Cleanroom and HVAC Systems

Praphon Angtrakool

Food and Drug Administration

Some PIC/S GMP Deficiencies Recently Observed

- Inadequate air filtration to manufacturing areas
  - No knowledge of grade of filters used
- Potential for penicillin/cephalosporin cross contamination
  - from environment and personnel
- Change area without mirrors/visual gowning instructions
- Poorly controlled water treatment systems
- Endotoxins in steriles APIs
- No cleaning validation
- Poorly defined “release for supply” procedures
- QC test data not genuine
- Effectiveness of GMP training not assessed

R W Tribe
Chief GMP Auditor
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June 2002

Australia (TGA)

Critical deficiency : deficiency that has produced, or may result in a significant risk of producing, a product which is harmful to the user.

Examples of critical deficiencies include :

- *no or inadequate air filtration to minimise airborne contaminants*
- *lack of sterilisation (or other complex process for critical products) validation*
- *inadequate segregation of manufacturing of high risk products, such as penicillins, cephalosporins, antineoplastics, steroids, hormones, resulting in a risk of contamination*

Health Canada (HPFB)

Critical observation : *Observation describing a situation that is likely to result in a non-compliant product or a situation that may result in an immediate or latent health risk and any observation that involves fraud, misrepresentation or falsification of products or data.*

Premises C.02.004

- *No air filtration system to eliminate airborne contaminants that are likely to be generated during fabrication or packaging.*
- *Generalized malfunctioning of the ventilation system (s) with evidence of widespread cross-contamination.*
- *Inadequate segregation of manufacturing or testing areas from other manufacturing areas for high risk products.*

Health Canada (HPFB)

Major observation *: Observation that may result in the production of a drug not consistently meeting its marketing authorization.*

Premises C.02.004

- *Malfunctioning of the ventilation system that could result in possible localized or occasional cross-contamination.*
- *Maintenance / periodic verification such as air filter replacement, monitoring of pressure differentials not performed. (8)*
- *Accessory supplies (steam, air, nitrogen, dust collection, etc...) not qualified.*
- *Heat Ventilation Air Conditioning (HVAC) and purified water (PW) system not qualified.*

Production Area (WHO) (1)

12.30 Production areas should be effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity) appropriate to the products handled, to the operations undertaken and to the external environment. These areas should be regularly monitored during both production and non-production periods to ensure compliance with their design specifications.

12.31 Premises for the packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

Production Area (PIC/S) (2)

3.3 Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.

3.12 Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.

3.15 Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

Questions & answers on the Australian GMP code

12 The new Code does not reference a specific standard for air quality for non-sterile manufacturing areas. Could you please advise the relevant Australian or ISO standard, and the correct area designations and standards we should apply?

There are no standards specific to non-sterile medicine manufacture. The various grades of air quality for the production of non-sterile medicines will require further consultation with industry before a TGA policy is issued on this topic.

International Society for Pharmaceutical Engineering (ISPE)

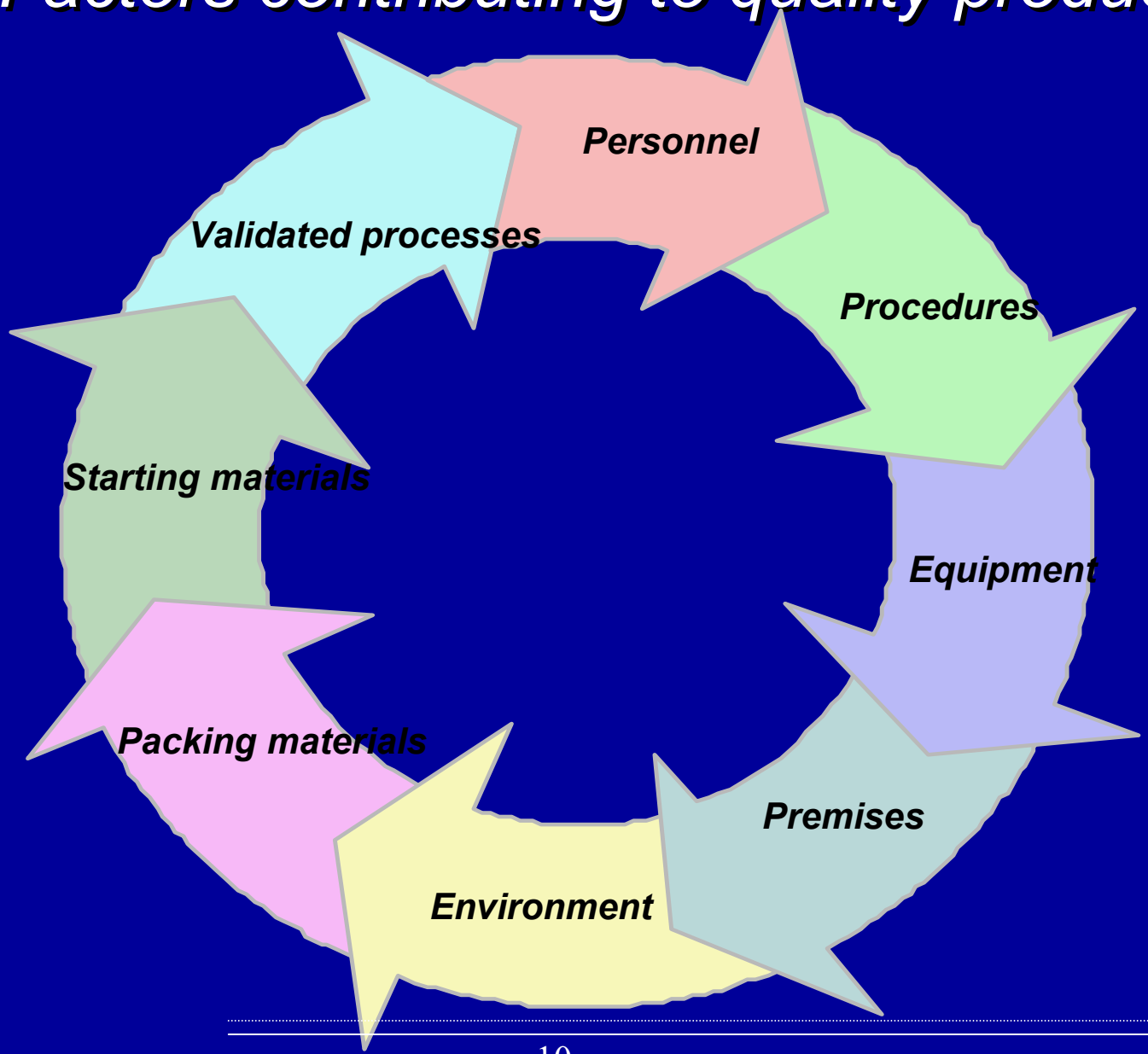
- *The ISPE OSD Baseline Guide further states that there are no particulate classification requirements for OSD facilities, such as those that exist for aseptic processing. The level of protection and air cleanliness for different areas should be evaluated based on the product being manufactured, the process and the product's susceptibility to degradation.*
- *The most common applied classification for open product zones in a solid dosage plant is a grade D classification. This equates to particulate level classification of ISO 14644-1 Class 8, "at rest", measured against particles size of 0.5 μm and 5 μm*

Factors that contribute to quality products

- *Starting materials and packaging materials*
- *Validated processes*
- *Personnel*
- *Procedures*
- *Equipment*
- *Design and quality of premises*
- *Manufacturing environment*

Inadequacies in the above factors will lead to sub-standard products.

Factors contributing to quality products



The manufacturing environment is critical for product quality

- *Light*
- *Temperature*
- *Humidity*
- *Air movement*
- *Microbial contamination*
- *Particulate contamination*
- *Uncontrolled environment can lead to product degradation*
  - *product contamination*
  - *loss of product and profit*

What are contaminants ?

Contaminants are

- *Products or substances other than product manufactured*
- *Foreign products*
- *Particulate matter*
- *Micro-organisms*
- *Endotoxins (degraded micro-organisms)*

Cross-contamination is a particular case of contamination

Cross-Contamination (1)

What is Cross-Contamination ?

Definition of Cross-Contamination:

Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

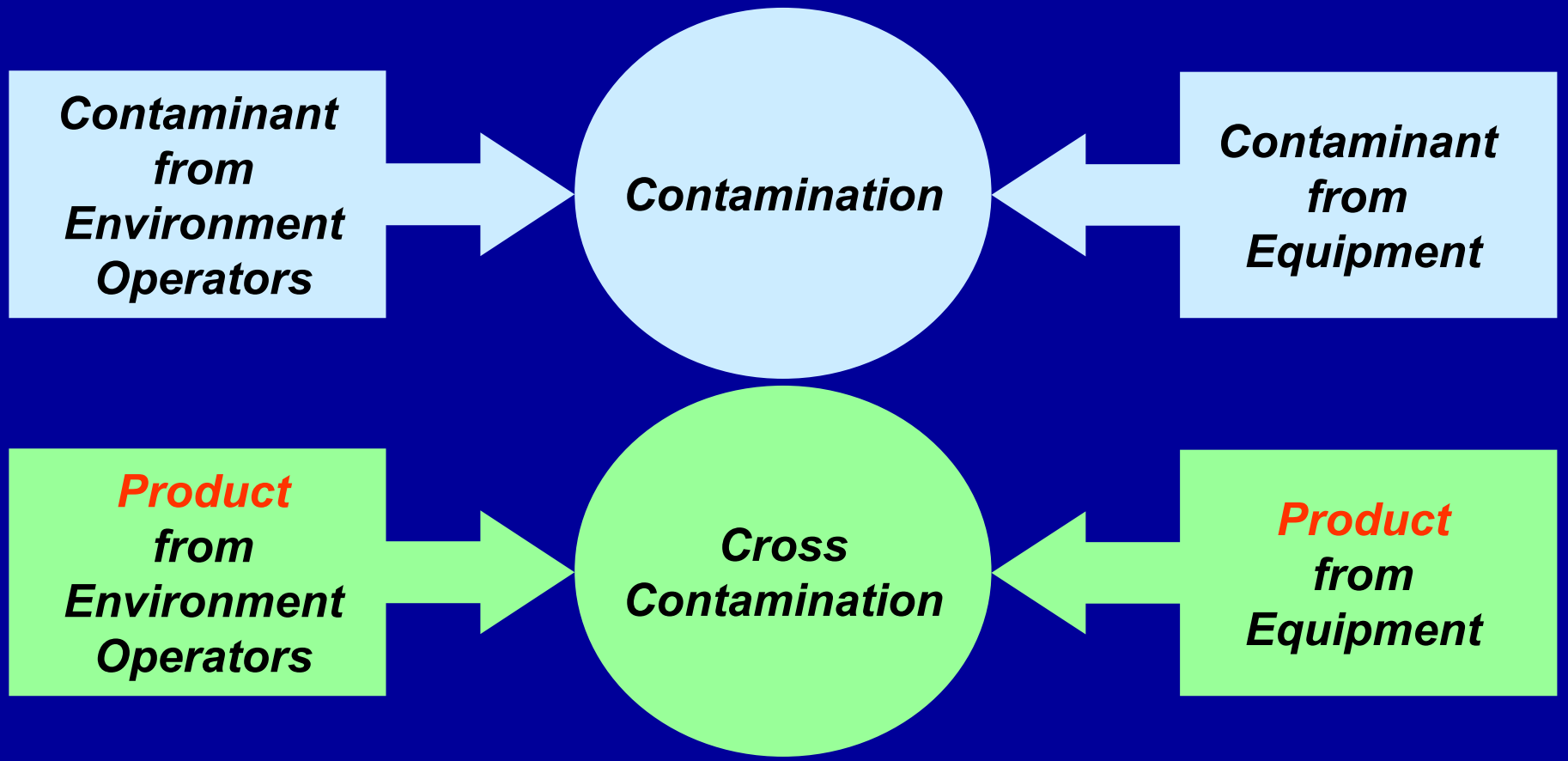
(WHO) **Annex 1, Glossary**

Cross-Contamination (2)

From where does Cross-Contamination originate?

