10 COMMON TRAPS IN DESIGNING A CLEANROOM

Cleanrooms Australia

Executive summary

Cleanrooms provide a controlled environment with a low level of pollutants. They are typically used for manufacturing or scientific research activities that need to be protected from small particle contamination. Cleanrooms are also used where temperature, humidity and pressure levels need to be precisely controlled.

How do cleanrooms work?

All air coming into a cleanroom is passed through a filter to trap particles and stop them from entering the cleanroom environment. The air inside a cleanroom is also constantly filtered, and the finer the filter used, the cleaner the cleanroom becomes. In most situations this air is pumped into the cleanroom, creating higher pressure in the cleanroom which keeps contaminating particles out.

Depending on the cleanliness level of the cleanroom, personnel working inside cleanrooms may also enter and exit the cleanroom through airlocks or air showers, and may wear full suits and masks that prevent contaminants entering the room from the person's skin, hair and breath.

Cleanrooms utilise positive and negative pressure to help remove existing particles and stop new particles entering clean zones.

For example, air is removed from a cleanroom to create negative pressure, which keeps personnel outside the cleanroom safe from whatever dangerous particles are within the space by sweeping away contaminants in areas where materials, personnel or manufacturing processes generate particles or other contaminates that may be dangerous.

Once the particles and contaminates are removed from the cleanroom through negative pressure, the cleanroom must then be refilled with clean air. Air is either exhausted or passed through a suitable filtration system and then returned into the cleanroom, thus creating positive pressure that stops new contaminants entering the clean zone.

How are cleanrooms classified?

Cleanrooms are classified by the size and volume of particles per cubic metre of air. The classification of the rooms will depend on which governing authority presides over the inspection of the process carried out within the cleanroom and will be set out as:

ISO standards -- predominantly for manufacturing and research

GMP -- predominantly for manufacturing under TGA licence

PIC/S -- predominantly for single dose compounding

ISO classification

There are nine classes of ISO classification.

ISO Class 1 is the highest classification according to ISO 14644–1 before moving to other filtration scales. Every cleanroom needs to be thoroughly tested to validate its ISO classification, and the filtration, which may include HEPA filters, will depend on the classification level you need to achieve.

The table below sets out the different ISO classifications based on the maximum number of particles per cubic metre and micro particle size (µm).

ISO 14644-1 Cleanroom Standards

Class	Maximum particles per m3					
	≥0.1 µm	≥0.2 µm	≥0.3 µm	≥0.5 µm	≥1 µm	≥5 µm
ISO 1	10	2.37	1.02	0.35	0.083	0.0029
ISO 2	100	23.7	10.2	3.5	0.83	0.029
ISO 3	1,000	237	102	35	8.3	0.29
ISO 4	10,000	2,370	1,020	352	83	2.9
ISO 5	100,000	23,700	10,200	3,520	832	29
ISO 6	$1.0x10^6$	237,000	102,000	35,200	8,320	293
ISO 7	$1.0x10^7$	$2.37x10^6$	1,020,000	352,000	83,200	2,930
ISO 8	$1.0x10^8$	$2.37x10^7$	$1.02x10^7$	3,520,000	832,000	29,300
ISO 9	$1.0x10^9$	$2.37x10^8$	$1.02x10^8$	35,200,000	8,320,000	293,000

Australian medicine manufacturers - PIC/S or TGA

Australian medicine **manufacturers** are required to hold a licence to manufacture from the therapeutic goods administration (TGA) demonstrating their compliance to the TGA GMP, or must demonstrate compliance with the Pharmaceutical Inspection Convention (PIC/S) Guide to Good Manufacturing Practice (GMP).

The air standards covers all aspects of production. This includes everything from the assessment of raw materials through to examination of the premises and production machinery, and evaluation of staff training and hygiene procedures.

Full documentation of TGA manufacturing principles for medicinal product can be found at **tga.gov.au/**.

PIC/S

PIC/S GMP standards call for detailed written operational procedures that cover the following areas:

- Quality control and risk management
- Personnel training and hygiene
- Premises and equipment including production, storage and ancillary areas
- Generation, control and retention of documentation
- Production, processing and packaging operations, including cross-contamination prevention
- Outsourced activities
- Complaints and product recall

Full PIC/S documentation is available at **picscheme.org/**.

What are the three states of cleanrooms?

