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Annex 5

Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms

1. Introduction

Heating, ventilation and air-conditioning (HVAC) play an important role in ensuring the manufacture of quality pharmaceutical products. A well designed HVAC system will also provide comfortable conditions for operators.

These guidelines mainly focus on recommendations for systems for manufacturers of solid dosage forms. The guidelines also refer to other systems or components which are not relevant to solid dosage form manufacturing plants, but which may assist in providing a comparison between the requirements for solid dosage-form plants and other systems.

HVAC system design influences architectural layouts with regard to items such as airlock positions, doorways and lobbies. The architectural components have an effect on room pressure differential cascades and cross-contamination control. The prevention of contamination and cross-contamination is an essential design consideration of the HVAC system. In view of these critical aspects, the design of the HVAC system should be considered at the concept design stage of a pharmaceutical manufacturing plant.

Temperature, relative humidity and ventilation should be appropriate and should not adversely affect the quality of pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

This document aims to give guidance to pharmaceutical manufacturers and inspectors of pharmaceutical manufacturing facilities on the design, installation, qualification and maintenance of the HVAC systems. These guidelines are intended to complement those provided in *Good manufacturing practices for pharmaceutical products (1)* and should be read in conjunction with the parent guide. The additional standards addressed by the present guidelines should, therefore, be considered supplementary to the general requirements set out in the parent guide.

2. Scope of document

These guidelines focus primarily on the design and good manufacturing practices (GMP) requirements for HVAC systems for facilities for the manufacture of solid dosage forms. Most of the system design principles for facilities manufacturing solid dosage forms also apply to other facilities such as those manufacturing liquids, creams and ointments. These guidelines do not cover requirements for manufacturing sites for the production of sterile pharmaceutical products. These guidelines do not cover the specific requirements relating to facilities handling hazardous products. Guidelines for hazardous product facilities are covered in a separate WHO guideline.

These guidelines are intended as a basic guide for use by pharmaceutical manufacturers and GMP inspectors.

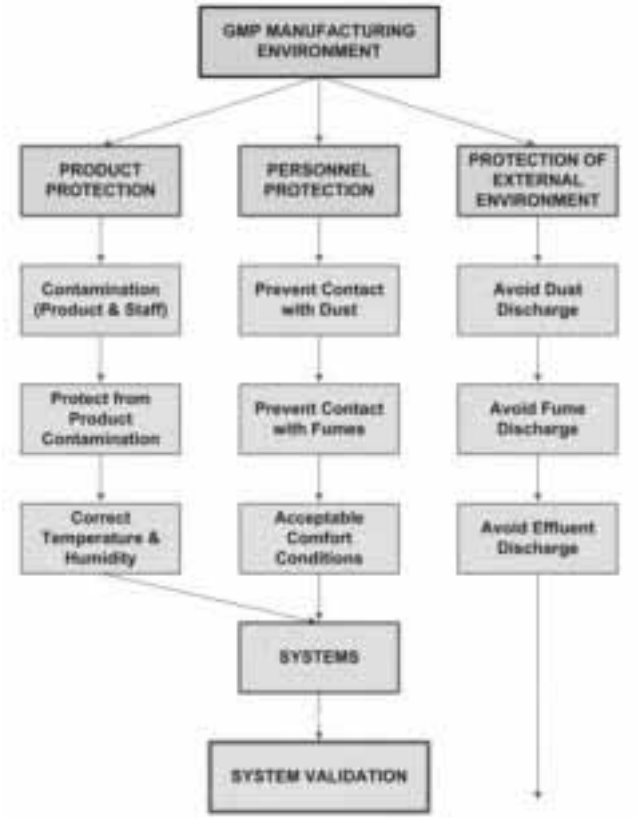
They are not intended to be prescriptive in specifying requirements and design parameters. There are many parameters affecting a clean area condition and it is, therefore, difficult to lay down the specific requirements for one particular parameter in isolation.

Many pharmaceutical manufacturers have their own engineering design and qualification standards and requirements may vary from one manufacturer to the next. Design parameters and user requirements should, therefore, be set realistically for each project, with a view to creating a cost-effective design, yet still complying with all regulatory standards and ensuring that product quality and safety are not compromised. The three primary aspects addressed in this manual are the roles that the HVAC system plays in product protection, personnel protection and environmental protection (Figure 1).

Cognisance should be taken of the products to be manufactured when establishing system design parameters. A facility manufacturing multiple different products may have more stringent design parameters with respect to cross-contamination control, compared with a single product facility.

Figure 1

The guidelines address the various system criteria according to the sequence set out in this diagram



3. Glossary

The definitions given below apply to terms used in these guidelines. They may have different meanings in other contexts.

acceptance criteria

Measurable terms under which a test result will be considered acceptable.

action limit

The action limit is reached when the acceptance criteria of a critical parameter have been exceeded. Results outside these limits will require specified action and investigation.

air changes per hour (ACPH)

The volume of air supplied to a room, in m^3/hr, divided by the room volume, in m^3.

air-handling unit (AHU)

The air-handling unit serves to condition the air and provide the required air movement within a facility.

airlock

An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods (PAL, personnel airlock; MAL, material airlock).

alert limit

The alert limit is reached when the normal operating range of a critical parameter has been exceeded, indicating that corrective measures may need to be taken to prevent the action limit being reached.

as-built

Condition where the installation is complete with all services connected and functioning but with no production equipment, materials or personnel present.

at-rest

Condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.

central air-conditioning unit (see air-handling unit)

change control

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated

status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

clean area (cleanroom)[1]

An area (or room or zone) with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

closed system

A system where the product or material is not exposed to the manufacturing environment.

commissioning

Commissioning is the documented process of verifying that the equipment and systems are installed according to specifications, placing the equipment into active service and verifying its proper action. Commissioning takes place at the conclusion of project construction but prior to validation.

containment

A process or device to contain product, dust or contaminants in one zone, preventing it from escaping to another zone.

contamination

The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediate, during production, sampling, packaging or repackaging, storage or transport.

controlled area

An area within the facility in which specific environmental facility conditions and procedures are defined, controlled, and monitored to prevent degradation or cross-contamination of the product.

critical parameter or component

A processing parameter (such as temperature or relative humidity) that affects the quality of a product, or a component that may have a direct impact on the quality of the product.

critical quality attribute (CQA)

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality.

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[1] Note: Clean area standards, such as ISO 14644-1, provide details on how to classify air cleanliness by means of particle concentrations, whereas the GMP standards provide a grading for air cleanliness in terms of the condition (at-rest or operational), the permissible microbial concentrations, as well as other factors such as gowning requirements. GMP and clean area standards should be used in conjunction with each other to define and classify the different manufacturing environments.

cross-contamination

Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

design condition

Design condition relates to the specified range or accuracy of a controlled variable used by the designer as a basis for determining the performance requirements of an engineered system.

design qualification (DQ)

Design qualification is the documented check of planning documents and technical specifications for conformity of the design with the process, manufacturing, GMP and regulatory requirements.

direct impact system

A system that is expected to have a direct impact on product quality. These systems are designed and commissioned in line with good engineering practice (GEP) and, in addition, are subject to qualification practices.

exfiltration

Exfiltration is the egress of air from a controlled area to an external zone.

facility

The built environment within which the clean area installation and associated controlled environments operate together with their supporting infrastructure.

good engineering practice (GEP)

Established engineering methods and standards that are applied throughout the project life-cycle to deliver appropriate, cost-effective solutions.

hazardous substance or product

A product or substance that may present a substantial risk of injury to health or to the environment

indirect impact system

This is a system that is not expected to have a direct impact on product quality, but typically will support a direct impact system. These systems are designed and commissioned according to GEP only.

infiltration

Infiltration is the ingress of air from an external zone into a controlled area.

installation qualification (IQ)

Installation qualification is documented verification that the premises, HVAC system, supporting utilities and equipment have been built and installed in compliance with their approved design specification.

no-impact system

This is a system that will not have any impact, either directly or indirectly, on product quality. These systems are designed and commissioned according to GEP only.

non-critical parameter or component

A processing parameter or component within a system where the operation, contact, data control, alarm or failure will have an indirect impact or no impact on the quality of the product.

normal operating range

The range that the manufacturer selects as the acceptable values for a parameter during normal operations. This range must be within the operating range.

operating limits

The minimum and/or maximum values that will ensure that product and safety requirements are met.

operating range

Operating range is the range of validated critical parameters within which acceptable products can be manufactured.

operational condition

This condition relates to carrying out room classification tests with the normal production process with equipment in operation, and the normal staff present in the room.

operational qualification (OQ)

Operational qualification is the documentary evidence to verify that the equipment operates in accordance with its design specifications in its normal operating range and performs as intended throughout all anticipated operating ranges.

oral solid dosage (OSD)

Usually refers to an OSD plant that manufactures medicinal products such as tablets, capsules and powders to be taken orally.

pass-through-hatch (PTH) or pass box (PB)

A cabinet with two or more doors for passing equipment or product, whilst maintaining the pressure cascade and segregation between two controlled zones. A passive PTH has no air supply or extract. A dynamic PTH has an air supply into the chamber.

performance qualification (PQ)

Performance qualification is the documented verification that the process and/or the total process related to the system performs as intended throughout all anticipated operating ranges.

point extraction

Air extraction to remove dust with the extraction point located as close as possible to the source of the dust.

pressure cascade

A process whereby air flows from one area, which is maintained at a higher pressure, to another area at a lower pressure.

qualification

Qualification is the planning, carrying out and recording of tests on equipment and a system, which forms part of the validated process, to demonstrate that it will perform as intended.

quality critical process parameter (CPP)

A process parameter which could have an impact on the critical quality attribute.

relative humidity

The ratio of the actual water vapour pressure of the air to the saturated water vapour pressure of the air at the same temperature expressed as a percentage. More simply put, it is the ratio of the mass of moisture in the air, relative to the mass at 100% moisture saturation, at a given temperature.

standard operating procedure (SOP)

An authorized written procedure, giving instructions for performing operations, not necessarily specific to a given product or material, but of a more general nature (e.g. operation of equipment, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

turbulent flow

Turbulent flow, or non-unidirectional airflow, is air distribution that is introduced into the controlled space and then mixes with room air by means of induction.

unidirectional airflow (UDAF)

Unidirectional airflow is a rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (see also turbulent flow).

validation

The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

validation master plan (VMP)

Validation master plan is a high-level document which establishes an umbrella validation plan for the entire project, and is used as guidance by the project team for resource and technical planning (also referred to as master qualification plan).