- *Poorly designed air handling systems and dust extraction systems*
- *Poorly operated and maintained air handling systems and dust extraction systems*
- *Inadequate procedures for personnel and equipment*
- *Insufficiently cleaned equipment*

Cross-Contamination (3)



Cross-Contamination (4)

Cross-contamination can be minimized by :

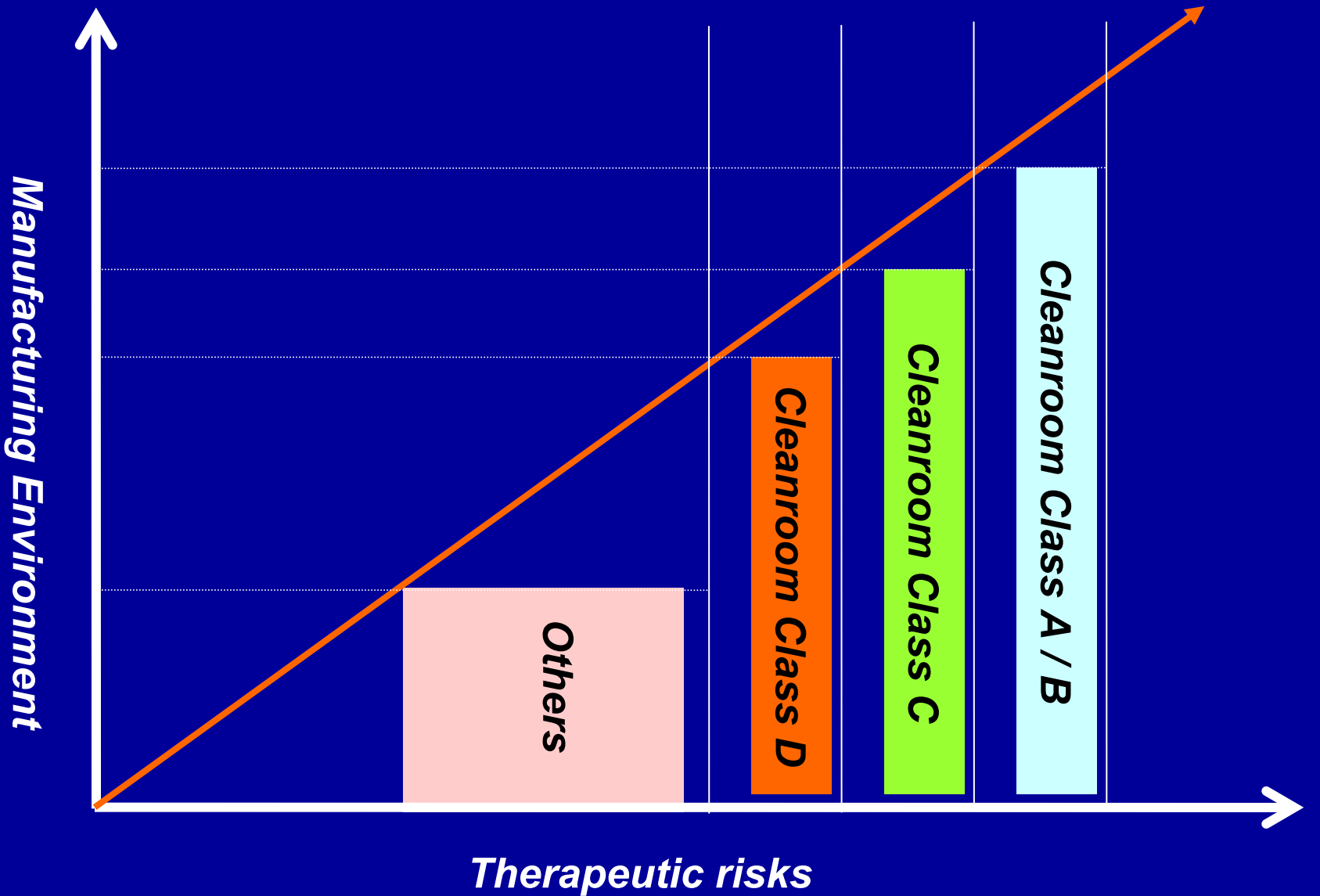
- *Personnel procedures*
- *Adequate premises*
- *Use of closed production systems*
- *Adequate, validated cleaning procedures*
- *Appropriate levels of protection of product*
- *Correct air pressure cascade*

Level of Protection Concept

Defines environmental requirements

- *Helps prevent contamination and cross-contamination*
- *Allows production under optimal hygiene conditions*
- *Takes into account*
  - *product sensitivity to contamination*
  - *therapeutic risk*

Therapeutic risks



Levels of Protection

Parameters to be defined :

- *Air cleanliness requirements (filters type and position, air flow patterns, air changes, pressure differentials, contamination levels by particulate matter and micro-organisms)*
- *Personnel and material transfer methods*
- *Permitted operations*
- *Building design and finishes*

Annex 1, 17.3, 17.4

Dust classification

Dust can be roughly classified by size according to :

- *Coarse dust with size range of 50 to 500 μm (settles rapidly)*
- *Fine dust with size range of 1 to 50 μm (settles slowly)*
- *Ultra fine dust with size range <0.5 μm to 1.0 μm (remains constantly suspended)*
- *Particles <0.05 μm are considered to vapors and not dust*

Only dust particles that are greater than 10 μm are visible to the naked eye with good lighting and good eyesight

Sources of Contamination (General information only)

Type of contamination	Example	Derived from (Examples)	Dealt with by (Examples)
- Non-viable (particulate)	- Metal specks - Clothing fiber	- Equipment - People's clothing - Outside air - Water supply	- Airborne particles are HEPA filtered - Contact part are cleaned and sterilized - Water purification systems
- Viable (micro-organism)	- Bacteria - Yeast molds	- People - Water - Outside air - Equipment, tools - Excipients - Active ingredients	- Limit aseptic core interventions - Airborne particles are HEPA filtered - Sterile filtration of solutions (0.2 μm) - Steam sterilization or irradiation of components
- Endotoxins (not normally associated with airborne bacteria)	- Arising from cell wall debris from certain organisms (often water borne)	- Wet equipment change parts, or container/closure after a period of time exposure	- Caustic soda solution with heat - High temperature (> 200 ^{0}C) time dependent

Particles Shedding

Activity	No. of particle generated/min
Sitting or standing still	100,000
Sitting, Small movement of arms or head	500,000
Sitting, moving arms , legs or head	1,000,000
Standing up	2,500,000
Walking slowly	5,000,000
Walking normally	7,500,000
Walking with speed (2.5m/s)	10,000,000
Performing work-out	15-30 x 1,000,000

Bacterial skin populations
Contact plate method

Hand & Neck

Site	Plate count
Forehead	348
Temple	560
Nose	TNTC
Upper lip	TNTC
Cheek	584
neck	316

Bacterial skin populations
Contact plate method

Upper trunk and arms

Site	Plate count
Upper arm	42
Elbow	8
Forearm	41
Wrist	TNTC
hand	224

Bacterial skin populations
Contact plate method

Lower Trunk and Arms

Site	Plate count
Shoulder	43
Breast	50
Perineum	TNTC
Hip	104
Inner thigh	TNTC

What is Cleanroom ?

- *Federal Standard 209 E*

  “A room in which the concentration of airborne particles is controlled and which contains one or more clean zone”

- *ISO 14644-1*

  “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 in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary”

What is Clean area ?

- *WHO TRS 908, 2003, Annex 4*

  "An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area"

- *PIC/S (1 July 2004)*

  "An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area"

  Note : The different degree of environmental control are defined in the Supplementary Guidelines for the Manufacture of sterile medicinal products

Airborne particulate classification for manufacture of sterile pharmaceutical preparation (WHO)

Grade	At rest		In operation	
	Maximum number of particles permitted/m ^{3}		Maximum number of particles permitted/m ^{3}	
	0.5 – 5.0 μm	> 5.0 μm	0.5 – 5.0 μm	> 5.0 μm
A	3500	0	3500	0
B	3500	0	350 000	2000
C	350 000	2000	3 500 000	20 000
D	3 500 000	20 000	Not defined	Not defined

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Good manufacturing practices for sterile pharmaceutical products

ISO airborne particulate cleanliness classes

ISO 14644-1 Class	Maximum permitted number of particles/m^3 equal to or above			
	At rest		In operation	
	0.5 μm	5 μm	0.5 μm	5 μm
Class 5 (LF)	3 500	30	3 500	30
Class 5 (Tur.)	3 500	30	35 000	300
Class 6	35 000	300	350 000	3 000
Class 7	350 000	3 000	3 500 000	30 000
Class 8	3 500 000	30 000	35 000 000	300 000
Class 9	35 000 000	300 000	Not defined	Not defined

LF = uni-directional flow or laminar air flow ; Tur. = turbulent or non uni-directional flow

ISO airborne particulate cleanliness classes for cleanroom and clean zones

Classification numbers (N)	Maximum concentration limits (particles/m^3 of air) for particles equal to and larger than the considered sizes shown below					
	0.1 μm	0.2 μm	0.3 μm	0.5 μm	1 μm	5.0 μm
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1000	237	102	35	8	
ISO Class 4	10 000	2370	1020	352	83	
ISO Class 5	100 000	23 700	10 200	3520	832	29
ISO Class 6	1 000 000	237 000	102 000	35 200	8320	293
ISO Class 7				352 000	83 200	2930
ISO Class 8				3 520 000	832 000	29 300
ISO Class 9				35 200 000	8 320 000	293 000

ISO classification is based on the equation :

$$C_n = 10^N + [0.1/D]^{2.08}$$

C_n *represents the maximum permitted concentration (in particle/m^3 of air) of airborne particles that are equal to or larger than the considered particle size; C_n is rounded to the nearest whole number*

N is the ISO classification number, which shall not exceed the value of 9. Intermediate ISO classification numbers may be specified, with 0.1 the smallest permitted increment of N

D is the considered particle size in μm

0.1 is a constant with a dimension of μm

International Standard : ISO 14644

ISO 14644 consists of the following parts, under the general title Cleanrooms and associated controlled environments :

- Part 1 : Classification of air cleanliness
- Part 2 : Specifications for testing and monitoring to prove continued compliance with ISO 14644-1
- Part 3 : Metrology and test methods

International Standard : ISO 14644

- Part 4 : Design, construction and start-up
- Part 5 : Operation
- Part 6 : Term and definitions
- Part 7 : Separative devices (clean air hoods, gloveboxes, isolators and mini-environments)
- Part 8 : Classification of airborne molecular contamination

Comparison of different airborne particulate classification system for clean areas

WHO GMP	United States (209E)	United States (Customary)	ISO/TC (209)	EEC GMP
Grade A	M 3.5	class 100	ISO 5	Grade A
Grade B	M 3.5	class 100	ISO 5	Grade B
Grade C	M 5.5	class 10 000	ISO 7	Grade C
Grade D	M 6.5	class 100 000	ISO 8	Grade D

EEC : European Commission;

ISO/TC : International Organization for Standardization Technical Committee

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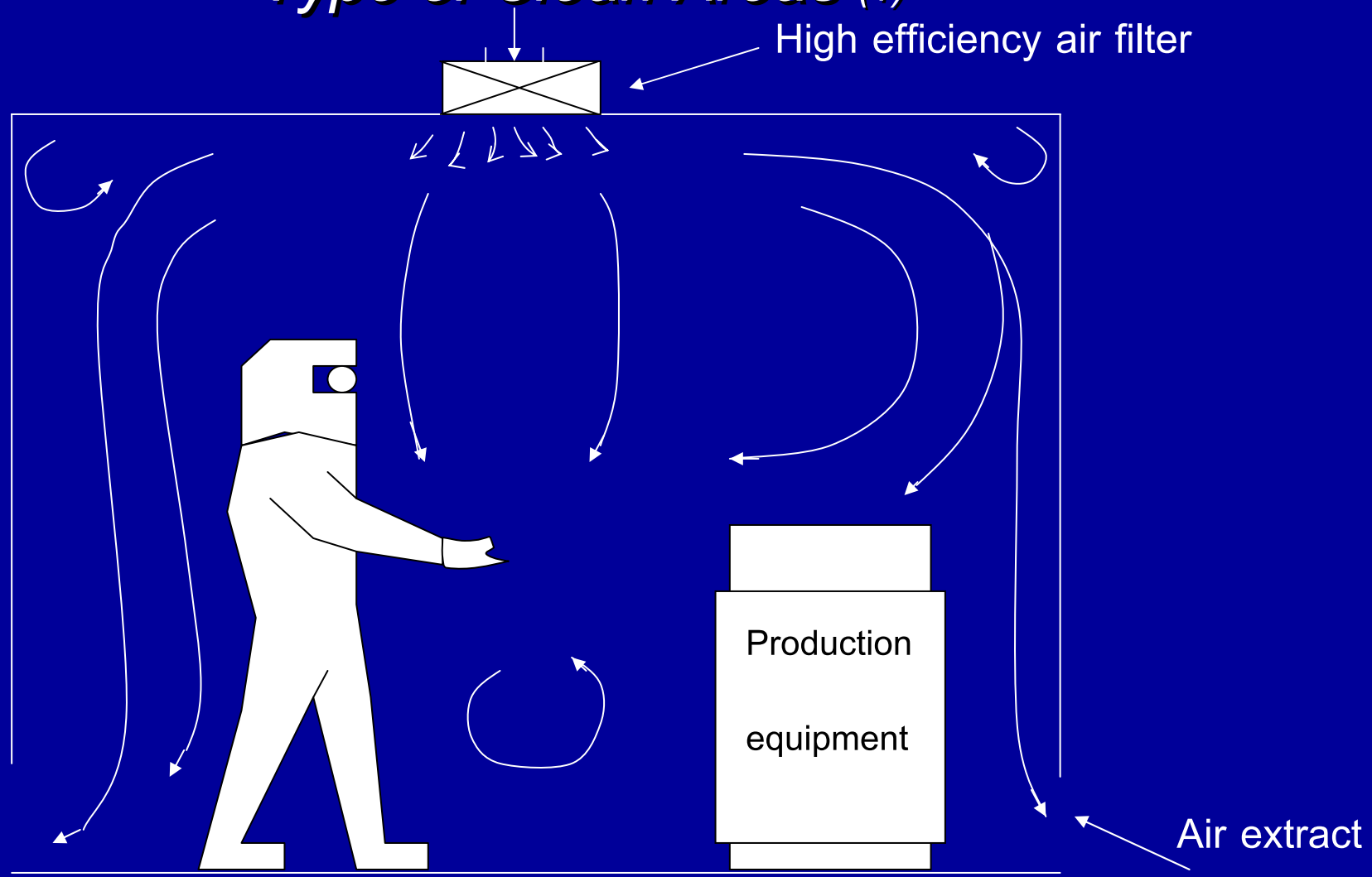
Good manufacturing practices for sterile pharmaceutical products

