



Cleanrooms and Air Quality – A Risk-Based Approach

By Dr. Tim Sandle (Email: tim.sandle@bpl.co.uk or timsandle@btinternet.com; website: www.pharmig.blogspot.com)

Introduction

Cleanrooms are highly controlled environments where the air quality is monitored to ensure the extreme standards of cleanliness required for the manufacture of pharmaceutical, electronic, and healthcare goods. These stringent standards usually require high fresh air rates, extensive filtering, temperature, and humidity control - all of which results in increased energy usage. Protection from uncontrolled ingress of external ambient air is achieved by creating a pressure differential between the cleanroom and its surroundings.

Contamination control is the primary consideration in cleanroom design; however, the relationships between contamination control and airflow are not well understood. Contaminants such as particles or microbes are primarily introduced to cleanrooms by people, although processes in cleanrooms may also introduce contamination (Reinmüller, 2001). During periods of inactivity or when people are not present, it is possible to reduce airflow and maintain cleanliness conditions. To design the cleanroom, the following factors must be accounted for:

- Minimize clean space
- Correct cleanliness level
- Optimize air change rate
- Consider use of minienvironments
- Optimize ceiling coverage
- Consider cleanroom protocol and cleanliness class
- Minimize pressure drop (air flow resistance)
- Consider location of large air handlers – close to end use
- Provide adequate sizing and minimize length of ductwork
- Provide adequate space for low pressure drop air flow
- Low face velocity
- Use of variable speed fans
- Optimize pressurization
- Consider air flow reduction when unoccupied
- Efficient components
- Face velocity
- Fan design
- Motor efficiency
- HEPA filters' differential pressures (ΔP)
- Fan filter efficiency
- Electrical systems that power air systems

The performance of a cleanroom is defined by a set of complex interactions between the airflow, sources of contamination and heat, position of vents, exhausts and any objects occupying the space. Consequently changes to any of these elements will potentially affect the operation of the cleanroom and could invalidate aspects of the room design (Ljungqvist and Reinmüller, 1997).

In the pharmaceutical industry, airflow is the answer to many contamination problems. There are four principles which apply to the control of airborne microorganisms in cleanrooms (Halls, 1994). These are:

- Filtration
- Dilution
- Directional Air Flow
- Air Movement

These principles are examined below.

This case study examines a cleanroom used for aseptic filling. It is an EU GMP Grade B / ISO Class 7 room containing a microenvironment: an EU GMP Grade A / ISO Class 5 clean area.

The Case Study

The cleanroom considered in this case study is a room six meters wide and nine meters long. Within the cleanroom is a unidirectional airflow cabinet, within which aseptic operations take place. This is illustrated in Figure 1 below:

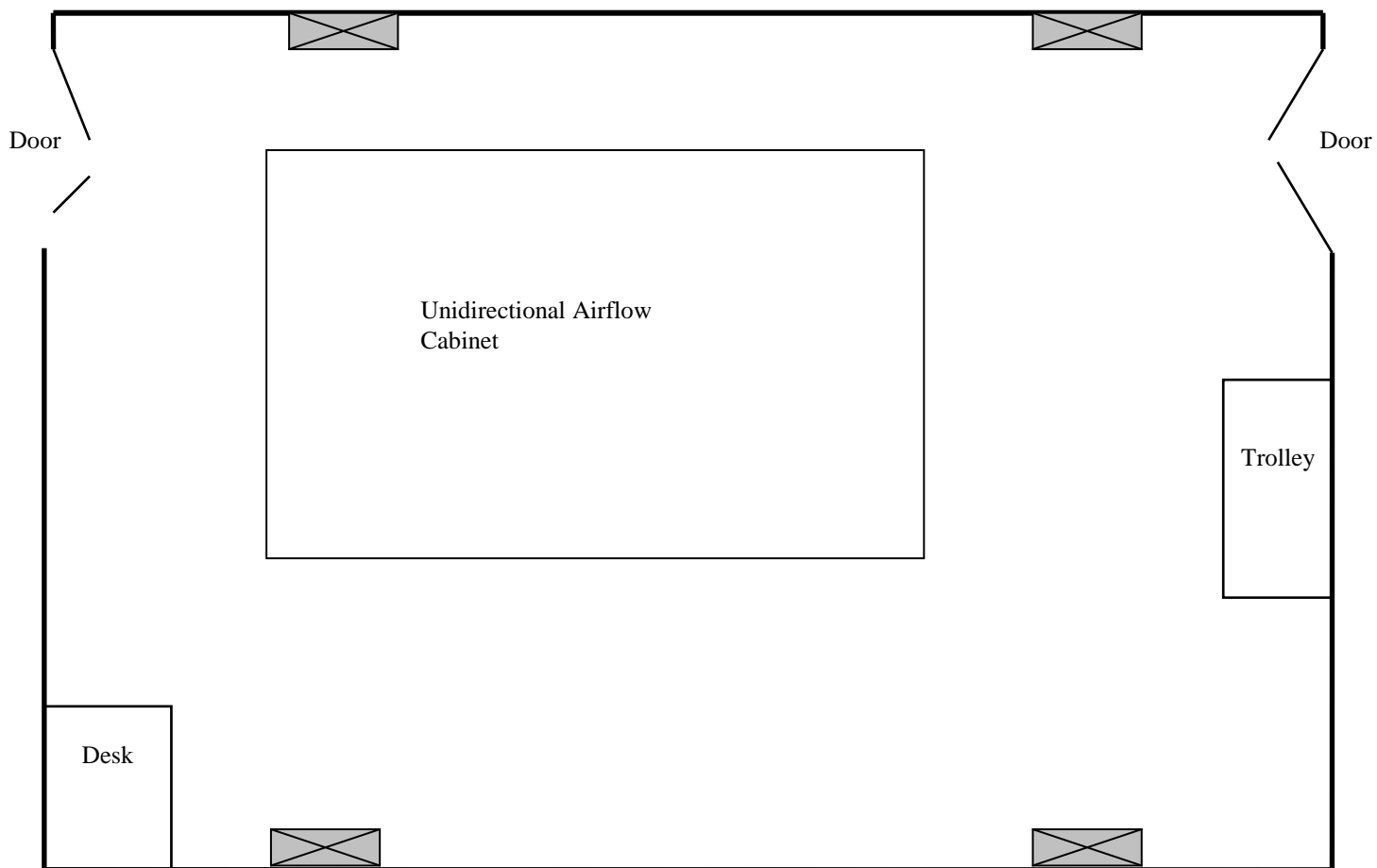


Figure 1: Schematic of the Cleanroom

The key design consideration for the cleanroom is the HVAC (Heating, Ventilation, and Air Conditioning) system (Whyte, 2001). For this, airflow and air changes must be controlled, and

the temperature and humidity of the air must be maintained at appropriate levels. In addition, the air must be filtered, and for this, the cleanroom requires appropriate HEPA (High Efficiency Particulate Air) systems.

The HVAC system operates on the basis of mechanical ventilation. An example of the air supply is illustrated in Figure 2 below:



Figure 2: Typical Air Ventilation Supply

Temperature and Humidity

A design consideration for air includes temperature and humidity control. High temperatures and humid environments can encourage microbial growth, where microorganisms are deposited from the air stream onto surfaces. These parameters are controlled via HVAC systems. HVAC systems normally have two preheated coils. The first coil recovers waste heat from chillers, while the second supplements this as required, followed by a spray humidifier, and finally a chilling battery. The heating and cooling coils are utilized only for temperature control.

Filtration

Filtration removes microorganisms. In cleanrooms, this is achieved through HEPA filters, which are designed to remove up to 99.997% of particles from air. HEPA filters are protected from blockage by prefilters, which remove up to about 90% of particles from the air. Therefore, if air contains about 3×10^8 particles per m^3 , and there is one prefilter and one HEPA Filter, the prefilter removes a sufficient number of particles to leave about 3×10^7 per m^3 as a challenge to the HEPA filter. The terminal HEPA filter will leave about 10^3 per m^3 to enter the cleanroom. In EU GMP, this relatively low number is within the limits for Grade A / ISO Class 5 and Grade B / ISO Class 7 “at rest” (Annex 1.4).

