Technical requirements for a cleanroom for the production of cytotoxic products

Cleanroom technology

The term cleanroom technology describes the chain of technical or operational measures that are necessary to prevent harmful effects from contamination of products or humans /
the environment

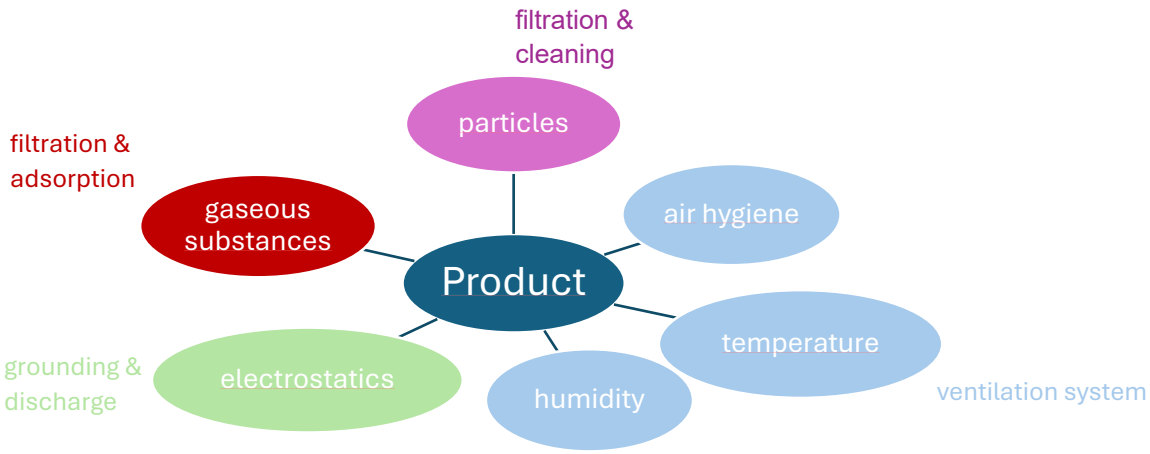
Therefore, the task is:

- to protect the products,
- protect the personnel,
- protect the environment

Protection of the product

Various structural measures are intended to prevent the following sources of contamination:

- Chemical contamination (e.g. residues of the previous process)
- Microbioogical contamination (e.g.bacteria, molds)
- Particulate contamination (e.g. fibres, hair, skin particles)



Protection of staff & environment

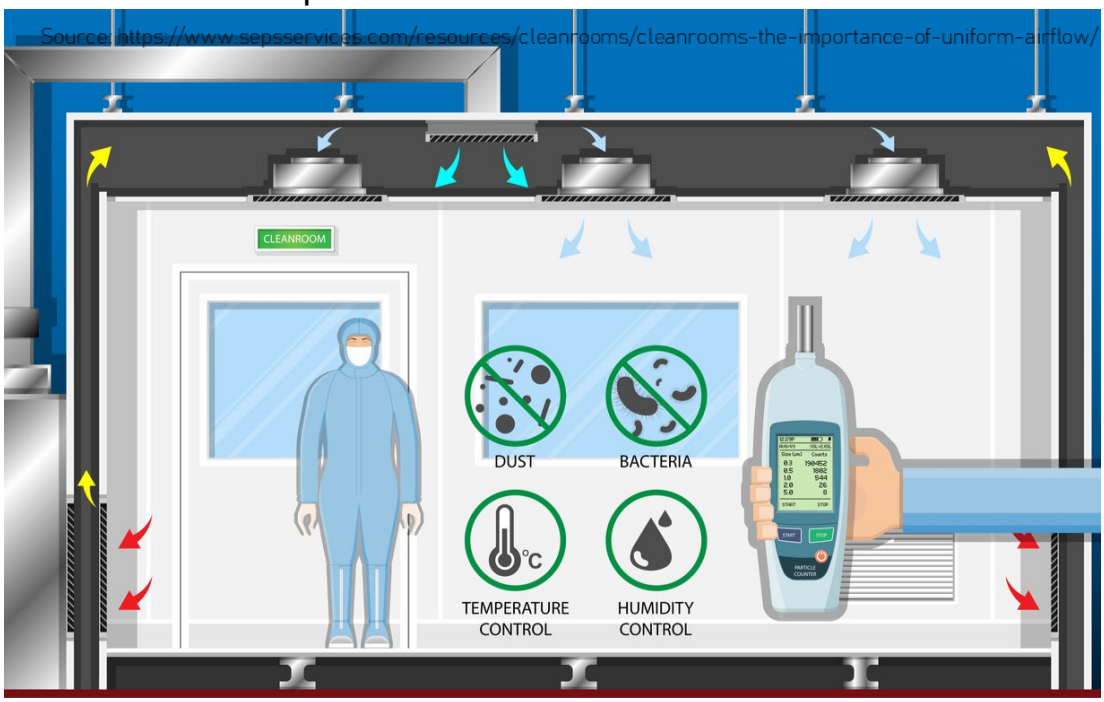
- air flow / barrier systems
- contaminated air removal
- HEPA filters