Comparison of ISO 14644-1 and some replaced US Standards

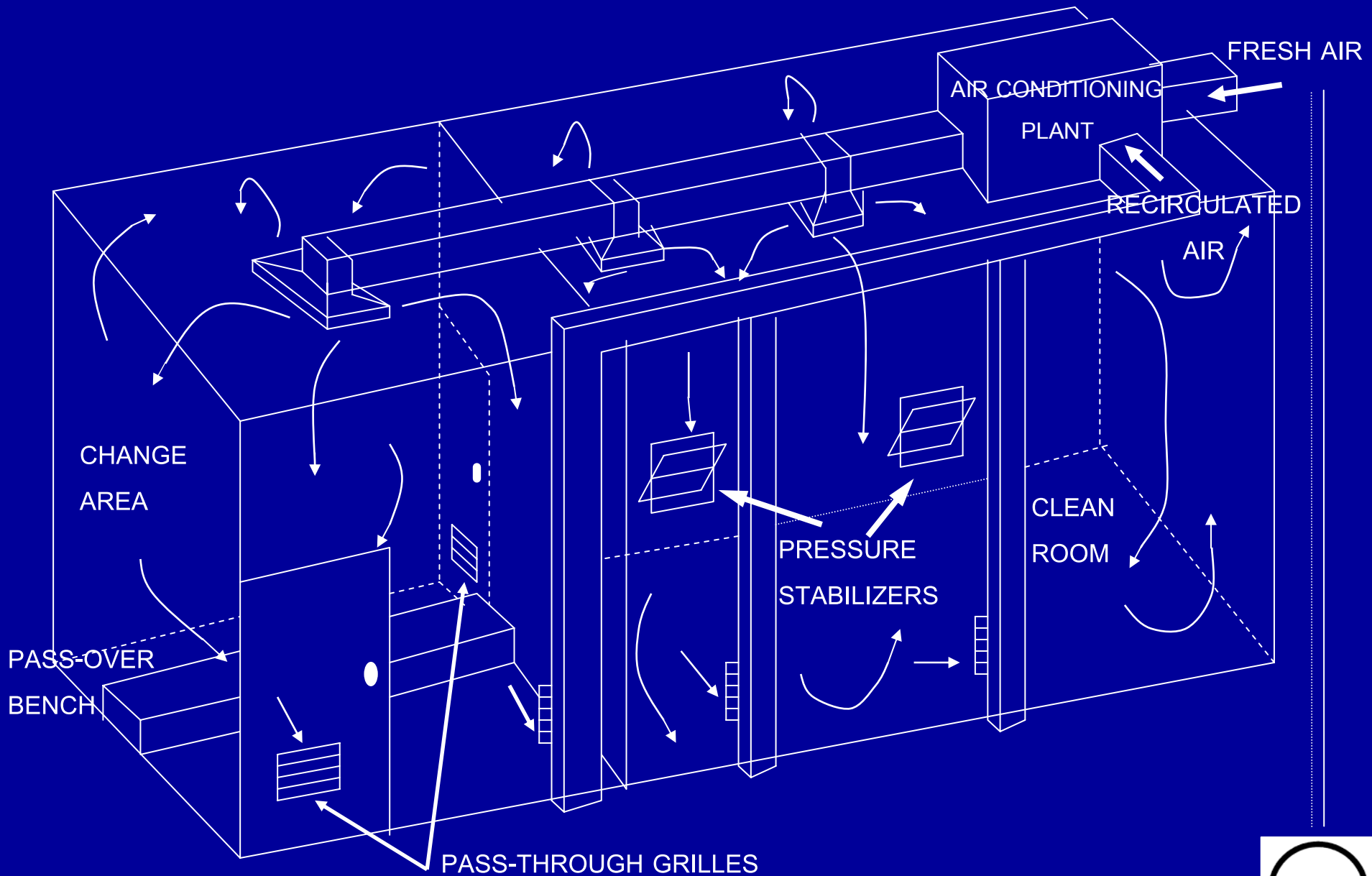
Some standard replaced by EN ISO 14644-1 : 1999								
ISO EN 14644-1 1999 Classes	*Particles per m³ ≥ 0.5 micron*	*US 209E 1992 Metric*	*US 209E 1992 particle/cu.ft.*	*EU cGMP 1997 Cleanliness*	*France AFNOR 1989 Classes*	*Germany VDI 2083 1990 Classes*	*Britain BS 5295 1989 Classes*	*Japan JIS B 9920 1989 Classes*
	1							
2	3.5					0		2
	10	M 1						
3	35	M 1.5	1			1		3
	100	M 2						
4	352	M 2.5	10			2		4
	1 000	M 3						
5	3 520	M 3.5	100	A + B*	4 000	3	E or F	5
	10 000	M 4						
6	35 200	M 4.5	1 000			4	G or H	6
	100 000	M 5						
7	352 000	M 5.5	10 000	C*	400 000	5	J	7
	1 000 000	M 6						
8	3 520 000	M 6.5	100 000	D*	4 000 000	6	K	8
	10 000 000	M 7						
9	100 000 000	M 7.5	1 000 000		40 000 000		L	9

Type of Clean Areas (1)



1. Conventional (non-unidirectional flow or turbulently ventilated) the air being supplied by air supply diffusers or filters in the ceiling

Conventionally ventilated clean room

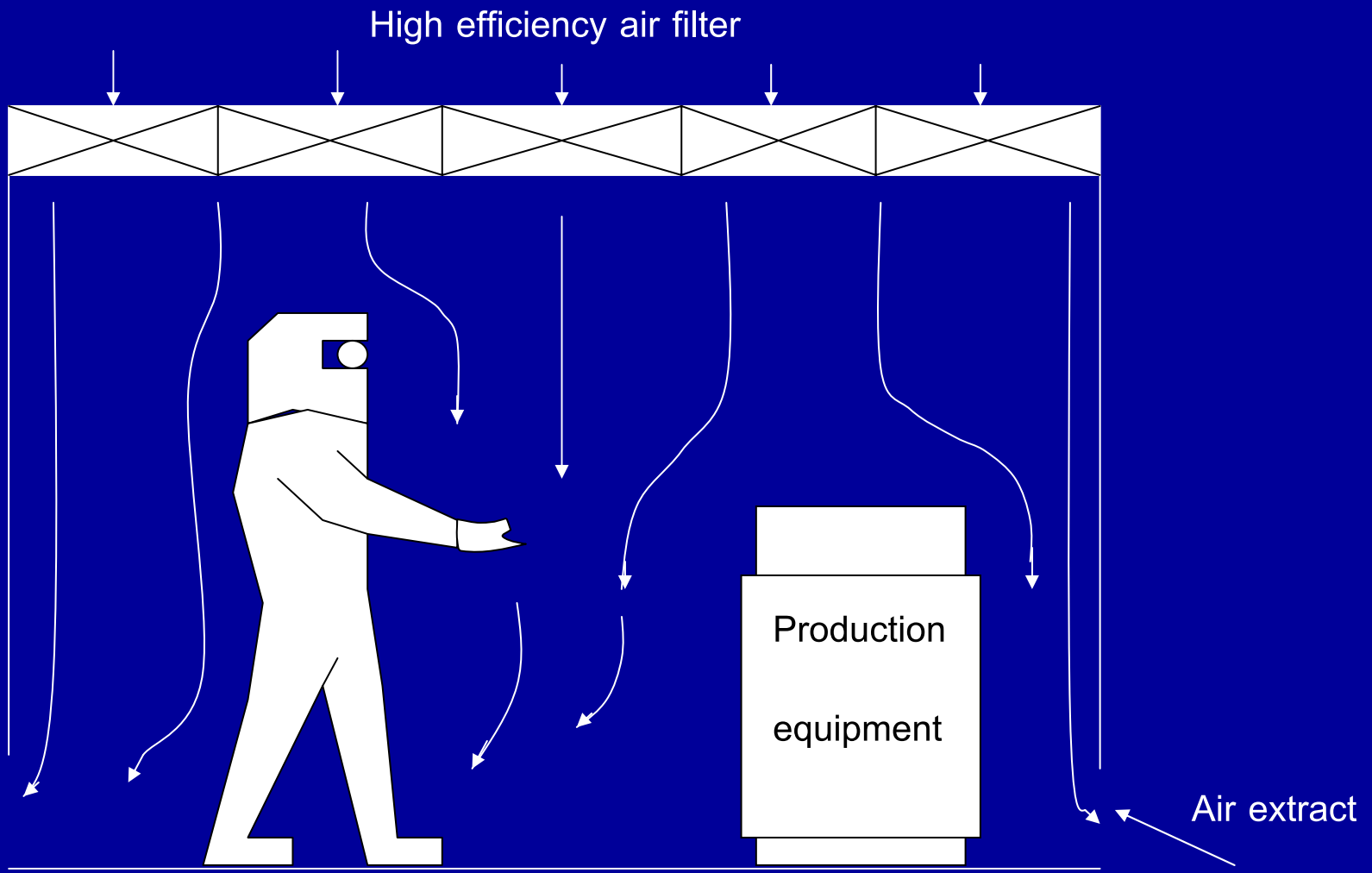


Type of Clean Areas (2)

Cleanroom differs from an ordinary ventilated room in a number of ways :

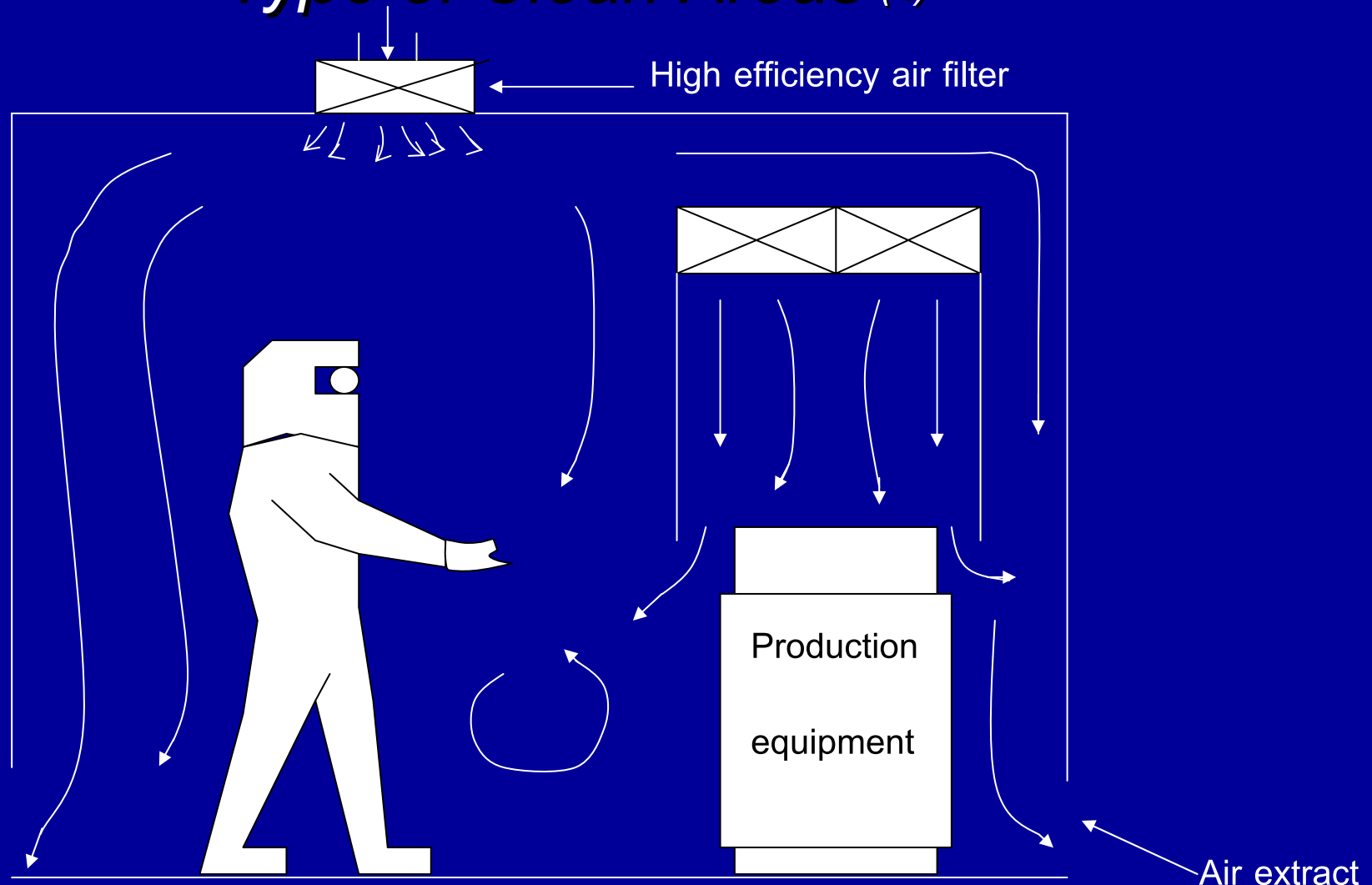
- *Increased air supply*
  - *office or shop (2 - 10 air change per hours)*
  - *cleanroom (20 - 60 air change per hours)*
- *High Efficiency Filter*
  - *High Efficiency Particle Air (HEPA) > 99.97 % efficient in removing particles greater than 0.3* μm
- *Terminal air filter*
- *Room pressurization and pass-though grilles*
  - *pass-through grilles or dampers will usually be seen at a low level on walls or doors*