4. Protection

4.1 Products and personnel

4.1.1 Areas for the manufacture of pharmaceuticals, where pharmaceutical starting materials and products, utensils, primary packing materials and equipment are exposed to the environment, should be defined as "clean areas", "clean zones", "controlled areas" or "cleanrooms".

4.1.2 The achievement of a particular clean area condition depends on a number of criteria that should be addressed at the design and qualification stages. A suitable balance between the different criteria will be required in order to create an efficient clean area.

4.1.3 Some of the basic criteria to be considered which affects room cleanliness should include:

- building finishes and structure
- air filtration
- air change rate or flushing rate
- room pressure
- location of air terminals and directional airflow
- temperature
- relative humidity
- material flow
- personnel flow
- gowning procedures
- equipment movement
- process being carried out (open or closed system)
- outside air conditions
- occupancy
- type of product
- cleaning standard operating procedures (SOPs).

4.1.4 Air filtration and air change rates should be set to ensure that the defined clean area condition is attained.

4.1.5 The air change rates should be determined by the manufacturer and designer, taking into account the various critical parameters using a risk based approach with due consideration of capital and running costs and

energy usage. Primarily the air change rate should be set to a level that will achieve the required clean area condition.

4.1.6 Air change rates are normally determined by the following considerations (could normally vary between 6 and 20 air changes per hour):

- area condition required: whether a specific room cleanliness condition is in fact required and whether the room condition is rated for an "at rest" condition or an "operational" condition (air change rate should be selected on need rather than tradition)
- the product characteristics (e.g. odours, hygroscopicity, etc)
- the quality and filtration of the supply air
- particulates generated by the manufacturing process
- particulates generated by the operators
- configuration of the room and air supply and extract locations
- sufficient air to achieve containment effect and to clean up the area
- sufficient air to cope with the room heat load
- sufficient air to balance extract rates
- sufficient air to maintain the required room pressure.

4.1.7 If a cleanroom classification is specified the manufacturer should state whether this is achieved under "as-built" (Figure 2), "at-rest" (Figure 3) or "operational" (Figure 4) conditions.

4.1.8 Room classification tests in the "as-built" condition should be carried out on the bare room, in the absence of any equipment or personnel.

4.1.9 Room classification tests in the "at-rest" condition should be carried out with the equipment operating where relevant, but without any operators. Because of the amounts of dust usually generated in a solid dosage facility, the clean area classifications would be rated for the "at-rest" condition.

4.1.10 Room classification tests in the "operational" condition are normally carried out during the normal production process with equipment operating, and the normal number of personnel present in the room. Generally a room that is tested for an "operational" condition should be able to be cleaned up to the "at-rest" clean area classification after a short clean-up time. The clean-up time should be determined through validation and is generally of the order of 20 minutes.

4.1.11 Materials and products should be protected from contamination and cross-contamination during all stages of manufacture (see also section 4.5 for cross-contamination control).

Note: contaminants may result from inappropriate premises (e.g. poor design, layout or finishing), poor cleaning procedures, contaminants brought in by personnel, poor manufacturing process and a poor HVAC system.

Figure 2
“As-built” condition

Figure 3
“At-rest” condition

Figure 4
"Operational" condition

4.1.12 Airborne contaminants should be controlled through effective ventilation and filtration.

4.1.13 External contaminants should be removed by effective filtration of the supply air (see Figure 5 for an example of a shell-like building layout to enhance containment and protection from external contaminants).

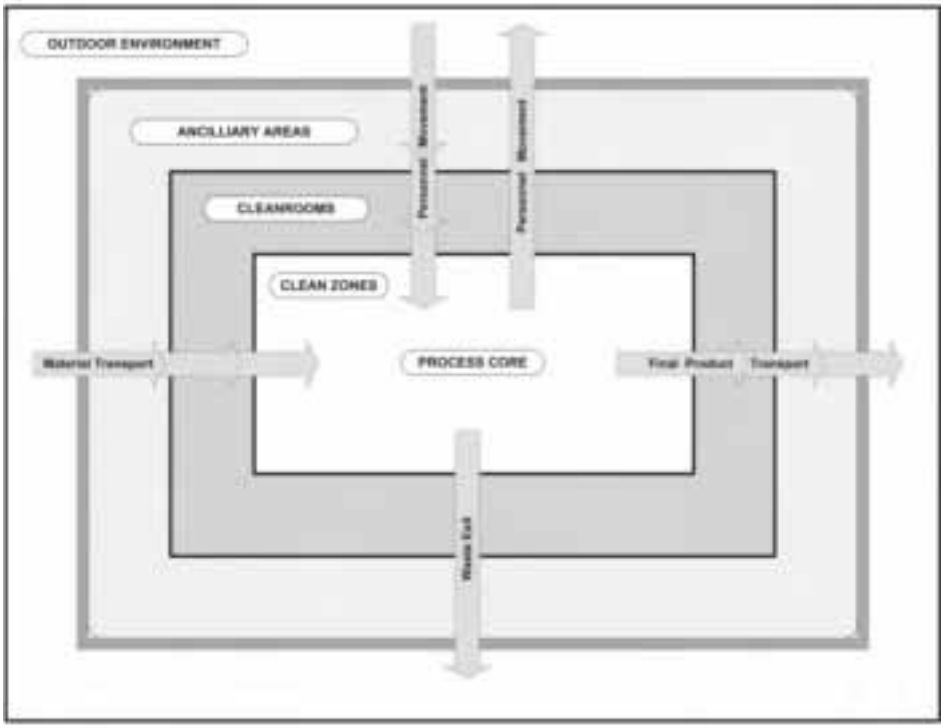
4.1.14 Internal contaminants should be controlled by dilution and flushing of contaminants in the room, or by displacement airflow (See Figures 6 and 7 for examples of methods for the flushing of airborne contaminants).

4.1.15 Airborne particulates and the degree of filtration should be considered critical parameters with reference to the level of product protection required.

4.1.16 Personnel should not be a source of contamination.

4.1.17 The level of protection and air cleanliness for different areas should be determined according to the product being manufactured, the process being used and the product's susceptibility to degradation (Table 1).

Figure 5
Shell-like containment control concept



4.2 Air filtration

Note: The degree to which air is filtered plays an important role in the prevention of contamination and the control of cross-contamination.

4.2.1 The type of filters required for different applications depends on the quality of the ambient air and the return air (where applicable) and also on the air change rates. Table 2 gives the recommended filtration levels for different levels of protection in a pharmaceutical facility. Manufacturers should determine and prove the appropriate use of filters.

4.2.2 Filter classes should always be linked to the standard test method because referring to actual filter efficiencies can be very misleading (as different test methods each result in a different value for the same filter). (Referring to filter classifications such as an 85% filter or a 5 μm filter are not valid classifications and should not be used, as this can lead to the incorrect filter being installed. Only the EN 779 and EN 1822 classifications, as per the table below, should be used.)

Figure 6
Turbulent dilution of dirty air

Low-level extract is ideal for dust suppression purposes, but is not essential. (Low-level extract is essential for Grade A, B & C areas.)

Figure 7
Unidirectional displacement of dirty air

Table 1

Examples of levels of protection (based on ISPE oral solid dosage (OSD) Guideline criteria)

Level	Condition	Example of area
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.

Table 2

Levels of protection and recommended filtration

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)

Note: The filter classifications referred to above relate to the EN 1822 and EN 779 test standards (EN 779 relates to filter classes G1 to F9 and EN 1822 relates to filter classes E10 to U17). Refer to Figure 8 for comparative classifications of other filter standards.

4.2.3 In selecting filters, the manufacturer should have considered other factors, such as particularly contaminated ambient conditions, local regulations and specific product requirements. Good pre-filtration extends the life of the more expensive filters downstream.

4.2.4 Materials for components of an HVAC system should be selected with care so that they do not become a source of contamination. Any component with the potential for liberating particulate or microbial contamination into the air stream should be located upstream of the final filters.

Figure 8

Comparison of filter test standards

Eurovent 4/5 Rating	ASHRAE 52.2	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	EN 779 & EN 1822		
(superseded)	Merv Rating	Average Arrestance A_m (%)	Average Dust Spot Efficiency E_m (%)	MPPS Integral Overall Efficiency (%)	EN Rating	
				99.999995	U17	EN 1822: 2009
				99.99995	U16	
EU 14				99.9995	U15	
EU 13	Merv 18			99.995	H14	
EU 12	Merv 17			99.95	H13	
EU 11				99.5	E12	
EU 10				95	E11	
EU 9	Merv 16		>95	85	E10	
EU 9	Merv 15		95		F9	EN779: 2002
EU 8	Merv 14		90		F8	
	Merv 13	>98	85	MPPS = Most Penetrating Particle Size	F7	
EU 7		>98	80			
	Merv 12	>95	75			
EU 6		>95	70		F6	
	Merv 11	>95	65			
		>95	60			
	Merv 10	>95	55			
EU 5	Merv 9	>95	50		F5	
	Merv 8	>95	45			
		>95	40			
	Merv 7	>90	35			
EU 4		>90	30		G4	
	Merv 6	90	25			
EU 3	Merv 5	85	20		G3	
		80	<20			
	Merv 4	75				
EU 2	Merv 3	70			G2	
	Merv 2	65				
EU 1	Merve 1	<65			G1	

4.2.5 Where possible ventilation dampers, filters and other services should be designed and positioned so that they are accessible from *outside* the manufacturing areas (service voids or service corridors) for maintenance purposes.

