

# Annex 2

## Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products

### Part 2: Interpretation of *Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products*

#### Background

The World Health Organization (WHO) published the first edition of its *Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* in 2006 (1).

Having considered various comments and the recommendations through public consultation over several years, the WHO Expert Committee on Specifications for Pharmaceutical Preparations agreed, during its Fifty-first meeting held in October 2017, that the *Supplementary guidelines for good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* guidelines, as amended, be adopted as Part 1 (2).

It was agreed that Part 1 consists of guidelines that contain recommendations on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile products, and further agreed that Part 1 be supported by an additional document that reflects the interpretation of the recommendations in Part 1.

This document is Part 2 and will be considered for adoption as such after consultation.

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# 1. Introduction and scope

This document represents Part 2 of the guidelines for good manufacturing practices (GMP) for heating, ventilation and air-conditioning (HVAC) systems. It contains non-binding examples, drawings, technical representations and interpretation in support of Part 1 of the HVAC systems guidelines (2).

It is intended to be a basic and explanatory guide for use by pharmaceutical manufacturers and GMP inspectors. It is not intended to be prescriptive in specifying requirements and design parameters but it attempts to facilitate a harmonized understanding of expectations for HVAC systems for manufacturers and regulators of non-sterile products.

Part 1 and Part 2 focus on good practices for HVAC systems for non-sterile products. Where applicable, some of the principles referred to may be considered in the HVAC design and approach for other dosage forms. These two documents are, however, not intended to be used as criteria for the design or review of HVAC systems for, for example, active pharmaceutical ingredients or sterile products.

Other relevant national and international standards, as applicable, should be considered when Part 1 and Part 2 are used. These include, but are not limited to, current publications such as ISO 14644 (3) and American Society of Heating and Air-Conditioning Engineers (ASHRAE) standards.

In general, HVAC systems can play an important role in facilitating a suitable environment for the manufacture of quality pharmaceutical products. Therefore, careful consideration should be given to their design. When designing an HVAC system, careful consideration should also be given to the building design and layout of areas, as these may influence the decision and design relating to, for example, the number of air-handling units (AHUs), components in AHUs, room pressure, pressure differentials, pressure cascades, levels of filtration, humidification, dehumidification, and heating and cooling of air. These may, in turn, have an impact on the quality of materials and products, as well as the functioning of equipment and instruments.

The conditions of areas should be defined and should be appropriate for storage, manufacture and use, as appropriate, of equipment, instruments, materials and products. It should further ensure that comfortable conditions are maintained for operators.

## 2. Risk assessment and design

### 2.1 Risk assessment

In line with the current approach in GMP, risk identification should be done for utilities such as HVAC systems. A science-based, comprehensive exercise of risk assessment should be used to determine risks related to possible failure of

the HVAC system and AHUs (including their components and subcomponents). An appropriate risk-assessment tool, such as failure modes and effects analysis or fault tree analysis, should be selected. Controls should be identified to eliminate the risks, or minimize the risk to an acceptable level. For example, the effect of failure of one or more AHUs in the HVAC system; failure of dust-extraction systems; or failure of AHU components such as filters, heating coils, cooling coils and fans should be assessed, and appropriate controls should be identified and implemented.

For more information on risk assessment, refer to the current WHO [World Health Organization] *guidelines on quality risk management* (4).

## 2.2 Design parameters

Manufacturers should define the design parameters of the HVAC system, to ensure appropriate operation and functioning of the system, which is needed for all the areas. Special consideration should be given to the required conditions for storage, manufacture and handling of materials and products, equipment and instrument functioning, personnel (operator) requirements and contamination control.

## 3. Glossary

For definitions and abbreviations, see Part 1 (2).

## 4. Premises

### 4.1 Premises design

Both the architectural design of the building and that of the HVAC system should be carefully considered when attempting to achieve the general objectives of preventing contamination and cross-contamination and ensuring an appropriate environment for the production and control of pharmaceutical products. It is important to ensure that the required environmental conditions, cleanliness and containment are achieved and maintained.

The infiltration of contamination from outside air should be minimized by the use of appropriate filtration, room pressure differentials and airlocks. Manufacturing facilities should normally be maintained at a positive pressure relative to the outside, to limit the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to the ambient pressure, special precautions should be taken to avoid ingress and egress of contaminant.

Risks of contamination should be controlled, especially in the case of potent contaminants, to ensure protection of materials, products, operators and the environment.

Where necessary, air locks, change rooms and pass-through hatches may be considered and provided with effective ventilation and filtered air. Special attention should be given to door design, as gaps between doors and floors, doors opening into low-pressure areas, and sliding doors can result in changes in the pressure differential between areas. An interlocking system and a visual and/or audible warning system may be used, where required, to prevent opening of more than one door at a time where required.

In addition to the design of the premises, general controls should be in place to ensure protection of materials, products and personnel. The HVAC system can play a role in achieving this objective. Where identified, areas should be maintained within defined limits for temperature, relative humidity, and viable and non-viable particles. To ensure that the clean area is maintained at the defined limits, areas are normally classified. When classifying the area, the manufacturer should state whether the classification is for the “as built”, “at rest” or “in operation” condition. For details, including definitions, see ISO 14644 (3).

Manufacturers may use different terms when classifying areas, including Grade A, B, C, D, or ISO 7, ISO 8, or Level 1, Level 2 or others (5) (see Table A2.1). When classifying an area, the class selected should be defined and described (see also Section 7).

Table A2.1

**Examples of area classification (5)**

<b>Level</b>	<b>Example of area</b>
Level 1	General area with normal housekeeping and maintenance, where there is no potential for product contamination, e.g. warehousing
Level 2	Protected area in which steps are taken to protect the pharmaceutical starting material or product from direct or indirect contamination or degradation, e.g. secondary packing, warehousing, first-stage change rooms
Level 3	Controlled area in which specific environmental conditions are defined, controlled and monitored, to prevent contamination or degradation of the pharmaceutical starting material or product, e.g. where product, starting materials and components are exposed to the room environment; plus equipment wash and storage areas for equipment product contact parts

The following describes approaches (with illustrations by means of diagrams) of different room arrangements and room pressures.