Apart from factors such as staff training, defined and validated cleaning procedures, as well as validated entry procedures and disinfection, attempts are already made to prevent contamination through technical and structural measures.

Various factors must be considered when it comes to the technical requirements.

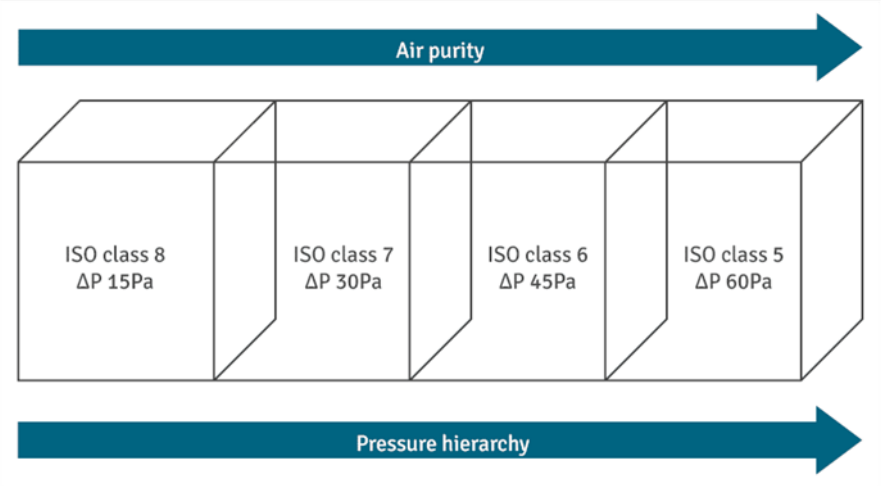
For example:

- Air pressure & air flow
- Temperature
- Humidity
- Measurements of particles



Air pressure

In cleanroom enviroments, pressure cascades refer to a system where different areas are maintained at progressively lower air pressures. The cleanest area has the highest pressure, and each adjacent, less clean zone has a slightly lower pressure.
This creates an airflow from clean to less clean areas, preventing contaminations from entering critical zones.



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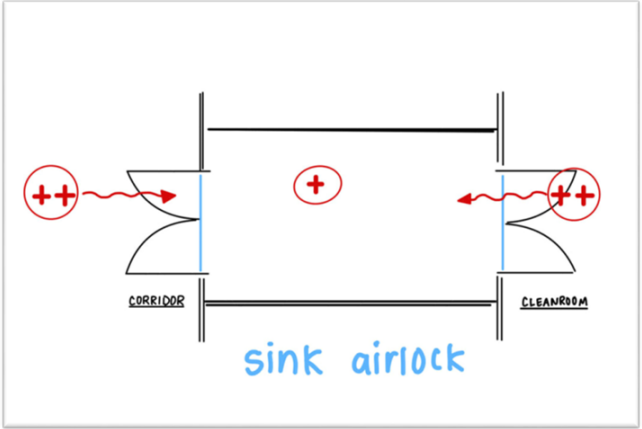
When working with cytostatic substances, it is not advisable to work strictly according to this principle, as otherwise cytotoxic substances could be released into the environment and thus harm humans and the environment.
To prevent this, additional airlocks are used.
As shown in the illustration, both rooms adjacent to the airlock have a higher air pressure than the airlock itself. This prevents airborne particles from entering the cleanroom from the outside and also prevents hazardous substances from getting outside.