4.2.6 Directional airflow within production or primary packing areas should assist in preventing contamination. Airflows should be planned in conjunction with operator locations, so as to minimize contamination of the product by the operator and also to protect the operator from dust inhalation.

4.2.7 HVAC air distribution components should be designed, installed and located to prevent contaminants generated within the room from being spread.

4.2.8 Supply air diffusers should be selected with care taking consideration of, e.g. room requirements and positions of equipment and operators in the room. Supply air diffusers of the high induction type (e.g. those typically used for office-type air-conditioning) should where possible not be used in clean areas where dust is liberated. Air diffusers should be of the non-induction type, introducing air with the least amount of induction so as to maximize the flushing effect. In rooms where the process results in high dust liberation; perforated plates or low induction swirl diffusers with low level extract or return should be used (to contain the dust at the lower level of the room) (see Figures 9–11 for illustrations of the three types of diffuser). In cases where dust liberation is low, ceiling return air grilles may be acceptable.

4.2.9 Induction and certain swirl diffusers induce room air vertically up to the diffuser to mix with the supply air. These diffusers create good dilution of contaminants in the room and may be used in rooms where there is low dust liberation. However, if used in rooms where excessive dust is generated, the distribution of dust in the room could be hazardous for the operators in the room.

4.3 Unidirectional airflow

4.3.1 Unidirectional airflow (UDAF) should be used for weighing booths or sampling booths to provide operator and product protection and should also have a slight air in-flow from the room to enhance containment. Dust containment at the weigh booth should be demonstrated by smoke airflow pattern tests, or other appropriate tests. UDAF can also be used to provide protection of other dusty processes.

4.3.2 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 the further processing of the product.

Figure 9
Induction diffuser

Figure 10
Perforated plate diffuser

Figure 11
Swirl diffuser

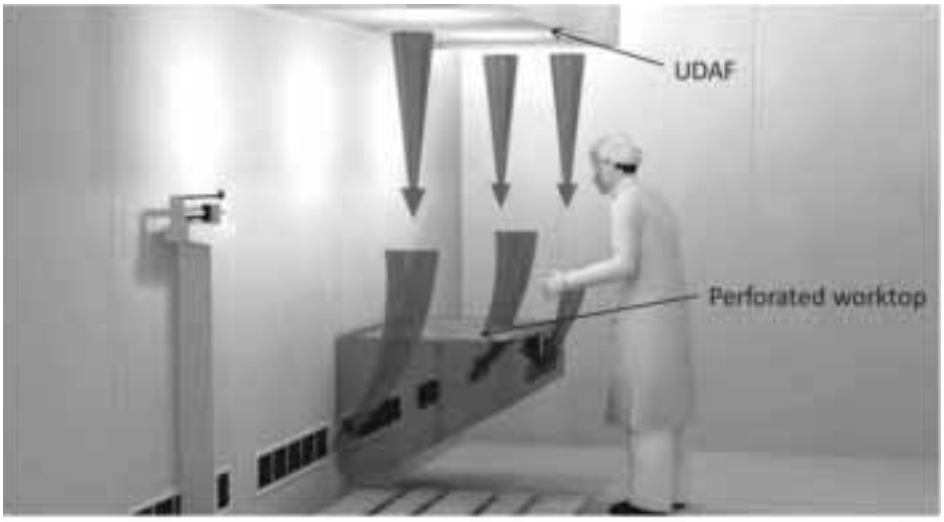
4.3.3 In a weighing booth situation, the aim of the UDAF is to provide dust containment and operator protection.

Example: In Figure 12 the dust generated at the weighing station is immediately extracted through the perforated worktop, thus protecting the operator from dust inhalation, but at the same time protecting the product from contamination by the operator by means of the vertical unidirectional airflow stream.

4.3.4 The unidirectional flow velocity should be such that it does not disrupt the sensitivity of balances in weighing areas. Where necessary the velocity may be reduced to prevent inaccuracies during weighing, provided that sufficient airflow is maintained to provide containment. Conventional unidirectional airflow systems, where a Grade A condition is required, have a guidance airflow velocity of 0.36 to 0.54 m/s. However, in a weigh booth or sampling booth a lower velocity can be used as a Grade A condition is not required. It is often necessary to reduce velocities to a lower level in order not to influence balance readings. The airflow velocity and directional flow should still ensure product containment. For this type of application it is sometimes better to refer to the unit as an airflow protection booth (APB) rather than a UDAF, in order to avoid confusion, with a Grade A requirement.

4.3.5 The position in which the operator stands relative to the source of dust liberation and airflow should be determined to ensure that the operator is not in the path of an airflow that could lead to contamination of the product (Figure 13).

Figure 12
Operator protection at weighing station



4.3.6 Once the system has been designed and qualified with a specific layout for operators and processes, this should be maintained in accordance with an SOP.

4.3.7 There should be no obstructions in the path of a unidirectional flow air stream that may cause the operator to be exposed to dust.

Figure 14 illustrates the incorrect use of a weighing scale which has a solid back. The back of the weighing scale should not block the return air path as this causes air to rise vertically, resulting in a hazardous situation for the operator.

Figure 15 illustrates a situation where an open bin is placed below a vertical unidirectional flow distributor. The downward airflow should be prevented from entering the bin, and then being forced to rise again, as this would carry dust up towards the operator's face. In such an occurrence it may be necessary to add a partial cover over the bin to limit the entry of air. Point extraction could also be used but this can result in the excessive loss of product.

Figure 16 shows that a solid worktop can sometimes cause deflection of the vertical unidirectional airflow resulting in a flow reversal. A possible solution would be to have a 100 mm gap between the back of the table and the wall, with the air being extracted here.

Figure 13
Operator protection by horizontal airflow

4.3.8 The manufacturer should select either vertical or horizontal unidirectional flow (Figure 17) and an appropriate airflow pattern to provide the best protection for the particular application.

4.3.9 Return or exhaust air grilles in rooms or at weigh or sampling booths should preferably be of the perforated grille types, which are easy to clean. Return/exhaust air filters can either be installed at the room terminal or in the air-handling unit. Maintenance and cleaning of filters and ducts should be addressed to ensure constant airflow.

4.4 Infiltration

4.4.1 Air infiltration of unfiltered air into a pharmaceutical plant should not be a source of contamination.

Figure 14

Operator subject to powder inhalation due to obstruction

Figure 15

Operator subject to powder contamination due to airflow reversal in bin

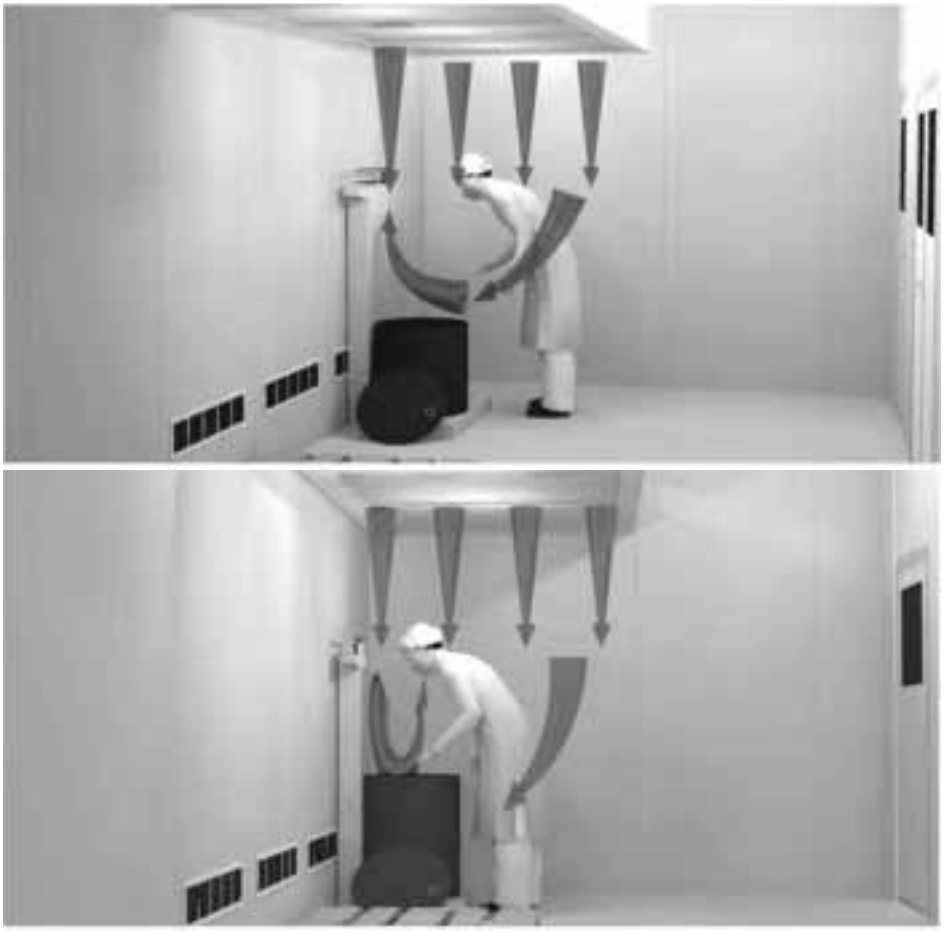


Figure 16
Operator subject to powder inhalation due to worktop obstruction

4.4.2 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. Refer to the WHO guideline for hazardous products, for further guidance on negative pressure facilities.

4.4.3 The location of the negative pressure facility should be carefully considered with reference to the areas surrounding it, particular attention being given to ensuring that the building structure is well sealed.

4.4.4 Negative pressure zones should, as far as possible, be encapsulated by surrounding areas with clean air supplies, so that only clean air can infiltrate into the controlled zone.