## 4.2 Weighing/dispensing and sampling areas

A room for weighing (e.g. dispensing of materials) should be of appropriate design (for examples, see Figs A2.1 and A2.2). It is often advantageous to have several rooms associated with the weighing activity. These may include a pre-weighing staging area, personnel airlock, material airlock, weighing area with a containment booth, post-weighing staging area, washing area and provision for waste removal. The HVAC system for such areas should ensure that the areas have at least the same area classification as other production areas where materials and products are exposed to the environment, logical flow of material and personnel, and an appropriate number of AHUs, as well as appropriate pressure differentials, containment, dust control, and rate of air exchange.

The objective of having a booth in a weighing room is to provide dust containment and operator protection. For example, the dust generated at the weighing location should be extracted through a perforated worktop, thus protecting the operator from dust inhalation, but at the same time protecting the material and product from contamination by the operator by means of the vertical airflow stream. The airflow velocity should be such that it does not disrupt the sensitivity of balances.

Fig. A2.1  
Example of a weighing area

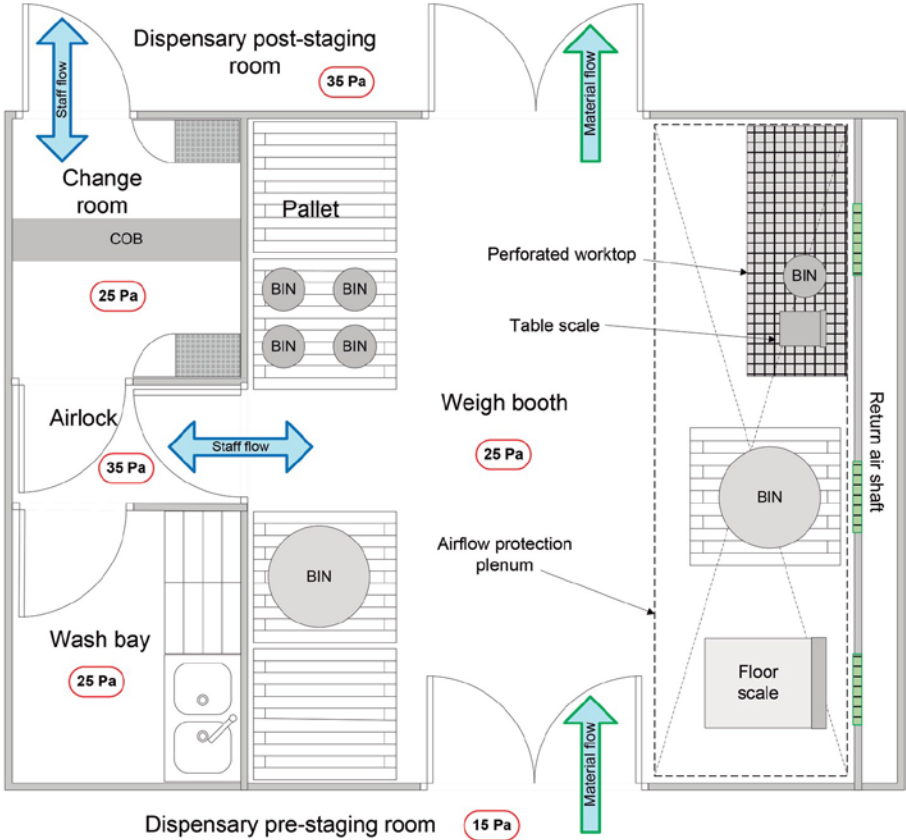


Fig. A2.2  
Examples of weighing areas

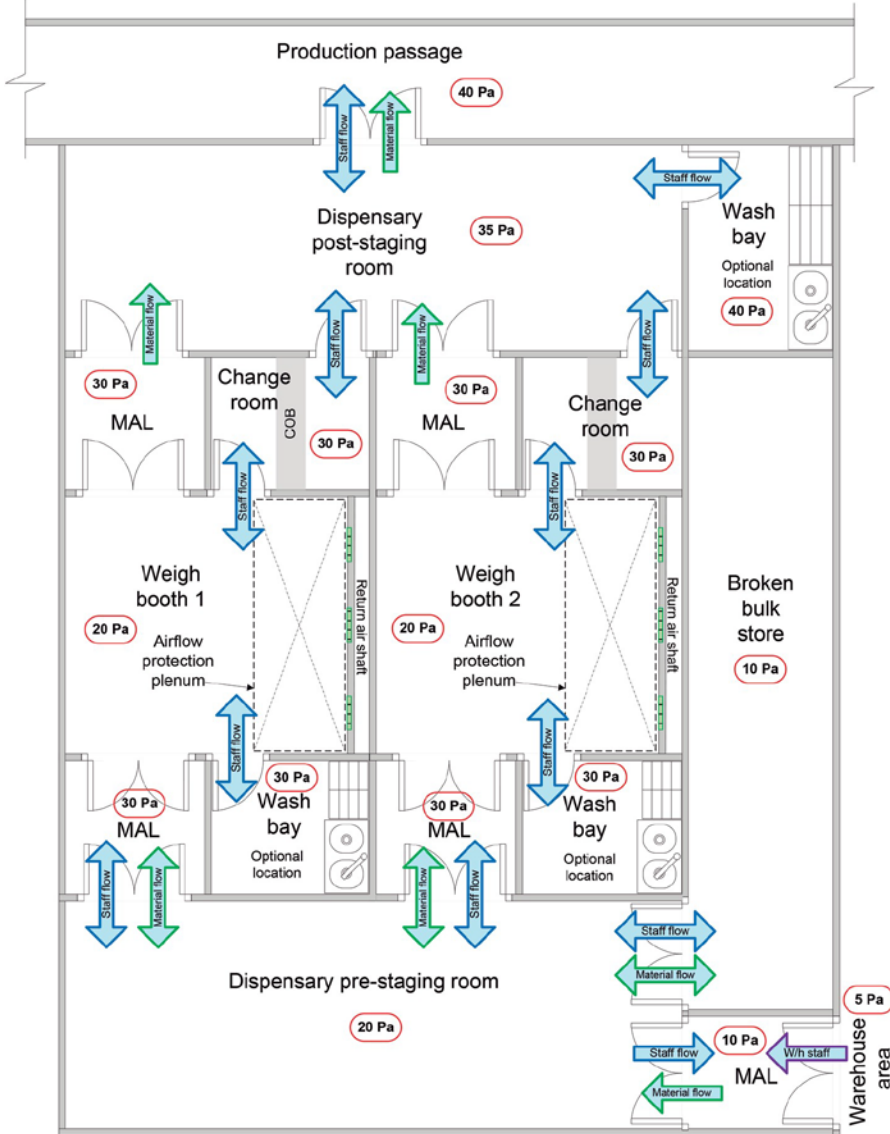
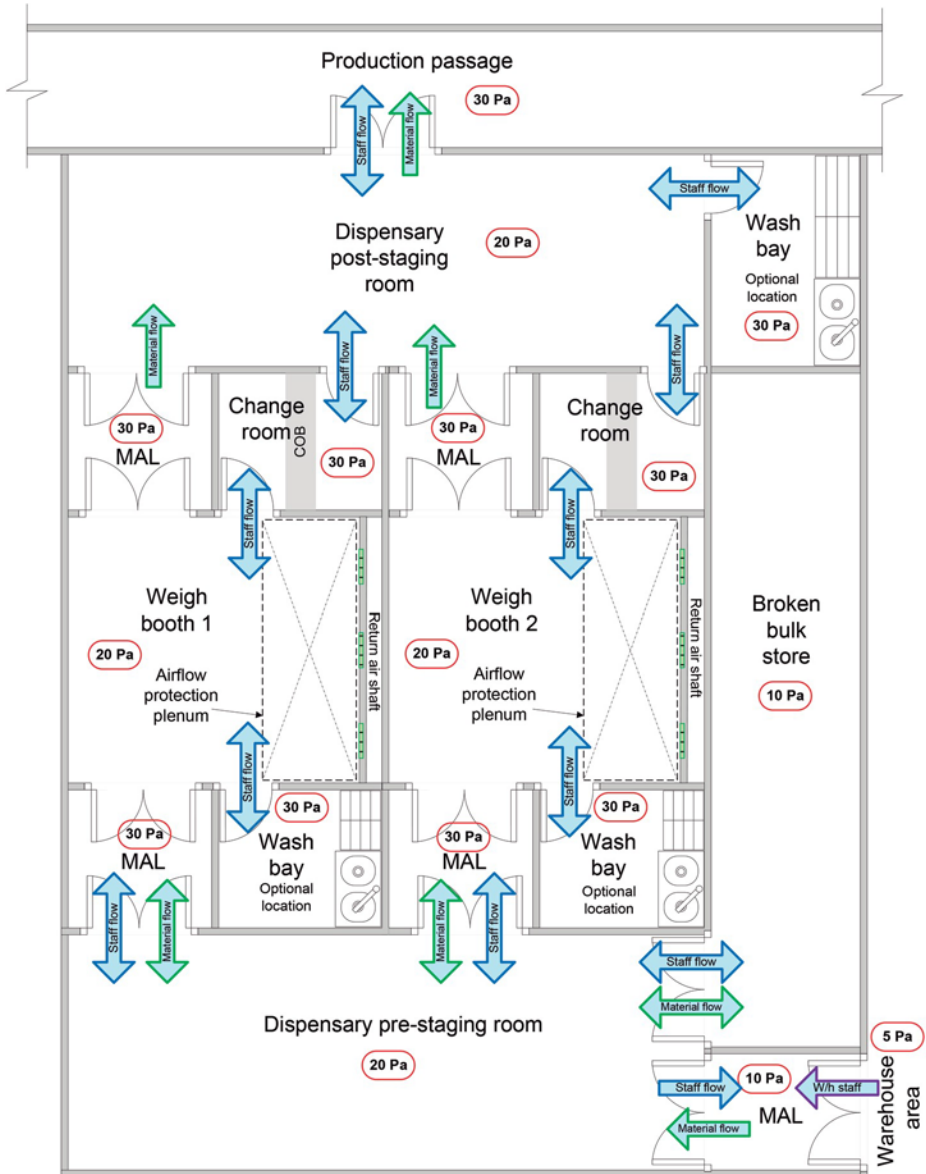




Fig A2.2 continued



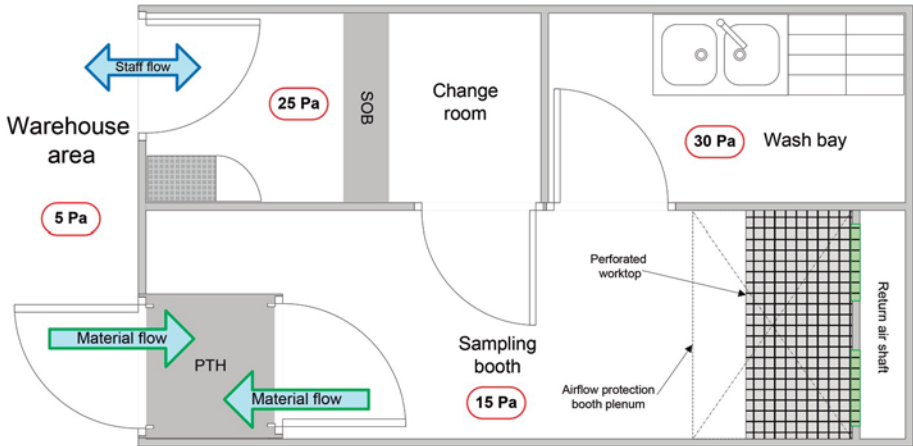
Note that the adjacent room pressures impact on determining the dispensary pressures.

COB: cross-over bench; MAL: material airlock; W/h: warehouse.

Similar aspects may be considered when designing a sampling area, as materials and primary components may be exposed to the environment during sampling (for examples, see Figs A2.3 and A2.4).

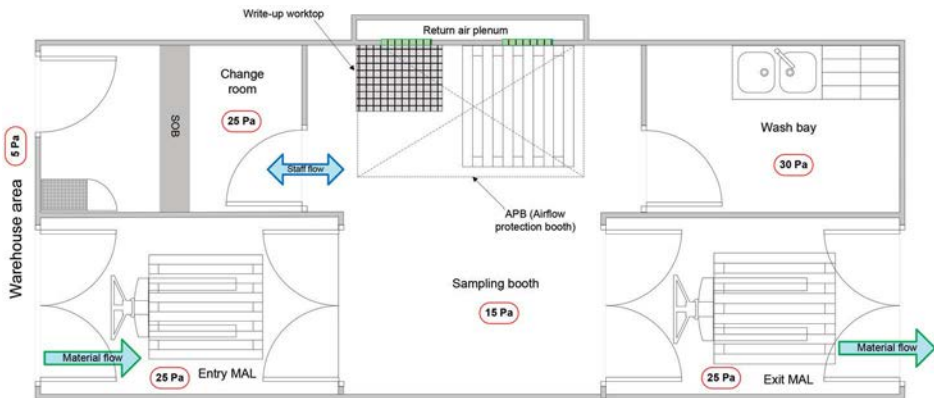
Sampling of materials such as starting materials, primary packaging materials and products, should be carried out in the same environmental conditions that are required for further processing of the product.