Type of Clean Areas (3)



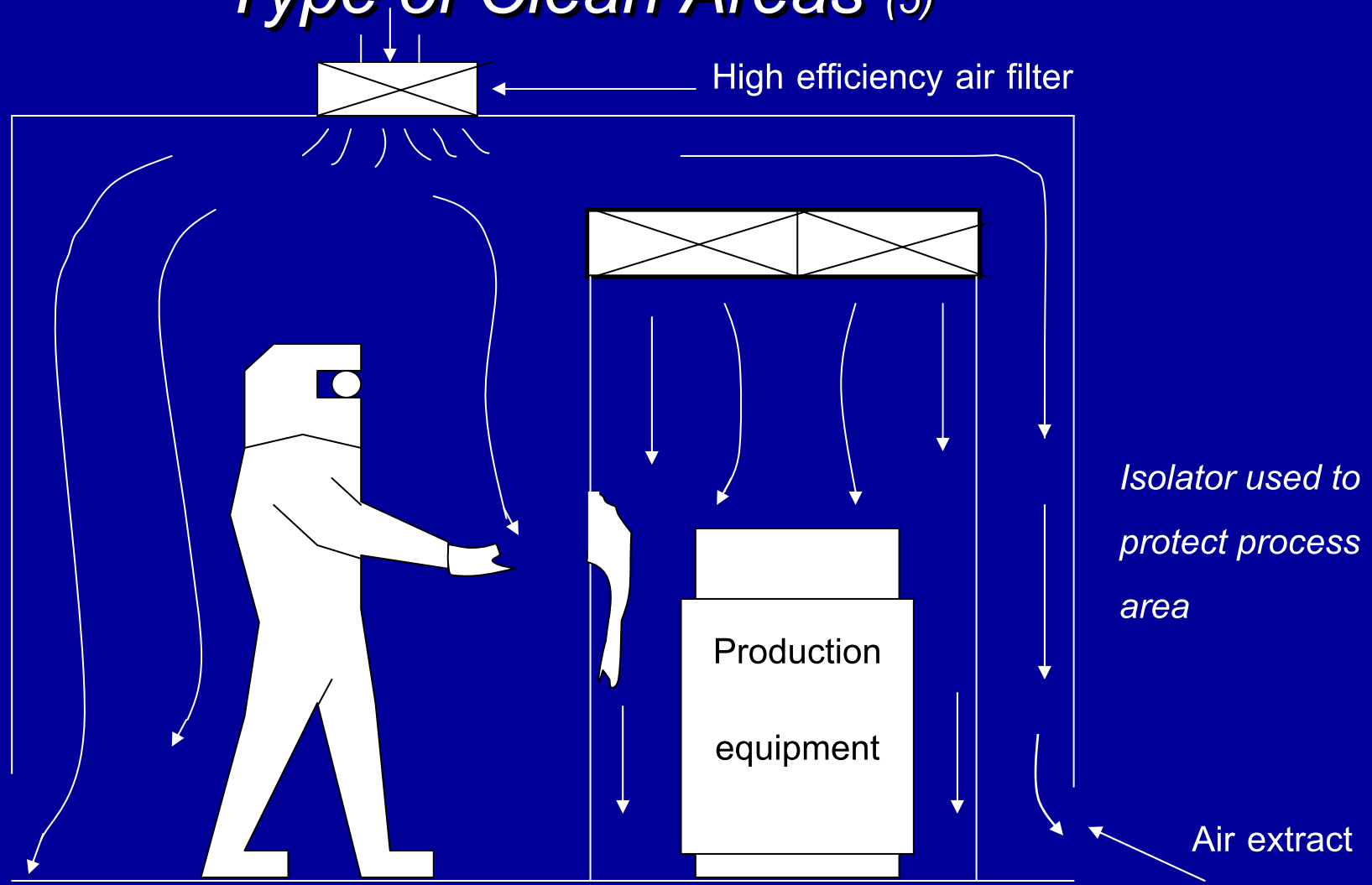
2. Unidirectional flow (laminar flow) clean air is supplied from a bank of high efficiency filters and passes in a unidirectional manner though the room

Type of Clean Areas (4)



3. *Mixed flow clean room with non- unidirectional flow in the room and unidirectional air flow protection the critical processing area*

Type of Clean Areas (5)



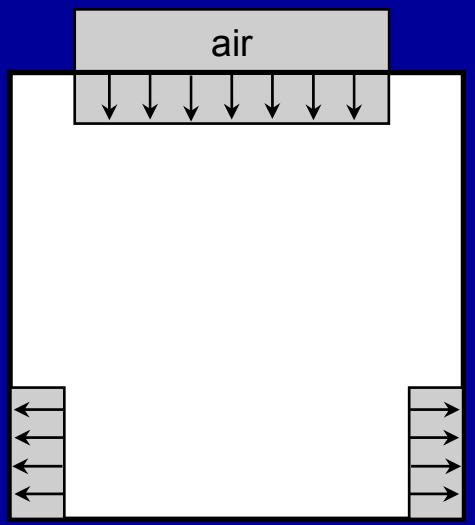
4. Isolators :(microenvironment) these are used within a cleanroom to give the highest level of protection against contamination.

Cleanroom condition

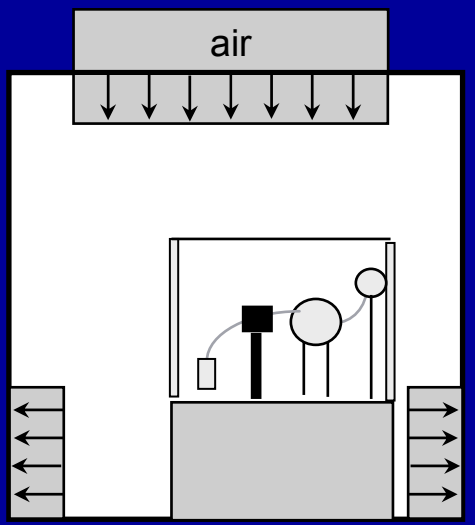
- *as built : condition where the installation is complete with all services connected and functioning but with no production equipment, materials, or personnel present*
- *at rest : condition where the installation is complete with equipment installed and operation in a manner agree upon by the customer and supplier, but with no personnel present*
- *operational : condition where the installation is functioning in the specified manner, with the specified number of personnel and working in the manner agreed upon*

Definition of Conditions

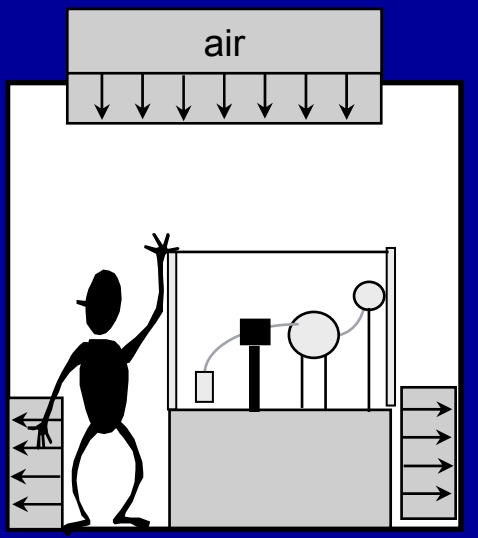
as built



at rest



in operation



Cleanroom classification standards can be divided into the following subgroups given below

Engineering Classes	These originate from Federal Standard 209, and are based on inanimate particles in air
Biocontamination (Pharmacy) Classes	These were originally based on Federal Standard 209 but developed to include living microorganisms. These standards are required for hygenic or sterile production. Guide to Good Manufacturing Practice and the CEN/ISO biocontamination standards cover this field.
Containment Classes	These are for areas where hazardous contaminants are used or can occur.

Type of Pharmaceutical Processes

- *Injectables*
  - *Aqueous products*
  - *Freeze-dried products*
  - *Powder products*

    - % RH

    - high potency
- *Topicals*
  - *class 100 000*
- *Oral Products*
  - *Pharmaceutical manufacturing facilities where products are exposed to the environment should be classified as "cleanrooms*
  - *cross-contamination between products or between product and people*

Level of Protection (Oral solid dosage form) *(1)*

- *Level 1 (General) : An area with normal housekeeping and maintenance. (e.g. Warehousing, Secondary Packing)*
- *Level 2 (Protected) : An area in which steps are taken to protect the exposed drug substance from contamination or degradation. (e.g. Manufacturing, Primary Packing, Dispensing, etc.)*
- *Level 3 (Controlled) : An area in which specific environmental conditions are defined, controlled and monitored to prevent contamination or degradation of the drug substance.*

Level of Protection (Oral solid dosage form) (2)

- *Level 1 protection and Pharmaceutical conditions can be equated with an ISO Class 9 condition.*
- *The most common applied classification for open product zones in a solid dosage plant is a grade D classification.*
- *Grade D equates to particulate level classification of ISO 14644-1 Class 8, at rest, measured against particles size of 0.5 μm and 5 μm*

Typical Zone	Level of Protection		Typical Dress Code
	GMP Guides	ISO Class Equivalent	
Street, canteen	External	External	Outdoor clothes
Receipt & dispatch	Level 1 or Unclassified	ISO Class 9	Appropriate to area
Warehousing, offices	Level 1 or Unclassified	ISO Class 9	Appropriate to area
Weighing & dispensing	Level 2 – background Level 3 – open product	ISO Class 8 – background ISO 6 or 7 – open product	Clean garments
Blending	Level 2 or 3	ISO Class 8 or 7	Clean garments
Granulation	Level 2 or 3	ISO Class 8 or 7	Clean garments
Milling	Level 3	ISO Class 8 or 7	Clean garments
Encapsulation & compression	Level 2	ISO Class 8	Clean garments
Coating	Level 2	ISO Class 8	Clean garments
Primary packing	Level 2 or 3	ISO Class 8 or 7	Clean garments
Secondary packing	Level 1 or Pharmaceutical	ISO Class 9	Captive coat, hat and overshoes
Non-sterile processing	Controlled or Class 100000 (in operation)	ISO Class 8	Clean garments
Rooms where filling takes place	Clean or Class 10000 (in operation)	ISO Class 6 or 7	Sterile garments
Point of fill or other aseptic operations	Critical or Class 100 (in operation)	ISO Class 5	Sterile garments
Change rooms & airlocks	The same classification as the area they serve	The same classification as the area they serve	Change to garments for the higher classification

Parameters influencing Levels of Protection (1)

- *Number of particles in the air*
- *Number of micro-organisms in the air or on surfaces*
- *Number of air changes for each room*
- *Air velocity*
- *Air flow pattern*
- *Filters (type, position)*
- *Air pressure differentials between rooms*
- *Temperature, humidity*