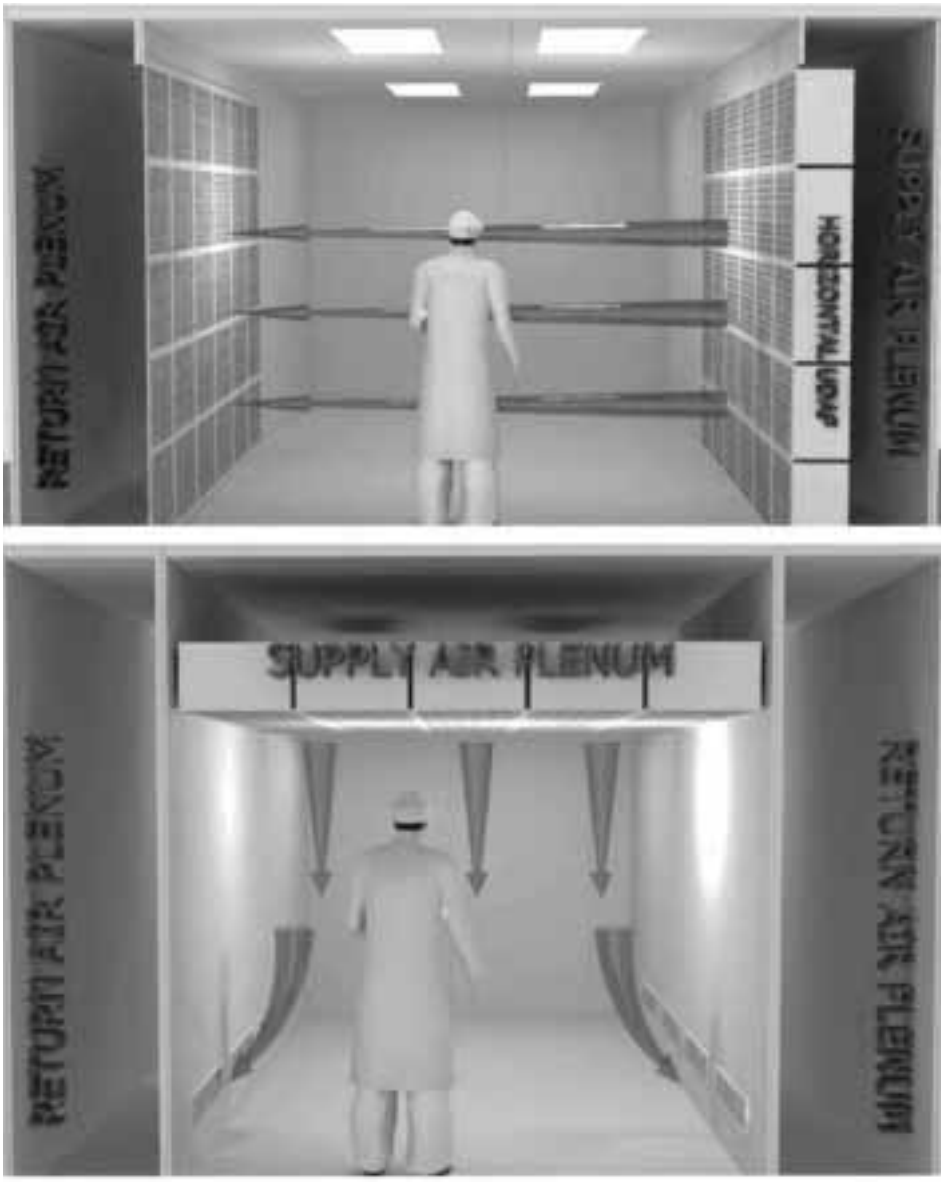
4.5 Cross-contamination

4.5.1 Where different products are manufactured at the same time, in different areas or cubicles, in a multiproduct OSD manufacturing site, measures should be taken to ensure that dust cannot move from one cubicle to another.

4.5.2 Correct directional air movement and a pressure cascade system can assist in preventing cross-contamination. The pressure cascade should be such that the direction of airflow is from the clean corridor into the cubicles, resulting in dust containment.

4.5.3 The corridor should be maintained at a higher pressure than the cubicles, and the cubicles at a higher pressure than atmospheric pressure.

Figure 17
Diagram indicating horizontal and vertical unidirectional flow



4.5.4 Containment can normally be achieved by application of the displacement concept (low pressure differential, high airflow), or the pressure differential concept (high pressure differential, low airflow), or the physical barrier concept.

4.5.5 The pressure cascade regime and the direction of airflow should be appropriate to the product and processing method used.

4.5.6 Highly potent products should be manufactured under a pressure cascade regime that is negative relative to atmospheric pressure.

4.5.7 The pressure cascade for each facility should be individually assessed according to the product handled and level of protection required.

4.5.8 Building structure should be given special attention to accommodate the pressure cascade design.

4.5.9 Ceilings and walls, close fitting doors and sealed light fittings should be in place, to limit ingress or egress of air.

4.6 Displacement concept (low pressure differential, high airflow)

Note: This method of containment is not the preferred method, as the measurement and monitoring of airflow velocities in doorways is difficult. This concept is commonly found in production processes where large amounts of dust are generated.

4.6.1 Under this concept the air should be supplied to the corridor, flow through the doorway, and be extracted from the back of the cubicle. Normally the cubicle door should be closed and the air should enter the cubicle through a door grille, although the concept can be applied to an opening without a door.

4.6.2 The velocity should be high enough to prevent turbulence within the doorway resulting in dust escaping.

4.6.3 This displacement airflow should be calculated as the product of the door area and the velocity, which generally results in fairly large air quantities.

Note: Although this method of containment may still exist on older facilities, it is not the preferred method, as the measurement and monitoring of doorway velocities is difficult. In addition, simultaneously maintaining the correct room pressure and the correct room air change rate is often not achieved.

4.7 Pressure differential concept (high pressure differential, low airflow)

Note: The pressure differential concept may normally be used in zones where little or no dust is being generated. It may be used alone or in combination with other containment control techniques and concepts, such as a double door airlock.

4.7.1 The high pressure differential between the clean and less clean zones should be generated by leakage through the gaps of the closed doors to the cubicle.

4.7.2 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.

4.7.3 In considering room pressure differentials, transient variations, such as machine extract systems, should be taken into consideration.

4.7.4 A pressure differential of 15 Pa is often used for achieving containment between two adjacent zones, but pressure differentials of between 5 Pa and 20 Pa may be acceptable. Where the design pressure differential is too low and tolerances are at opposite extremities, a flow reversal can take place. For example, where a control tolerance of ± 3 Pa is specified, the implications of rooms being operated at the upper and lower tolerances should be evaluated. It is important to select pressures and tolerances such that a flow reversal is unlikely to occur.

4.7.5 The pressure differential between adjacent rooms could be considered a critical parameter, depending on the outcome of risk analysis. The limits for the pressure differential between adjacent areas should be such that there is no risk of overlap in the acceptable operating range, e.g. 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in the failure of the pressure cascade, where the first room is at the maximum pressure limit and the second room is at its minimum pressure limit.

4.7.6 Low pressure differentials may be acceptable when airlocks (pressure sinks or pressure bubbles) are used to segregate areas.

4.7.7 The effect of room pressure tolerances are illustrated in Figure 18.

4.7.8 The pressure control and monitoring devices used should be calibrated and qualified. Compliance with specifications should be regularly verified and the results recorded. Pressure control devices should be linked to an alarm system set according to the levels determined by a risk analysis.

4.7.9 Manual control systems, where used, should be set up during commissioning, with set point marked, and should not change unless other system conditions change.

4.7.10 Airlocks can be important components in setting up and maintaining pressure cascade systems and also to limit cross-contamination.

4.7.11 Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock (Figures 19–21):

- cascade airlock: higher pressure on one side of the airlock and lower pressure on the other;
- sink airlock: lower pressure inside the airlock and higher pressure on both outer sides;

Figure 18

Examples of pressure cascades

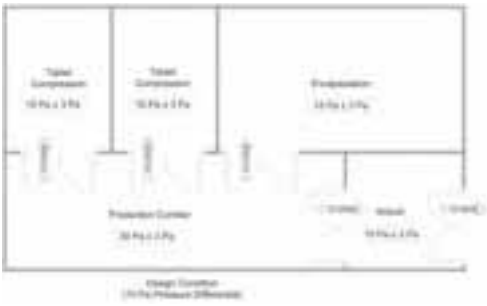


Image of room pressure gauge indicating colour coded normal, alert & action parameters

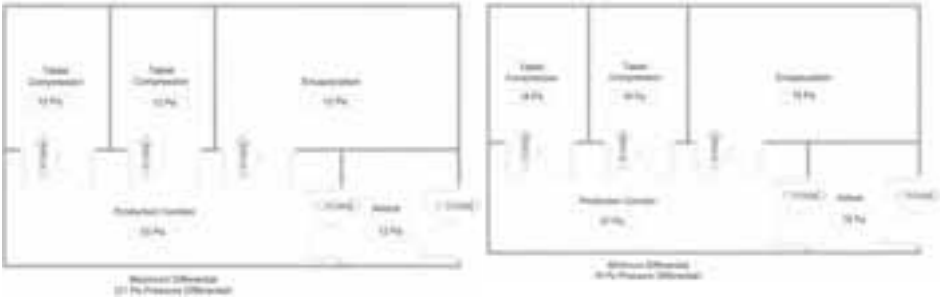


Figure 19

Example of 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 criteria.)