Fig. A2.3  
**Example of a sampling area**



PTH: pass-through hatch.

Fig. A2.4  
**Example of a sampling area**



MAL: material airlock.

A clean corridor concept is usually recommended for non-sterile oral solid-dosage form production areas, where there is then a higher pressure in the corridor compared to airlocks or production rooms. This is to facilitate containment of dust and contaminants that may have been generated in production rooms (see also the principles mentioned in the text on weighing/dispensing and sampling areas) (for an example, see Fig. A2.5).

To further support containment, consideration may also be given to having material airlocks (MALs) and personnel airlocks (PALs), where needed, for entry and exit of processing areas (for an example, see Fig. A2.6). Appropriately designed airlocks can assist in ensuring containment. Additional controls, such as pressure differentials between areas, an appropriate number of air changes in an area, and sufficient filtration of air, should be in place. The use of airlocks assists in ensuring containment; however, other means may be considered to achieve this objective, such as closed systems and pressure gradients between adjacent areas.

Fig. A2.5

#### Example of a change room and some production areas

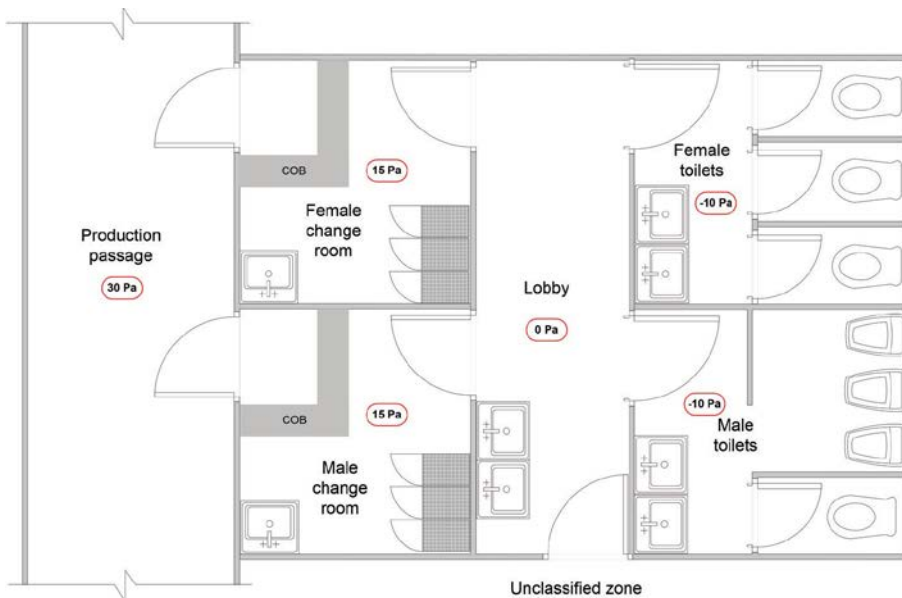
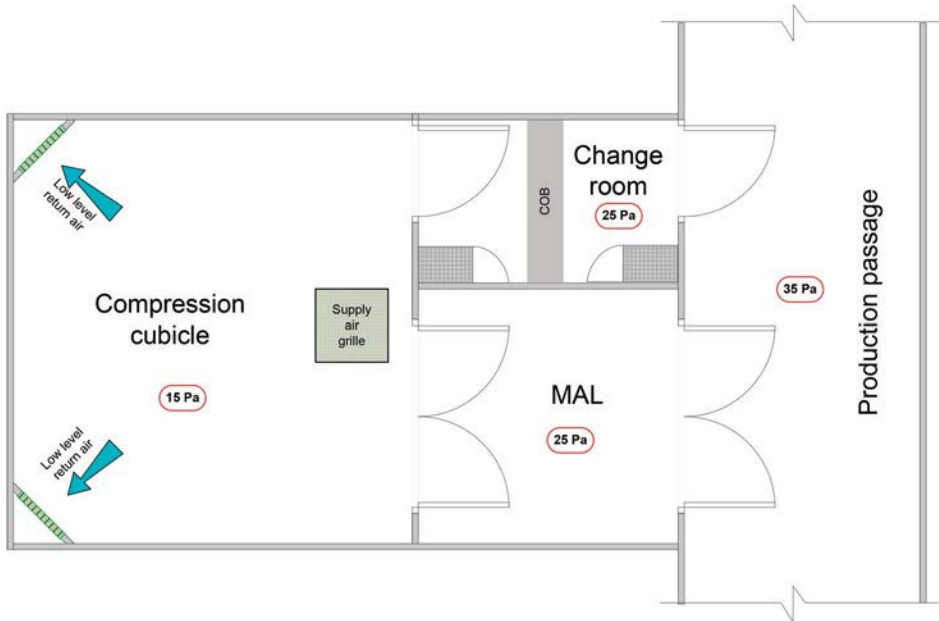