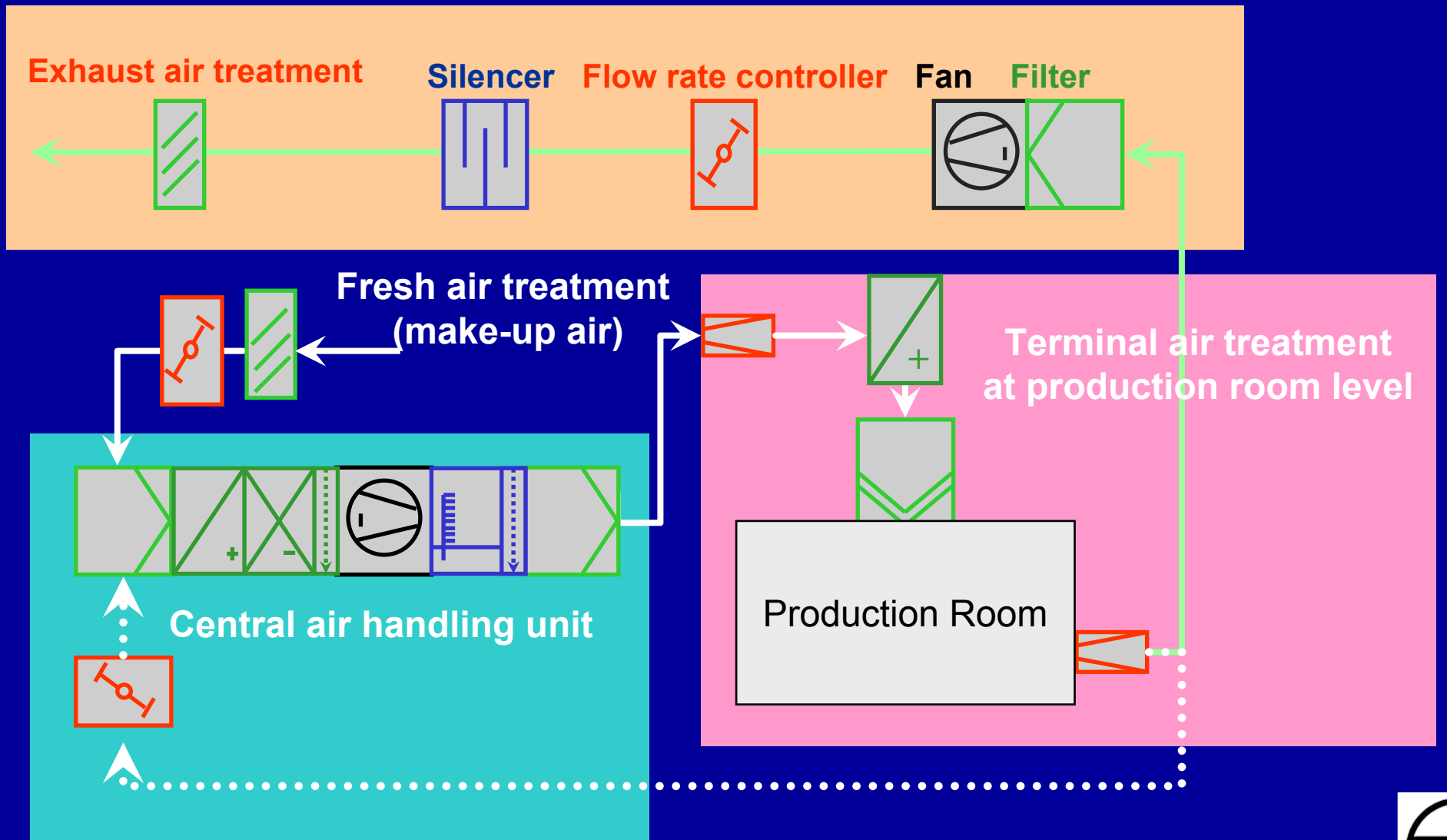
Parameters influencing Levels of Protection (2)

Air handling systems:

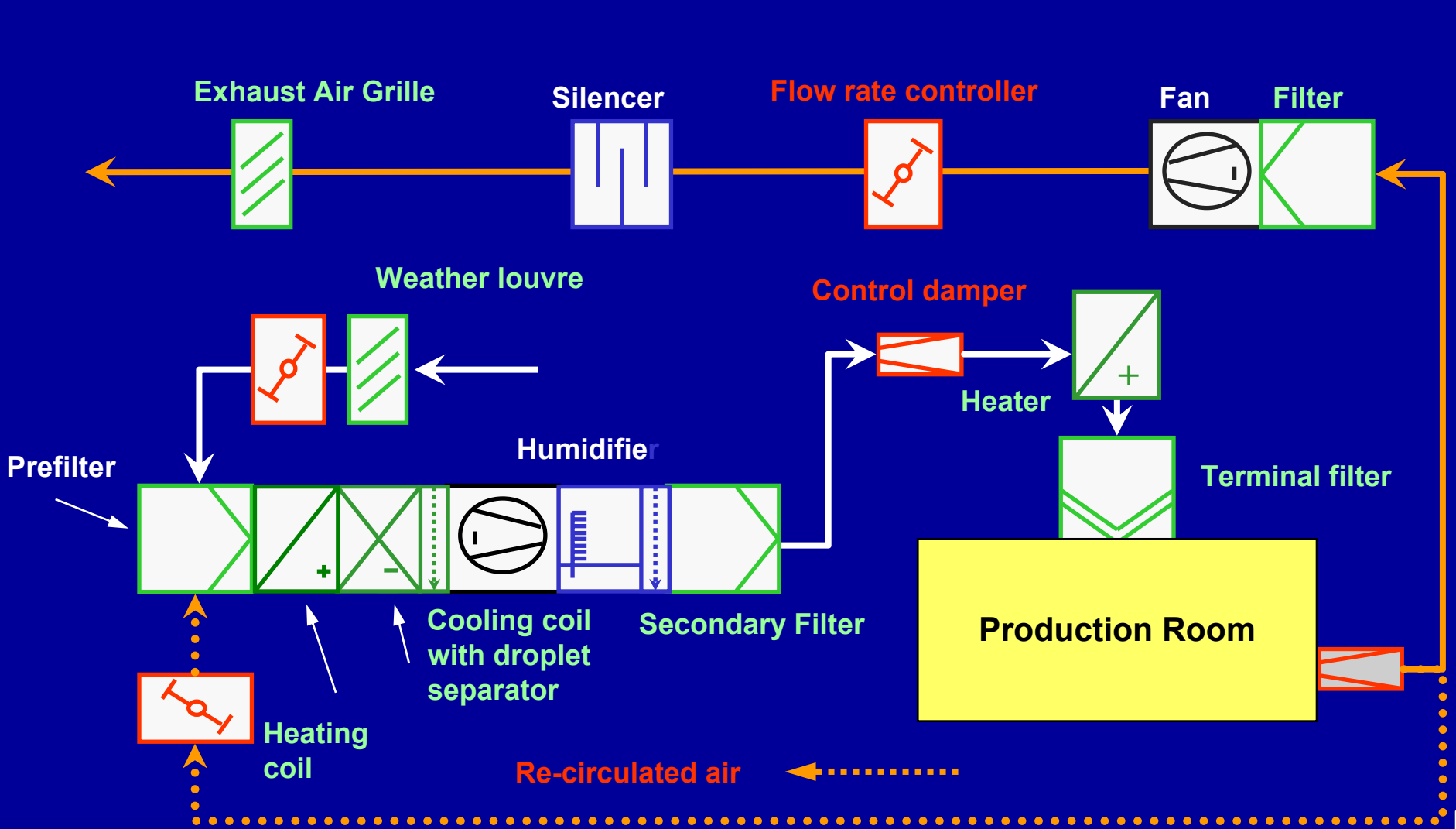
- *Are the main tool for reaching required parameters*
- *But are not sufficient as such*
- *Need for additional measures such as*
  - *appropriate gowning (type of clothing, proper changing rooms)*
  - *validated sanitation*
  - *adequate transfer procedures for materials and personnel*

Annex 1, 17.10 to 17.16

Main subsystems



Overview components



Characteristics of air handling systems

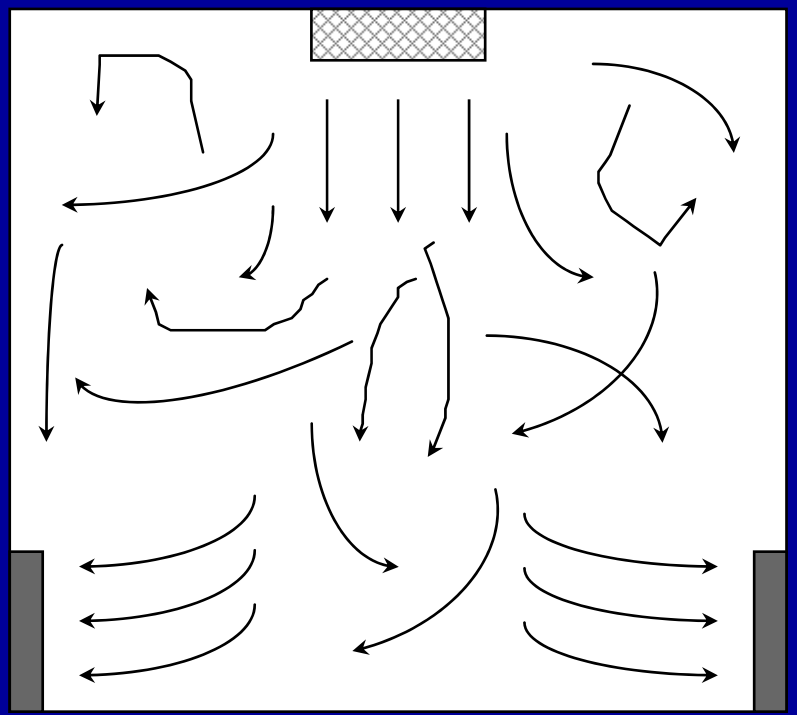
In the following slides, we will study alternatives in air handling systems

- *Turbulent or uni-directional airflows*
- *Filter position*
- *Air re-circulation vs fresh air*
- *Return air systems (positions)*
- *Overpressure requirements*

Air flow patterns (1)

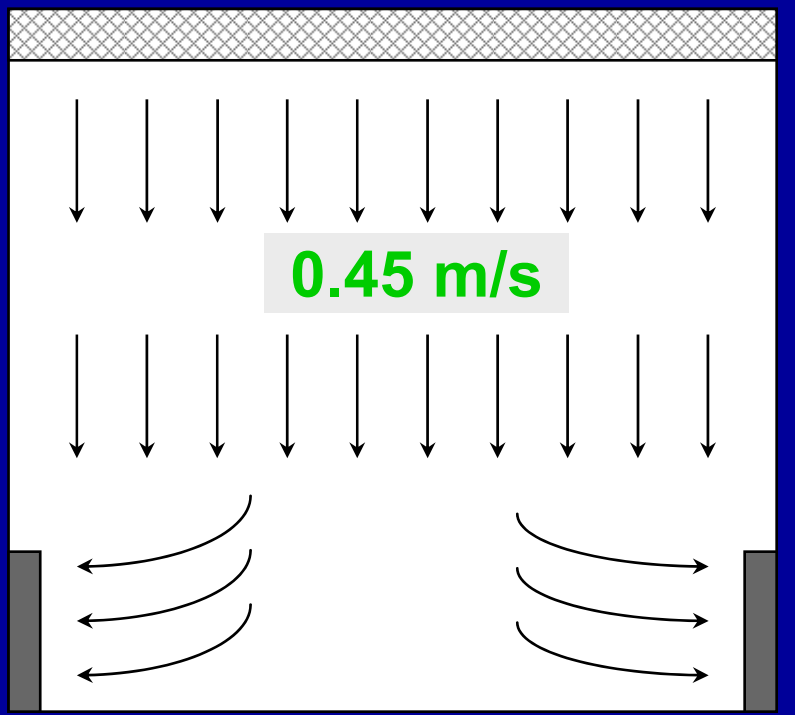
Turbulent

dilution of dirty air



Uni-directional / laminar

displacement of dirty air



Annex 1, 17.3

Air flow patterns (2)

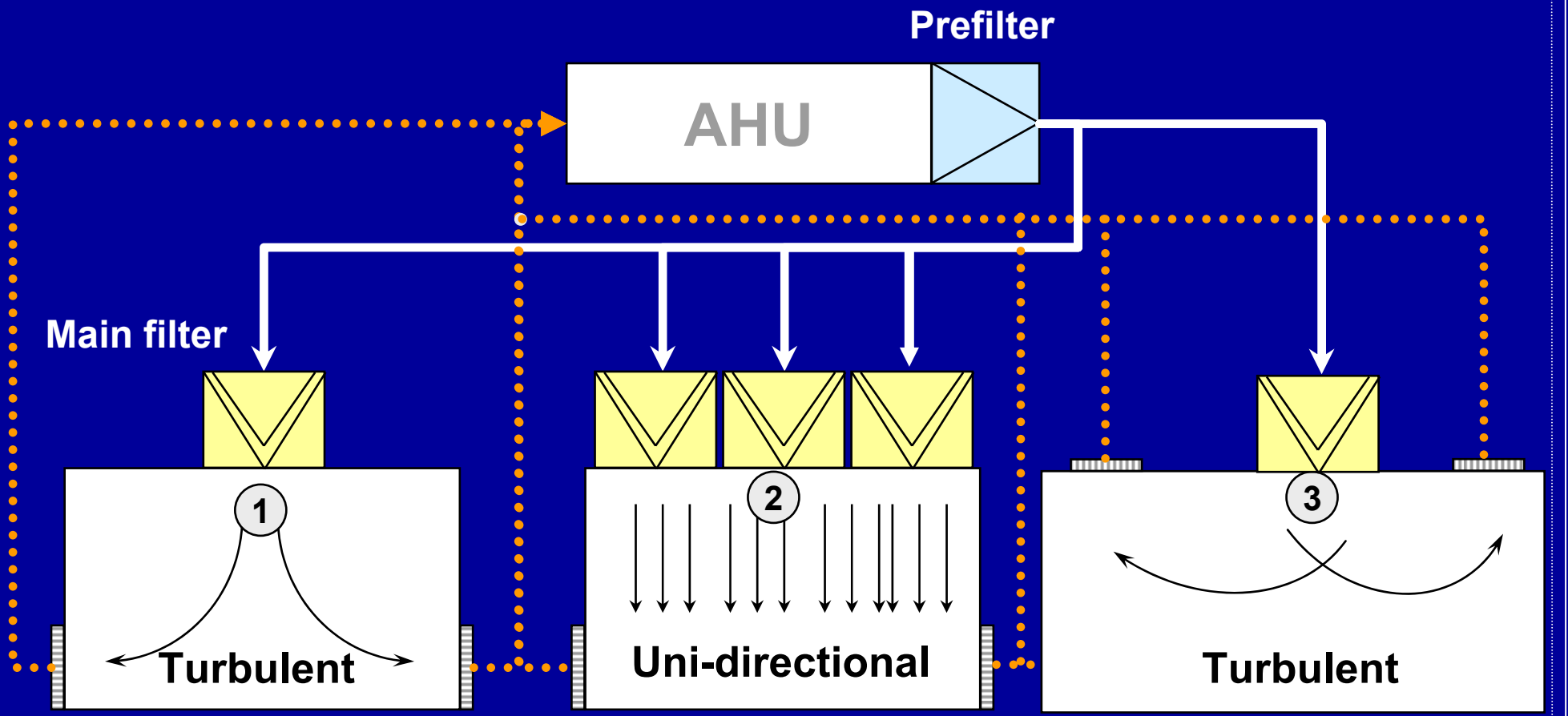
Filtered air entering a production room or covering a process can be

- *turbulent*
- *uni-directional (laminar)*
  - *GMP aspect*
  - *economical aspect*

New technologies: barrier technology/ isolator technology.