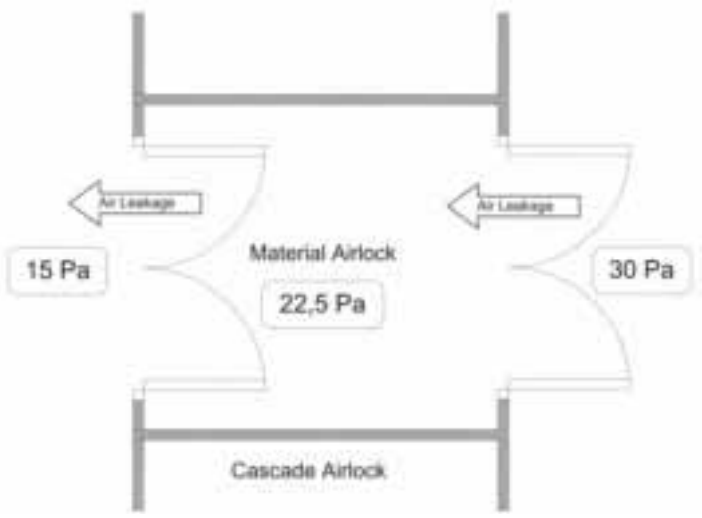


Figure 20
Example of sink airlock

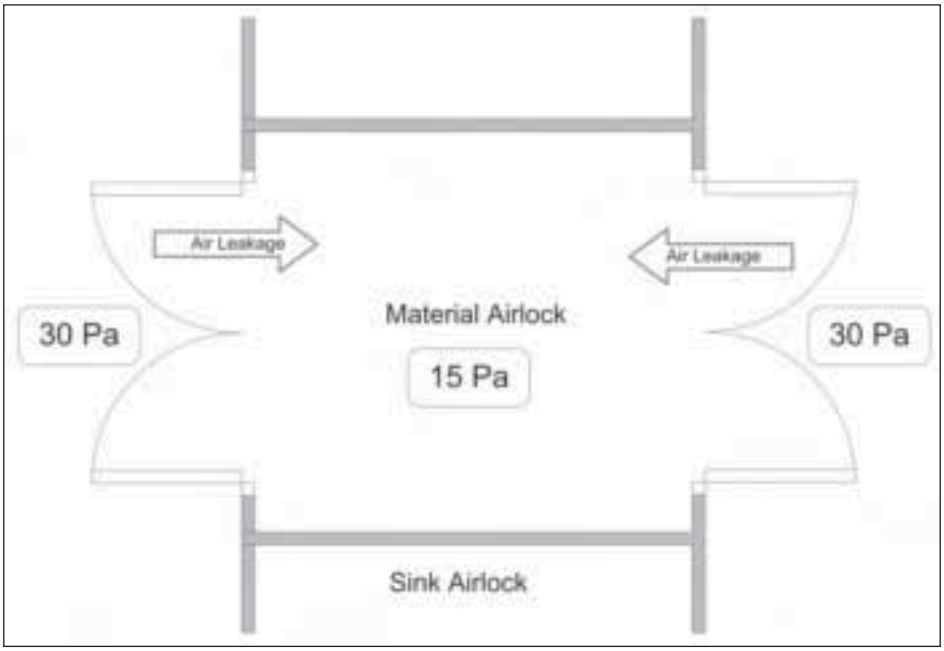
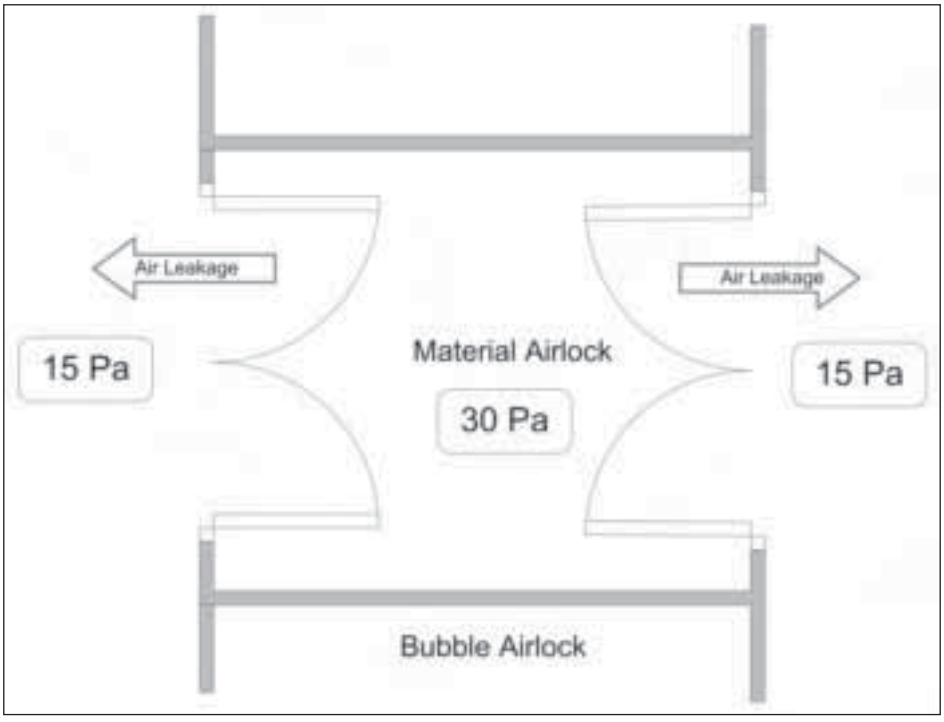


Figure 21
Example of bubble airlock



- bubble airlock: higher pressure inside the airlock and lower pressure on both outer sides.

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 pressure differential from room to room.

4.7.12 Doors should open to the high pressure side, so that room pressure assists in holding the door closed and in addition be provided with self-closers. Should the doors open to the low pressure side, the door closer springs should be sufficient to hold the door closed and prevent the pressure differential from pushing the door open. There should be a method to indicate if both doors to airlocks are open at the same time, or alternatively these should be interlocked. The determination of which doors should be interlocked should be the subject of a risk assessment study.

4.7.13 Central dust extraction systems should be interlocked with the appropriate air-handling systems, to ensure that they operate simultaneously.

4.7.14 Room pressure differential between adjacent cubicles, which are linked by common dust extraction ducting, should be avoided.

4.7.15 Air should not flow through the dust extraction ducting or return air ducting from the room with the higher pressure to the room with the lower pressure (this would normally occur only if extract or return systems were inoperative). Systems should be designed to prevent dust flowing back in the opposite direction in the event of component failure or airflow failure.

4.7.16 Adequate room pressure differential indication should be provided so that each critical room pressure can be traced back to ambient pressure (by summation of the room pressure differentials), in order to determine the room actual absolute pressure. Room pressure indication gauges should have a range and graduation scale which enables the reading to an accuracy, as appropriate; normal operating range, alert and action limits should be defined and displayed at the point of indication. A colour coding gauge may be helpful.

Room pressure indication may be either analogue or digital, and may be represented as either pressure differentials or absolute pressures. Which ever system is used any out-of-specification condition should be easily identifiable.

4.7.17 Material pass-through-hatches (PTH) or pass boxes (PB) can also be used for separating two different zones. PTHs fall into two categories, namely a dynamic PTH or a passive PTH. Dynamic PTHs have an air supply to or extraction from them, and can then be used as bubble, sink or cascade PTHs.

4.8 Physical barrier concept

4.8.1 Where appropriate, an impervious barrier to prevent cross-contamination between two zones, such as closed systems, pumped or vacuum transfer of materials, should be used.

4.9 Temperature and relative humidity

4.9.1 Where appropriate, temperature and relative humidity should be controlled, monitored and recorded, where relevant, to ensure compliance with requirements pertinent to the materials and products and provide a comfortable environment for the operator where necessary.

4.9.2 Maximum and minimum room temperatures and relative humidity should be appropriate. Alert and action limits on temperatures and humidities should be set, as appropriate.

4.9.3 The operating band, or tolerance, between the acceptable minimum and maximum temperatures should not be made too close. Tight control tolerances may be difficult to achieve and can also add unnecessary installation and running costs.

4.9.4 Cubicles, or suites, in which products requiring low relative humidity are processed, should have well-sealed walls and ceilings and should also be separated from adjacent areas with higher relative humidity by means of suitable airlocks.

4.9.5 Precautions should be taken to prevent moisture migration that increases the load on the HVAC system.

4.9.6 Humidity control should be achieved by removing moisture from the air, or adding moisture to the air, as relevant.

4.9.7 Dehumidification (moisture removal) may be achieved by means of either refrigerated dehumidifiers or chemical dehumidifiers.

4.9.8 Appropriate cooling media for dehumidification such as low temperature chilled water/glycol mixture or refrigerant should be used.

4.9.9 Humidifiers should be avoided if possible as they may become a source of contamination (e.g. microbiological growth). Where humidification is required, this should be achieved by appropriate means such as the injection of steam into the air stream. A product-contamination assessment should be done to determine whether pure or clean steam is required for the purposes of humidification.

4.9.10 Where steam humidifiers are used, 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. Only appropriate additives should be added to the boiler system.

4.9.11 Humidification systems should be well drained. No condensate should accumulate in air-handling systems.

4.9.12 Other humidification appliances such as evaporative systems, atomizers and water mist sprays, should not be used because of the potential risk of microbial contamination.

4.9.13 Duct material in the vicinity of the humidifier should not add contaminants to air that will not be removed by filtration further downstream.

4.6.14 Air filters should not be installed immediately downstream of humidifiers, as moisture on the filters could lead to bacterial growth.

4.9.15 Cold surfaces should be insulated to prevent condensation within the clean area or on air-handling components.

4.9.16 When specifying relative humidity, the associated temperature should also be specified.

4.9.17 Chemical driers using silica gel or lithium chloride are acceptable, provided that they do not become sources of contamination.

5. Dust control

5.1 Wherever possible, dust or vapour contamination should be removed at source. Point-of-use extraction, i.e. as close as possible to the point where the dust is generated, should be employed. Spot ventilation or capture hoods may be used as appropriate.

5.2 Point-of-use extraction should be either in the form of a fixed high velocity extraction point or an articulated arm with movable hood or a fixed extraction hood.

5.3 Dust extraction ducting should be designed with sufficient transfer velocity to ensure that dust is carried away, and does not settle in the ducting. Periodic checks should be performed to ensure that there is no build up of the dust in the ducting.

5.4 The required transfer velocity should be determined: it is dependent on the density of the dust (the denser the dust, the higher the transfer velocity should be, e.g. 15–20 m/s).