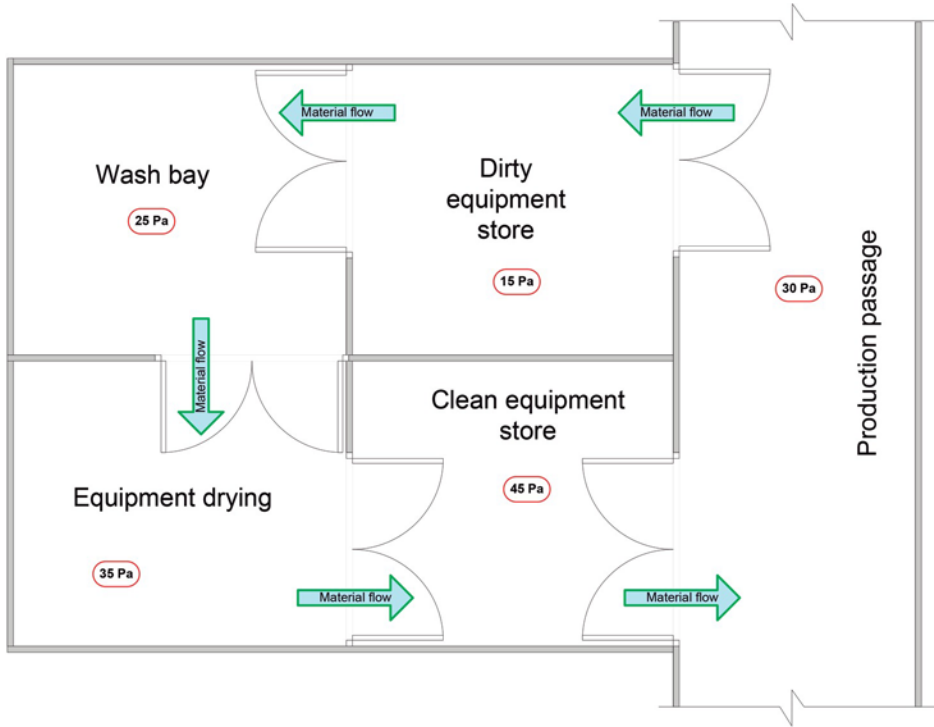
Fig. A2.6

**Example of a compression cubicle with material (MAL) and personnel (PAL) airlocks (also used as an area to change garments)**



Washing areas should be designed and used in such a manner that equipment and components will not be re-contaminated after cleaning. The system supplying and extracting air from the area(s) should be suitably designed to ensure that this objective is achieved. Principles that may be considered include (but are not limited to) filtration of air, pressure differentials between areas, air changes per hour and airflow directions (for an example, see Fig. A2.7).

Fig. A2.7

**Example of a washing area**

## 5. Design of HVAC systems and components

The HVAC system should be appropriately designed, taking into consideration the design of the facility, with various rooms or areas for storage of materials and in-process materials or products, processing, and movement of materials, products and personnel. The required cleanliness classification should be achieved, as well as other parameters, such as air filtration, airflow velocity, air volumes, pressure differentials, temperature, relative humidity, viable and non-viable particle counts and containment. Conditions and limits should be specified, based on need. Manufacturers should determine and define limits for these. These should be realistic, appropriate and scientifically justifiable at rest, in operation and as built at the time of design. In determining these, relevant factors and risks should be considered, including but not limited to possible failures of AHUs, seasonal variations, properties and types of materials and products, numbers of personnel and risks of cross-contamination.

Other aspects, such as the number of AHUs, dust-collecting or dust-extraction systems, the need for recirculation of air, percentage of fresh air (in

the case of recirculated air) and the level of filtration of air should be defined by the manufacturer when considering the design of the facility and activities in different areas and rooms.

Manufacturers should maintain schematic drawings of the HVAC system, AHUs and components. These should reflect the initial design and installation, as well as the current situation. Changes made during the life-cycle of the system should be reflected in change-control records and qualification protocols and reports, as appropriate.

The components selected in an HVAC system should be of sufficient capacity to ensure that the design objectives are met (e.g. for heating, cooling, humidification, dehumidification, airflow volumes), taking impacting factors into consideration, such as loss of air due to leakage and seasonal variations. Materials for construction of components, and their placement, should be such that these do not become the source of contamination. For example, components should not shed particles and the sequence of components should be logical; for example, filters should be placed in such a manner that any possible contaminants generated in the system can be retained by filters and not be introduced into the production area.

To prevent contamination of areas, components such as ventilation dampers, filters and other services should be accessible from outside the manufacturing areas (such as service corridors).

The overall design should be such that there is no possibility of undesired, unfiltered air or contaminants entering manufacturing areas.

## 5.1 Containment

Manufacturers should ensure that appropriate measures are taken to contain product dust in a manufacturing area, thus preventing or minimizing the risk of contamination of other areas and possible cross-contamination. In some cases, it may be advisable to have airlocks or pass-through hatches between rooms or areas. In addition, sufficient dilution, pressure differentials (recommended minimum values of 5 Pa) and airflow directions can further support containment in an area.

## 5.2 Cleanliness

Areas should be maintained at the defined levels of cleanliness and classifications. The HVAC system can support this through, for example, appropriate levels of filtration of air, dilution and dust removal. Equipment, containers, personnel and other related components should be appropriately located or placed in areas so as not to obstruct airflow and the effectiveness of the HVAC system.

Recontamination should be prevented by ensuring that movement of material and personnel is within the same area classification and not back

and forth between areas of different classification. Where such back-and-forth movement is unavoidable, appropriate controls should be identified and implemented, to ensure that moving from a higher class to a lower-classified area and back to a higher-classified area will not result in contaminants being brought into the cleaner classified area.

### 5.3 Automated monitoring systems

The performance of the HVAC system achieving and maintaining the desired results for parameters such as temperature, relative humidity, airflow and pressure differential should be carefully controlled and monitored. This is to ensure that there is no departure from these limits during manufacturing. Monitoring systems should be in place to ensure that the system operates within its design limits. Manual or automated (computerized) systems may be used.

Automated monitoring systems may provide possibilities for ongoing monitoring with better assurance of compliance with the defined limits. Where these automated systems are considered to be good practice (GXP) systems, these should be appropriately validated. The scope and extent of validation of the computerized system should be determined, justifiable and appropriately executed. This includes, but is not limited to, access and privileges to the software, setting of limits, monitoring and acknowledging alarms, audit trails, controls, and reporting.

### 5.4 Switching off air-handling units

It is recommended that the HVAC system be operational on an ongoing basis. Where a manufacturer decides to use energy-saving modes or switch some selected AHUs off at specified intervals, such as overnight, at weekends or for extended periods of time, care should be taken to ensure that materials and products are not affected. In such cases, the decision, procedures and records should be sufficiently documented and should include risk assessment, standard operating procedures, records and validation. This includes procedures and records for the start-up and shut-down sequence of AHUs.

