing and depyrogenation stations terminally sterilized filling are shown as ISPE CNC+, which is Grade D.

* Grade 5, 7, 8 , CNC+ are ISPE Grades per ISPE grading system

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Argument

- As may be seen in most applications, for example, ISO-5 technical requirements are not maintained for the background for aseptic filling, or ISO 7 requirements for the background for terminally sterilized filling.
- Thus, considering not the `at rest´ but the `in-operation´ state is established as the practical and widespread application.

Then:

	GMP		ISPE		ISO
Open aseptic filling area	Grade A	≅	Grade 5	≅	ISO-5
Background for aseptic filling	Grade B	≅	Grade 7	≅	ISO-7
Background for terminally sterilized filling	Grade C	≅	Grade 8	≅	ISO-8
Monitored, controlled but not classified area	Grade D	≅	CNC+	≅	not defined

CNC+: monitored CNC
CNC : Controlled but Not Classified

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Counter argument

- **On the other hand, PIC/S GUIDE TO GOOD PRACTICES FOR MEDICINAL PRODUCTS Annex 1, dated 2017, and the GMP Guides issued in 2017 by TR Ministry of Health, or TR Ministry of Food, Agriculture and Livestock state that the clean areas for manufacturing of sterile products should be designed to reach certain specified air cleanliness level in the `at rest´ state, in order to meet the `in-operation´ conditions.**

Then:

	GMP		ISPE		ISO
Open aseptic filling area	Grade A	≅	Grade 5	≅	ISO-5
Background for aseptic filling	Grade B	≅	Grade 5	≅	ISO-5
Background for terminally sterilized filling	Grade C	≅	Grade 7	≅	ISO-7
Monitored, controlled but not classified area	Grade D	≅	Grade 8	≅	ISO-8

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Back to square one...

- **Which one is to be recognized?**
  - **`A´ required by EU GMP?..**

	GMP		ISPE		ISO
Open aseptic filling area	Grade A	≅	Grade 5	≅	ISO-5
Background for aseptic filling	Grade B	≅	Grade 5	≅	ISO-5
Background for terminally sterilized filling	Grade C	≅	Grade 7	≅	ISO-7
Monitored, controlled but not classified area	Grade D	≅	Grade 8	≅	ISO-8

  - **`B´ common practice?..**

	GMP		ISPE		ISO
Open aseptic filling area	Grade A	≅	Grade 5	≅	ISO-5
Background for aseptic filling	Grade B	≅	Grade 7	≅	ISO-7
Background for terminally sterilized filling	Grade C	≅	Grade 8	≅	ISO-8
Monitored, controlled but not classified area	Grade D	≅	CNC+	≅	not defined

CNC+: monitored CNC
CNC : Controlled but Not Classified

This is an open question, still...
If `A´ was to be followed, then many of the cleanrooms designed and built to `B´ would be discarded.

CLEANROOM

DESIGN

- Architectural, HVAC, materials, construction and operational disciplines, standards and requirements are all together considered in the design of cleanrooms.
- Cleanroom design -like all other engineering works- is an engineering effort, which requires consideration of energy efficient and cost effective operation, in addition to those binding, stringent requirements of cleanliness, temperature, humidity and air flow control, high operational reliability, ease in maintenance, and safety/security.
- Those technical criteria for cleanroom design and construction are to be taken as guides to the designer, rather than a set of absolute rules to be followed in every situation. They receive common acceptance by the industry, because they have provided guidance for many successful implementations.

CLEANROOM

DESIGN

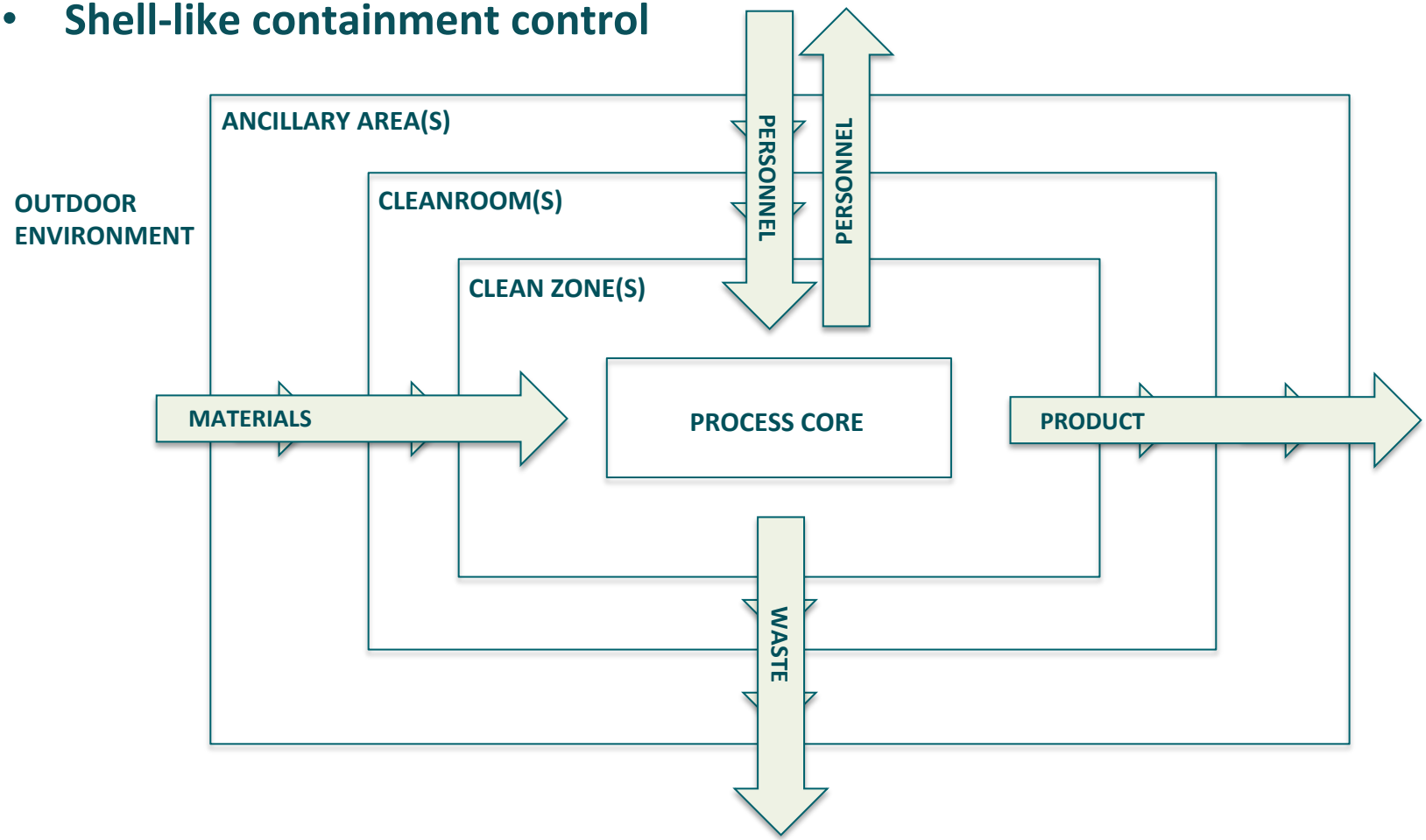
- **Air handling (for clean air supply and climatization - HVAC), as well as selection of the materials (for wall and ceiling panels and floor) constitute the most important elements of cleanroom design.**

- **Elements, such as the process in the cleanroom, and the operational conditions, architectural lay-out, automation, safety/security and fire protection and extinguishing system, distribution lines (for product, solutions, water, air, gas, etc.), type and placement of the equipment inside, convenience in installation and maintenance, all play significant role in the design of a cleanroom...**
  and the budget and schedule, for sure...

CLEANROOM

PREMISES

- **Shell-like containment control**



CLEANROOM

PREMISES

Basic rules

- **The determiners of the criteria per the current GMP(*), which must be followed in cleanroom lay-out and passages:**

  (*) -- *1 October 2017 Version 2017/01* ***Republic of Turkey, Ministry of Health, Turkish Medicines and Medical Devices Agency***
  GOOD MANUFACTURING PRACTICES (GMP) GUIDE FOR MANUFACTURING PLANTS OF HUMAN MEDICINAL PRODUCTS *(Compatible with PIC/S GMP Guide version: PE 009-13)*

  -- *2 Mart 2017 Rev. 02* ***Türkiye Cumhuriyeti Gıda, Tarım ve Hayvancılık Bakanlığı***
  VETERİNER TIBBİ ÜRÜNLER İÇİN İYİ ÜRETİM UYGULAMALARI (GMP)

  -- *1 January 2017 PE 009-13 (Part I)* ***PIC/S GUIDE TO GOOD PRACTICES FOR MEDICINAL PRODUCTS***

- **In addition:**

  -- *2015 ISO-14644* ***Cleanrooms and Associated Controlled Environments***

  -- *2011 WHO TRS 961* ***Expert Committee on Specifications for Pharmaceutical Preparations***

  -- *September 2004 FDA Guidance for Industry* ***Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice***

- **In case of conflict, the criteria as per the current GMP(*) is applicable.**

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CLEANROOM

PREMISES

Basic rules

- Classified cleanrooms should be on one level, as possible.
- Buildings and facilities should have adequate space for orderly placement of equipment and materials, and the flow of personnel and materials should be designed to prevent mix-ups and contamination.
- Transfer of personnel, materials, equipment, components or products between cleanrooms should be by means of airlocks and pass-thru transfer hatches (transfer boxes, pass boxes) with interlock mechanism.
  Dynamic transfer boxes with clean air flushing should be used for the passages between the cleanrooms of different grades; while static pass boxes can be used for the passages between the same grades.
- Components, containers, equipment and any other article required in a clean area where aseptic processing takes place should be sterilized and passed into the area through double-ended sterilizers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination.

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CLEANROOM

PREMISES

Basic rules

- Conveyor belts should not pass through a partition between Grade A or B area and an area of lower grade, unless the belt itself is continuously sterilized.
- Sinks or drains should be prohibited in Grade A or B areas used for aseptic processing.
  In other areas, air breaks should be fitted between the machine or sink and the drainage system. Floor drains should be fitted with traps or water seals to prevent backflow.

CLEANROOM

PREMISES

Basic rules

- Each cleanroom should be dimensioned to the size necessary to do the job (maybe a little larger); unnecessary oversizing should be avoided.

  Ventilating and conditioning unnecessarily large volumes will increase the cost, because ventilation and air conditioning comprise the highest cost item in cleanroom operations.
  Moreover, it gets difficult to maintain the requested airflow pattern in large volumes (which is an issue for ISO-5 and cleaner class cleanrooms).
- A filtered air supply should maintain a positive (or negative) pressure and airflow relative to surrounding areas of different grade, and flush the area effectively.
- Adjacent cleanrooms of different grades should have a pressure differential of 10-15 Pascal. (guidance values)

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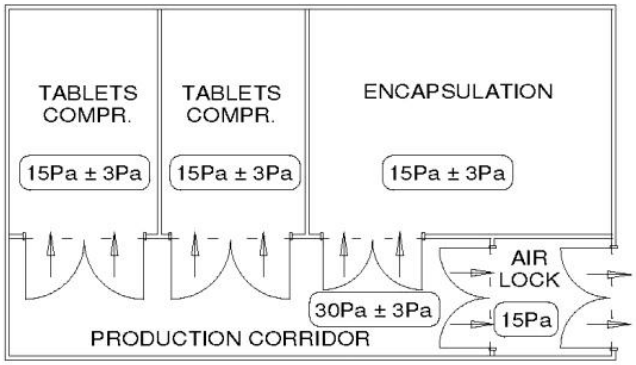
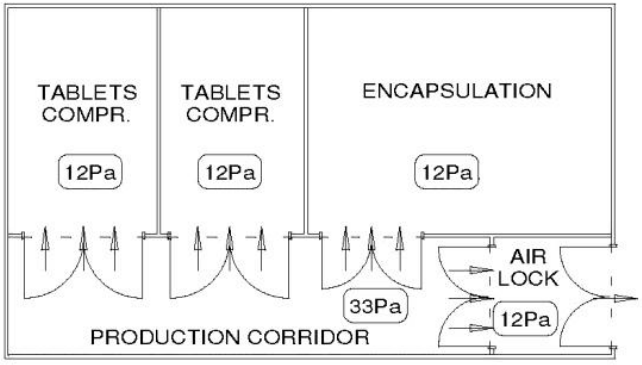
CLEANROOM

PREMISES

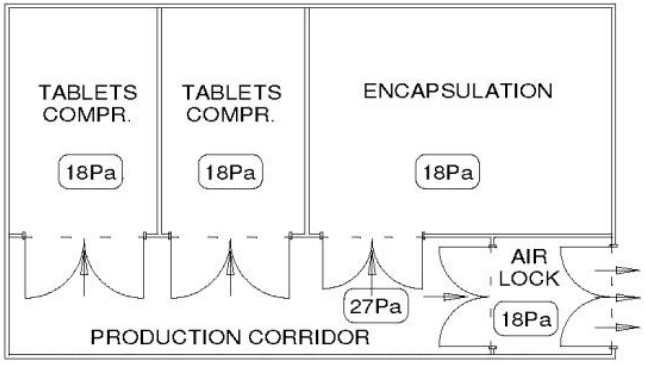
Pressure differential



DESIGN CONDITION



MAXIMUM DIFFERENTIAL



MINIMUM DIFFERENTIAL

* lower pressure in the cleaner processing areas for tablet manufacturing

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CLEANROOM

PREMISES

Basic rules

- 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.
- There should be changing (gowning) rooms and airlocks for personnel and material transfer between the classified cleanrooms.
- An airlock is designed for and used by either people or materials and equipment.
- More than one doors of the airlock should not be opened simultaneously. An interlocking mechanism, or a visual and/or audible warning system should be employed to prevent opening of more than one door at a time.
- The door between two areas (e.g., airlock and cleanroom) which have a pressure differential should open towards the higher pressure. However, if there is a mechanism which ensures closing of the door tightly, then it may open towards the lower pressure.

