ANNEX 6: 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 are intended as a basic guide for use by 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 manufacturers have their own engineering design and qualification standards and requirements may vary from one manufacturer to the next.

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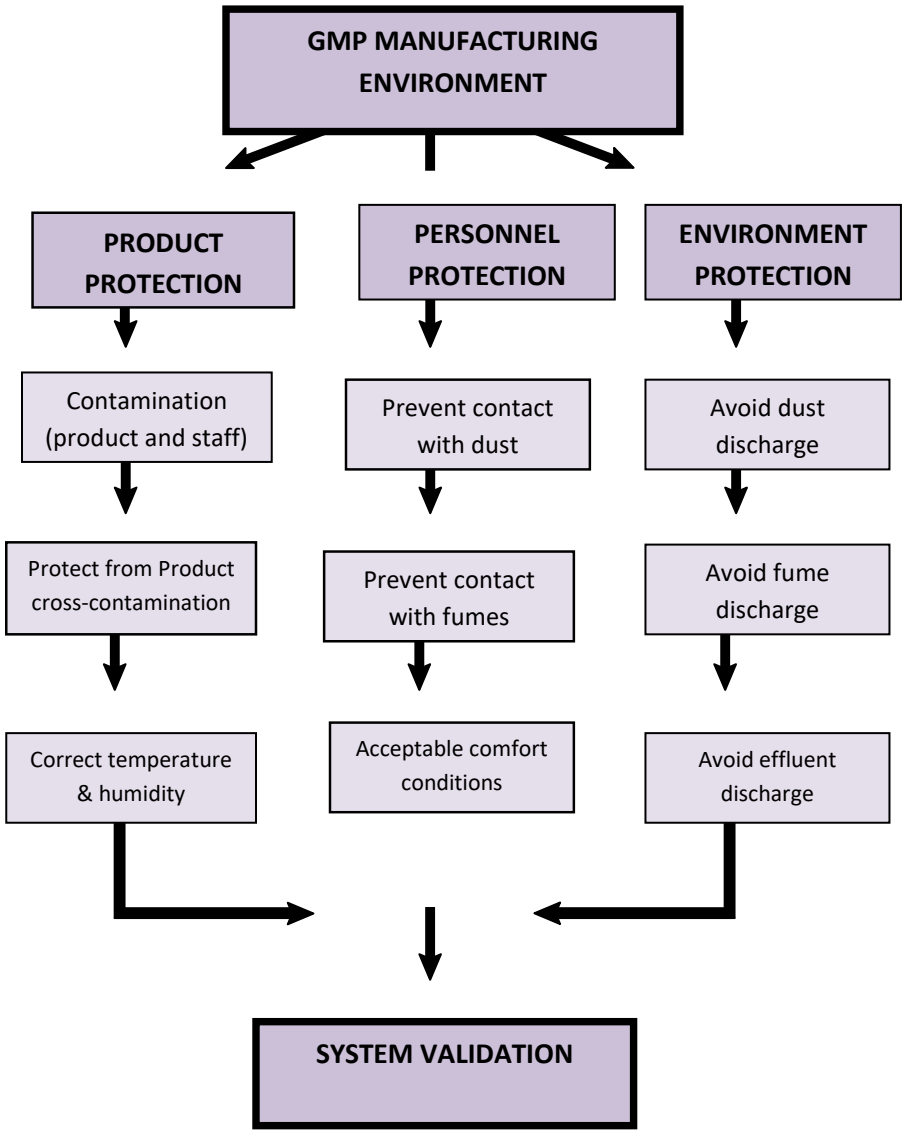

Figure 1: The guidelines address the various system criteria according to the sequence set out in this diagram

Design parameters should, therefore, be set realistically for each project, with a view to creating a cost-effective design, yet still complying with all regulatory standard 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 (Fig. 1).

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-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 para- meter 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 (clean room)[1]
An area (or room) with defined environmental control of particulate and micro- bial contamination, constructed and used in such a way as to reduce the intro- duction, generation and retention of contaminants within the area.

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 pro- duction, sampling, packaging or repackaging, storage or transport.

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

Cross-contamination

[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.

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Contamination of a starting material, intermediate product or finished product with another starting material or material 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)
DQ is the documented check of planning documents and technical specifica- tions 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.

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.

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 contaminated air from an external zone into a clean area.

Installation qualification (IQ)
IQ is documented verification that the premises, HVAC system, supporting util- ities 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 parame- ter 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)
OQ is the documentary evidence to verify that the equipment operates in accor- dance 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.

Performance qualification (PQ)
PQ 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.

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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.

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 intro- duced 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). (Modern standards no longer refer to laminar flow, but have adopted the term unidirectional airflow.)

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)
VMP 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 Product and personnel

4.1.1 Areas for the manufacture of pharmaceuticals, where pharmaceutical starting materials and products, utensils and equipment are exposed to the environment, should be classified as “clean areas”.