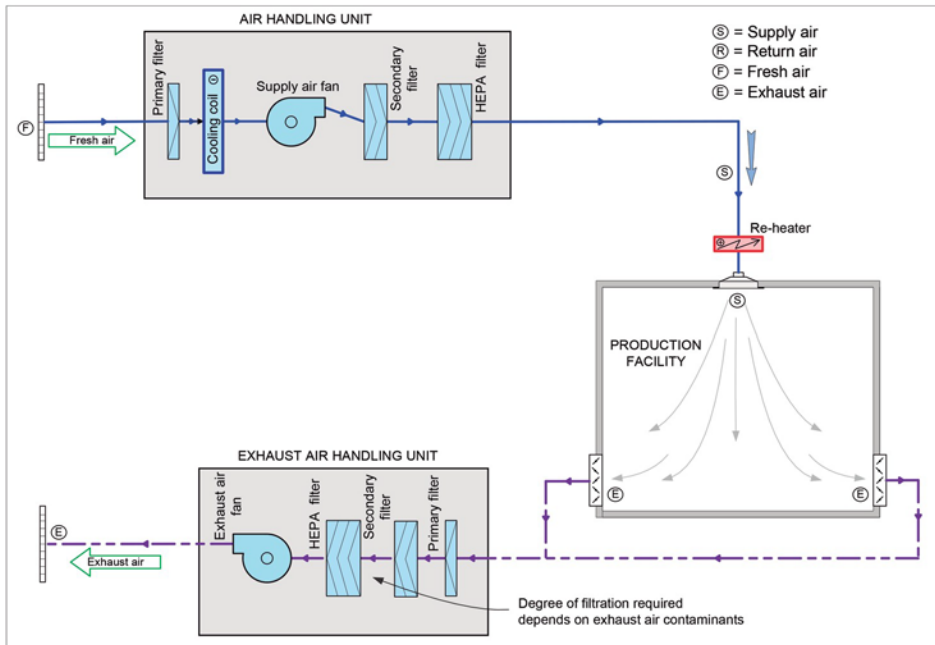
## 6. Full fresh air systems and recirculation systems

Manufacturers may select to have full fresh air systems (for an example, see Fig. A2.8) or recirculate treated air supplied to production areas (in a full fresh air system, no air is recirculated; in recirculation systems, a defined percentage of the air is recirculated). In both cases, the air supplied to the production areas should be appropriately treated, to ensure that the environmental conditions specified are met and that the risks for contamination and cross-contamination are controlled.

Manufacturers using recirculation systems should determine the percentage of fresh air to be supplied to the relevant manufacturing areas, as required by national and international standards. This volume of air should be verified during qualification.

In both scenarios, appropriate levels of filtration should be applied, to prevent contamination and cross-contamination. Manufacturers should ensure that when high-efficiency particulate air (HEPA) filters are used, these are appropriately installed, not damaged and thus suitable for the intended use (see tests described in Section 12).

Fig. A2.8  
**Example of a full fresh air system**



HEPA: high-efficiency particulate air filter.

## 7. Air filtration, airflow direction and pressure differentials

Effective ventilation and appropriate levels of filtration are recommended in basic GMP guidelines. Manufacturers should determine which classes of filters should be used in ensuring that contaminants from outside are not introduced into manufacturing areas and that where recirculation systems are used, filtration of recirculated air is carried out effectively, to ensure that there is no risk of cross-



contamination. Where different products are manufactured in different rooms in the same facility at the same time, appropriate controls should be in place to ensure containment and prevention of contamination and cross-contamination.

Filters selected for air filtration should be determined and specified. When a manufacturer chooses to install HEPA filters to achieve the desired degree of filtration of air, these filters may be placed in the AHU, or may be installed terminally near the supply grille.

Filters have an impact on the cleanroom class or level of protection. The different levels of protection and recommended filter grades are presented in Table A2.2.

Table A2.2

### Levels of protection and recommended filtration (5)

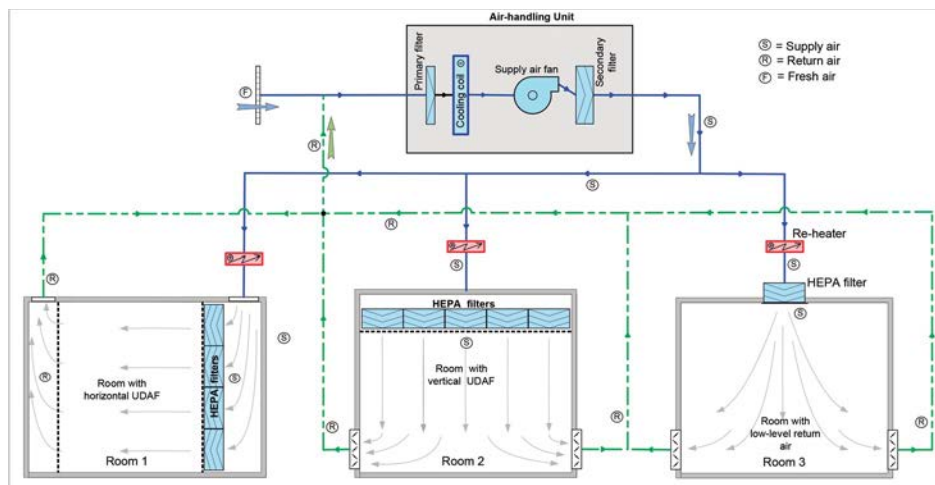
Level of protection	Recommended filtration
Level 1	Primary filters only (e.g. EN 779 G4 filters)
Level 2	Protected areas operating on 100% outside air: primary plus secondary filters (e.g. EN 779 G4 plus F8 or F9 filters)
Level 3	Production facility operating on recirculated plus ambient air, where potential for cross-contamination exists: primary plus secondary plus tertiary filters (e.g. EN 779 G4 plus F8 plus EN 1822 H13 filters; for full fresh air system, without recirculation, G4 and F8 or F9 filters are acceptable)

The number of air changes or air-exchange rates should be sufficient. A guidance value is between 6 and 20 air changes per hour. Manufacturers should also establish how much time it takes for a room that is out of its classification to return within the specified class. This is often referred to as clean-up or recovery time. A guidance time period for clean-up or recovery is about 15–20 minutes.

Airflow directions should be specified and proven to promote containment and not be adversely affected or obstructed by equipment, utilities, containers or personnel. The location of supply and return or exhaust air grilles should facilitate appropriate airflow directions in an area.

Fig. A2.9 is a schematic diagram of an example of an air-handling system serving rooms with horizontal directional flow, vertical directional flow and turbulent flow, for rooms 3, 4 and 5, respectively. In these rooms, the HEPA filters are indicated to have been placed terminally mounted in the rooms and not in the AHU. Whenever HEPA filters are terminally mounted, it can assist with preventing cross-contamination from room to room in the event of a fan failure.

Fig. A2.9

**Example of horizontal airflow, vertical flow and turbulent flow**

UDAF: unidirectional airflow.