5.5 Airflow direction should be carefully chosen, to ensure that the operator does not contaminate the product, and also so that the operator is not put at risk by the product.

5.6 Point extraction alone is usually not sufficient to capture all of the contaminants, and general directional airflow should be used to assist in removing dust and vapours from the room.

5.7 Typically, in a room operating with turbulent airflow, the air should be introduced from ceiling diffusers, located at the door entry side of the room and extracted from the rear of the room at low level to help give a flushing effect in the room. Correct flushing of the rooms may be verified by airflow visualization smoke tests.

5.8 When dealing with particularly harmful products, additional steps, such as handling the products in glove boxes or using barrier isolator technology, should be used.

6. Protection of the environment

6.1 General

6.1.1 It should be noted that protection of the environment is not addressed in this guideline, and discharges into the atmosphere should be compliant with relevant local and national environmental legislation and standards.

6.1.2 Dust, vapours and fumes could be possible sources of contamination; therefore, care should be taken when deciding on the location of the inlet and exhaust points relative to one other.

6.2 Dust in exhaust air

6.2.1 Exhaust air discharge points on pharmaceutical equipment and facilities, such as from fluid bed driers and tablet-coating equipment, and exhaust air from dust extraction systems, carry heavy dust loads and should be provided with adequate filtration to prevent contamination of the ambient air.

6.2.2 Where the powders are not highly potent, final filters on a dust exhaust system should be fine dust filters with a filter classification of F9 according to EN 779 filter standards.

6.2.3 Where reverse-pulse dust collectors are used for removing dust from dust extraction systems, they should usually be equipped with cartridge filters containing a compressed air lance, and be capable of continuous operation without interrupting the airflow.

6.2.4 Alternative types of dust collectors (such as those operating with a mechanical shaker, requiring that the fan be switched off when the mechanical shaker is activated) should be used in such a manner that there is no risk of cross-contamination. There should be no disruption of airflow during a production run as the loss of airflow could disrupt the pressure cascade.

6.2.5 Mechanical-shaker dust collectors should not be used for applications where continuous airflow is required, in order to avoid unacceptable fluctuations in room pressures, except in the case where room pressures are automatically controlled.

6.2.6 When wet scrubbers are used, the dust-slurry should be removed by a suitable means, e.g. a drainage system or waste removal contractor.

6.2.7 The quality of the exhaust air should be determined to see whether the filtration efficiency is adequate with all types of dust collectors and wet scrubbers.

6.2.8 Where necessary, additional filtration may be provided downstream of the dust collector.

6.3 Vapour and fume removal

6.3.1 Vapour should be extracted at the point of generation. When planning the system for the extraction of residual vapours, the density of the vapour should be taken into account. If the vapour is lighter than air, the extract grilles should be at a high level, or possibly at both high and low levels.

6.3.2 The systems for fume, dust and effluent control should be designed, installed and operated in such a manner that they do not become possible sources of contamination or cross-contamination, e.g. an exhaust-air discharge point located close to the HVAC system fresh air inlet.

6.3.3 Fumes should be removed by means of wet scrubbers or dry chemical scrubbers (deep-bed scrubbers).

6.3.4 Wet scrubbers for fume removal normally require the addition of various chemicals to the water to increase the adsorption efficiency.

6.3.5 Deep-bed scrubbers should be designed with activated carbon filters or granular chemical adsorption media. The chemical media for deep-bed scrubbers should be specific to the effluent being treated.

6.3.6 The type and quantity of the vapours to be removed should be known to enable the appropriate filter media, as well as the volume of media required to be determined.

7. Design of HVAC systems and components

7.1 General

7.1.1 The required degree of air cleanliness in most OSD manufacturing facilities can normally be achieved without the use of high-efficiency particulate air (HEPA) filters, provided the air is not recirculated or

in the case of a single-product facility. Many open product zones of OSD form facilities are capable of meeting ISO 14644-1 Class 8 or Grade D, "at-rest" condition, measured against particle sizes of 0.5 ìm and 5 ìm, but cleanliness may not necessarily be classified as such by manufacturers.

A risk assessment should be carried out to determine the cleanroom conditions required and the extent of validation required.

7.1.2 There are two basic concepts of air delivery to pharmaceutical production facilities: a recirculation system, and a full fresh air system (100% outside air supply). For recirculation systems the amount of fresh air should not be determined arbitrarily on a percentage basis, but, for example, by the following criteria:

- sufficient fresh air to compensate for leakage from the facility and loss through exhaust air systems;
- sufficient fresh air to comply with national building regulations; and[2]
- sufficient fresh air for odour control.

7.1.3 Where automated monitoring systems are used, these should be capable of indicating any out-of-specification condition without delay by means of an alarm or similar system. Sophisticated computer-based data monitoring systems may be installed, which can aide with planning of preventive maintenance and can also provide trend logging.

(This type of system is commonly referred to as a building management system (BMS), building automation system (BAS) or system control and data acquisition (SCADA) system.) If these systems are used for critical decision-making, they should be validated.

7.1.4 Failure of a supply air fan, return air fan, exhaust air fan or dust extract system fan can cause a system imbalance, resulting in a pressure cascade malfunction with a resultant airflow reversal.

7.1.5 All critical alarms should be easily identifiable and visible and/or audible to relevant personnel.

7.1.6 Appropriate alarm systems should be in place to alert personnel if a critical fan fails. A fan interlock failure matrix should be set up, such that if a fan serving a high pressure zone fails, then any fans serving surrounding lower pressure areas should automatically stop, to prevent an airflow reversal and possible cross-contamination.

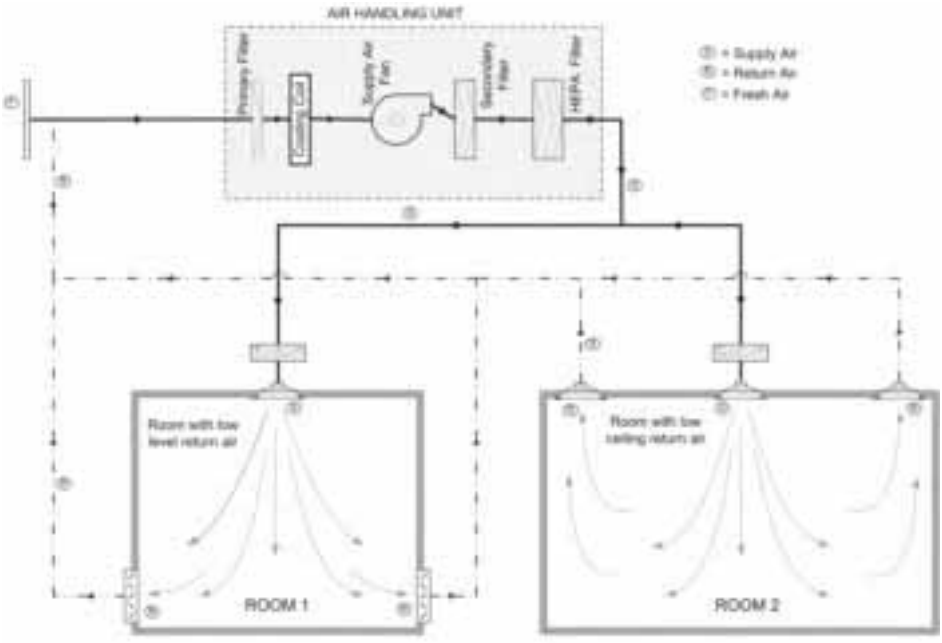
[2] Depending on occupant density, between 1 and ACPH will often satisfy occupancy requirements.

7.2 Air distribution

7.2.1 The positioning of supply and extract grilles should be such as to provide effective room flushing. Low-level return or exhaust air grilles are usually preferred. However, where this is not possible, a higher air change rate may be needed to achieve a specified clean area condition, e.g. where ceiling return air grilles are used.

7.2.2 There may be alternative locations for return air. For example, referring to Figure 22, Room 1 (low-level return air) and Room 2 (ceiling return air). The airflow diagram in Figure 22 is an example of a typical system with a lower clean area condition.

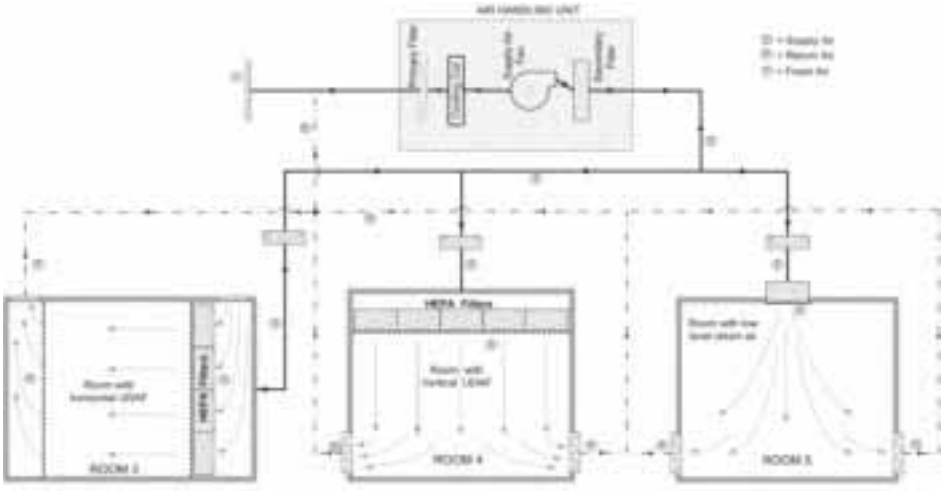
Figure 22
Air-handling system with high-efficiency particulate air filters in air-handling unit



The airflow schematics of the two systems (Figures 22 and 23) indicate air-handling units with return air or recirculated air, having a percentage of fresh air added. Depending on product characteristics and dust loading it is sometimes preferable to fit filters on return air outlets or in return air ducting.