https://pharmaceuticalupdates.com/

Air flow

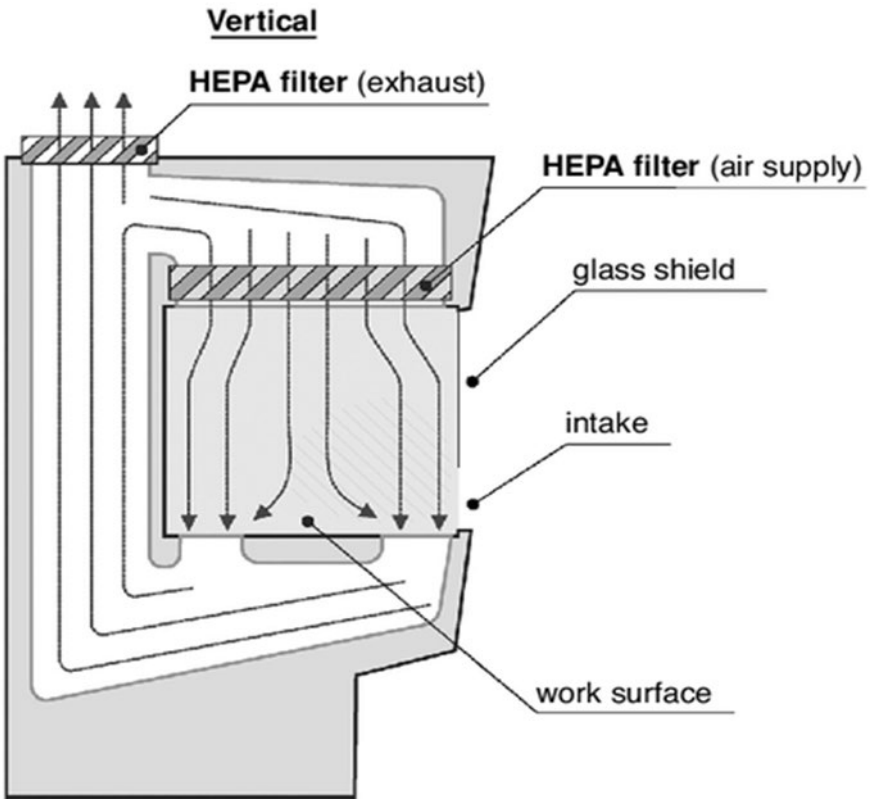
To protect employees and products from contamination, a regulated laminar air flow system is used.
The example on the right is a laminar airflow workbench.

This is a specific method of air movement desgined to minimize contamination and maintain a controlled, clean anviroment.

As shown in the image, laminar airflow means the air flows in parallel layers, moving at the same speed and in the same direction, with no turbulences or swirls.
The air particles follow smooth, straight paths.

It typically flows vertically from the ceiling of the laminar flow hood to the work surface and prevents stirring up particles and keeps them from settling on critical surfaces.

The incoming air is cleaned by a HEPA filter. Similarly, the outgoing air is further cleaned of pollutants by one or more HEPA filters in succession.

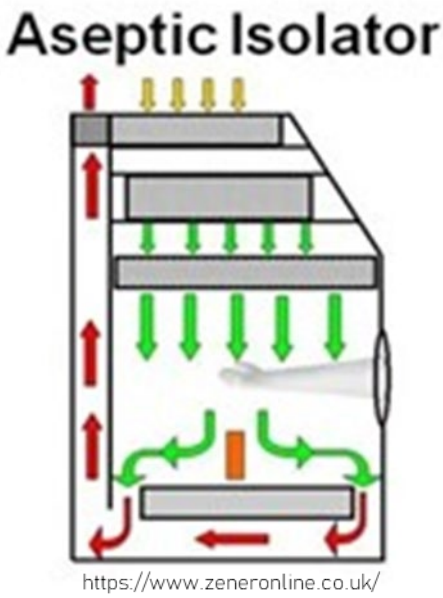


https://www.researchgate.net/

Isolators, which are increasingly being used, also represent a similar principle.