CLEANROOM

PREMISES

Basic rules

- Hand washing facilities should be provided only in the first stage of the changing room.
- Separate changing rooms for entering and leaving the clean areas may sometimes be desirable.
- Changing rooms should be designed as airlocks, and used to provide physical separation of the different stages of changing.
- These areas (changing rooms, airlocks) should be flushed effectively with filtered air.
- The final stage of the changing room should, in at-rest state, be the same grade as the area into which it leads.

  - For example, an airlock opening into a Grade B cleanroom, which is the background for aseptic processing, should conform to ISO-5 standards.

  - Likewise, an airlock opening into a Grade C cleanroom should conform to ISO-7.

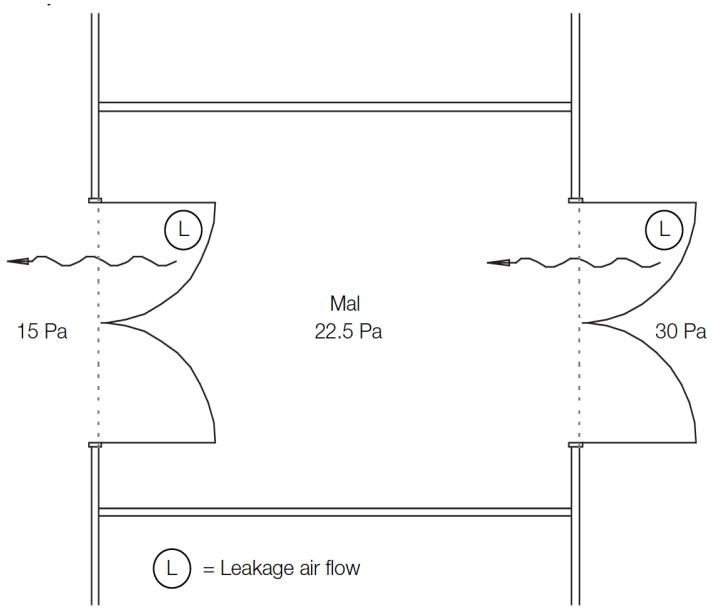
CLEANROOM

PREMISES

Airlock

- **Airlocks may be of three different types:**

(cascade) higher pressure on one side, lower pressure on the other.



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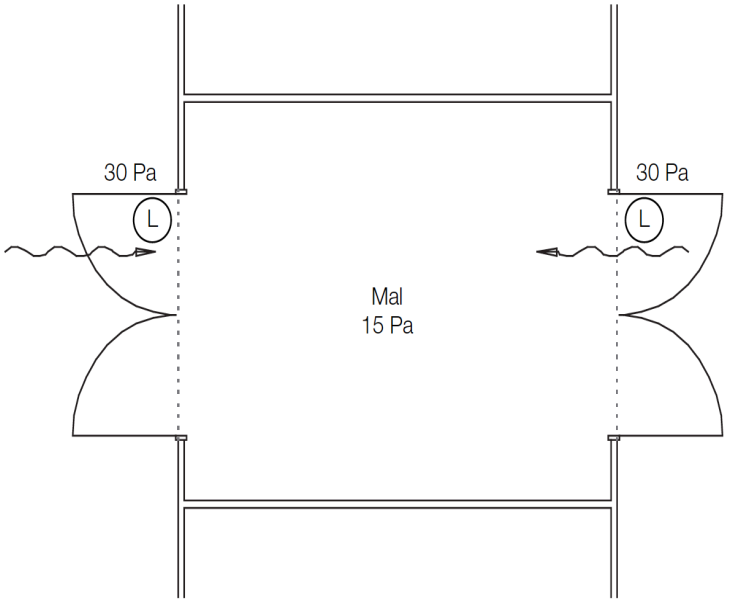
CLEANROOM

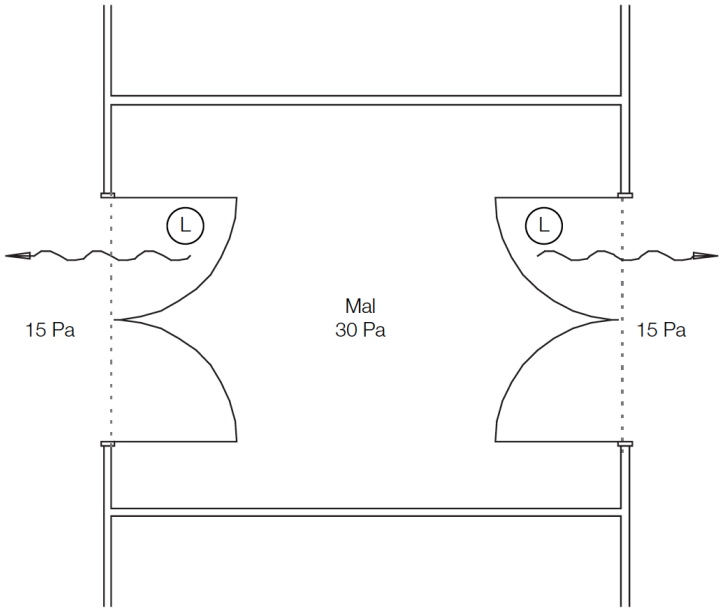
PREMISES

Airlock

(sink) lower pressure in the airlock, and higher pressures on both sides.



(bubble) higher pressure in the airlock and, lower pressures on both sides.



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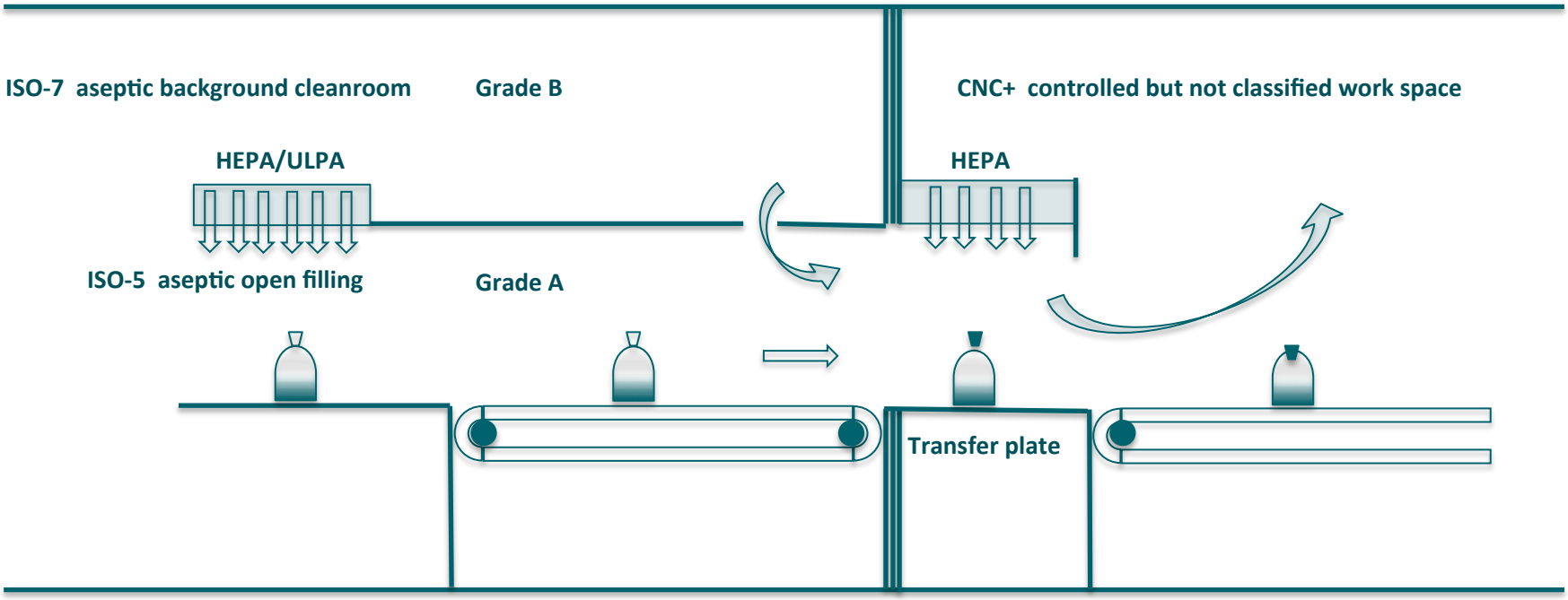
CLEANROOM

PREMISES

Conveyor passage

- Conveyor belt should not pass through a partition between Grade A or B area and an area of lower grade, unless the belt itself is continuously sterilized.



CLEANROOM

MATERIALS

- A cleanroom -by definition- is supposed to not generate or adsorb contaminants, and maintain clean air distribution.
- In order for not generating and adsorbing contaminants, selection of materials for the wall and ceiling panels, doors and windows and the floor is important. The coatings for the doors, windows, walls, ceiling and floor are:

  - anodized or oven-dried painted or coated aluminum
  - galvanized or oven-dried painted or coated steel
  - passivated stainless steel
  - coated gypsum-board
  - composite (FRP, GRP) panel
  - tempered glass
  - epoxy, acrylic or vinyl coating

CLEANROOM

MATERIALS

- Surface of the doors, windows, ceiling and wall panels must be of easily cleanable material which does not generate and adsorb contaminants.
- Floor must be of easily cleanable material which does not generate and adsorb contaminants.
- Joints of the panels and the joining elements must not generate and retain contamination.
- Door handles, hinges, ventilating and lighting fixture and alike must not generate and retain contamination.
- Wall and ceiling panels, floor, doors, windows and other hardware must not be affected by the cleaning method and chemicals.
- The coating material must not wear or tear because of mechanical and chemical impacts, hence generate and retain contamination during normal usage of the cleanroom.

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CLEANROOM

MATERIALS

- The structure and/or isolation under the coating must maintain its strength and durability, and not generate and retain contaminants throughout the lifecycle of the cleanroom.
  Those panels with isolation material made of rock wool, glass wool, plastic foam, wood shavings, gypsum, etc. tend to become a source of contamination in time.
- The ceiling and floor covings of the wall panels must be concave and one-piece as possible.
- The floor must be strong enough to not get damaged by the weight and movement of the personnel and machinery.

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CLEANROOM

MATERIALS

- The fixtures for ventilating, lighting, electric power distribution, fire detection and suppression must be of the types which, to the extent possible, do not retain contamination.
- Structural integrity and durability of the panels and the doors are important.
- It is required that the panels, doors and other hardware be flame and fire retardant and/or resistant.
- It is preferred the the panels, doors and other apertures, as well as the ventilation grill or fixture attachments are modifiable or reparable on site.
- It is preferred that the panels, doors and other hardware do not generate electrostatic charge or dissipate it quickly.