Figure 23 is a schematic diagram of an air-handling system serving rooms with horizontal unidirectional flow, vertical unidirectional flow and turbulent flow, for rooms 3, 4 and 5, respectively.

Figure 23
Horizontal unidirectional flow, vertical unidirectional flow and turbulent flow



7.3 Recirculation system

7.3.1 There should be no risk of contamination or cross-contamination (including by fumes and volatiles) due to recirculation of air.

7.3.2 Depending on the airborne contaminants in the return-air system it may be acceptable to use recirculated air, provided that HEPA filters are installed in the supply air stream (or return air stream) to remove contaminants and thus prevent cross-contamination. The HEPA filters for this application should have an EN 1822 classification of H13.

7.3.3 HEPA filters may not be required where the air-handling system is serving a single product facility and there is evidence that cross-contamination would not be possible.

7.3.4 Recirculation of air from areas where pharmaceutical dust is not generated such as secondary packing, may not require HEPA filters in the system.

7.3.5 HEPA filters may be located in the air-handling unit or placed terminally. Where HEPA filters are terminally mounted they should

preferably not be connected to the ducting by means of flexible ducting. Due to the high air pressure required for the terminal filter, this connection should preferably be a rigid duct connection. Where flexible ducting is used, it should be as short as possible and properly fixed to withstand duct pressure.

7.3.6 Air containing dust from highly toxic processes and/or solvents or flammable vapours should never be recirculated to the HVAC system.

7.4 Full fresh-air systems

Figure 24 indicates a system operating on 100% fresh air and would normally be used in a facility dealing with toxic products or solvents, where recirculation of air with contaminants should be avoided.

7.4.1 The required degree of filtration of the exhaust air depends on the exhaust air contaminants and local environmental regulations. HEPA filters in the exhaust system would normally only be required when handling hazardous materials.

Figure 24
Full fresh-air system

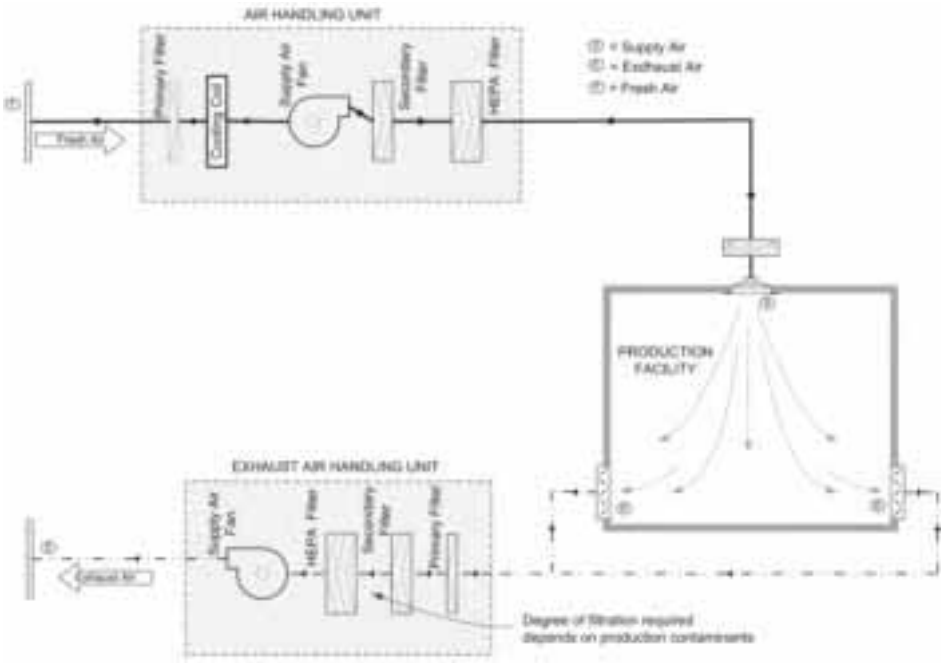
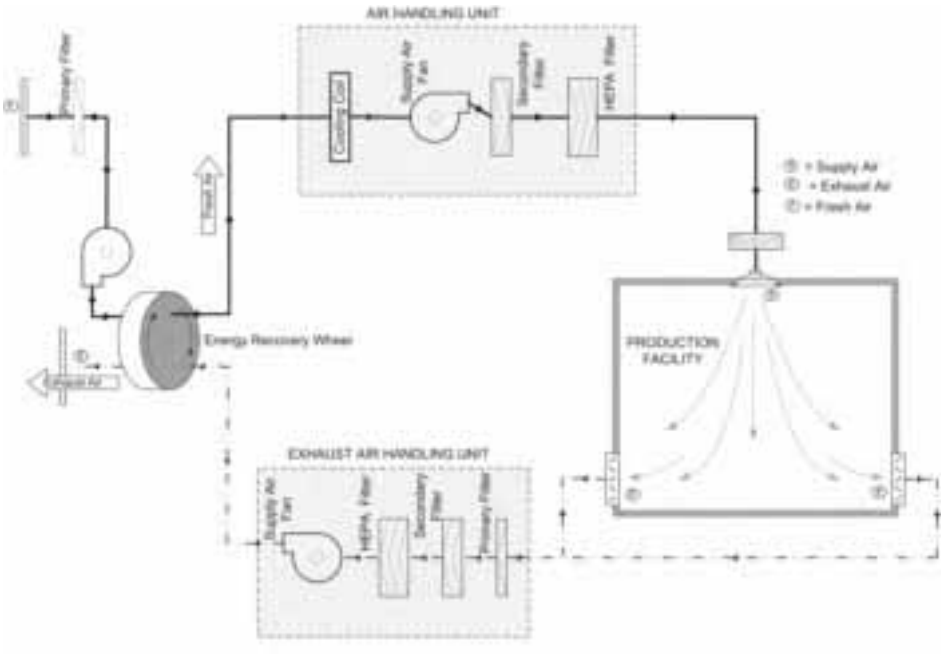


Figure 25
Full fresh-air system with energy recovery



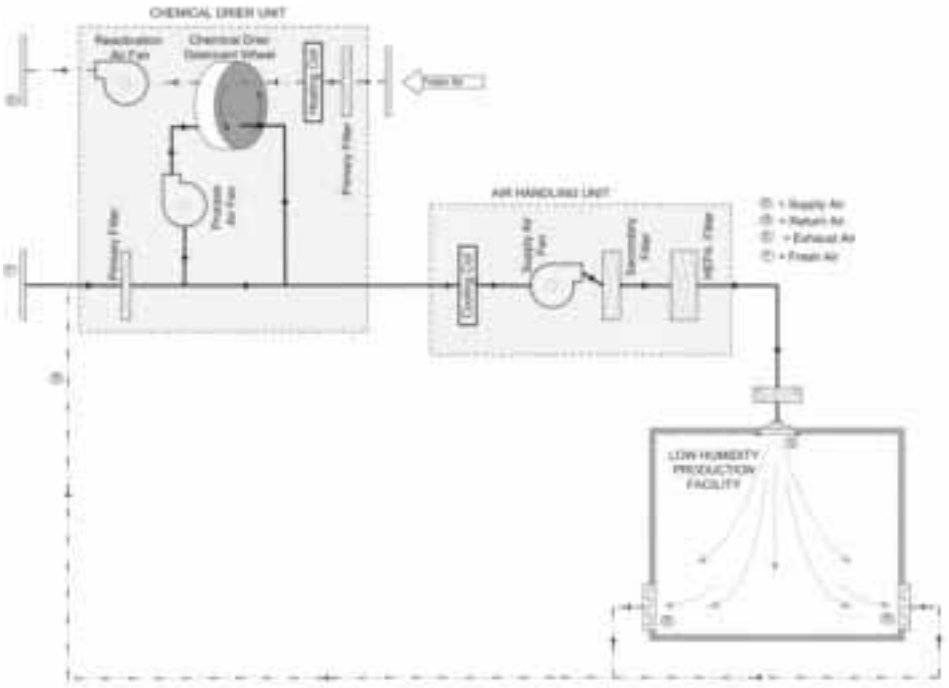
7.4.2 Energy-recovery wheels if used in multiproduct facilities should have been subjected to a risk assessment to determine if there is any risk of cross-contamination. When such wheels are used they should not become a source of possible contamination (see Figure 25). *Note*: *Alternatives to the energy-recovery wheels, such as crossover plate heat exchangers and water-coil heat exchangers, may be used in multiproduct facilities.*

7.4.3 The potential for air leakage between the supply air and exhaust air as it passes through the wheel should be prevented. The relative pressures between supply and exhaust air systems should be such that the exhaust air system operates at a lower pressure than the supply system.

7.5 Additional system components

7.5.1 A schematic diagram of the airflow for a typical system serving a low relative humidity suite is represented in Figure 26. Air can be dried with a chemical drier (e.g. a rotating desiccant wheel which is continuously regenerated by means of passing hot air through one segment of the wheel). Alternative methods of drying air are also available.

Figure 26
Air-handling system with chemical drying



7.5.2 The figure illustrates the chemical drier handling part of the fresh air/return air mixture on a bypass flow. The location of the chemical drier should be considered in the design phase. The practice of locating the complete chemical drier unit in the production cubicle is not recommended as this could be a source of contamination or cross-contamination. Examples of appropriate locations for the drying wheel could include:

— full flow of fresh/return air;
— partial handling of fresh/return air (bypass airflow);
— return air only;
— fresh air only; or
— pre-cooled air with any of the above alternatives.

7.5.3 Possible additional components that may be required in air handling should be considered depending on the climatic conditions and locations. These may include items such as:

— frost coils on fresh air inlets in very cold climates to preheat the air;
— reheaters for humidity control
— automatic air volume control devices
— sound attenuators

— snow eliminators to prevent snow entering air inlets and blocking airflow
— dust eliminators on air inlets in arid and dusty locations
— moisture eliminators in humid areas with high rainfall
— fresh air precooling coils for very hot or humid climates.