In fact, most pharmaceutical air handling systems recirculate up to 80% of the air supplied to cleanrooms. Therefore, the initial challenge to the HEPA filters is probably only about 10^6 particles per m^3 . So, in practice, there are normally no more than 3×10^2 particles per m^3 supplied to pharmaceutical cleanrooms. This level is even further within the limits of Grade A / ISO Class 5 and Grade B / ISO Class 7 “at rest” in the EU GMP (Annex 1.4).

A typical HEPA filter installation looks like this:

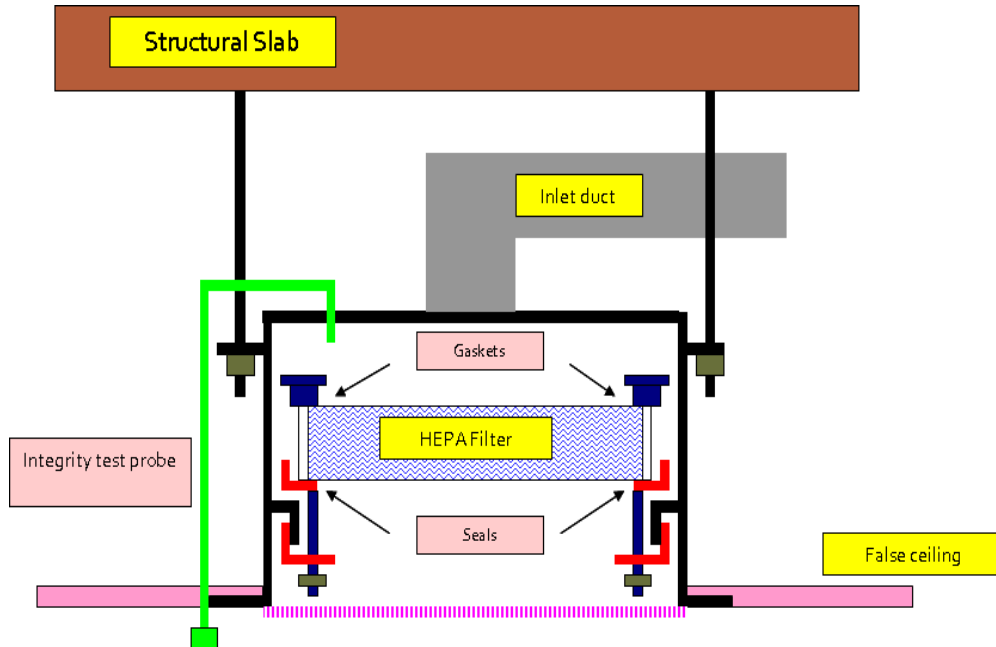


Figure 3: HEPA Filter

Dilution

Particles build up in enclosed spaces where there is no ventilation. Ventilation is the process by which any particles generated in cleanrooms (in addition to those which pass the filters) are carried away, and any particles remaining in the room will be diluted with new “clean” air. The minimum ventilation rate expected in pharmaceutical cleanrooms is 20 air changes per hour (the modern requirement up to twice as many as this, and up to 75 for a changing room). With 20 air changes per hour, the air in a cleanroom is replaced at least every three minutes. In comparison, an office with standard air conditioning might have only two to three air changes per hour. Although 20 air changes is the accepted minimum standard, air change rate recommendations were developed decades ago with little scientific research to back them up. The recommended design ranges for an ISO Class 5 clean area in terms of air change rates are from 250 to 700 air changes per hour.

Recirculation air change rates are an important factor in determining fan and motor sizing for a recirculation air handling system. Air handling sizing and air path design directly impact the capital costs and configuration of a building. In assessing the requirement of airflow and air supply, airflow modeling is undertaken during the design stage. The key information gathered from such modeling relates to the establishment of appropriate air change rates. Such modeling allows for the performance of the cleanroom environment to be assessed prior to construction and to thus make changes to the layout of the cleanroom. The standard modeling approach is Computational Fluid Dynamics (CFD).