4.1.2 The achievement of a particular clean area classification 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 should include:

- building finishes and structure
- air filtration
- air change rate or flushing rate
- room pressure
- location of air terminals and directional airflow
- temperature
- humidity
- material flow
- personnel flow
- equipment movement
- process being carried out
- outside air conditions
- occupancy
- type of product.

4.1.4 Air filtration and air change rates should ensure that the defined clean area classification is attained.

4.1.5 The air change rates should be determined by the manufacturer and designer, taking into account the various critical parameters. Primarily the air change rate should be set to a level that will achieve the required clean area classification.

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

- level of protection required
- 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
- sufficient air to cope with the room heat load
- sufficient air to maintain the required room pressure.

4.1.7 In classifying the environment, the manufacturer should state whether this is achieved under “as-built” (Fig. 2), “at-rest” (Fig. 3) or “operational” (Fig. 4) conditions.

Figure 2. “As-built” condition

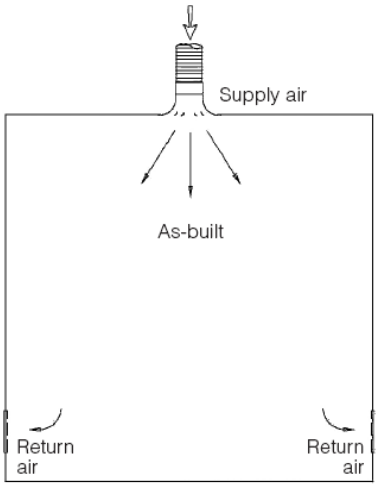


Figure 3. "At-rest" condition

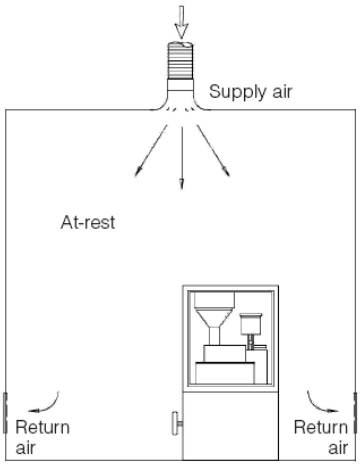
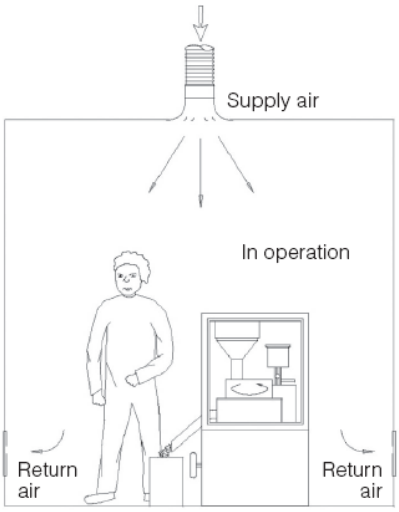


Figure 4: "Operational" Condition



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 most clean area classifications are rated for the "at-rest" condition.

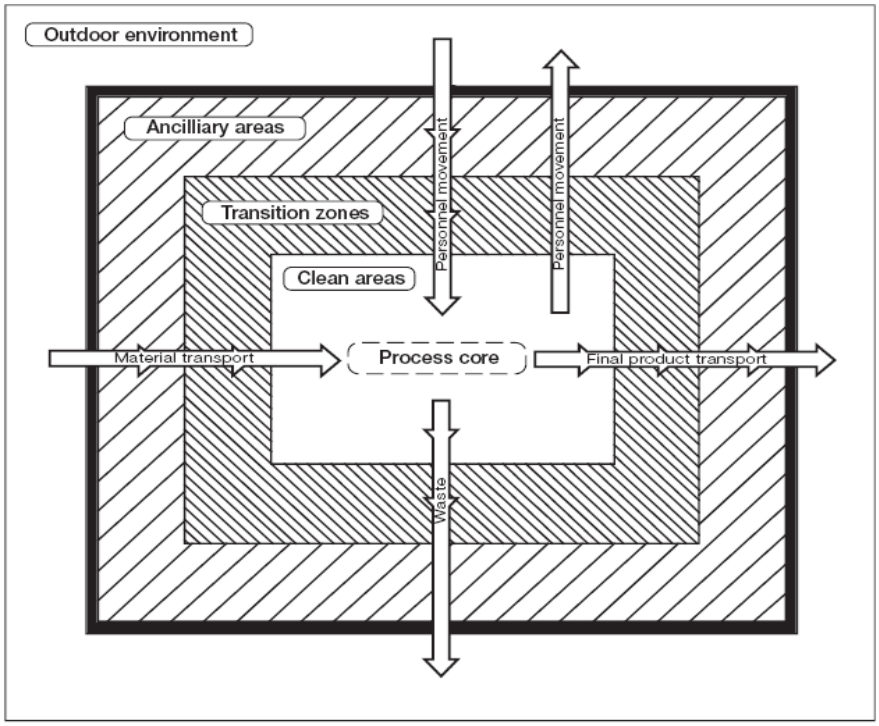
4.1.10 Room classification tests in the “operational” condition should be carried out during the normal production process with equipment operating, and the normal number of personnel present in the room. Generally a room that is tested for an “operational” condition should be able to be cleaned up to 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 5.5 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, and a poor HVAC system.