These are a closed systems into which materials must first be introduced.

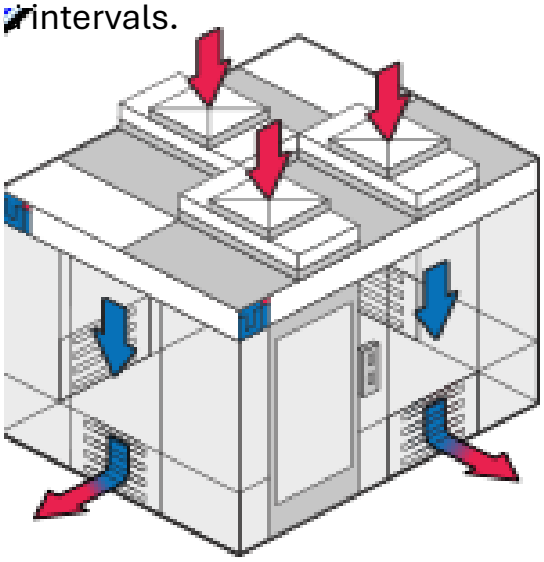
The manufacturer can access the isolator through designated access points using attached gloves.



Air flow - remove contaminated air

The air used, both in the laminar flow bench and in the room, is extracted and filtered several times using HEPA-filters H14.

These must be checked and replaced regularly for the purpose of requalification or at fixed intervals.



Temperature & humidity

https://www.terrauniversal.com/

Temperature and humidity are precisley controlled and documented to ensure stable environmental conditions and product safety.

This is managed by a central HVAC system, which continously cools, heats, humidifies, or dehumidifies the air.

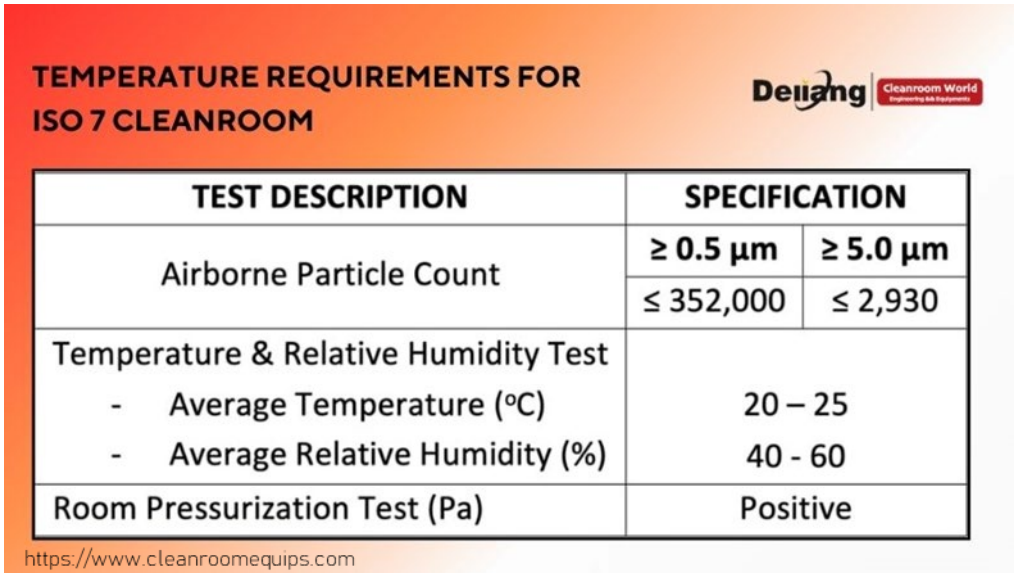
Sensors in the room constantly monitor actual values and trasmit data to a building management system.

If deviations occur, the system can automatically adjust to maintain the defined setpoints.

Additionally, alram funktions are often implemented to enable immediate response in case limit violations.