Air Movement

In relation to an assessment of air change rates, the cleanroom requires assessment for airflow. In aseptic manufacture, it is critical that contamination is avoided. Products or equipment can become contaminated from airborne microorganisms if microorganisms settle out of the air. If particles and microorganisms stay suspended in the air, they are less of a problem; it is only when they settle out that they become an actual cause of contamination. Therefore, controlling air movement is an important control step. Air movement is used in two beneficial ways in cleanrooms:

- Turbulent air flow
- Unidirectional air flow (UDAF)

Most cleanrooms are of the turbulent air flow type. Here, air is driven in through grills and ducts at ceiling height and removed through low level ducts. Whilst the air is in the room, its initial supply velocity is sufficient to keep it in constant turbulence, which prevents particles and microorganisms from settling out (this is ideal, because dead air can occur beneath tables, etc). It is important to know where dead areas occur (these can be shown through airflow visualization studies using smoke). If they cannot be avoided, monitoring should be targeted at these locations.

The idea of unidirectional airflow is that if air is supplied at a very high velocity through specially designed grills, it will flow for quite a distance in straight lines. Unidirectional air flow blows away all the contamination and particles that come into its path. Unidirectional airflow is capable of sweeping up microorganisms that are sitting on surfaces, thereby cleaning the surfaces up. This is the principle behind unidirectional airflow (UDAFs) units and “laminar” (LAF) airflow cabinets, under which aseptic operations are performed.

This can be illustrated as follows:

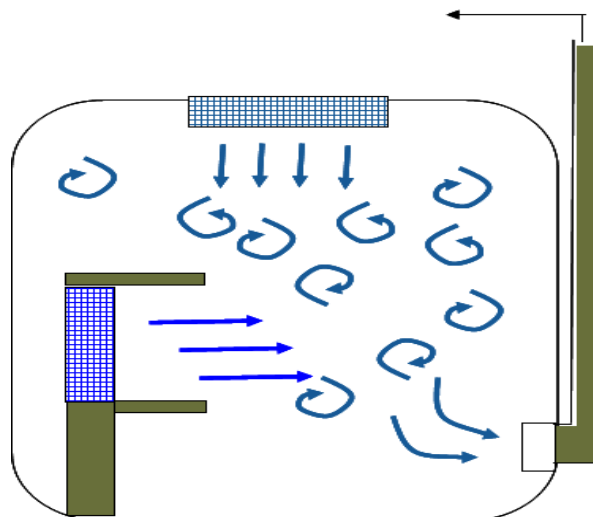


Figure 4: Illustration of Air Movement: UDAF Unit (Laminar Flow) Within a Turbulent Flow Cleanroom

Airflow is examined through airflow visualization mapping, whereby smoke is generated, and the behavior of the smoke is studied and then captured onto a video camera. With the cleanroom, above the UDAF, the air is drawn from the room through high-level returns. The air is then



filtered and resupplied to the room through the HEPA filters. Careful consideration must be made of equipment and other obstacles in the room. Where air strikes an object, any contamination in the air can be deposited, or where air becomes trapped, then dead air spots can develop.

An example of airflow visualization is illustrated below:

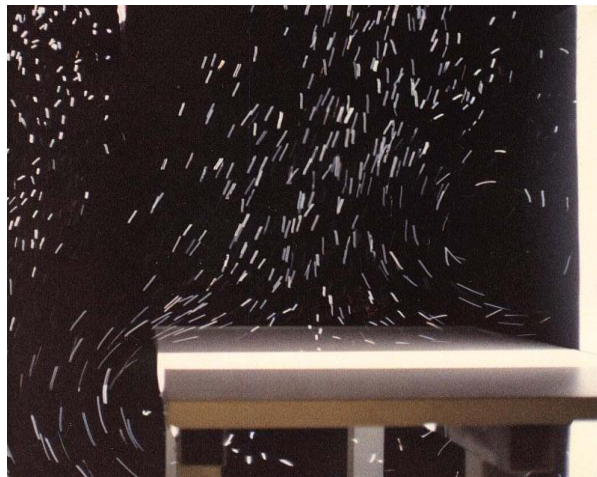


Figure 5: An Example of Airflow Visualization (Turbulent Flow)

Microenvironments or Minienvironments

Within the cleanroom is a UDAF unit. A UDAF is classified as a minienvironment. This is a localized environment created by an enclosure to isolate a product or process from the surrounding environment. The advantages in using a minienvironment include the following:

- Minienvironments may create better contamination control and process integration.
- Minienvironments may maintain better contamination control by better control of pressure difference or through the use of unidirectional airflows.
- Minienvironments may potentially reduce energy costs.