CLEANROOM

MATERIALS

- **Paint**
  - ✓ available in various colors
  - ✓ may be fire retardant
  - ✗ requires supporting panel
  - ✗ not resistant against many cleaning agents
  - ✗ not resistant against impacts
  - ✗ not resistant against scratches
  - ✗ may be contaminated when impacted or scratched

- **Epoxy coating**
  - ✓ available in various colors
  - ✓ may be fire retardant
  - ✓ resistant against many cleaning agents
  - ✗ requires supporting panel
  - ✗ not resistant against impacts
  - ✗ not resistant against scratches
  - ✗ may be contaminated when impacted or scratched

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CLEANROOM

MATERIALS

- **Vinyl laminate coating**
  - ✓ available in various colors
  - ✓ may be fire retardant
  - ✓ resistant against many cleaning agents
  - ✓ resistant against scratches
  - ✗ requires supporting panel
  - ✗ not resistant against impacts
  - ✗ in case of deep scratches or tears, the supporting panel is exposed, which may contaminate
  - ✗ difficult to disassemble since the joints are fixed chemically

- **Phenolic laminate coating**
  - ✓ available in various colors
  - ✓ may be fire retardant
  - ✓ resistant against many cleaning agents
  - ✓ several mm thick, self supporting panels (or may require support)
  - ✓ resistant against scratches
  - ✗ not resistant against impacts
  - ✗ … … …

CLEANROOM

MATERIALS

- **Galvanized steel**
  - ✓ fire retardant
  - ✓ not accumulating static charge
  - ✓ resistant against many cleaning agents
  - ✓ several mm thick, self supporting panels (or may require support)
  - ✗ one color (grey)
  - ✗ if scratched, metal is exposed, which may be contaminated (rust)

- **Stainless steel (AISI 304 or AISI 316)**
  - ✓ resistant against many cleaning agents
  - ✓ if scratched, renews itself, hence contaminated material is not exposed
  - ✓ fire retardant
  - ✓ not accumulating static charge
  - ✓ several mm thick, self supporting panels (or may require support)
  - ✗ one color (grey)
  - ✗ high cost
  - ✗ hard to work with
  - ✗ joints may be troublesome
  - ✗ not resistant against impacts

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CLEANROOM

MATERIALS

- **Polystyrene (Styropor, Styrofoam) Polyurethane isolation**
  - ✓ cheap
  - ✓ easy to work with
  - ✗ not fire retardant
  - ✗ prone to contamination in humid environments
- **Rockwool, Glasswool isolation**
  - ✓ good sound and heat isolation
  - ✓ flame and fire retardant
  - ✗ prone to contamination in humid environments
- **Aluminum honeycomb**
  - ✓ good sound and heat isolation
  - ✓ flame and fire retardant
  - ✓ light and sturdy

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CLEANROOM

MATERIALS

- **FRP (Fiber Reinforced Plastic) or GRP (Glass Reinforced Plastic)**

  Fiberglass Reinforced Polymer, Glass Reinforced Polymer, Glass Reinforced Polyester

  ✓ resistant against many cleaning agents

  ✓ resistant against scratches

  ✓ resistant against impacts

  ✓ self supporting panel (support structure not required)

  ✓ suitable for walkable ceiling

  ✓ isolation not required

  ✓ easy to work with

  ✓ available in various colors

  ✓ flame and fire retardant

  ✓ dissipates electrostatic charge

  ✓ easy to repair or modify

  ✗ high investment cost

  ✓ low total cost of ownership (low TOC), good return on investment (good ROI)

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CLEANROOM

MATERIALS

Usually, the GRP (Glass Reinforced Polyester) composite panels, which are part of FRP (Fiber Reinforced Plastic) group of materials are preferred in construction of the cleanrooms because of their advantages, such as:

- chemical and mechanical durability (resistant to water [H_2O] and hydrogen peroxide [H_2O_2]);
- panels in large dimensions, eliminating many joints;
- air ducts and fixture openings can be pre-cast;
- structural integrity and strength;
- not requiring isolation;
- reparable and modifiable in place;
- reusable for many years;
- modularity;
- flame and fire resistance;
- dissipating electrostatic charge.

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CLEANROOM

MATERIALS

			Floor
ISPE Grade 5 ISPE Grade 7	ISO 5 Class 100 ISO 7 Class 10,000 (in-operation)	**GMP Grade A** **GMP Grade B**	Should be solid, nonporous, cleanable and sanitizable. Should not have joints causing microbial growth. Coved wall base integral with the floor. Floor drains or sinks are not permitted. Acrylic, epoxy , coating resistant to chemicals, welded seam vinyl, terrazo.
ISPE Grade 8	ISO 8 Class 100,000	**GMP Grade C**	Should be smooth and cleanable. Drains should be capped. Acrylic, epoxy, coating resistant to chemicals, welded seam vinyl, vinyl tile, terrazo, sealed concrete.
CNC+	not defined	**GMP Grade D**	Standard construction practices are generally acceptable. Surfaces should be easily cleanable. Epoxy, coating resistant to chemicals, welded seam vinyl, vinyl tile, terrazzo, sealed concrete.
CNC	not defined	**not defined**	Standard construction practices are generally acceptable. Terrazzo, sealed concrete or coatings resistant to dust generation.

* Grade 5, 7, 8 , CNC+ are ISPE Grades per ISPE grading system

CLEANROOM

MATERIALS

			Interior walls
ISPE Grade 5 ISPE Grade 7	ISO 5 Class 100 ISO 7 Class 10,000 (in-operation)	**GMP Grade A** **GMP Grade B**	Crevice free, smooth, nonporous, robust wall construction. Must not have joints or seams where microbial growth may occur. Joints to the ceiling and the floor must be coved, and rounded corners are used to enhance cleanability. Aseptic processing are subject to rigorous cleaning and bio-decontamination. Surfaces must be resistant to corrosion and degradation from such agents. Gypsum board finished with chemically resistant paint or coating, welded seam vinyl, sprayed on wall finishes, panels with vinyl surface finish, glass reinforced composite panel.
ISPE Grade 8	ISO 8 Class 100,000	**GMP Grade C**	Crevice free, smooth, nonporous, robust wall construction. Wall surface must be covered with material meeting the durability and cleanability requirements. Substrate materials include concrete blocks, gypsum board or metal panels.
CNC+	not defined	**GMP Grade D**	Standard construction practices are generally acceptable. Wall surface must be covered with material meeting the durability and cleanability requirements. Concrete, gypsum board, metal, glazed tiles.
CNC	not defined	**not defined**	Standard construction practices are generally acceptable. Not required to separate operations by walls. If proper identification procedures are in place , portable partitions or chains may be used to serparate the stored materials.

* Grade 5, 7, 8 , CNC+ are ISPE Grades per ISPE grading system

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CLEANROOM

MATERIALS

			Ceiling
ISPE Grade 5 ISPE Grade 7	ISO 5 Class 100 ISO 7 Class 10,000 (in-operation)	**GMP Grade A** **GMP Grade B**	Crevice free, smooth, nonporous, robust wall construction. Must not have joints or seams where microbial growth may occur. Joints to the walls must be coved, and rounded corners are used to enhance cleanability. Aseptic processing are subject to rigorous cleaning and bio-decontamination. Surfaces must be resistant to corrosion and degradation from such agents. Grade 5 (Grade A) aseptic processing areas usually require unidirectional airflow. In order to achieve this, the ceiling is formed into a grid, holding an array of necessary number of HEPA filters. (Air passes through the filters at a defined speed to ensure the required unidirectional airflow.) Fixtures should be flush mounted, or not have horizontal surfaces below the ceiling. Maintenance access from outside the room should be considered. Where possible, sprinkler heads should be recessed and fusibly capped for cleanliness, but not caulked. Gypsum board finished with chemically resistant paint or coating, welded seam vinyl, sprayed on wall finishes, panels with vinyl surface finish, glass reinforced composite panel.
ISPE Grade 8	ISO 8 Class 100,000	**GMP Grade C**	Should provide protection from contaminants from not-controlled areas above the ceiling. Caulked in place , clipped and sealed in place suspended ceiling (Mylar, FRP/GRP, metal or similar, nonporous, easily cleanable.)
CNC+	not defined	**GMP Grade D**	Ceilings are generally required in these areas. suspended ceiling (Mylar, FRP/GRP, metal or similar, nonporous, easily cleanable.)
CNC	not defined	**not defined**	Ceilings are generally not required in these areas if material or product is not exposed.

* Grade 5, 7, 8 , CNC+ are ISPE Grades per ISPE grading system

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CLEANROOM

MATERIALS

			Joint details (ceiling-wall wall-wall wall-floor)
ISPE Grade 5 ISPE Grade 7	ISO 5 Class 100 ISO 7 Class 10,000 (in-operation)	**GMP Grade A** **GMP Grade B**	Caulked, coved or splayed integral floor bases are required. In addition, wall to wall, and wall to ceiling covings should be provided.
ISPE Grade 8	ISO 8 Class 100,000	**GMP Grade C**	Coved or splayed integral floor bases are not required, but are commonly used to ease cleaning and to protect wall bases, particularly when walls are made of materials like gypsum board. Rounded or splayed wall-wall or wall-ceiling joining details are not required, but are commonly used to ease cleaning.
CNC+	not defined	**GMP Grade D**	Coved or splayed integral floor bases are not required, but are suggested to protect wall bases particularly when walls are made of materials like gypsum board. Rounded or splayed wall-wall or wall-joining details are not required.
CNC	not defined	**not defined**	Standard construction details are generally appropriate.

* Grade 5, 7, 8 , CNC+ are ISPE Grades per ISPE grading system

CLEANROOM

MATERIALS

			Doors, windows
ISPE Grade 5 ISPE Grade 7	ISO 5 Class 100 ISO 7 Class 10,000 (in-operation)	**GMP Grade A** **GMP Grade B**	Doors and frames: stainless steel metal*, vinyl, PVC, FRP/GRP in frequently washed, corrosive areas; Windows: normal or tempered glass, Plexiglas, Lexan or similar. *Stainless steel may be used for the doors, but not mandatory. All surfaces should be reachable for cleaning. Door hardware (handles, hinges, etc.) should be recessed and concealed where possible, but accessible for cleaning; and made of stainless steel or plated metal.
ISPE Grade 8	ISO 8 Class 100,000	**GMP Grade C**	Doors and frames: painted metal, vinyl, PVC, FRP/GRP in frequently washed, corrosive areas; Windows: normal or tempered glass, Plexiglas, Lexan or similar. Horizontal surfaces should be reachable for cleaning. Flush glazing is not required, but should be considered for easy cleaning. Drop sills on doors are not required if the HVAC can accommodate air leakage. Door hardware (handles, hinges, etc.) should be designed for easily cleanable; and made of stainless steel or plated metal.
CNC+	not defined	**GMP Grade D**	Should meet general building code requirements. Door and window hardware should comply with general building codes; and are recommended to be suitable for industrial use.
CNC	not defined	**not defined**	Should meet general building code requirements. Door and window hardware should comply with general building codes; and are recommended to be suitable for industrial use.

* Grade 5, 7, 8 , CNC+ are ISPE Grades per ISPE grading system

CLEANROOM

MATERIALS

			Lighting fixtures
ISPE Grade 5 ISPE Grade 7	ISO 5 Class 100 ISO 7 Class 10,000 (in-operation)	**GMP Grade A** **GMP Grade B**	Fixtures should be sealed to prevent contamination. Consideration should be given to providing maintenance access from outside the cleanroom. Should be positioned to avoid disturbance of the unidirectional airflow required in Grade 5 (Grade A) zones.
ISPE Grade 8	ISO 8 Class 100,000	**GMP Grade C**	Fixtures can be flush mounted or surface mounted tight to the ceiling to avoid any horizontal surfaces below the ceiling.
CNC+	not defined	**GMP Grade D**	Fixtures can be flush mounted or surface mounted tight to the ceiling to avoid any horizontal surfaces below the ceiling.
CNC	not defined	**not defined**	Industrial type fixtures can be mounted, suspended from the ceiling structure.

