Med Val Pharma
LIMITED
CONSULTANTS

WHAT IS A CLEAN ROOM?

A clean room is an extremely sophisticated work environment, designed and built with the express purpose of providing a high level of cleanliness for a production or research facility.

Strictly controlled in terms of:

- Clean room classification
- Air particles
- Pressure
- Air filtration
- Temperature and humidity
- Entry of people and parts

Clean room classification

The UK standards are ISO 14644-1 (2015) and EU GMP.

Air particles

The control of airborne particles is critical to the contamination control within the clean room.

Pressure

Pressure is positive within the clean room and higher than that of the surrounding areas, controlled to comply with ISO 14644-1.

Air filtration

Air filtration is critical to the clean room as this removes particles to a high level. Normally via H.E.P.A. (High Efficiency Particulate Air) filters.

Temperature and humidity

Temperature and humidity is controlled for comfort and for critical production requirements.

Entry of people and parts

The entry to clean rooms is strictly controlled to authorised personnel trained in the discipline of hygiene and gowning techniques. Parts entry is also critical so as not to contaminate the clean room environment.

Why do we need clean rooms?

We need clean rooms to ensure medicines and critical components which can be put into humans (or animals) are not contaminated at production/dispensing stage.

We also need clean rooms in the Micro electronic industry, to ensure no particulate is present in the air where complex Microelectronic devices are assembled.

Clean rooms can be found in many industries

- Pharmaceuticals, pharmacies (hospitals), cell therapy.
- Medical device manufacturers, biotechnology.
- Microbiology, aerospace, avionics.
- Semi-conductor assembly, wafer fabrication.
- Microelectronics, optical devices.
- Fibre optics, plastics moulding.
- Forensic science.
- Food industry, brewing industry.
- Paint spraying.
- Cosmetic, plastic surgery.

The clean room facility offers improved product quality and reliability when manufactured within a classified clean room.

Definition of clean air flow

Airflow patterns within a clean room are;

- Non-uni-directional – turbulent flow
- Uni-directional – laminar flow
-

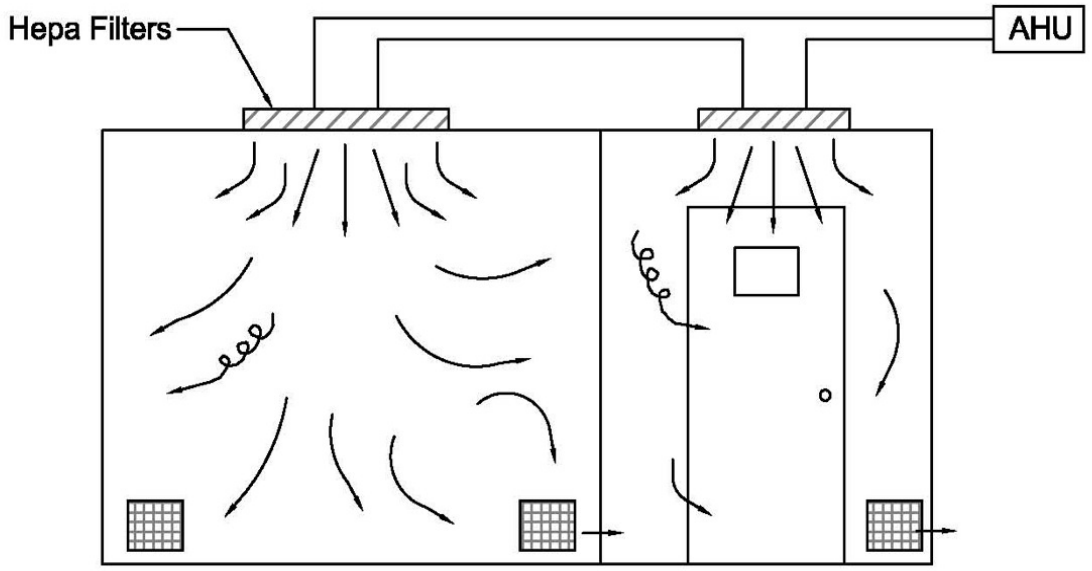
Non-uni-directional (turbulent flow)

This air is forced into the clean room and flows freely in a turbulent manner to provide effective flushing of the clean area. This airflow removes micronized particles through the designed re-circulatory air system. Air enters at ceiling level with exhaust air leaving at low level.