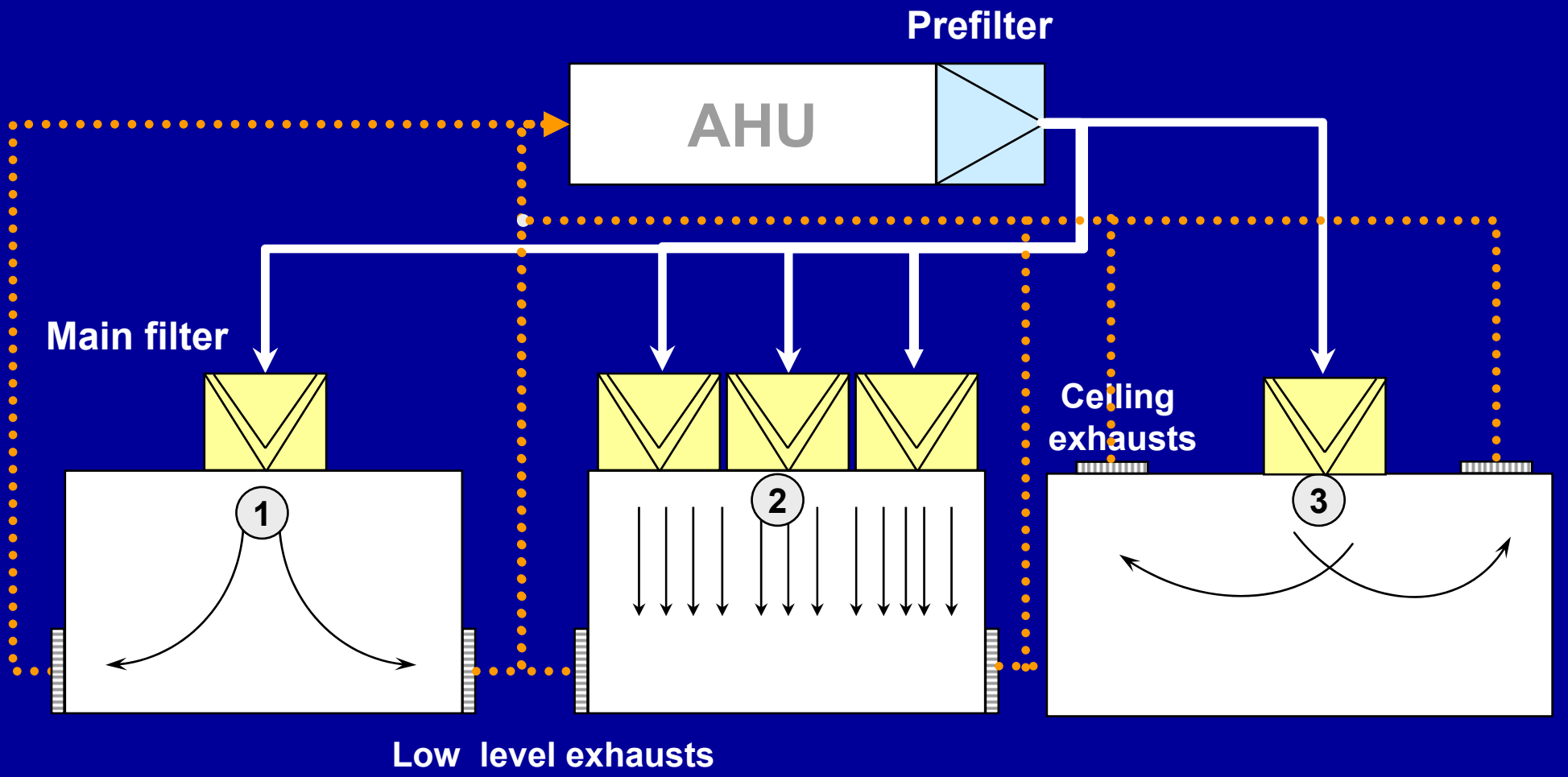
Annex 1, 17.3, 17.4

Air flow patterns (3)

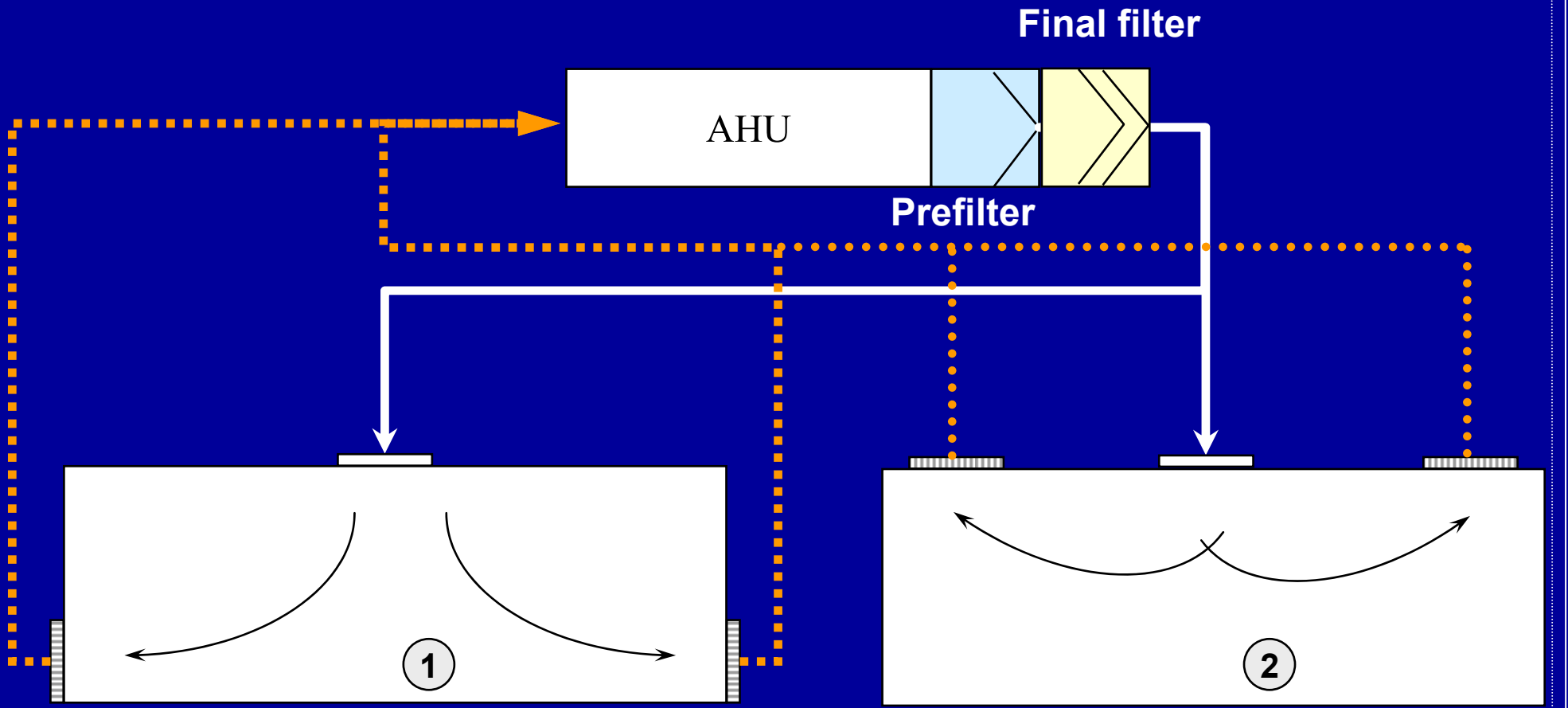


Annex 1, 17.3

Positioning of filters (1)



Positioning of filters (2)



Air re-circulation

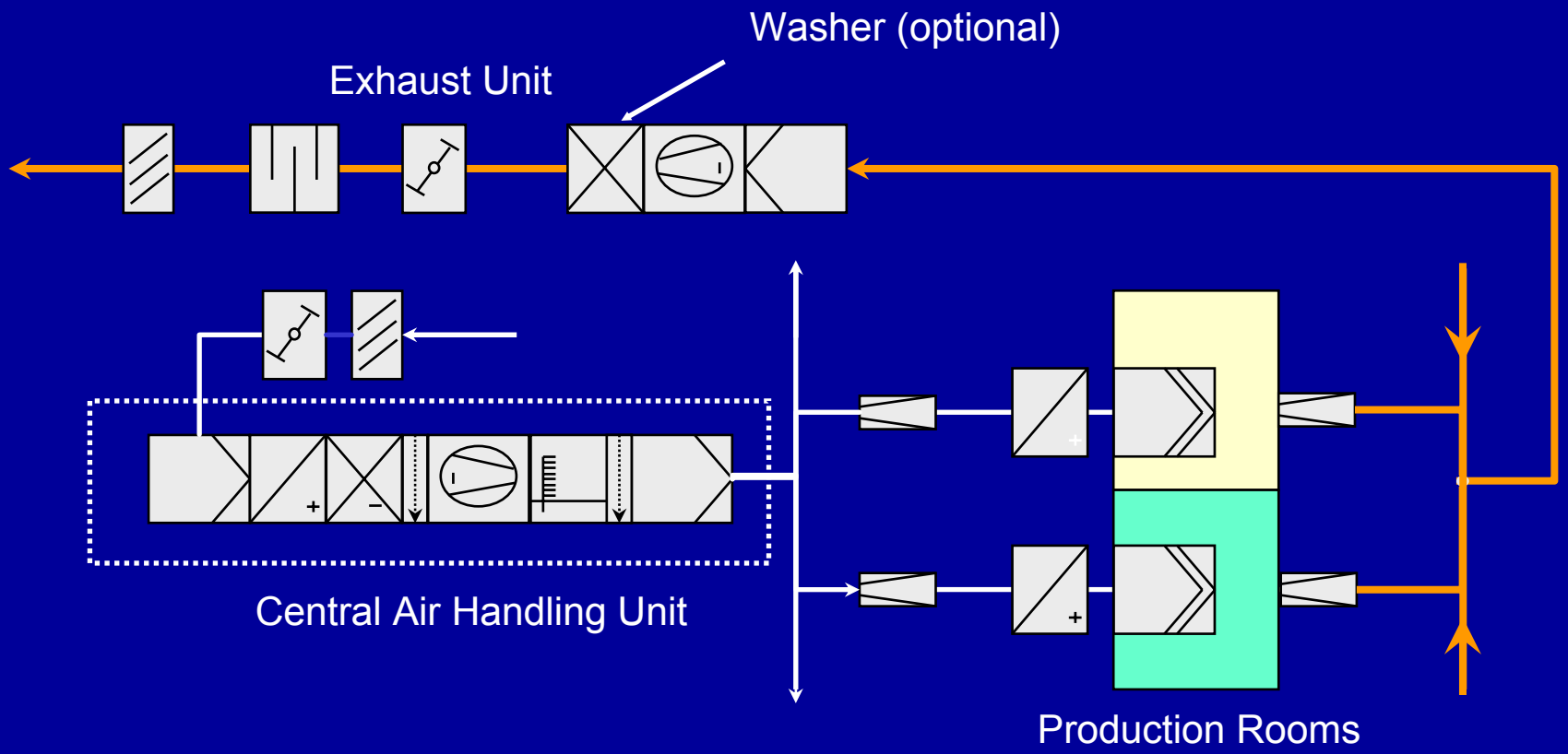
The filtered air entering a production room can be

- *100% exhausted or*
- *a proportion re-circulated*
  - *GMP aspect*
  - *Economical reasons*