* Grade 5, 7, 8 , CNC+ are ISPE Grades per ISPE grading system

CLEANROOM

MATERIALS

			Fire extinguishing sprinklers
ISPE Grade 5 ISPE Grade 7	ISO 5 Class 100 ISO 7 Class 10,000 (in-operation)	**GMP Grade A** **GMP Grade B**	Sprinkler system may be wet or dry. Pipes should be concealed. Sprinklers should be recessed or flush head in order to facilitate cleaning. Sprinkler heads that do not disrupt unidirectional airflow should be used in Grade 5 (Grade A) zones.
ISPE Grade 8	ISO 8 Class 100,000	**GMP Grade C**	Sprinkler system may be wet or dry. Pipes should be concealed. Sprinkler heads may be the conventional type, passing through the ceiling. Where there is concern about cleaning, recessed or flush sprinkler heads should be considered.
CNC+	not defined	**GMP Grade D**	Sprinkler system may be wet or dry. Pipes should be concealed. Sprinkler heads may be the conventional type, passing through the ceiling.
CNC	not defined	**not defined**	Sprinkler system may be wet or dry. Pipes may be exposed. Sprinkler heads may be exposed.

* Grade 5, 7, 8 , CNC+ are ISPE Grades per ISPE grading system

CLEANROOM

MATERIALS

			Penetrations
ISPE Grade 5 ISPE Grade 7	ISO 5 Class 100 ISO 7 Class 10,000 (in-operation)	**GMP Grade A** **GMP Grade B**	Penetrations should be sealed with caulk, to prevent cross-contamination between areas. Silicone caulking is generally acceptable, or an escutcheon, if the fire resistant sealant does not provide a smooth finish.
ISPE Grade 8	ISO 8 Class 100,000	**GMP Grade C**	Penetrations should be sealed with caulk, to prevent cross-contamination between areas. Silicone caulking is generally acceptable, or an escutcheon, if the fire resistant sealant does not provide a smooth finish.
CNC+	not defined	**GMP Grade D**	Penetrations should be sealed with caulk, with escutcheon plate suggested.
CNC	not defined	**not defined**	Sealing is generally not required, except as necessary for fire resistance or thermal requirements.

* Grade 5, 7, 8 , CNC+ are ISPE Grades per ISPE grading system

CLEANROOM

INSTALLATION

- Walls and ceiling must be made of least number of panels with minimum joints.
- Walls should be coved at the wall-floor and wall-ceiling joints.
- Placement of the equipment and furniture in the cleanroom must not disrupt the designed airflow.
- Windows should not protrude inwards; there should not be windowsill, skirting, cable duct, etc.
- No cable should be drawn over the panels; there should not be any surface mounted hardware like switches, power outlets, etc.
- Transfer boxes, door handles, benches, racks, etc. must be stainless steel or FRP/ GRP; monolithic, as possible; and there shouldn't be recesses or joints that may retain contamination.
- Ventilation grilles, lighting fixtures, etc. should be flush (as possible) with the wall or ceiling surface.

CLEANROOM

INSTALLATION

- Joining hardware like rivets, round head screws, bolts and nuts, etc. should be avoided.
- Transfer boxes should be mounted extending intothe lower class cleanroom.
- There should not be drains or sinks in Grade A or B aseptic processing areas.
- Construction and installation techniques which may generate and retain contamination should not be preferred.

CLEANROOM

HVAC

- **Significant parameters in HVAC (Heating, Ventilating, Air Conditioning) design:**
  - provisioning of clean air (number and type of HEPA filters)
  - air change rate
  - airflow direction and speed
  - air pressure differential
- **In addition, temperature and humidity should be considered, according to the the type of operation carried out in the cleanroom.**
- **There should be at least 10-15 Pascal pressure differential (when door is closed) between the adjoining rooms of different classification with passage to each other.**

5 Pa = 0.02 inch H_2O = 0.51 mm H_2O = 0.038 mm Hg
10 Pa = 0.04 inch H_2O = 1.02 mm H_2O = 0.075 mm Hg
12 Pa = 0.05 inch H_2O = 1.22 mm H_2O = 0.09 mm Hg
15 Pa = 0.06 inch H_2O = 1.53 mm H_2O = 0.11 mm Hg
10 Pa = 0.08 inch H_2O = 2.04 mm H_2O = 0.15 mm Hg

CLEANROOM

HVAC

- Depending on the type of operation, some pressure differential is usually preferred between the rooms having the same cleanliness grade (class).
- Minimum 12.5 Pa pressure differential should be maintained at all times between an aseptic processing room and the adjoining unclassified room. In case the difference drops below this value, it should be confirmed that the aseptic conditions are restored.
- It is recommended that the pressure differentials betwen the cleanrooms are continuously monitored throughout each shift, and recorded. Alarms should be documented, and the deviations from established limits should be investigated.
- The rate of air change in a ISO-8 (Class 100,000) cleanroom should be 20, at least. (Significantly higher air change rates are normally required for the cleaner class cleanrooms.)

FDA Guidance for Industry Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice September 2004

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CLEANROOM

HVAC

- **EU GMP, PIC/S GUIDE TO GMP**

Grade A: Tha local zone for high risk operations (e.g., filling, stoppered bowls, open ampoules or vials, making aseptic connections, etc.).
Laminar airflow systems should provide a homogeneous (unidirectional) air speed of 0.36 - 0.54 m/s (guidance value) at the working zone, which should be demonstrated and validated.
Unidirectional airflow and lower air speeds may be used in closed isolators and glove boxes.

Grade B: Background environment for Grade A zone for aseptic preparation and filling.

Grade C or Grade D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

CLEANROOM

HVAC

- **ISO-14644-4**

Cleanroom examples for aseptic processing of healthcare products			
ISO class air cleanliness (in operation)	**airflow type**	**average airflow velocity** m/s	**application examples**
ISO-5 (≥0.5 µm)	unidirectional - U	> 0.2	aseptic processing
ISO-7 (≥0.5 µm)	not unidirectional (N or M)	not applicable	other processing zone directly supporting aseptic processing
ISO-8 (≥0.5 µm)	not unidirectional (N or M)	not applicable	support zones for aseptic processing, including controlled processing zone

Note a. **Occupancy states associated with ISO Class should be defined and agreed in advance of establishing optimum design conditions.**

Note b. **Airflow types: U = unidirectional, N = non-unidirectional, M = Mixed (U and N combined)**

CLEANROOM

HVAC

- **ISO-14644-4**

Cleanroom examples for microelectronics				
ISO class air cleanliness (in operation)	**airflow type**	**average airflow velocity** m/s	**air changes per hour** h^{-1}	**application examples**
ISO-4	unidirectional - U	0.3 - 0.5	not applicable	work zones
ISO-5	unidirectional - U	0.2 - 0.5	not applicable	work zones
ISO-6	not unidirectional (N or M)	not applicable	70 - 160	work zones
ISO-7	not unidirectional (N or M)	not applicable	30 - 70	service zones, surface treatment
ISO-8	not unidirectional (N or M)	not applicable	10 - 20	service zones

Note a. **Occupancy states associated with ISO Class should be defined and agreed in advance of establishing optimum design conditions.**

Note b. **Airflow types: U = unidirectinal, N = non-unidirectional, M = Mixed (U and N combined)**

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ISO-14644-4 definitions for airflow models:

- **Unidirectional: Controlled airflow through the entire cross-section of a clean zone with a steady velocity and approximately parallel streamlines.**
  Note: This type of airflow results in a directed transport of particles from the clean zone.

- **Non-unidirectional airflow: Air distribution where the supply air entering the clean zone mixes with the internal air by means of induction.**

- **Mixed airflow cleanrooms combine both unidirectional and non-unidirectional airflow in the same room.**

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For cleanrooms of ISO-5 and cleaner classes (in-operation) the airflow patterns are often unidirectional.

Non-unidirectional or mixed airflow pattern is typical for cleanrooms of ISO-6 or less clean (in-operation).

Unidirectional airflow may either be vertical or horizontal.
Unidirectional airflow relies upon a final filtered air supply and return inlets, which are nearly opposite one another in order to maintain an airstream in as straight a flow pattern as possible.
In both vertical or and horizontal airflow, the important design feature is the ability to ensure that the airflow pattern is disrupted as little as possible at the process core.

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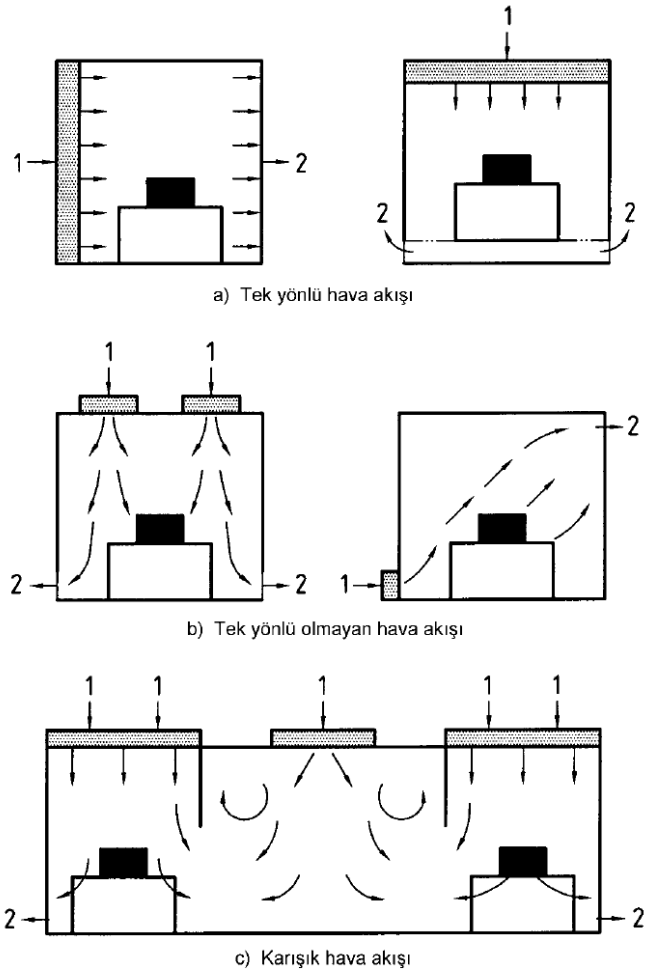
- **Unidirectional airflow**
- **Non-unidirectional airflow**
- **Mixed airflow**



Şekil A.2 - Temiz odalarda hava akış düzenleri

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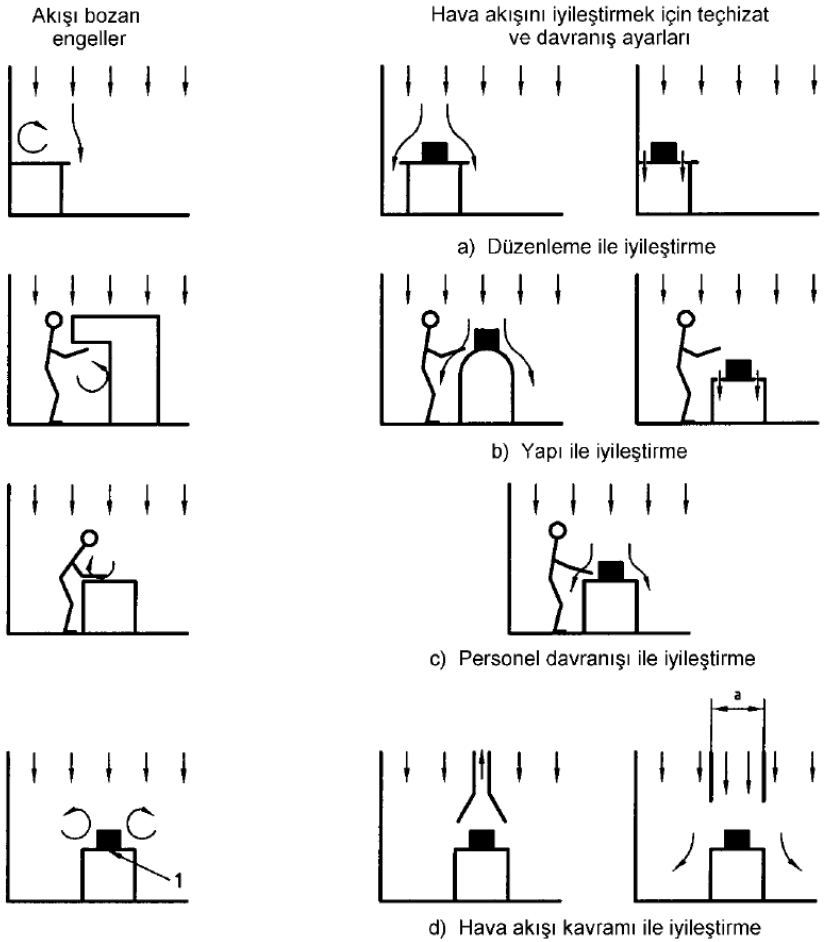
- **Influence of personnel and objects on unidirectional airflow**