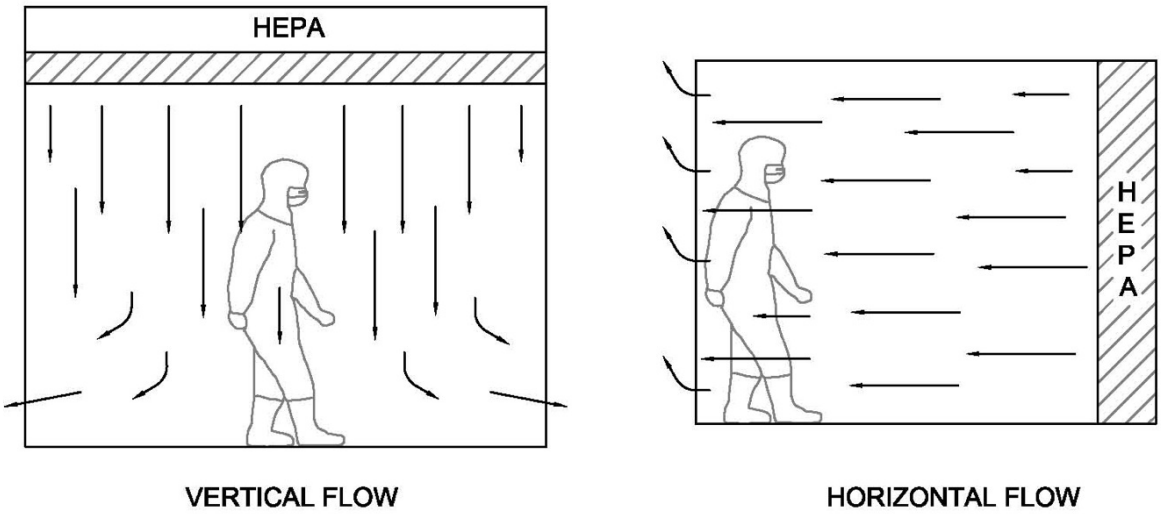
Uni-directional laminar flow

This air forces all particles to flow in a regimented path. The uni-directional flow can be vertical or horizontal and is normally directly from a H.E.P.A. filter or flow screen. Uni-directional flow devices can be cabinets, modules and even a full clean room.

Non-unidirectional flow (turbulent flow)



Uni-directional (laminar flow)



VERTICAL FLOW

HORIZONTAL FLOW

Standard for UK ISO 14644-1 (2015)

Maximum concentration limits (particles per m3 of air) for particles equal to or greater than considered sizes below (values up to three significant figures).

ISO 14644-1 (2015)

Class	0.1 um	0.2 um	0.3 um	0.5 um	1 um	5.0 um
ISO 1	10	d	d	d	d	e
ISO 2	100	24	10b	d	d	e
ISO 3	1000	237	102	35b	d	e
ISO 4	10000	2370	1020	352	83b	e
ISO 5	100000	23700	10200	3520	832	def
ISO 6	1000000	237000	102000	35200	8320	293
ISO 7	c	c	c	352000	83200	2930
ISO 8	c	c	c	3520000	832000	29300
ISO 9	c	c	c	35200000	8320000	293000

EU GMP ORANGE GUIDE

Grade	Maximum permitted number of particles/m3 equal to or above			
	At rest		In operation	
	0.5 um	5 um	0.5 um	5 um
A	3520	20	3520	20
B	3520	29	352000	2900
C	352000	2900	3520000	29000
D	3520000	29000	Not defined	Not defined

PARTICLES

Particulate contamination is measured by the units micro metre or micron and is signified as µ and µgm

1µg is thirty nine millionths of an inch.

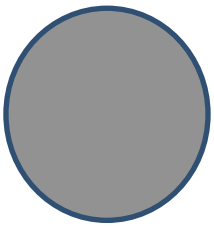
Or

One millionth of a metre.

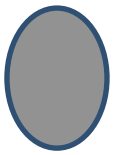
The control of particulate contamination is measured in microns and in general is compliant with one or more of the standards classification.

Particle size example

A human hair on end magnified to a 1000 times larger
Non-viable
Non-living particles



100 microns



10 microns

Viable
Living organisms

5 microns

- **.5 microns**

Most particulate contamination or most particle penetrating sizes are between 0.3 µm and 0.5 µm.
Viable (living) organisms which are mostly bacteria range from 0.5 µm to 5 µm and are usually found in colony-forming units.

Viruses range from 0.003 to 0.05 µm.

Bacteria particle

Smaller particles will gather together to form a “raft” upon which bacteria may prosper.