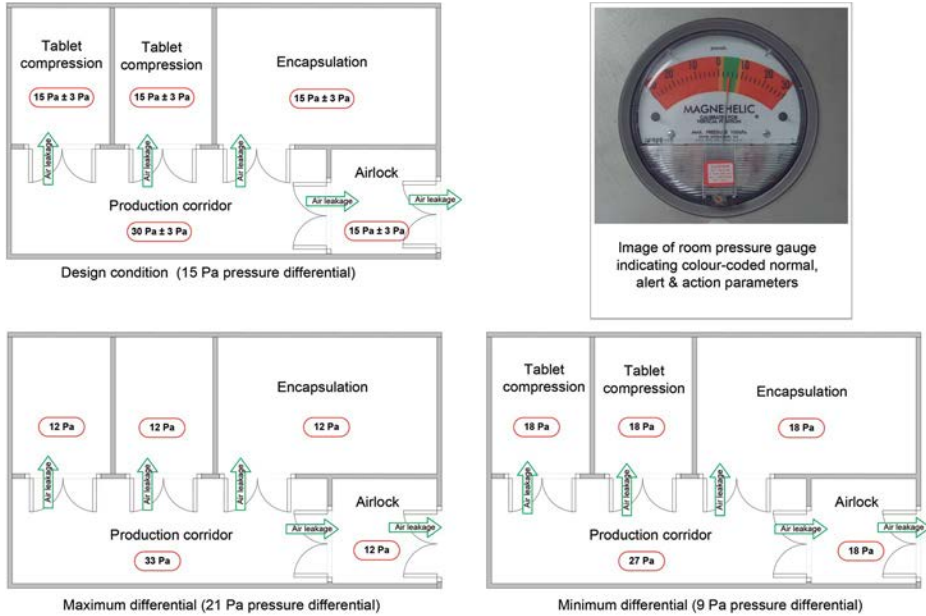
The pressure differential should be of sufficient magnitude to ensure containment and prevention of flow reversal, but should not be so high as to create turbulence problems. It is suggested that pressure differentials of between 5 Pa and 20 Pa be considered. Where the design pressure differential is too low and tolerances are at opposite extremities, a flow reversal can take place. There should be no risk of overlap in the acceptable operating range, for example, 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in failure of the pressure cascade (for examples, see Fig. A2.10). The upper and lower limits for pressure differentials between areas in a facility should be defined by the manufacturer. Where there are interleading rooms, the limits should be appropriate to ensure that there is no overlap in actual values, as this may result in loss in pressure differential between areas and even reversal of air flow.

Cumulative tolerances for the instruments measuring pressure differential should not cause a situation where an undetected reversal of airflow is possible. This can be accomplished by setting the limits such that there is no overlap in the differential between adjacent rooms at the extremes of acceptable tolerances, or by using a common reference point such as the corridor outside of a suite of rooms.

The pressure control and monitoring devices used should be calibrated and, where possible, be linked to an alarm system set according to the determined levels.

Fig. A2.10

## Examples of pressure cascades



## 7.1 Airlocks

Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubbleairlock:

- *cascade airlock*: higher pressure on one side of the airlock and lower pressure on the other (for an example, see Fig. A2.11);
- *sink airlock*: lower pressure inside the airlock and higher pressure on both outer sides (for an example, see Fig. A2.12);
- *bubble airlock*: higher pressure inside the airlock and lower pressure on both outer sides (for an example, see Fig. A2.13).

Fig. A2.11

**Example of a cascade airlock: in most cases, the internal pressure of the airlock is not critical; the pressure differential between the two outer sides is the important criterion**

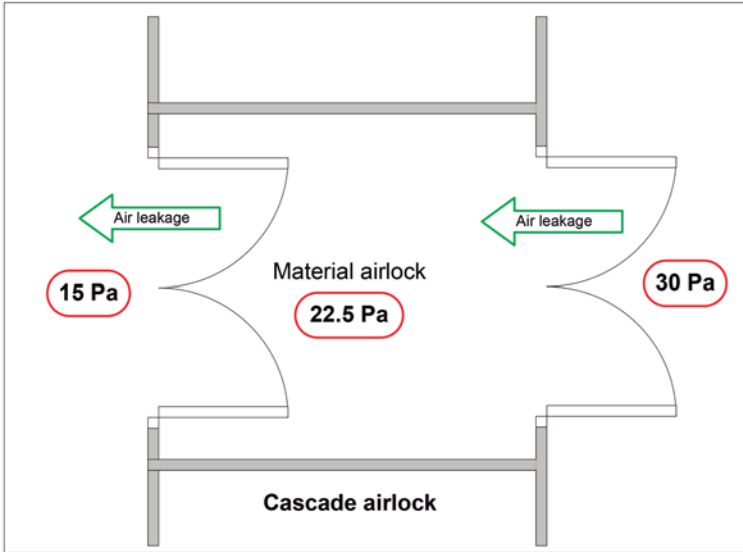


Fig. A2.12

**Example of a sink airlock**

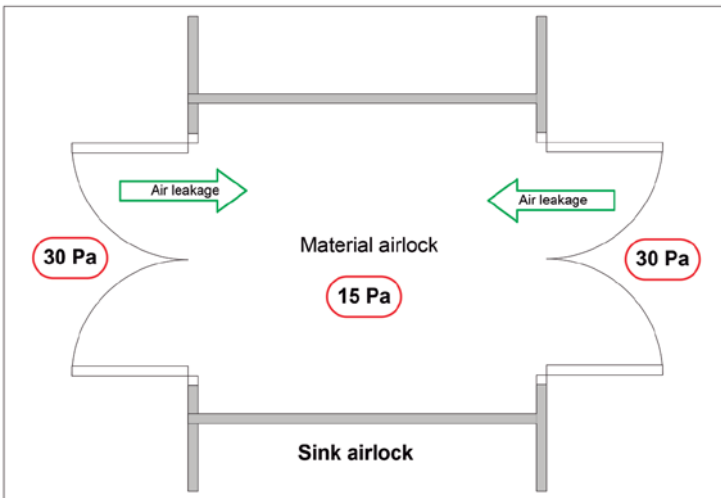
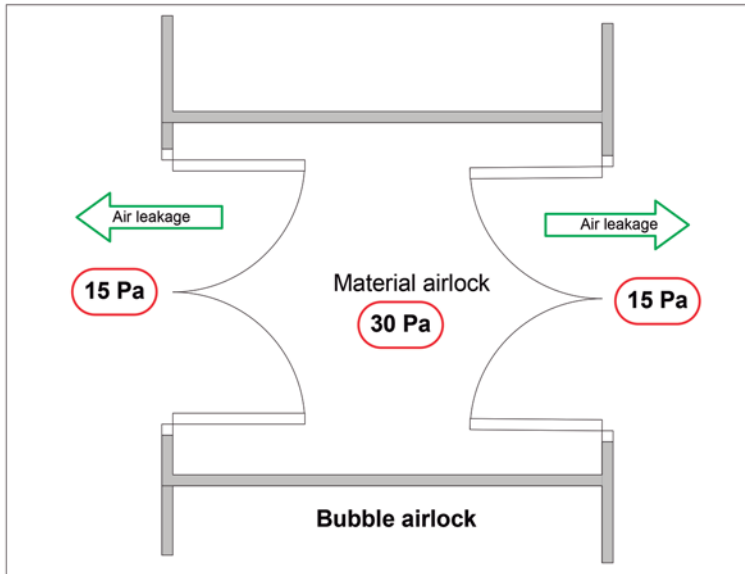