Şekil A.3 - Tek yönlü hava akışında personelin ve malzemelerin etkisi

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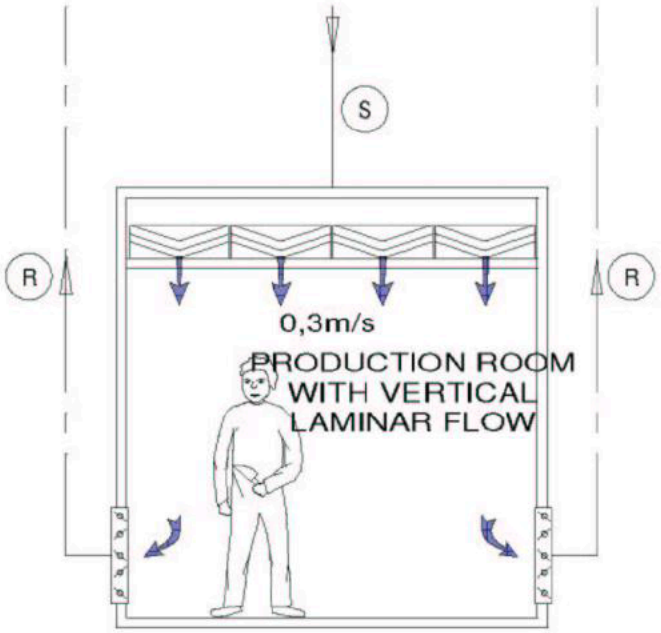
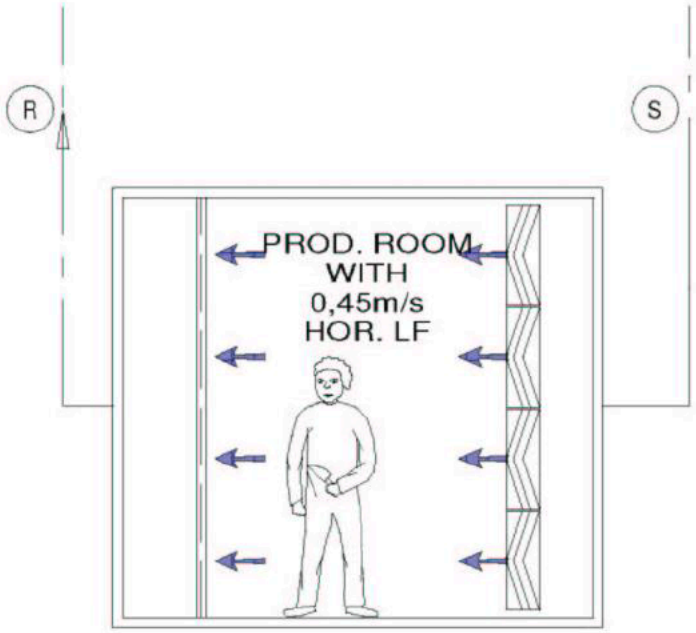
Unidirectional (U) vertical and horizontal airflow models





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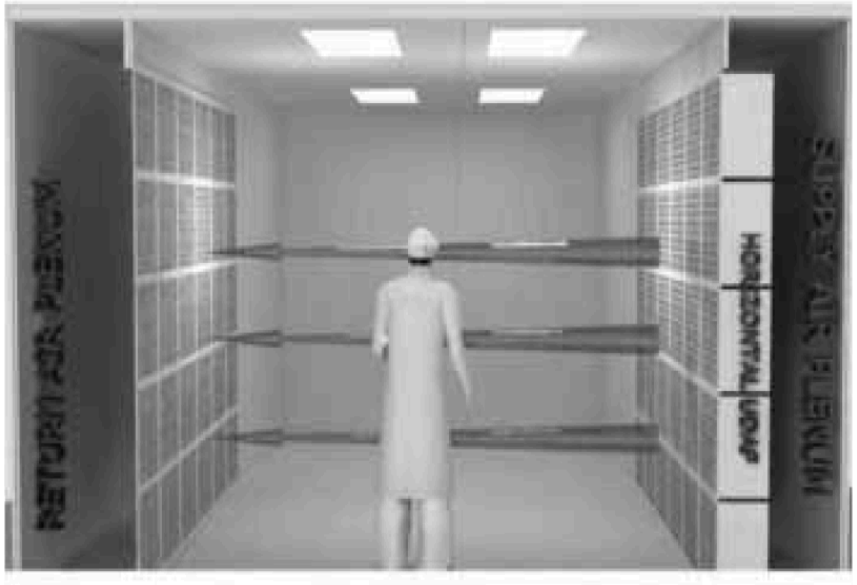
Unidirectional (U) vertical and horizontal airflow models

Diagram indicating horizontal and vertical unidirectional flow



WHO EXPERT COMMITTEE ON SPECIFICATIONS FORPHARMACEUTICAL PREPARATIONS
WHO Technical Report Series TRS 961 2011

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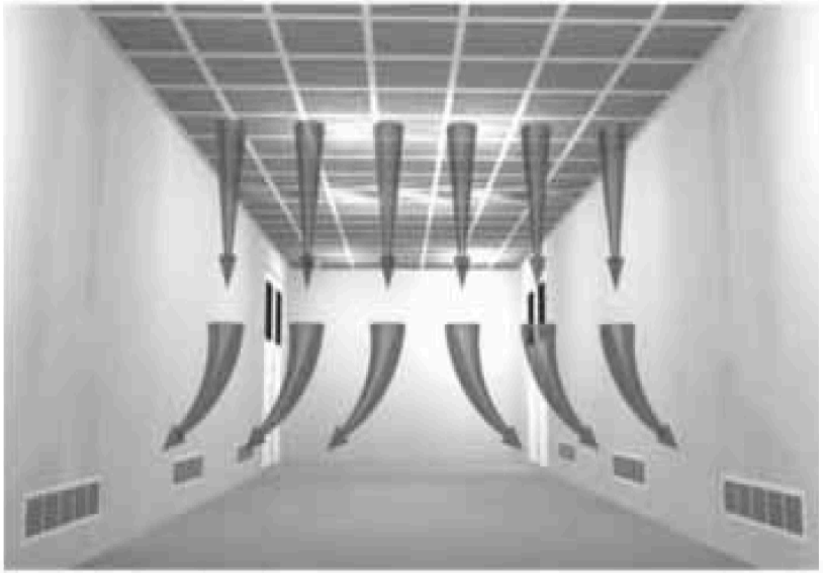
Unidirectional (U) and Non-unidirectional (N) airflow models



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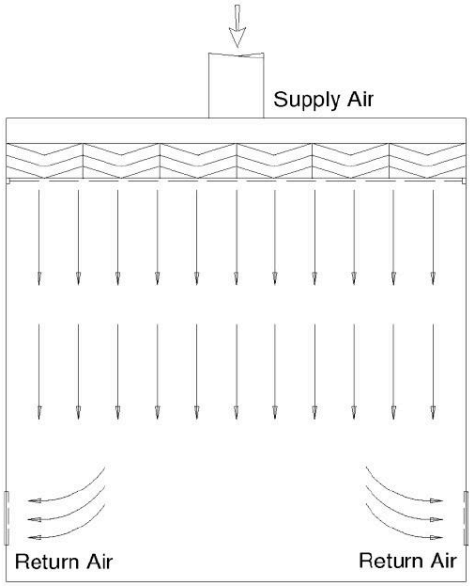
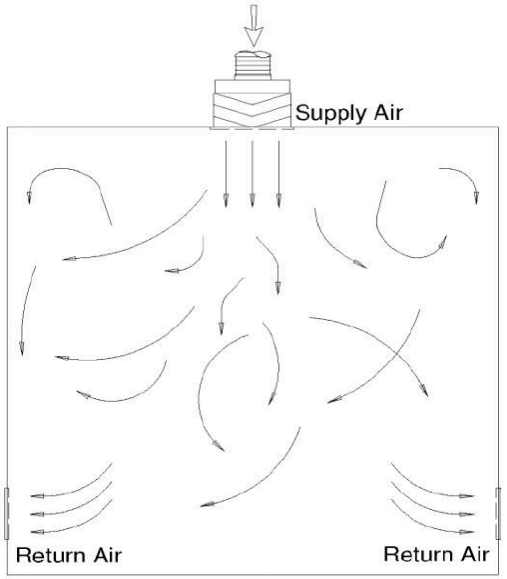
Unidirectional (U) and Non-unidirectional (N) airflow models

Unidirectional



Turbulent



Cleanroom Technology: Fundamentals of Design, Testing and Operation
W. Whyte, University of Glasgow, UK
John Wiley & Sons, Ltd. 2001

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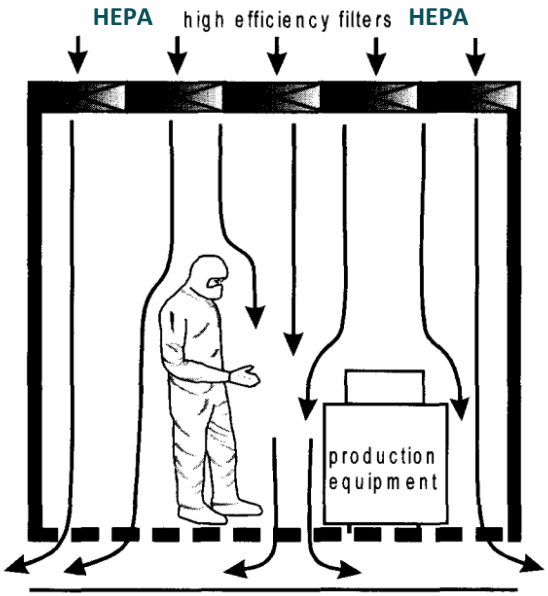
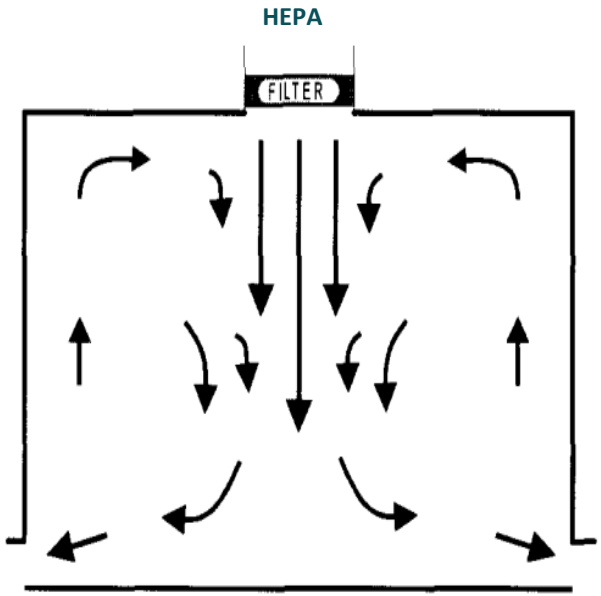
Unidirectional (U) and Non-unidirectional (N) airflow models





Cleanroom Technology: Fundamentals of Design, Testing and Operation
W. Whyte, University of Glasgow, UK
John Wiley & Sons, Ltd. 2001

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ISO-14644-4 definitions

Clean zones may be segregated from each other by the following means:

- **Low pressure differential, high airflow $v \geq 0.2$ m/s**
- **High pressure differential, low airflow $\Delta P = 5 - 20$ Pa**
- **Physical barrier (wall, separator, etc.)**

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Airflow types and airspeeds and number of air changes recommended for cleanrooms

Class of cleanroom	Airflow type	Average velocity (ft/min)	Air changes/hr	air velocity m/s
ISO 8 (100,000)	N/M	1-8	5-48	0,005 - 0,04
ISO 7 (10,000)	N/M	10-15	60-90	0,05 - 0,075
ISO 6 (1,000)	N/M	25-40	150-240	0,127 - 0,2
ISO 5 (100)	U/N/M	40-80	240-480	0,2 - 0,4
ISO 4 (10)	U	50-90	300-540	0,25 - 0,45
ISO 3 (1)	U	60-90	360-540	0,3 - 0,45
better than ISO 3	U	60-100	360-600	0,3 - 0,5

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Airflow speeds and number of air changes and HEPA coverage recommended for cleanrooms