A percentage of these bacteria would be pathogenic.

Particulate by itself is capable of producing an embolism.

This is an obvious danger to a clean room or aseptic facility, producing injectable or parental drugs.

Operator contamination

Operator contamination generates more than 50% of particles within a clean room. Human contamination is of both viable and non-viable particulate contamination.

- 90% of microbe spectrum within the clean room is composed of staphylococci micrococci of human origin.
- An operator at rest sheds around 250,000 particles of >0.5 micron per minute rising by a factor of three or four when in motion.
- Bacteria carrying cells released from a male operator average as much as 5,000 particles per minute.
- Operators shed a complete skin every 20 working days.

UN-GOWNED OPERATOR CONTAMINATION

Operators shed	Particulate	Skin flakes Eyelashes Cosmetics Tobacco
Operators produce	Chemical and organic matter	Sodium, magnesium Calcium Oral effluvia Iron
Operators generate	Biological	Bacteria Viruses Pathogens
Operators outer clothing street generate	High levels of particulate	Silicone dust Fibres Cellulose Nylon Wool

Cosmetics

Lipstick sheds 1,000,000,000 > 0.5 µm particles

Blusher sheds 1,600,000,000 > 0.5 µm particles

Powder sheds 1,300,000,000 > 0.5 µm particles

Eye shadow sheds 3,300,000,000 > 0.5 µm particles

Controlling contamination

Controlling contamination within a clean room is critical to maintaining its classification and also to protect the product or process, which is being produced.

By gowning and ensuring operators understand the need for entry procedures contamination can be controlled.

Contamination can be by particulate or electrostatic discharge.

To control/combat contamination to the product/process additional mini classified clean environments can be introduced within the clean room.

Often these mini classified environments are of a higher quality air class than the general room environment.

Example: Uni-directional laminar flow cabinet.

Clean room principles for entry

Clean room operators should fully understand the need for a correct entry discipline.

Clean room operators should be clean and healthy. They should not enter clean rooms without having a good level of personal hygiene and should not enter if feeling unwell.

Personal hygiene	Medical health
Wash/bathe frequently	Be aware of allergies
Shampoo hair frequently	Be aware of respiratory dis orders
Wear clean under garments daily	Be aware of skin rashes
Wear clean outer wear regularly	Be aware of spots
Avoid scratching	Be aware of diseases
Shave daily (male)	Be aware of mental phobias
Keep hair under control	Do not enter if unsure

Strict No's for a clean room operative

- No cosmetics
- No jewellery
- No eating of drinking
- No paper
- No high heel shoes
- No unclean people

Clean room disciplines

All clean rooms should have a strict Entry/Exit S.O.P. for all staff to view and comply with:

In general:

- Wear clean room specified clothing
- Wear over shoes
- Wear gloves
- Wear hair cover
- Wear face masks as required
- Wear glasses/goggles as required
- Use tacky mats

Different classes of clean rooms require different levels of clothing; the more critical the operation or process, the higher the level of clothing required to contain contamination.

Summary:

- No eating or smoking or chewing
- Wear protective clothing
- Keep talk to a minimum
- Never comb hair
- Never apply cosmetics
- Keep pockets empty
- Keep paper out
- Entry always through Change Room
- Understand S.O.P. for entry
- Wash hands as per S.O.P.
- Remove outer street clothing (if required)
- Ensure doors are closed and not wedge open
- Do not take anything into the clean room that is not required
- Smokers should rinse with mouth wash before entering
- Entry of parts/tools should be under a strict clean policy
- Airlocks should be segregated as In or Out
- Do not Exit via Airlock, always use Exit Change.

Cleaning and maintenance

The cleaning of clean rooms is critical to control contamination. A rigorous S.O.P. for cleaning should be used and all cleaning materials validated prior to use.

Maintenance of clean rooms should take into consideration the contamination it may generate, general engineering shut downs require full clean down on completion.

Validation testing

To comply with ISO 14644-1 (2015) and EU GMP Class requirements, the clean room will require independent validation testing to comply with ISO 14644-2 and ISO 14644-3. Validation testing is a statutory requirement for classification.

Useful publications list

- ISO 14644-1
- ISO 14644-2
- ISO 14644-3
- ISO 14644-4
- EU GMP Orange Guide#
- www.s2c2.co.uk Clean Room Society for Contamination Control
- HTM 05-03 Health and Technical Memorandum
- ISPE Baseline Pharmaceutical Engineering Guide.