Fig. A2.13

**Example of a bubble airlock**

*Note:* The diagrams above and the differential pressures shown here are for illustration purposes only. Pressures indicated in these examples are absolute pressures, whereas the local pressure indication would most likely be the pressure differential from room to room.

Additional controls should be identified through risk identification and risk assessment. For example, where possible, personnel should not move between different areas during production (such as compression rooms and in process control laboratories), unless there is no risk of contamination of other areas. Personnel often become sources of contamination, as they may carry dust from one area to another. Controls may include airlocks or gowning procedures.

## 8. Temperature and relative humidity

Manufacturers should set appropriate upper and lower limits for temperature and relative humidity for different areas. The required storage conditions specified for the materials and products should be considered when the limits are defined. The HVAC system should be designed in such a manner that these limits can be achieved and maintained through all seasons.

Systems for dehumidification or humidification require special considerations, owing to their contamination risk (e.g. condensate formation, bacterial and fungal contamination, contaminated steam and risks when using

mobile systems between different areas). Chemicals such as corrosion inhibitors or chelating agents, which could have a detrimental effect on the product, should not be added to the boiler system. Humidification systems should be well drained. No condensate should accumulate in air-handling systems. Other humidification appliances such as evaporative systems, atomizers and water mist sprays, should not be used, because of the potential risk of microbial contamination. Air filters should not be installed immediately downstream of humidifiers, as moisture on the filters could lead to bacterial growth. Cold surfaces should be insulated to prevent condensation within the clean area or on air-handling components. Chemical driers using silica gel or lithium chloride are acceptable, provided they do not become sources of contamination.

## 9. Dust, vapour and fume control

Manufacturers should ensure that dust-generated vapours and fumes are effectively removed from the manufacturing areas. Extraction or collecting systems should be designed and qualified to demonstrate this. Sufficient air velocity should be maintained in such systems to effectively remove dust and vapours.

A dust extractor should normally not serve different rooms where different products can be processed at the same time, owing to the risks such as backflow or flow from room to room, resulting in possible contamination and cross-contamination.

Wherever possible, dust or vapour contamination should be removed at source, that is, as close as possible to the point where the dust is generated. Ducting for dust extraction should be designed with sufficient transfer velocity (determined by the manufacturer, depending on materials and products processed), to ensure that dust is carried away, and does not settle in the ducting (a guidance value is 15–20 m/s). As vapours can be problematic, extraction may be supported by directional airflow to assist in the removal. The density of the vapour should be taken into consideration, with extract grilles at a high level or possibly at both high and low levels.

## 10. Protection of the environment

Manufacturers should have controls in place to ensure that air from production areas, including contaminated air from equipment such as fluid bed driers, is passed through appropriate levels of filtration, to ensure that the environment is not polluted. Manufacturers should consult national and international environmental legislation.

## 11. Commissioning

Where manufacturers perform commissioning, this should be clearly documented.

## 12. Qualification

Manufacturers should consider all stages of qualification for their HVAC systems. This includes, where appropriate, user requirement specification, design qualification, factory acceptance test, site acceptance test, installation qualification, operational qualification and performance qualification. Qualification to be done over the life-cycle of the HVAC system should be described and executed, including, for example, when changes are made to the system.

Validation master plan(s), protocols, reports and source data for tests should be available. The scope and extent of qualification should be determined based on risk assessment. Parameters with limits included in qualification (such as temperature test, airflow direction, viable and non-viable particle counts) should be justified by manufacturers. The procedures followed for the performance of the tests should generally be in line with the standard as described in ISO 14644(3).

Some of the typical HVAC system parameters that should be included in the tests during qualification are listed next and the selection of the parameters should be justified (for examples, see Table A2.3). It is recommended that the tests be done at defined intervals. The tests typically cover:

- temperature;
- relative humidity;
- supply air quantities;
- return air or exhaust air quantities;
- room air-change rates;
- room pressures and pressure differentials;
- airflow pattern tests;
- unidirectional airflow velocities;
- containment system velocities;
- HEPA filter penetration tests;
- room particle count tests;
- duct leakage tests;
- materials of construction;
- microbiological counts;
- de-dusting and dust extraction systems.

Table A2.3

**Considerations for test parameters and procedures**

Test parameter	Test procedure	Note
Temperature	ISO 14644 (3) and WHO Technical Report Series, No. 961 (6)	Adapt ISO tests in case of longer periods, and consider the temperature mapping test as described in WHO Technical Report Series
Relative humidity	ISO 14644 (3) and WHO Technical Report Series, No. 961 (6)	Adapt ISO tests in case of longer periods, and consider the temperature mapping test as described in WHO Technical Report Series
Pressure differential	ISO 14644 (3)	Consider extended periods to show consistency in performance
Airflow volumes	ISO 14644 (3)	
Installed filter leakage	ISO 14644 (3)	
Particle counts	ISO 14644 (3)	
Airflow direction	ISO 14644 (3) or company procedure (smoke test)	Ensure a continuous capture of the process, e.g. video, with correct angles to demonstrate air flow direction, and appropriate records and labelling indicating date, time, signatures and area filmed and recorded in a traceable manner
Airflow velocity	ISO 14644 (3)	
Recovery	In-house procedure	
Air-change rate		

## 13. Maintenance

Manufacturers should maintain current documentation for HVAC systems, including operation and maintenance manuals, schematic drawings, procedures and records.

Repairs, maintenance and preventive maintenance (including cleaning, replacement of components, changes, qualification) should be executed in accordance with procedures. Records for these should be maintained for an appropriate time.



## References

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