Air Change Rates / Ceiling HEPA Coverage

Class ISO 146144-1 (Federal Standard 209E)	Average Airflow Velocity m/s (ft/min)	Air Changes Per Hour	Ceiling Coverage
ISO 8 (Class 100,000)	0.005 – 0.041 (1 – 8)	5 – 48	5 – 15%
ISO 7 (Class 10,000)	0.051 – 0.076 (10 -15)	60 – 90	15 – 20%
ISO 6 (Class 1,000)	0.127 – 0.203 (25 – 40)	150 – 240	25 – 40%
ISO 5 (Class 100)	0.203 – 0.406 (40 – 80)	240 – 480	35 – 70%
ISO 4 (Class 10)	0.254 – 0.457 (50 – 90)	300 – 540	50 – 90%
ISO 3 (Class 1)	0.305 – 0.457 (60 – 90)	300 – 540	60 – 100%
ISO 1 – 2	0.305 – 0.508 (60 – 100)	360 – 600	80 – 100%

Uni-directional air flow in cleanroom applies to ISO-5 and cleaner

300 ACH = 45 CFM/SF in a cleanroom with a 9' ceiling

% of cleanroom ceiling area occupied by filter modules

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Number of air changes and HEPA coverage recommended for cleanrooms

Recommended Air Changes and Ceiling Coverage

ISO Class	Air Changes Per Hour	Ceiling Coverage
ISO 1	500-750	80-100%
ISO 2	500-750	80-100%
ISO 3	500-750	60-100%
ISO 4	400-750	50-90%
ISO 5	240-600	35-70%
ISO 6	150-240	25-40%
ISO 7	60-150	15-25%
ISO 8	5-60	5-15%

How to Select a Cleanroom, Clean Air Products

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Airflow speeds and number of air changes and HEPA coverage recommended for cleanrooms

CLEAN ROOM DESIGN CRITERIA (Mechanical Practices)					
Criteria	Class Limits				
	ISO-4	ISO-5	ISO-6	ISO-7	ISO-8
FED-209 CLASS	10	100	1000	10000	100000
AirChanges Per hr	600	300-480	150-250	60-120	10- 40
HEPAFilter Coverage %	100	70-100%	30-60%	10 - 30%	5-10%
CFM per Sq. Ft.	90	65 - 36	32 -18	16- 9	8 - 5
TypicalFilter Efficiency	99.9997	99.997	99.997	99.997	99.97
TypicalFilter Velocity	60-110 FPM m/s 0.3 – 0.55	50-90 FPM 0.25 – 0.45	40-90 FPM 0.2 – 0.45	25-40 FPM 0.13 – 0.2	10-30 FPM 0.05 – 0.15
AirFlow Type	Unidirect-ional	Unidirect-ional	M i xed	M i xed	M i xed

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Airflow speeds and number of air changes recommended for cleanrooms

Class per ISO 14644 (Old FS 209 e)	Average Airflow (Across Entire Room)	Air Changes (per hour)
ISO 8 (Class 100,000)	0.005 – 0.041 m/sec (1 – 8 ft/min)	5 – 48
ISO 7 (Class 10,000)	0.051 – 0.076 m/sec (10 – 15 ft/min)	60 – 90
ISO 6 (Class 1,000)	0.127 – 0.203 m/sec (25 – 40 ft/min)	150 – 240
ISO 5 (Class 100)	0.203 – 0.406 m/sec (40 – 80 ft/min)	240 – 480
ISO 4 (Class 10)	0.254 – 0.457 m/sec (50 – 90 ft/min)	300 – 540
ISO 3 (Class 1)	0.305 – 0.457 m/sec (60 – 90 ft/min)	360 – 540
ISO 2 and cleaner	0.305 – 0.508 m/sec (60 – 100 ft/min)	360 – 600

Note: Actual average velocity and air changes required may vary depending on the application, floor plan and number of personnel. Typical face velocity from the filter is 90 feet per minute. Average airflow is determined by airflow readings from several interior points.

http://www.cleanroomswest.com/air-flow-rates/

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HEPA coverage recommended for cleanrooms

Class – ISO 14644 (per Fed. Stnd 209e)	Ceiling Coverage
ISO 8 (Class 100,000)	5 – 15%
ISO 7 (Class 10,000)	15 – 20%
ISO 6 (Class 1,000)	25 – 40%
ISO 5 (Class 100)	50 – 100%
ISO 4 (Class 10)	100% *
ISO 3 (Class 1)	100% *
ISO 2 and cleaner	100%*
*ULPA filters required in Class 10 – 1 and cleaner applications. HEPA filters used in all others.	

http://www.cleanroomswest.com/ceiling-filter-coverage/

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- airspeed,
- air change rate,
- HEPA coverage

are important parameters in the design of cleanrooms.

applications in the industry ->

Table 1: Cleanroom HVAC requirements

(Recommended to meet and exceed Federal Standard 209 E, 209 Class 1 VLF, and ISO 14644-1)

ISO 14644-1 per cubic meter	209 E Intern. (SI)	209 E English (USA) per cubic ft.	Suggested minimum ceiling coverage	Suggested filter type	Suggested minimum air velocity @ ceiling level	Suggested minimum cleanroom air changes
Class 3 Particle counts ≥ 0.1 µm – 1,000 ≥ 0.5 µm – 35	Class M	Class 1 Particle counts ≥ 0.1 µm – 35 ≥ 0.5 µm – 1	100% ceiling coverage	ULPA filters providing efficiency of 99.99995% at 0.12 µm	75 to 90 fpm (0.38 to 0.46 m/sec)	500 to 640 ach
	Class M 1.5	Class 1 Particle counts ≥ 0.1 µm – 35 ≥ 0.5 µm – 1	100% ceiling coverage	ULPA filters providing efficiency of 99.99995% at 0.12 µm	75 to 90 fpm (0.38 to 0.46 m/sec)	450 to 640 ach
	Class M 2	Class 10 Particle counts ≥ 0.1 µm – 99.1 ≥ 0.5 µm – 2.83	100% ceiling coverage	ULPA filters providing efficiency of 99.99995% at 0.12 µm	70 to 80 fpm (0.36 to 0.41 m/sec)	420 to 600 ach
Class 4 Particle counts ≥ 0.1 µm – 10,000 ≥ 0.5 µm – 352	Class M 2.5	Class 10 Particle counts ≥ 0.1 µm – 345 ≥ 0.5 µm – 10	100% ceiling coverage	ULPA filters providing efficiency of 99.99995% at 0.12 µm	70 to 80 fpm (0.36 to 0.41 m/sec)	420 to 600 ach
	Class M 3	Class 100 Particle counts ≥ 0.1 µm – 991 ≥ 0.5 µm – 28.3	80% ceiling coverage	HEPA filters providing efficiency of 99.999% at 0.12 µm	50 to 70 fpm (0.26 to 0.36 m/sec)	300 to 480 ach
Class 5 Particle counts ≥ 0.1 µm – 100,000 ≥ 0.5 µm – 3,520	Class M 3.5	Class 100 Particle counts ≥ 0.1 µm – 3,450 ≥ 0.5 µm – 100	75% ceiling coverage	HEPA filters providing efficiency of 99.999% at 0.12 µm	50 to 70 fpm (0.26 to 0.36 m/sec)	300 to 480 ach
Class 6 Particle counts ≥ 0.1 µm – 1,000,000 ≥ 0.5 µm – 35,200	Class M 4.5	Class 1000 Particle counts ≥ 0.1 µm – 34,500 ≥ 0.5 µm – 1,000	40% ceiling coverage	HEPA filters providing efficiency of 99.999% at 0.12 µm	30 to 50 fpm (0.15 to 0.25 m/sec)	180 to 300 ach
Class 7 Particle counts ≥ 0.5 µm – 352,000	Class M 5.5	Class 10,000 Particle counts ≥ 0.1 µm – 345,000 ≥ 0.5 µm – 10,000	30% ceiling coverage	HEPA filters providing efficiency of 99.99% at 0.3 to 0.5 µm	20 to 30 fpm (0.10 to 0.15 m/sec)	60 to 100 ach
Class 8 Particle counts ≥ 0.5 µm – 3,520,000	Class M 6.5	Class 100,000 Particle counts ≥ 0.1 µm – 3,450,000 ≥ 0.5 µm – 100,000	15% ceiling coverage	HEPA filters providing efficiency of 99.99% at 0.3 to 0.5 µm	15 to 20 fpm (0.08 to 0.10 m/sec)	36 to 90 ach

Note: Air changes developed for cleanroom heights 9′ to16′

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- **Basic guidance values in the design of cleanrooms**

Basic Guide to Clean Room Design						
Classes (Fed 209 D)	1	10	100	1,000	10,000	100,000
Particles per m3 > 0.5 micron	35.3	353	3,530	35,300	353,000	3,530,000
Air Changes Per Hour	600	500	500	40-120	20-40	10-20
Room Pressure	15 Pa	15 Pa	15 Pa	10-15 Pa	10-15 Pa	5-10 Pa
Clean air inlets Cover as % of ceiling area	100%	100%	90%	20-50%	10-20%	5-10%
Clean air inlets Locations	Ceiling					Ceiling/High Wall
Filter Location	Ceiling					Ceiling/AHU
Return Locations	Floor		Low Level or Floor		Low Sidewall	Sidewall
Velocity at clean air inlets (m/s)	0.45			0.15-0.45		
Velocity at return air (m/s)	n/a			0.5-1	1-2.5	2.5
Airlock (required)	Yes					None
Area per occupant (m2)	40		30	20	10	5
Equipment in room	Minimum				30% Floor	50% Floor
Room Height	n/a			Minimum 3	Minimum 2.75	Minimum 2.25

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Basic guidance values in the design of cleanrooms

Classification of various cleanroom classes according to ISO 14644-1, U.S.F.S. 209 E and EU GMP standards:

Purity class by ISO 14644-1 standard		8	7	6	5	4	3
Purity class by U.S.Federal Standard 209 E		100 000	10 000	1 000	100	10	1
Purity class by EU GMP standard		D	C	B	A		
Maximum permitted number of particles (particle/m³) equal to or greater than	5.0 µm	29 300	2 930	293	29	-	-
	1.0 µm	832 000	83 200	8 320	832	83	8
	0.5 µm	3 520 000	352 000	35 200	3 520	352	35
	0.3 µm	-	-	102 000	10 200	1 020	102
	0.2 µm	-	-	237 000	23 700	2 370	237
	0.1 µm	-	-	1 000 000	100 000	10 000	1 000
Type of flow		Turbulent	Turbulent	Transition	Unidirectional	Unidirectional	Unidirectional
Maximum number of air changes i/h		36-90	60-100	180-300	300-480	420-600	500-640
Minimum velocity m/s		0.08-0.10	0.10-0.15	0.15-0.25	0.26-0.36	0.36-0.41	0.38-0.46
Minimum ceiling coverage by filters %		15	30	40	75	100	100
Filter type		H12	H12	H13	H14	U16	U16
Air diffusers		Ceiling swirl diffuser	Ceiling swirl diffuser	Ceiling filter diffuser	Ceiling filter diffuser	Ceiling filter diffuser	Ceiling filter diffuser
Exhaust air openings		Side wall	Low wall-mounted sideway	Low mounted sideway	Floor or low mounted sideway	Floor mounted	Floor mounted
Positive pressure in cleanroom Pa		10-15	10-15	10-15	10-15	1.5	1.5

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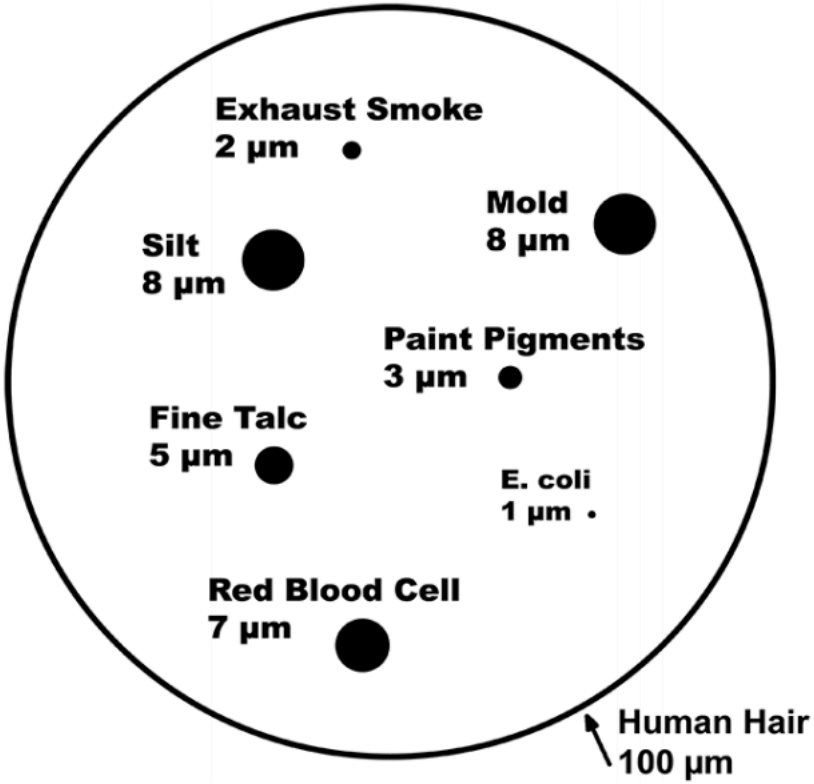
- **Particle sizes**