Annex 1, 15.10, 17.24

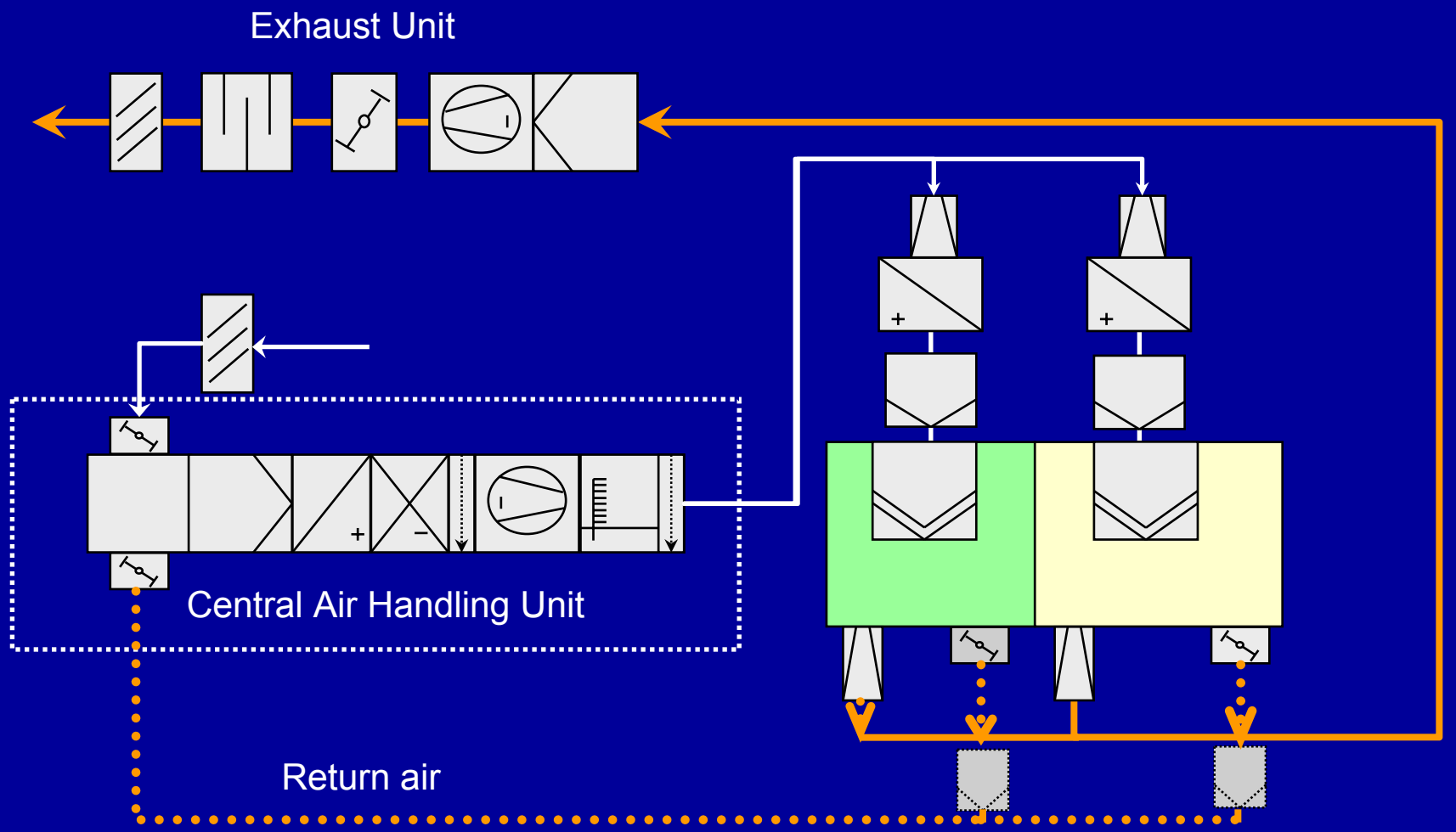
Ventilation with 100% fresh air

(no air re-circulation)



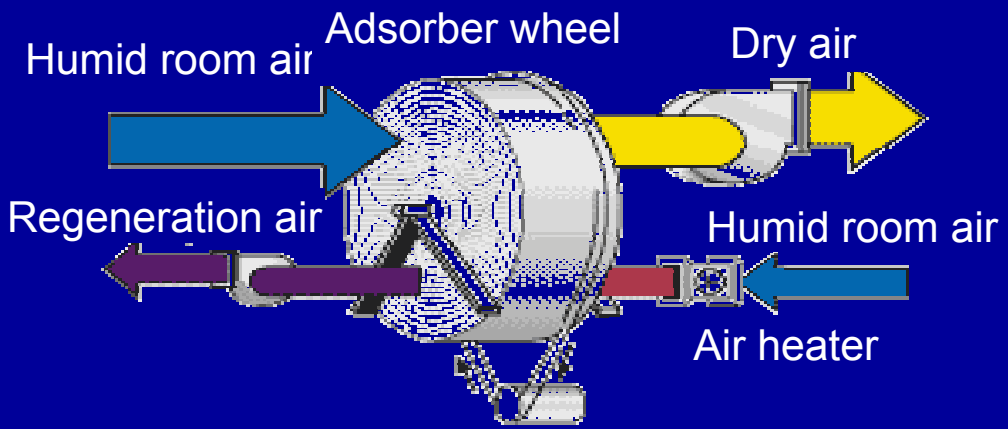
Annex 1, 17.24

Ventilation with re-circulated air + make-up air



Central Air Handling Unit

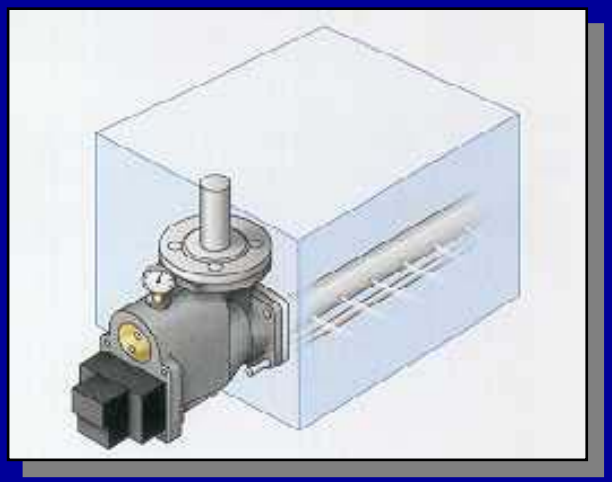
Control damper for air flow

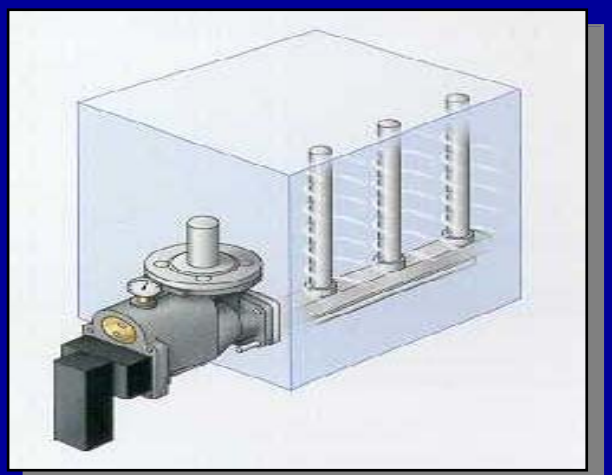


De-humidification

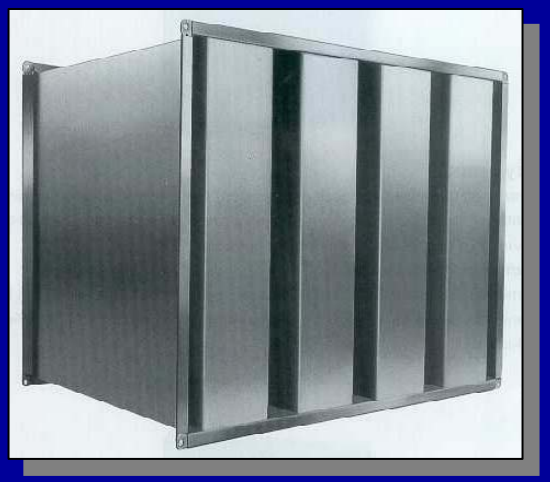
Air handling unit

Humidifier





Silencer

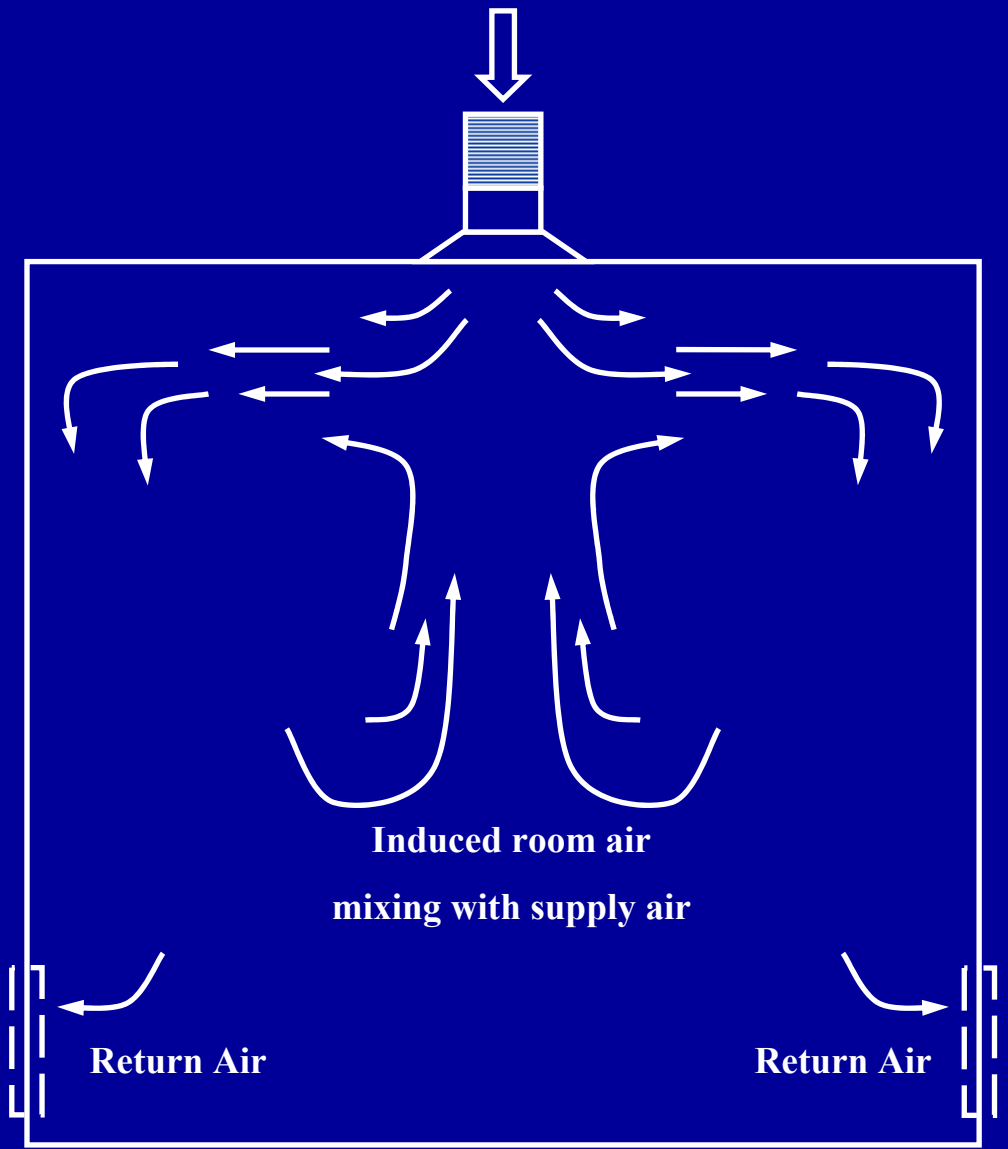


Heating and cooling units

Air flow patterns

- *Supply air diffusers of the high induction type should not be used in a cleanroom*
- *Air should be exhausted from rooms at a low level.*
- *Recommended supply air diffuser*
  - *Perforated plate diffuser*
  - *Swirl diffuser*