Directional Airflow

Directional airflow is essential for cleanrooms. To illustrate this, imagine there is a room full of “clean” air. Now imagine that personnel have free access to this room from a surrounding area containing normal environmental air. If this were the case, the less clean air will enter the cleanroom as personnel access it. To avoid this in pharmaceutical manufacturing, systems are designed to prevent “dirty” air from entering the cleanroom by ensuring that there is always a flow of air in an outward direction.

The way in which the “dirty” air is prevented from entering the cleanroom is by ensuring a very high rate of air supply to the cleanroom, thus keeping it at a higher pressure than its surroundings. If there is contact with “outside” air, any mixing of the two types of air takes place outside the cleanroom, because the direction of airflow is from the clean to the dirty area. This directional airflow is measured and monitored through pressure differentials. Thus, air will always move from an area where it is at a high pressure to one where there is a low pressure (this is due to the Law of Physics). Particles and microorganisms cannot “swim upstream” against a directional air flow.

To protect against pressure being lost too quickly, air locks are placed over the access and exit doors of cleanrooms.

An example of the “pressure differential” cascade is as follows:

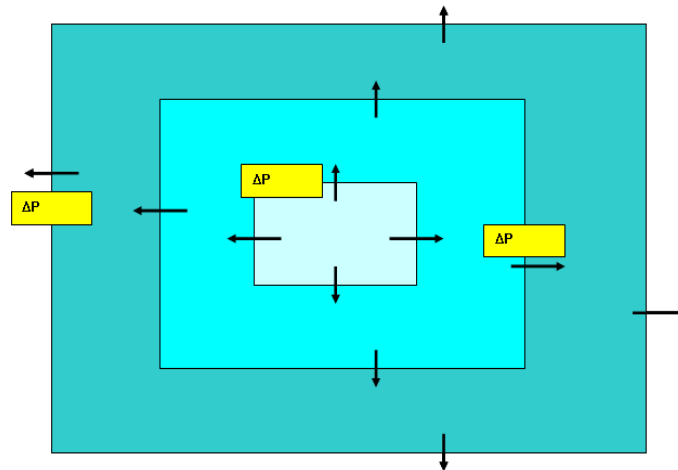


Figure 6: Pressure Cascade

Environmental Monitoring

With the critical air control parameters established within the cleanroom, and physical monitoring in place to ensure that the HVAC system functions as designed, the cleanroom must be subject to environmental monitoring to demonstrate if the room remains in control (Sandle, 2011a).

Monitoring consists of:

- Particle monitoring
- Viable monitoring

With particle monitoring, this is undertaken using mobile optical particle counters or particle counters linked to a facility monitoring system (FMS). The locations for monitoring are selected either by covering representative areas in the room or by orientating the monitoring towards the main activities within the room (Moldenhauer, 2008).

With the cleanroom examined in this case study (Figure 1), monitoring has been orientated towards the areas of greatest risk (Sandle, 2011b).

Justification for the locations for monitoring is as follows:



Locations for Monitoring	Sample Type	Justification
Room: Wall mounted	Particle Counting	This location is designed to detect particle levels from filling operations. The counter is close to both the filling machine and the access door leading from the adjacent corridor. Previous particle classification data had shown that no single point in the corridor had a higher number of particles than any other.
Grade A: Oversealing	Particle Counting	This location is the previous stopper location. It is currently located in the Grade B environment on the outer edge of the UDAF.
Grade A: Point of Fill	Particle Counting	This location is the previous stopper location. It is currently located in the Grade B environment on the outer edge of the UDAF.