Controllind temperature and humidity is crucial to ensure product quality, stability and sterility.

Uncontrolled conditions can lead to microbial groth, particle formation or changes in active ingredients.



TEST DESCRIPTION	SPECIFICATION	
Airborne Particle Count	≥ 0.5 µm	≥ 5.0 µm
	≤ 352,000	≤ 2,930
Temperature & Relative Humidity Test		
- Average Temperature (°C)	20 – 25	
- Average Relative Humidity (%)	40 - 60	
Room Pressurization Test (Pa)	Positive	

Measurements of particles

To monitor the number of particles and thus also the air quality according to GMP or ISO classifications, so-called particle counters are used.

These measuring devices are used to detect and count airborne particles by size by drawing in the air from the environment.

Particle counters are available as portable units (for routine checks) or fixed systems (for continuous monitoring) and draw in air to count particles by size.

Class	Maximum particles/m³, equal to or greater than the tabulated size			
	At Rest		In Operation	
	≥ 0,5 µm	≥ 5,0 µm	≥ 0,5 µm	≥ 5,0 µm
A	3,520 ISO 5	29 ISO M (29;≥ 5 µm; LSAPC)	3,520 ISO 5	29 ISO M (29;≥ 5 µm; LSAPC)
B	3,520 ISO 5	29 ISO M (29;≥ 5 µm; LSAPC)	352,000 ISO 7	2,930
C	352,000 ISO 7	2,930	3,520,000 ISO 8	29,300
D	3,520,000 ISO 8	29,300	Not defined	

https://www.testotis.de/

Other important measures concern the structural requirements:

- unnecessary objects in the cleanroom can impede the airflow. Therefore, limit your cleanroom equipment to the bare essentials.
- tools and furniture should be made of abrasion-resistant materials to minimize the adhesion of particles to surfaces. (e.g. stainless-steel cabinets /worktables)
- furniture, flooring, and wall coverings must be smooth and seamless to prevent particles from settling
- materials should be easy to clean and disinfect

- additional work materials such as notebooks, pens and paper must also be suitable for use in cleanrooms.

Guidelines

The most important regulatory framework for the qualification of cleanrooms in the pharmaceutical sector is formed by the EU GMP Guideline Annex 1 in combination with DIN EN ISO 14644.

DIN EN ISO 14644

DIN EN ISO 14644-1 is an international series of standards for the classification of cleanrooms, focused on particle concentration.

It defines nine cleanroom classes (ISO 1 to ISO 9) based on the maximum permissible particle concentration per cubic meter of air.

ISO classification number (N)	Maximum concentration limits (particulates/m^3 of air) for particles equal to and larger than the considered sizes shown below (concentration limits are calculated in accordance with equation (1) in 3.2)					
	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1 µm	5 µm
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1,000	237	102	35	8	
ISO Class 4	10,000	2,370	1,020	352	83	
ISO Class 5	100,000	23,700	10,200	3,520	832	29
ISO Class 6	1,000,000	237,000	102,000	35,200	8,320	293
ISO Class 7				352,000	83,200	2,930
ISO Class 8				3,520,000	832,000	29,300
ISO Class 9				35,200,000	8,320,000	293,000
NOTE: Uncertainties related to the measurement process require that concentration data with no more than three significant figures be used in determining the classification level.						

https://alliedcleanrooms.com/

Annex I

Annex 1 of the EU GMP Directive for the manufacture of sterile medicinal products supplements these requirements of DIN EN ISO 14644 and additionally specifies limits for microbiological load and recovery times of cleanrooms, which further specifies the requirements for air purity.

An important requirement of Annex 1 is the definition of recovery time, which states that a cleanroom must regain its required cleanliness class within a defined period of time after a disruption. According to VDI 2083-2, this must be carried out every 12 months at specified measuring points and critical locations.

Grade	Air Sample cfu/m^3	Settle Plates (Diameter 90 mm) cfu/4 Hours [a]	Contact Plates (Diameter 55 mm) cfu/plate
A[b]	1	1	1
B	10	5	5
C	100	50	25
D	200	100	50

https://health.ec.europa.eu/