All cleanrooms have three different states – **As Built**, **At Rest** and **Operational**. As Built refers to an empty cleanroom before equipment is installed. A cleanroom is classified as At Rest when equipment has been installed but workers are yet to begin using the cleanroom, and Operational refers to a cleanroom when it is in full working use.

There are likely to be changes in a cleanroom's particulate count through each state as machinery, materials and workers are introduced. As such, cleanrooms must be tested and validated for ISO classification throughout the three states.

All three states need to be tested to ensure your cleanroom is in compliance with the conditions that are required for your manufacturing process. The testing process should be addressed in your validation documentation and subsequent standard operating procedures (SOPs) so it is not overlooked.

Test results can be used to verify the effectiveness of your HEPA filter. For example, if your HEPA filter falls short of the particles for cubic metre required for your target ISO classification in the At Rest stage, you may need to consider upgrading before your cleanroom becomes operational.

Why is cleanroom classification so important?

As ISO standards protect people and expensive machinery, every aspect of cleanroom construction and maintenance must be thoroughly tested and validated. Without expert knowledge, expensive but avoidable mistakes are all too common.

You'll also need to conduct regular cleanroom validation to maintain your ISO classification. Regular validation will help you identify any contamination sources before they threaten the safety of your cleanroom, or cause damage that may be costly to fix.

Regular validation will reveal airborne particle counts, airflow abnormalities and other changes. Monitoring these results will ensure that your cleanroom is operating at maximum efficiency, which will keep your operating costs on budget. Maintaining your ISO classification through on-going validation will provide peace of mind for clients and protect your critical processes.

The scope and frequency of your cleanroom validations should be set out in your SOP and your monitoring plans should be aligned with your risk assessment in order to prevent unexpected maintenance costs and any operational time losses.

Maintaining proper validation and maintenance records is also vital should your cleanroom come under audit.

10 things to consider when designing a cleanroom

1. Power requirements

Power upgrades can be notoriously expensive, especially if they need to be done retrospectively. That's why it's so important to understand your power requirements from the early planning stage.

The good news is that power is an easy load to calculate, and if there is a large enough power supply to the building there isn't much to worry about. However, you may need to consider a redundant backup power supply such as a generator or uninterrupted power supplies (UPS). These can be included for either critical components or for the whole facility.

The predominant deciding factor with respect to auxiliary power supplies is how critical the cleanroom operation is. Shutting down mid-shift can be a costly affair if you're running large batches. This is especially true if the cleanroom is sterile. In this instance, the room may require a clean down and testing to confirm that no bacteria have found their way into the cleanroom while the power was off.

On the other hand, unless the cleanroom is used 24 hours per day, there are usually savings to be had with a night setback power option. This option usually runs the cleanroom at a percentage of its full running cost.

2. Clearance

Due to the high cost of real estate in Australia, we are all eager to use our factory space as economically and fully as possible. However, you may need to consider allowing clearance space between the ceiling and walls of your cleanroom and the ceiling and walls of your manufacturing facility for necessary services. We have in the past seen many different situations and found many ways to get services to the correct location.

And keep in mind that while higher ceilings in the cleanroom allow for a more flexible internal working space, it will also incur higher capital and running costs as the extra air volume will need to be filtered for the life of the facility. And as the cleanliness classification increases this cost also increases.

A simple trick to reduce costs is to reduce the size of the cleanroom. This includes the ceiling height of the cleanroom, which means there is less air volume to filter. It also saves on building materials and means that smaller equipment and mechanical services can be used.

3. Cold tracking

Cold tracking refers to the movement of temperate along a conductive material, and can cause condensation on the exterior walls, ceiling or windows of the cleanroom. This can cause a range of issues and create an occupational health and safety problem if dripping moisture causes a slipping hazard for your workers or causes electrical issues as water leaks into electrical components, or drips into the cleanroom and may affect microbial counts.

Cold tracking must be accounted for in the design phase of your cleanroom. Failure to do so may cause problems or delays as authorities request any cold tracking issues to be remedied before your cleanroom is approved.

4. Interior isolation

Interior isolation can be particularly effective and allow future flexibility in food and pharmaceutical processes to prevent dangerous cross contamination.

This might include providing a separate anteroom for gowning which is isolated from the main cleanroom in order to prevent contaminants entering the cleanroom environment on the street clothes of your workers.