8. Commissioning, qualification and maintenance

8.1 Commissioning

8.1.1 Commissioning should include the setting up, balancing, adjustment and testing of the entire HVAC system, to ensure that it meets all the requirements, as specified in the user requirement specification (URS), and capacities as specified by the designer or developer. The commissioning plan should start at the early stages of a project so that it can be integrated with qualification and verification procedures.

8.1.2 The installation records of the system should provide documented evidence of all measured capacities of the system.

8.1.3 Acceptance criteria should be set for all system parameters. The measured data should fall within the acceptance criteria.

8.1.4 Acceptable tolerances for all system parameters should be specified prior to commencing the physical installation.

8.1.5 Training should be provided to personnel after installation of the system, and should include operation and maintenance.

8.1.6 Commissioning should be a precursor to system qualification and process validation.

8.2 Qualification

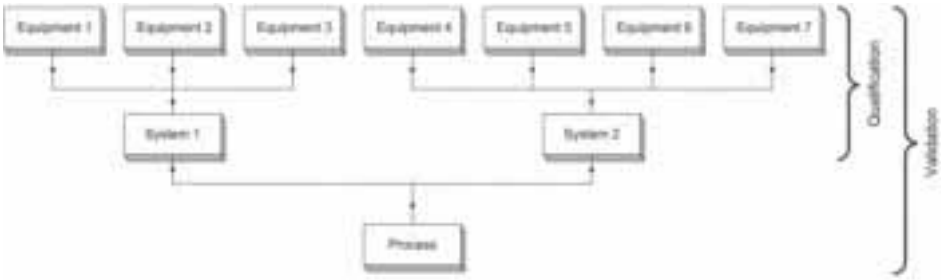
8.2.1 Validation is a many-faceted and extensive activity and is beyond the scope of these guidelines (*2*) (see also Figure 27).

A risk-based approach should be used to identify the extent to which the HVAC system requires qualification and verification. The basic concepts of qualification of HVAC systems are set out below.

8.2.2 The qualification of the HVAC system should be described in a validation master plan (VMP).

8.2.3 It should define the nature and extent of testing and the test procedures and protocols to be followed.

Figure 27
Qualification is a part of validation



8.2.4 Stages of the qualification of the HVAC system should include DQ, IQ, OQ and PQ.

8.2.5 Critical and non-critical parameters should be determined by means of a risk analysis for all HVAC installation components, subsystems and controls.

8.2.6 Any parameter that may affect the quality of the pharmaceutical product, or a direct impact component, should be considered a critical parameter.

8.2.7 All critical parameters should be included in the qualification process. *Note: A realistic approach to differentiating between critical and noncritical parameters is required, to avoid making the validation process unnecessarily complex.*

Example:

- *The relative humidity of the room where the product is exposed should be considered a critical parameter when a humidity-sensitive product is being manufactured. The humidity sensors and the humidity monitoring system should, therefore, be qualified. The heat transfer system, chemical drier or steam humidifier, which is producing the humidity controlled air, is further removed from the product and may not require operational qualification.*
- *A room cleanliness condition is a critical parameter and, therefore, the room air change rates and HEPA filters should be critical parameters and require qualification. Items such as the fan generating the airflow and the primary and secondary filters are non-critical parameters, and may not require operational qualification.*

8.2.8 Non-critical systems and components should be subject to GEP and may not necessarily require qualification.

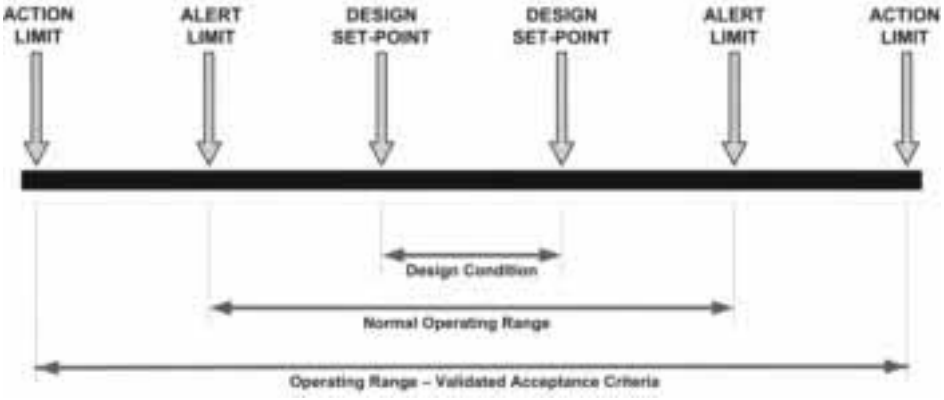
8.2.9 A change control procedure should be followed when changes are planned to the direct impact HVAC system, its components and controls that may affect critical parameters.

8.2.10 The design condition, normal operating ranges, operating range and alert and action limits should be defined and be realistic.

8.2.11 Out-of-limit results (e.g. action limit deviations) should be recorded and their impact should be investigated.

8.2.12 The relationships between design conditions, normal operating range and validated acceptance criteria (also known as proven acceptable range) are given in Figure 28.

Figure 28
System operating ranges



8.2.13 For a pharmaceutical facility, based on a risk assessment, some of the typical HVAC system parameters that should be qualified may include:

— temperature
— relative humidity
— supply air quantities for all diffusers
— return air or exhaust air quantities
— room air change rates
— room pressures (pressure differentials)
— room airflow patterns
— unidirectional flow velocities
— containment system velocities
— HEPA filter penetration tests

— room particle counts
— room clean-up rates
— microbiological air and surface counts where appropriate
— operation of de-dusting
— warning/alarm systems where applicable.

8.2.14 The maximum time interval between tests should be defined by the manufacturer. The type of facility under test and the product level of protection should be considered. Table 3 gives various tests that can be carried out. The required tests and intervals between testing should be determined through risk assessment.

Table 3
Tests to demonstrate compliance

Test parameter	Test procedure
Particle count test (Verification of cleanliness)	Dust particle counts to be carried out and result printouts produced. No. of readings and positions of tests to be in accordance with ISO 14644-1 Annex B5
Air pressure difference (To verify non cross-contamination)	Log of pressure differential readings to be produced or critical plants should be logged daily, preferably continuously. A 15 Pa pressure differential between different zones is recommended. In accordance with ISO 14644-3 Annex B5
Airflow volume (To verify air change rates)	Airflow readings for supply air and return air grilles to be measured and air change rates to be calculated. In accordance with ISO 14644-3 Annex B13
Airflow velocity (To verify unidirectional flow or containment conditions)	Air velocities for containment systems and unidirectional flow protection systems to be measured. In accordance with ISO 14644-3 Annex B4
Filter leakage tests (To verify filter integrity)	Filter penetration tests to be carried out by a competent person to demonstrate filter media, filter seal and filter frame integrity. Only required on HEPA filters. In accordance with ISO 14644-3 Annex B6
Containment leakage (To verify absence of cross-contamination)	Demonstrate that contaminant is maintained within a room by means of: • airflow direction smoke tests • room air pressures. In accordance with ISO 14644-3 Annex B4
Recovery (To verify clean-up time)	Test to establish time that a cleanroom takes to recover from a contaminated condition to the specified cleanroom condition. Should not take more than 15 min. In accordance with ISO 14644-3 Annex B13*

Test parameter	Test procedure
Airflow visualization (To verify required airflow patterns)	Tests to demonstrate air flows: • from clean to dirty areas • do not cause cross-contamination • uniformly from unidirectional airflow units Demonstrated by actual or video-taped smoke tests. In accordance with ISO 14644-3 Annex B7

8.2.15 Requalification should also be done when any change, which could affect system performance, takes place.

8.2.16 Clean-up or recovery times normally relate to the time it takes to "clean up" the room from one condition to another, e.g. the relationship between "at-rest" and "operational" conditions in the clean area may be used as the criteria for clean-up tests. Therefore, the clean-up time can be expressed as the time taken to change from an "operational" condition to an "at rest" condition.

8.2.17 If energy-saving procedures such as reducing the airflow during non-production hours are used, precautionary measures should be in place to ensure that the systems are not operated outside the defined relevant environmental conditions.

These precautionary measures should be based on a risk assessment to ensure that there is no negative impact on the quality of the product.

8.2.18 Documents that should be included in the qualification manuals should include system airflow schematics, room pressure cascade drawings, zone concept drawings, air-handling system allocation drawings, particle count mapping drawings, etc.

8.3 Maintenance

8.3.1 There should be a planned preventive maintenance programme, procedures and records for the HVAC system. Records should be kept.

8.3.2 Operating and maintenance (O&M) manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system. These documents should be kept up to date, containing any system revisions made.

8.3.3 Maintenance personnel should receive appropriate training.

8.3.4 HEPA filters should be changed either by a specialist or a trained person, and then followed by installed filter leakage testing.

8.3.5 Any maintenance activity should be assessed critically to determine any impact on product quality including possible contamination.

8.3.6 Maintenance activities should normally be scheduled to take place outside production hours, and any system stoppage should be assessed with a view to the possible need for requalification of an area as a result of an interruption of the service.

9. Premises

9.1 As the efficient operation of the air-handling system and cleanliness levels attained are reliant on the correct building layout and building finishes, the following items should be considered:

- adequate airlocks, such as personnel airlocks (PAL) and/or material airlocks (MAL), change rooms and passages should be provided to protect passage between different cleanliness conditions . These should have supply and extract air systems as appropriate;
- areas such as airlocks, change rooms and passages, should be designed so that the required pressure cascades can be achieved;
- detailed diagrams depicting pressure cascades, air flow directions and flow routes for personnel and materials should be prepared and maintained;
- where possible, personnel and materials should not move from a higher cleanliness zone to a lower cleanliness zone and back to a higher cleanliness zone; (if moving from a lower cleanliness zone to a higher cleanliness zone, changing /decontamination procedures should be followed); and
- the final stage of the changing room should, in the "at rest" state, be the same GMP classification grade as the area into which it leads.

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