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Recommendations in the standards and industry applications

ISO - 4 Class 10	Airflow type U, N, M	Airspeed m/s ft/m	Air change rate h^{-1}	HEPA coverage %	Filter efficiency %	
	U	0.3 - 0.5 60 - 100	not applicable			ISO 14644-4 Table B2 Microelectronics…
	U	0.25 - 0.45 50 - 90	300 - 540			IEST Recommended Practice RP CC012
		0.25 - 0.45 50 - 90	300 - 540	50 - 90		ASHRAE
		0.25 - 0.45 50 - 90	300 - 540	50 - 90		Terra Universal
	U	0.36 - 0.41 70 - 80	420 - 600	100	U 16	Klima Oprema
			400 - 750	50 - 90		How to Select a Cleanroom, Clean Air Products
	U	0.3 - 0.55 60 - 110	600	100	99,9997	ULPA U15
		0.25 - 0.45 50 - 90	300 - 540	100		ULPA
		0.35 - 0.4 70 - 80	420 - 600	100	99,99995	ULPA U16
			600	100		Area per occupant = 40 m2 Cafmil Farr

U: Unidirectional
N: Not unidirectional
M: Mixed

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ISO – 5 Class 100	Airflow type U, N, M	Airspeed m/s ft/m	Air change rate h^{-1}	HEPA coverage %	Filter efficiency %	
	U	> 0.2 > 40				ISO 14644-4 Table B1 Aseptic processing of healthcare prod…
	U	0.2 - 0.5 40 - 100	not applicable			ISO 14644-4 Table B2 Microelectronics…
		0.36 - 0.54 70 - 105				
	U / N / M	0.2 - 0.4 40 - 80	240 - 480			IEST Recommended Practice RP CC012
		0.2 - 0.4 40 - 80	240 - 480	35 - 70		ASHRAE
		0.2 - 0.4 40 - 80	240 - 480	35 - 70		Terra Universal
	U	0.25 - 0.45 50 - 90	300 - 480	75	H14	Klima Opera
			240 - 600	35 - 70		How to Select a Cleanroom, Clean Air Products
	U	0.25 - 0.45 50 - 90	300 - 480	70 - 100	99,997	HEPA H14
		0.2 - 0.4 40 - 80	240 - 480	50 - 100		HEPA
		0.25 - 0.35 50 - 70	300 - 480	75	99,999	HEPA
			500	90		Area per occupant = 30 m2 Cafmil Farr

U: Unidirectional
N: Not unidirectional
M: Mixed

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ISO – 6 Class 1,000	Airflow type U, N, M	Airspeed m/s ft/m	Air change rate h^{-1}	HEPA coverage %	Filter efficiency %	
	N / M	not applicable	70 - 160			ISO 14644-4 Table B2 Microelectronics…
	N / M	0.125 - 0.2 25 - 40	150 - 240			IEST Recommended Practice RP CC012
		0.125 - 0.2 25 - 40	150 - 240	25 - 40		ASHRAE
		0.125 - 0.2 25 - 40	150 - 240	25 - 40		Terra Universal
	N	0.15 - 0.25 30 - 50	180 - 300	40	H13	Klima Opera
			150 - 240	25 - 40		How to Select a Cleanroom, Clean Air Products
	M	0.2 - 0.45 40 - 90	150 - 250	30 - 60	99,997	HEPA
		0.125 - 0.2 25 - 40	150 - 240	25 - 40		HEPA
		0.15 - 0.25 30 - 50	180 - 300	40	99,999	HEPA
			40 - 120	20 - 50		Area per occupant = 20 m2 Cafmil Farr

U: Unidirectional
N: Not unidirectional
M: Mixed

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ISO – 7 Class 10,000	Airflow type U, N, M	Airspeed m/s ft/m	Air change rate h^{-1}	HEPA coverage %	Filter efficiency %	
	N / M	not applicable				ISO 14644-4 Table B1 Aseptic processing of healthcare products…
	N / M	not applicable	30 - 70			ISO 14644-4 Table B2 Microelectronics…
	N / M	0.05 - 0.075 10 - 15	60 - 90			IEST Recommended Practice RP CC012
		0.05 - 0.075 10 - 15	60 - 90	15 - 20		ASHRAE
		0.05 - 0.075 10 - 15	60 - 90	15 - 20		Terra Universal
	N / M	0.1 - 0.15 20 - 30	60 - 100	30	H12	Klima Opera
			60- 150	15 - 25		How to Select a Cleanroom, Clean Air Products
	M	0.125 - 0.2 25 - 40	60 - 120	10 - 30	99,997	HEPA H14
		0.05 - 0.075 10 - 15	60 - 90	15 - 20		HEPA
		0.1 - 0.15 20 - 30	60 - 100	30	99,99	HEPA
			20 - 40	10 - 20		Area per occupant = 10 m2 Cafmil Farr

U: Unidirectional
N: Not unidirectional
M: Mixed

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ISO – 8 Class 100,000	Airflow type U, N, M	Airspeed m/s ft/m	Air change rate h^{-1}	HEPA coverage %	Filter efficiency %	
	N / M	not applicable				ISO 14644-4 Table B1 Aseptic processing of healthcare products…
	N / M	not applicable	10 - 20			ISO 14644-4 Table B2 Microelectronics…
	N / M	0.005 - 0.04 1 - 8	5 - 48			IEST Recommended Practice RP CC012
		0.005 - 0.04 1 - 8	5 - 48	5 - 15		ASHRAE
		0.005 - 0.04 1 - 8	5 - 48	5 - 15		Terra Universal
	N / M	0.08 - 0.1 16 - 20	36 - 90	15	H12	Klima Optima
			5 - 60	5 - 15		How to Select a Cleanroom, Clean Air Products
	M	0.05 - 0.15 10 - 30	10 - 40	5 - 10	99,97	HEPA
		0.005 - 0.04 1 - 8	5 - 48	5 - 15		HEPA
		0.075 - 0.1 15 - 20	36 - 90	15	99,99	HEPA
			> 20 FDA Guidance GMP 2004	5 - 10		Area per occupant = 5 m2 Cafmil Farr

U: Unidirectional
N: Not unidirectional
M: Mixed

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Summary of the recommendations in the standards and industry applications

ISO-5 cleanroom
- airflow: should be unidirectional (GMP, ISO)
- airspeed: 0.36 - 0.54 m/s, 70 - 105 ft/m (GMP)
- air change: > 300 per hour
- filter coverage: %40 - 80 of ceiling area
- filter efficiency: ULPA U15, HEPA H14
- area per occupant: 30 m^2

ISO-6 cleanroom
- airflow: not unidirectional
- airspeed: > 0.15 m/s, > 30 ft/m
- air change: > 200 per hour
- filter coverage: %30 - 40 of ceiling area
- filter efficiency: HEPA H14
- area per occupant: 20 m^2

ISO-7 cleanroom
- airflow: not unidirectional
- airspeed: > 0.1 m/s, > 20 ft/m
- air change: > 60 per hour
- filter coverage: %15 -25 of ceiling area
- filter efficiency: HEPA H14
- area per occupant: 10 m^2

ISO-8 cleanroom
- airflow: not unidirectional
- airspeed: 0.05 - 0.1 m/s, 10 - 20 ft/m
- air change: > 20 per hour (FDA)
- filter coverage: %5 - 10 of ceiling area
- filter efficiency: HEPA H13, EPA E12
- area per occupant: 5 m^2

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Filter types recommended for cleanrooms

	SPECIFICATION		TYPICAL APPLICATIONS	
	Grade	EN		
	G2	EN779	Prefilter for fresh air,	
	G3	EN779	Filters for electrical equipment, cooker hood medias, prefilter for solder fumes	
	G4	EN779	Good general purpose prefilter for fresh air, minimum standard for air intakes to food areas	
	F5	EN779	Prefilter for Activated Carbon Filters, Above average prefilter for fresh air.	
	F6	EN779	Secondary filter to glass panel for low grade offices	
	F7	EN779	Secondary filter to pleated panel filters in offices and shopping malls where décor cleanliness is importa	
	F8	EN779	As F7 , low grade operating theatres	Efficiency
	F9	EN779	As F8, low grade clean rooms for storage or simila	to EN1822
E10	H10	EN1822	For removal of smoke (not 100%) low grade cleanroom Class 8 to EN1464	85
E11	H11	EN1822	Start of HEPA range not often usec	95
E12	H12	EN1822	Lower grade cleanrooms	99.5
	H13	EN1822	Cleanrooms, or asbestos removal - start of ensuring air is breathable quality, when used in industrial applicatic	99.95
	H14	EN1822	Cleanrooms, or asbestos removal - ensures air is breathable quality, when used in industrial applicatic	99.995
	U15	EN1822	Not often requestec	99.9995
	U16	EN1822	Cleanroom to Class 4 to EN1464	99.99995

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Comparison of HEPA and ULPA filters

ISO Filter Class	Efficiency	IEST* Filter Type	EN 1822**	Remarks
ISO 15 E	≥ 95%	-	E 11	
ISO 20 E	≥ 99%			
ISO 25 E	≥ 99.5%		E 12	
ISO 30 E	≥ 99.9%			
ISO 35 H	≥ 99.95%		H 13	
-	99.97%	A,B, E, H, I		Type A,B,E are traditional HEPA filters
ISO 40 H	≥ 99.99%	C, J, (K)		In current usage, higher performance Type K is prefered over Type J for added safety
ISO 45 H	≥ 99.995%	K	H 14	
ISO 50 U	≥ 99.999%	D		
ISO 55 U	≥ 99.9995%	F	U15	
ISO 60 U	≥ 99.9999%	G		
ISO 65 U	≥ 99.99995%	G	U 16	
ISO 70 U	≥ 99.999999%	G		
ISO 75 U	≥ 99.9999995%	G	U 17	

* IEST filter types A,B,C,D,E classified per tests using photometers according to Mil Standard 282.
Filter Types F,G,H, I,J,K are classified per test results using using particle counters.

** EN 1822 Filter class E 10 not within range of efficiencies in the ISO standard

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Comparison of HEPA and ULPA filters

HEPA / ULPA	Integral efficiency* for MPPS	Filter Class to EN 1822	DIN 24183	DIN 24184	BS 3928	US Mil. Std. 292
E10	≥ 85 %	H 10	EU 10	Q	EU 10	–
E11	≥ 95 %	H 11	EU 11	R	EU 11	≥ 95 %
E12	≥ 99.5 %	H 12	EU 12	–	EU 12	≥ 99.97 %
H13	≥ 99.95 %	H 13	EU 13	S	EU 13	≥ 99.99 %
H14	≥ 99.995 %	H 14	EU 14	–	EU 14	≥ 99.999 %
U15	≥ 99.9995 %	U 15	EU 15	–	–	–
U16	≥ 99.99995 %	U 16	EU 16	–	–	–
U17	≥ 99.999995 %	U 17	EU 17	–	–	–

* The integral efficiency is the mean value of all local efficiencies measured over the filter's face area.

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Comparison of HEPA and ULPA filters by EN-1822

EN-1822 High Efficiency Air Filters (EPA, HEPA and ULPA)

E10 - E12 EPA Efficiency Particulate Air Filter
H13 - H14 HEPA High Efficiency Particulate Air Filter
U15 - U17 ULPA Ultra Low Penetration Air Filter

Local Penetration ≤ 5 x Integral Penetration

Local penetratio should be less than five times the integral penetration
(20 times for U17)

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

[a] See 7.5.2 and FprEN 1822-4.