You may also need to include interior isolation dividers in the cleanroom design in order to keep different manufacturing processes separate and avoid cross contamination between work areas inside the cleanroom. Failure to do so could result in manufacturing shutdowns and even product recalls if cross contamination occurs.

5. Personnel and workflow

You must carefully consider how both personnel and materials will flow through your cleanroom. Many heavy items such as raw supplies, complicated products, and items for maintenance need to be regularly moved in and out of cleanrooms. Custom-built trolleys, pass-through hatches, and even electric monorail hoists can help to minimise the dangers of manual lifting.

And you'll need to consider the wellbeing of your staff. By their nature, some cleanrooms can feel like sparsely furnished, white-walled prison cells. A simple solution is to install windows that line up from inside the cleanest area of the room to the environment outside the cleanroom. This simple feature can increase staff retention rates and help create a more pleasant working environment.

Lack of product flow understanding leads to poor design, which means extra staff, extra cost, extra work, lost production, lost time, and extra consumables needed.

6. Static electricity and humidity control

Is your process sensitive to static electricity? There are a number of steps that can be taken during the construction phase to minimise dangers that may affect your product yield or component failure rates.

Humidity also impacts bio-load and static electricity, which is why humidity control in a cleanroom requires careful consideration. If it is too low, static electricity can build up. If it is too high, the room's bio-load can negatively affect how often you need to do sterile cleaning.

Depending on the level of humidity control required and what humidity level is specified, different types of capital equipment may be omitted, which can result in lower costs for the overall job.

7. Capital cost vs. running cost

In larger cleanrooms, there are a multitude of different design considerations and forms of equipment available to choose from for both the construction and operation of the room.

You must choose carefully, as some items are significantly more efficient than others in operation. The more efficient items usually cost more upfront, but may deliver significant savings over the lifecycle of the cleanroom.

That's why when assessing the 'price' of the cleanroom, it is imperative to understand what sort of system is being provided. For example, some more expensive equipment can pay for itself in just two years.

8. Standard operating procedures (SOP)

You must also establish and document cleanroom SOPs to ensure that your cleanroom is effectively operated to maintain air quality.

Your SOPs should set how you'll minimise potential contamination from your manufacturing activities, how you'll control staff access to the cleanroom, how the facility will be cleaned, and how air filters and air flow will be monitored.

9. Authorities and compliance

There are several standards that your cleanroom may need to comply with depending on your industry and the function of the cleanroom – and these must all be addressed during the design phase.

Standards you may need to comply with include ISO 14644, the Australian code of Good Manufacturing Practice (GMP), Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PICS), Australian Standard (AS) 1386 1989 and a range of Therapeutic Goods Administration (TGA) standards.

For example, to achieve GMP compliance all cleanroom surfaces must be easy to clean, not generate their own contamination (through corrosion or flaking), and be crease, crack, shatter and dent proof.

In order to qualify for GMP compliance, the TGA may request that you supply supporting documentation that may include the following:

- Quality Management System (QMS) documentation that demonstrates an internal audit and management review has been completed prior to a TGA audit.
- A risk management report that documents your risk analysis and demonstrates how your risk acceptability criteria has been determined.
- Sterilisation validation reports that detail the method or process of sterilisation, and sterilisation residue reports where applicable.
- Facility schematics along with process and personnel flow documentation and active ingredient management.

10. Future expansion

One of the most common pitfalls in cleanroom design in failing to consider how you'll expand it to meet your future needs. Simple choices regarding the selection and positioning of equipment in the initial planning stage may make expansion cheaper and easier to accommodate later down the track.

Identify where your business is positioning itself and any areas it is likely to move into over the next period so you can design a facility that will accommodate future requirements.

Next steps

We recommend that anyone designing a cleanroom purchase and read the relevant standard to assist in determining specific requirements for the cleanroom. We also strongly recommend filling in the questionnaire found in Annex H of standard ISO 14644.4 to help identify other items and issues that may not have been considered yet.

This process will help to establish some of the information required to successfully outline a conceptual design and ultimately construct an effective and compliant cleanroom.

We can help you with conceptual design, consultancy, or the creation of Room Data Sheets for the installation, followed by an order of probable cost, quotation, contract, construction and finally the at-rest validation.

For more information or to discuss your cleanroom project in detail please **contact us**.