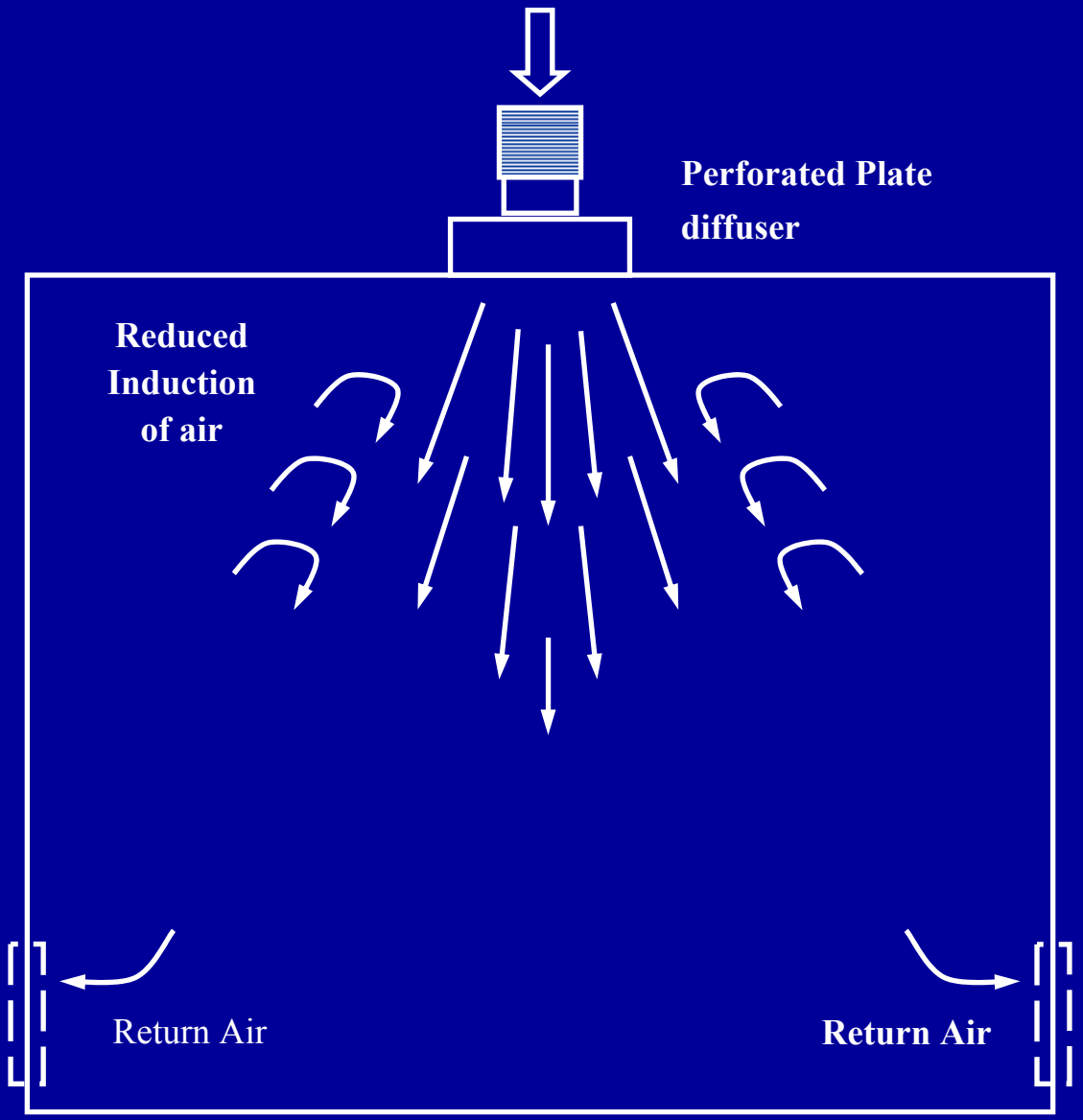
Induction diffuser (not recommended)



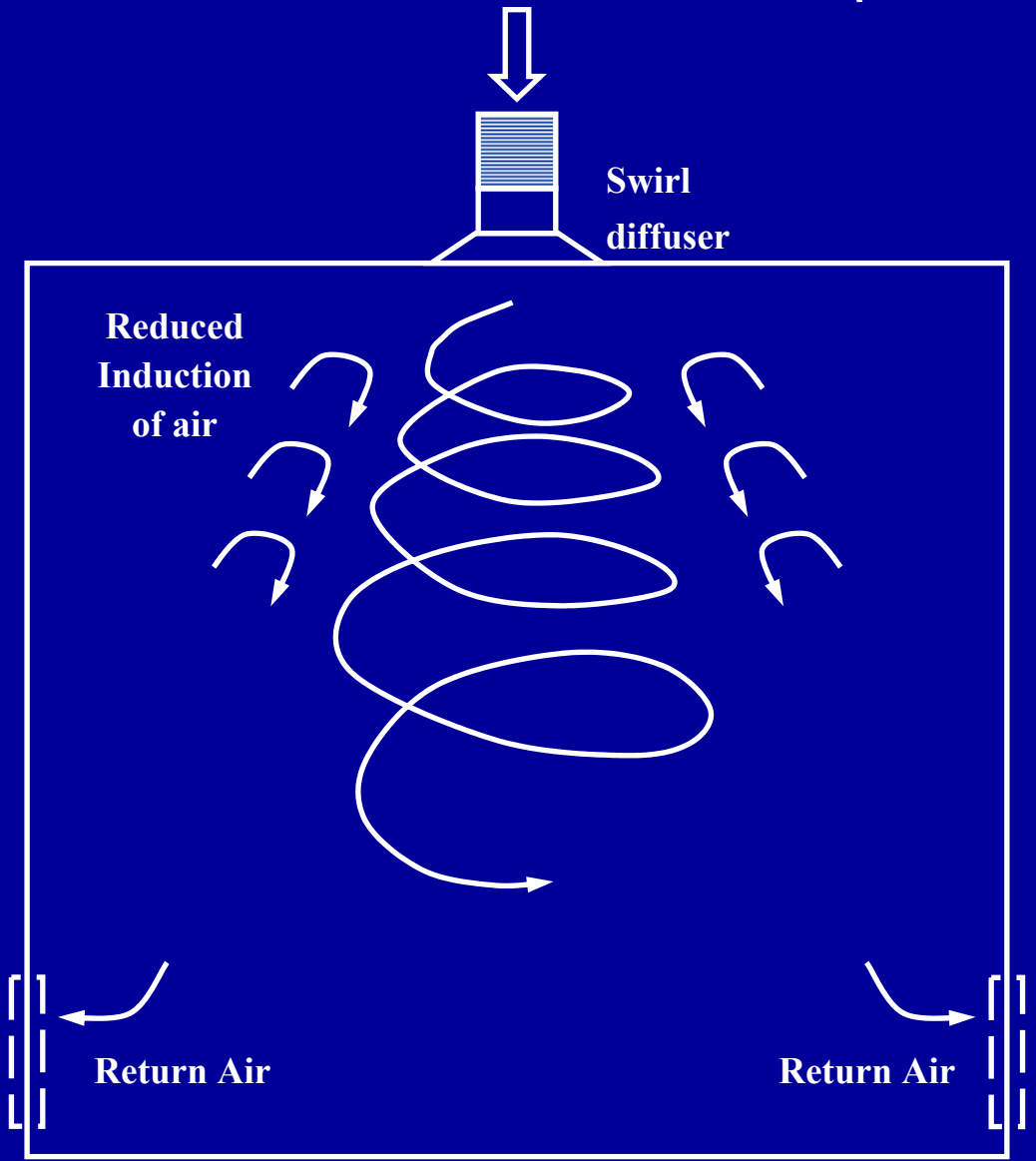
High induction office type diffuser

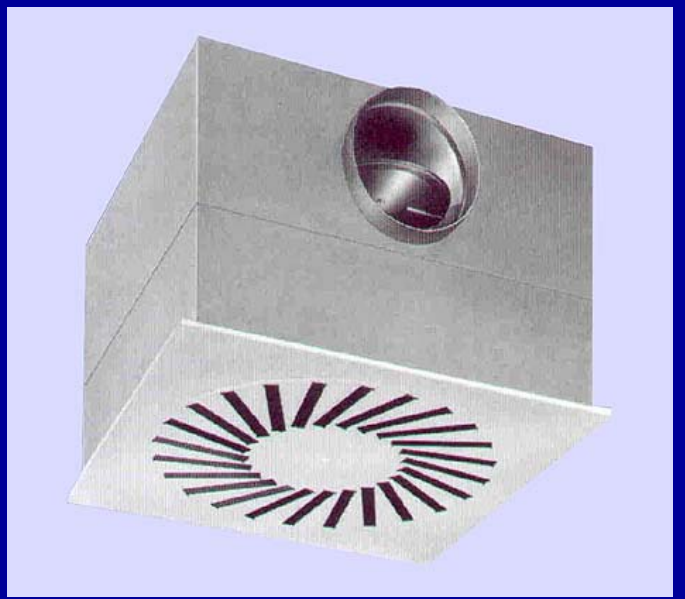
(avoid)

Perforated plate diffuser (recommended)



Swirl diffuser (recommended)

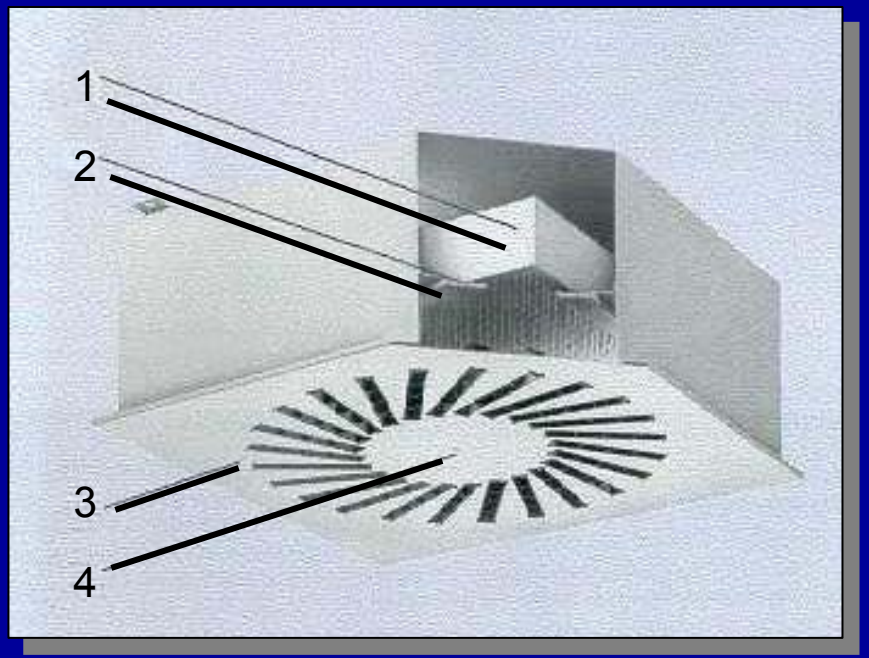


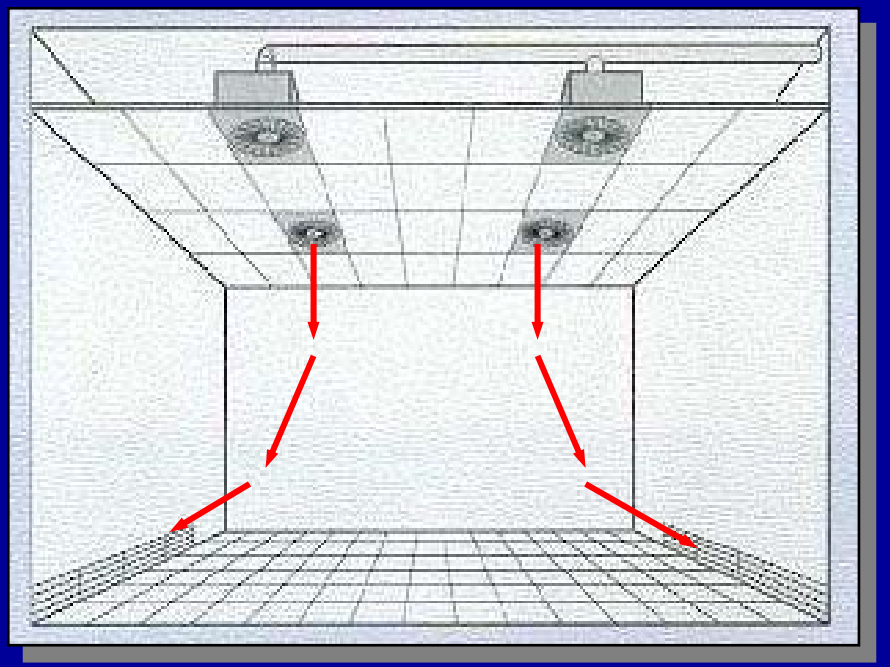


Low induction swirl diffuser

(preferred)

Swirl Type air diffusers with terminal filters





1 Filter

2 Tightening frame

3 Register outlet

4 Screw fixation for register

Components (1)

◆ *Weather louvre*	✓ *To prevent insects, leaves, dirt and rain from entering*
◆ *Silencer*	✓ *To reduce noise caused by air circulation*
◆ *Flow rate controller*	✓ *Automated adjustment of volume of air (night and day, pressure control)*
◆ *Control damper*	✓ *Fixed adjustment of volume of air*

Components (2)

Heating unit	To heat the air to the proper temperature
Cooling unit /dehumidifier	To cool the air to the required temperature or to remove moisture from the air
Humidifier	To bring the air to the proper humidity, if too low
Filters	To eliminate particles of pre-determined dimensions and/or micro-organisms
Ducts	To transport the air

Problems with components

Flow rate controller	Blocked
Control damper	Poorly adjusted, bad pressure differential system
Humidifier	Bad water/steam quality/poor drainage
Cooling battery	No elimination of condensed water/poor drainage
Filters	Incorrect retention rate/damaged/badly installed
Ducts	Inappropriate material/internal insulator leaking

The Containment Classes

Class	Explanation	Example
BL 1	Normal laboratory standard	Ordinary biochemistry labs, School and university labs
BL 2	Special training and routines to prevent lab infections. Appropriate waste handling	Diagnostic labs Health lab
BL 3	Special lab with negative pressure Air locks for people and material Autoclave in the room All work done in safety cabinet Special decontamination of waste	Special safety labs Tuberculosis labs
BL 4	Special labs with total separation between humans and microorganism in every respect, negative pressure, sterilization	High risk labs

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