With viable monitoring, monitoring is designed to ensure that critical activities and areas are assessed. Monitoring locations remain the same between monitoring sessions. It is not the practice to vary monitoring locations. By keeping a consistency of locations, trends over time can be more readily assessed. The draft guidance for ISO 14698-1 (“Cleanrooms and Associated Controlled Environments – Biocontamination Control, Part 1: General Principles”) recommends that the locations used for environmental monitoring are determined, reasoned, and justified.

For determining monitoring locations, representative locations can be selected or a risk assessment approach can be adopted. It is more typical to adopt the risk-based approach. Here, each location is given a risk rating (high, medium, or low). This is a qualitative assessment based upon proximity to the critical area (such as exposed product or vials) and taking into account the ease of transfer of any contamination towards product, vials, or other critical areas. This has been interpreted by using the following table:

Proximity to Critical Area	Ease of Transfer	Risk Rating
Near	High	A
Close	High	A
Far	High	B
Near	Medium	B
Close	Medium	B
Far	Medium	B
Near	Low	B
Close	Low	C
Far	Low	C



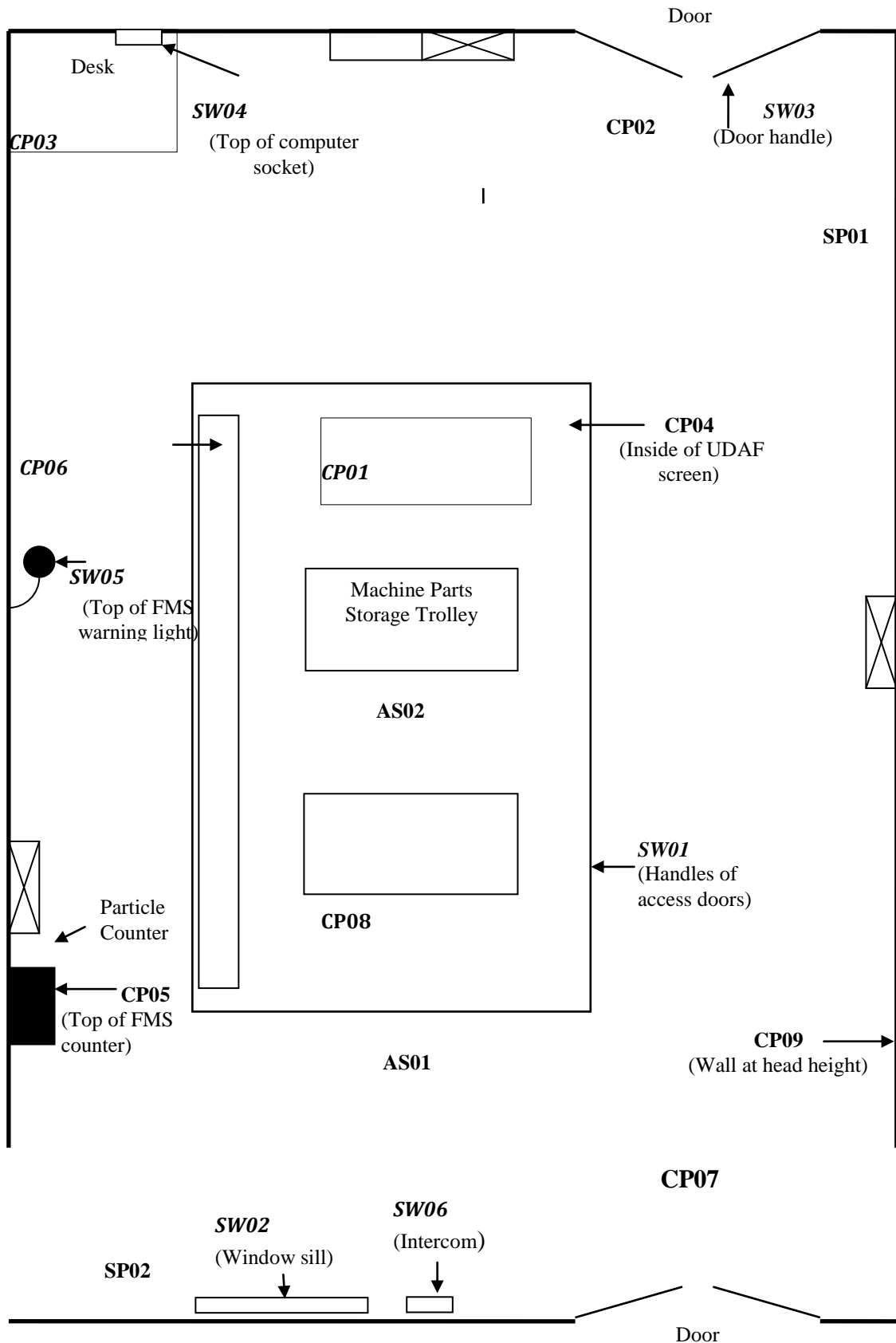
The sample types are normally a combination of:

- Active air samples (where a volume of air is sampled)
- Settle plates (which detect any microorganisms which might drop out of the air)
- Contact plates and swabs (which detect any microorganisms which might be on a surface)

The key for the room plan is:

CP	=	Contact plate (RODAC) ¹
SW	=	Swab
SP	=	Settle plate (passive air sampling)
AS	=	Active (volumetric) air sample

¹ Sometimes CPW (for contact plate at working height) and CPF (for contact plates from floors) are used in Microbiology documents.





The justification for the locations is:

Locations in Room	Sample	Proximity to Critical Area	Ease of Dispersion	Risk Rating	Justification
SW01	Swab	Near	High	B	Handles for the access doors to the UDAF. This sample checks the cleanliness of a key part of the room, which is potentially touched frequently by operators.
SW02	Swab	Far	Medium	B	Swab of a window sill. For this location, there is a potential for dust to settle and for contamination to build up.
SW03	Swab	Far	Medium	B	Door handle – an example of an area difficult to clean and frequently used.
SW04	Swab	Far	Medium	B	Test at the above floor level area and also an area difficult to clean.
SW05	Swab	Far	Medium	B	Check on FMS system cleanliness.
SW06	Swab	Far	Medium	B	Check on high areas that are difficult to clean (intercom).
CP01	Contact Plate	Near	High	A	Check of the trolley used to hold air-samplers when not in use. General surface cleanliness check.
CP02	Contact Plate	Far	Medium	B	General check of floor cleanliness along an access route.
CP03	Contact Plate	Far	Medium	B	Check of widely used area in room: desk.
CP04	Contact Plate	Near	High	A	Check of area that is difficult to clean or one which could potentially be missed, i.e., inside of the UDAF.
CP05	Contact Plate	Far	Medium	B	Example of high-level area and one difficult to clean.

CP06	Contact Plate	Near	High	A	Example of high-level area and one difficult to clean.
CP07	Contact Plate	Far	Medium	B	Check of general room floor surface cleanliness.
CP08	Contact Plate	Close	Medium	B	Check of room cleanliness.
CP09	Contact Plate	Far	Medium	B	Contact plate of wall at mid-height. The reason for adding the sample was to increase the number of samples taken at mid-height across the filling suite and to act as a general check of wall cleanliness.
SP01	Settle Plate	Far	Medium	B	Plate located towards one end of the room close to a main transit route (room exit). The sample is designed to indicate the level of contamination which might settle from the air.
SP02	Settle Plate	Far	Medium	B	Plate located towards one end of the room, diametrically opposite to the other settle plate. The sample is designed to indicate the level of contamination which might settle from the air.
AS01	Active Air Sample	Far	Medium	B	Located close to the UDAF where equipment is stored and therefore likely to be in an area where personnel presence is higher. General check of air cleanliness.
AS02	Active Air Sample	Near	High	A	Sample located within the UDAF. This sample will give an indication of the air quality in the environment where equipment is stored.

Conclusion

This case study has examined the importance of contamination control and the control of air in an EU GMP Grade B / ISO Class 7 cleanroom containing a Grade A / ISO Class 5 microenvironment. The case study has emphasized the importance of the physical design of



cleanrooms, particularly with reference to HVAC and HEPA filtration, and has considered the importance of a robust environmental monitoring regime.

Further Reading

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