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

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

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Comparison of HEPA and ULPA filters by ISO-29463

ISO-29463 High-efficiency filters and filter media for removing particles in air

Filter class		Overall Efficiency (%)	Local or leak
Penetration (%)	HEPA / ULPA		
ISO 15 E	E11	≥ 95	NA
ISO 20 E		≥ 99	NA
ISO 25 E	E12	≥ 99.5	NA
ISO 30 E		≥ 99.90	
ISO 35 H	H13	≥ 99.95	≤ 0.25
ISO 40 H[4]		≥ 99.99	≤ 0.05
ISO 45 H[4]	H14	≥ 99.995	≤ 0.025
ISO 50 U		≥ 99.999	≤ 0.005
ISO 55 U	U15	≥ 99.9995	≤ 0.0025
ISO 60 U		≥ 99.9999	≤ 0.0005
ISO 65 U	U16	≥ 99.99995	≤ 0.00025
ISO 70 U		≥ 99.99999	≤ 0.0001
ISO 75 U		≥ 99.999995	≤ 0.0001

Table 1 – ISO Filter Classes

99.995 -> 0.005 -> x5 -> 0.025 -> 99.975
integral local

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Typical calculation for number of HEPA filters for ISO-5 cleanroom

filter face area: 61 cm x 61 cm = 0.372 m^2	24"x 24" = 4 sqf
filter output airspeed: 0.45 m/s	89 fpm
0.37 x 0.45 = 0.167 m^3/s = 600 m^3/h	353 cfm
each HEPA filter provides 600 m^3/hour of clean air	21,180 ft^3/h
cleanroom volume: 50 m^2 x 3 m = 150 m^3	5.296 ft^3

600 ÷150 = 4 air changes/hour 21.180 ÷ 5296 = 4 /h

<u>at least</u> 75 ea HEPA filters are required for 300 air changes/hour

75 x 0.372 m^2 = 28 m^2 => 56% of the ceiling area

if 81 adet H14 HEPA filters are used, 60% coverage can be attained.

Hence, ISO-5 ✓

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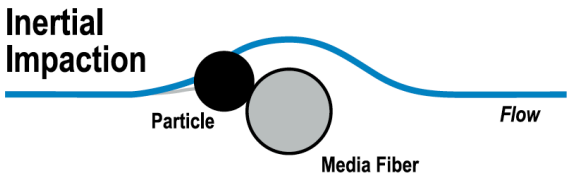
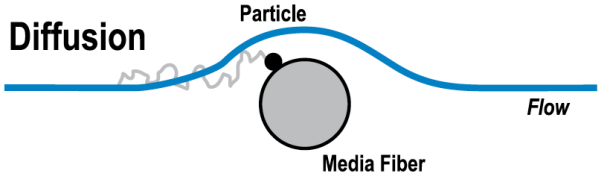
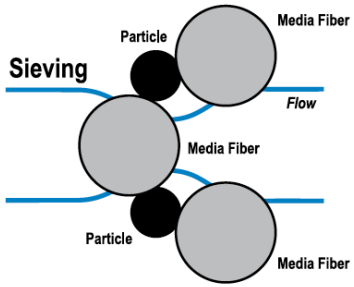
Filtering mechanisms in HEPA filters



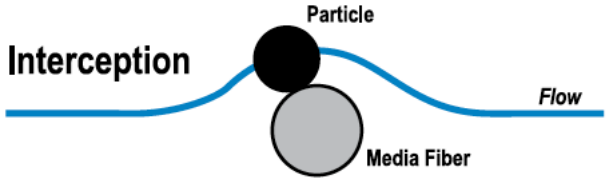
inertia: (large) heavy particles



diffusion: very small particles



sieving: particles which cannot penetrate the fiber space



interception: mid-size particles

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Filtering mechanisms in HEPA filters

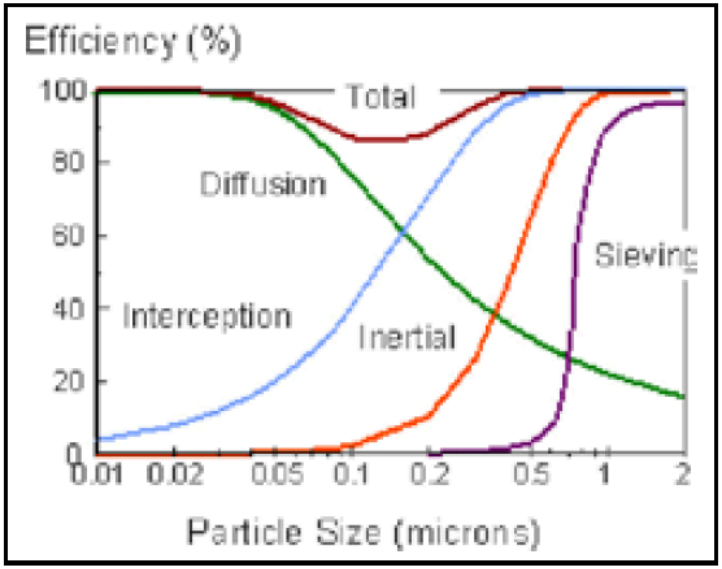

Figure 1 - Filter Efficiency vs. Particle Size

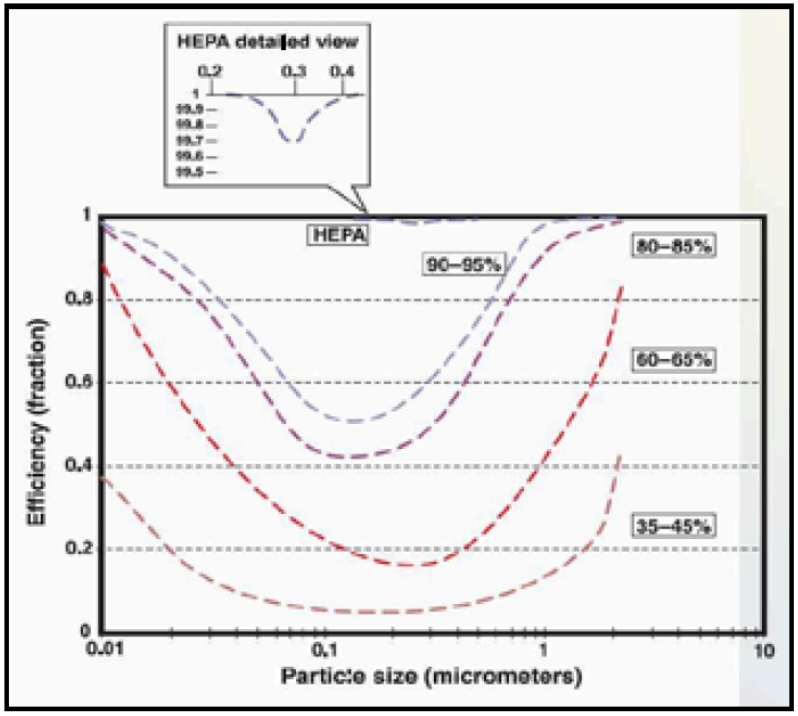

Figure 2 - Detail of HEPA Filter Efficiency vs. Particle Size

MMPS Most Penetrating Particle Size (most difficult to catch)
HEPA: 0.3 µm ULPA: 0.12 µm

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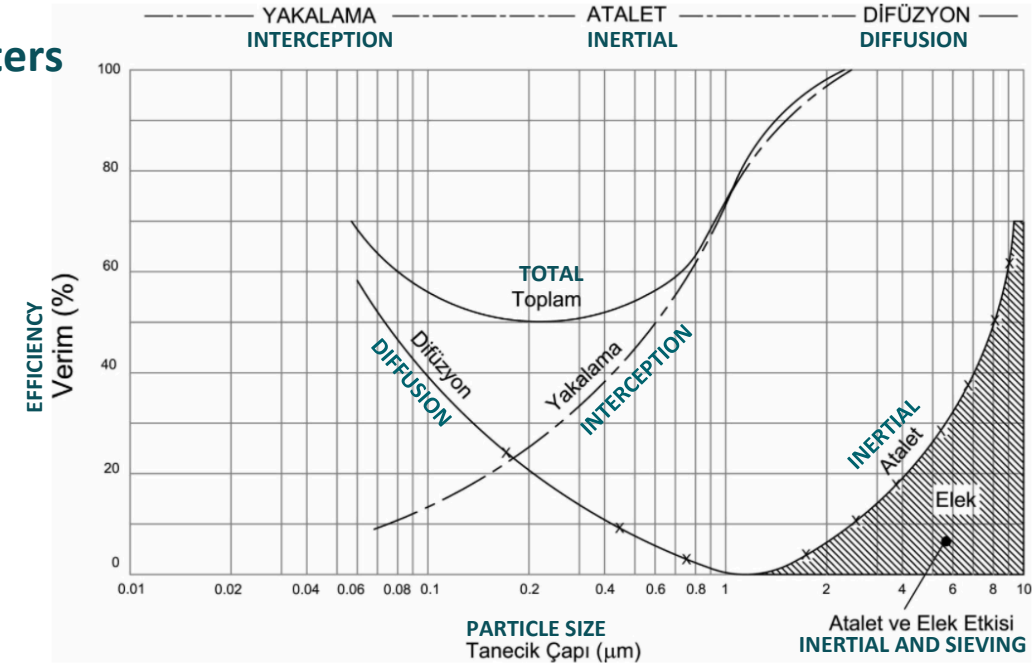
Filtering mechanisms in HEPA filters



Şekil – 1
Çeşitli filtrasyon mekanizmalarının tanecik çapına göre verime etkisi ve MPPS.

MMPS Most Penetrating Particle Size (most difficult to catch)

HEPA: 0.3 µm ULPA: 0.12 µm

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NOTES

Note 1

- WHO WHO TRS 961 WHO Expert Committee on Specifications for Pharmaceutical Preparations,
  - Annex 3 WHO Good Manufacturing Practices for Pharmaceutical Products: Main Principals
  - Annex 5 Supplementary Guidelines on Good Manufacturing Practices for Heating, Ventilation and Airconditioning Systems for Non-sterile Pharmaceutical Dosage Forms
- PIC/S Guide to Good Manufacturing Practice for Medicinal Products - Annexes
- T.C. Sağlık Bakanlığı Good Manufacturing Practices (GMP) Guide for Manufacturing Plants of Human Medicinal Products

dokümanlarında hava kilidi (airlock) şu şekilde tanımlanmaktadır:

<u>Airlock:</u> An enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods.

- **Bu tanımlarda yer alan `either... or...´ bağlacı Türkçe'ye mutlaka `ya... ya da ...´ olarak tercüme edilmeli ve uygulamada personel hava kilidi (Personnel Airlock - PAL) ve malzeme hava kilidi (Material Airlock - MAL) ayrı olmalı.**

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NOTES

Note 2

- **Common practice is that <u>two successive airlocks</u> have to be crossed when passing from one cleanroom to another with two classes (or grades) of separation.**
  (CNC > D > C > B > C > D > CNC)
- **However, there is no such requirement in the FED or ISO standards, or FDA or EU GMP guides.**
- **Only in the 2011 issue of** WHO TRS 961 WHO Expert Committee on Specifications for Pharmaceutical Preparations - Annex 6 WHO Good Manufacturing Practices for Sterile Pharmaceutical Products **under,** 11. Premises **just below paragraph** 11.7 **there was an amendment paragraph as:**

  There should <u>not be a change of more than one grade between airlocks or passages and changing rooms</u>, i.e. a Grade D passage can lead to a Grade C airlock, which leads to a Grade B changing room, which leads to a Grade B clean room.
- **In other words, the amendment paragraph in the 2011 issue of** WHO TRS 961 **states that when passing from Grade D clean area to Grade B, there should be a Grade C area (clean area, clean room, change room, airlock).**

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Note 2

- **This, above mentioned amendment was later removed from paragraph** 51. **in chapter** Premises **in** PIC/S Guide to Good Manufacturing Practice for Medicinal Products – Annex 1 Manufacture of Sterile Medicinal Products**, which was issued later (in 2017) and which was peer reviewed by the experts, for sure.**
- **This amendment paragraph is not in the GMP Guides issued in 2017 by TR Ministry of Health, or TR Ministry of Food, Agriculture and Livestock.**
- **There is no such requirement in the ISPE documents, which comply many of the engineering practices.**
- **This widely accepted practice (CNC > D > C > B > C > D > CNC) is followed without any reference to a current document.**

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- **Cleanroom ... to be continued...**

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Version: 2017/01 Effective Date: 01/10/2017 (Compatible with PIC/S GMP Guide version: PE 009-13)

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THANK YOU

Ruşen Eşref YAZGAN

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