4.1.12 Airborne contaminants should be controlled through effective ventilation.

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

Figure 5. Shell-like containment control concept



Note: The process core is regarded as the most stringently controlled clean zone which is protected by being surrounded by clean areas of a lower classification.

4.1.14 Internal contaminants should be controlled by dilution and flushing of contaminants in the room, or by displacement airflow. (See Figs 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 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).

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 depend 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 deter- mine and prove the appropriate use of filters.

Figure 6. Turbulent dilution of dirty air

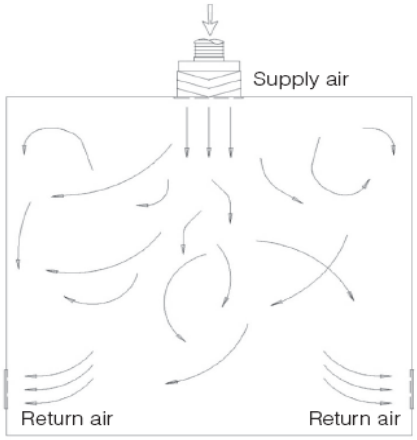


Figure 7. Unidirectional displacement of dirty air

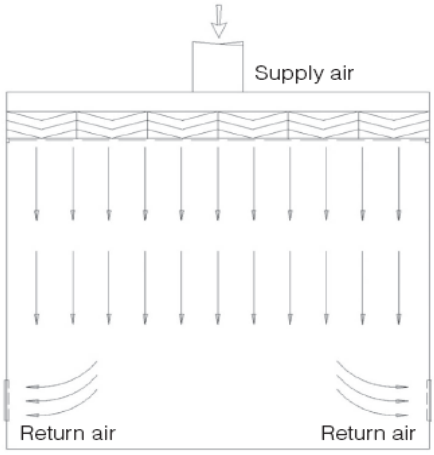


Table 1. Examples of levels of protection

Level	Condition	Example of area
Level 1	General Area	with normal housekeeping and maintenance, e.g. ware- housing, secondary packing

Level 2	Protected Area	in which steps are taken to protect the exposed pharmaceutical starting material or product from contamination or degradation, e.g. manufacturing, primary packing, dispensing
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

Table 2. Levels of protection and recommended filtration

Level of Protection	Example of area
Level 1	Primary filters only (e.g. EN779 G4 filters)
Levels 2 and 3	Production facility operating on 100% outside air: primary plus secondary filters (e.g. EN779 G4 plus F8 filters)
Levels 2 and 3	Production facility operating on recirculated plus ambient air, where potential for cross-contamination exists: Primary plus secondary plus tertiary filters (e.g. EN779 G4 plus F8 plus EN1822 H13 filters)

Note: The filter classifications referred to above relate to the EN1822 and EN779 test standards (EN 779 relates to filter classes G1 to F9 and EN 1822 relates to filter classes H10 to U16).

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) (Fig. 8).

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 the 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.

4.2.5 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.

Figure 8. Comparison of filter test standards

EU Class	Percentage (average)	Percentage (Integral value)	EN779	EN 1822
		99.99995		U16
		99.9995		U15
14		99.995		H14
13		99.95		H13
12				
11		99.5		H12
10		95		H11
9	95	85		F9/H10
8	90	75		F8
	85			F7
7	80			

EN?1822?

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		75			
6		70			F6
		65			
		60			
		55			
5		50			F5
		45			
	Percentage	40			
	(average)	35			
4	95	30			G4
	90	25			
3	85	20			G3
	80				
	75				
2	70				G2
	65				
					G1
Eurovent Class – Eurovent 4/5 (2-9) Eurovent 4/9 (2-9) Eurovent 4/4 (10-14)	Arrestance	Dust spot efficiency ASHRAE 52/76 BS6540 Part 1	MPPS, DEHS Aerosol EN1822	CEN/TC/195 WG1-G1-F9	

EN?779?

EN, European norm (Euronorm); EU, European Union.

This figure gives a rough comparison between the different filter standards (filter classes should always be connected to the standard test method).

4.2.6 Personnel should not be a source of contamination.

4.2.7 Directional airflow within production or 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.

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

4.2.9 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. (See Figs 9–11 for illustrations of the three types of diffuser.)

4.2.10 Whenever possible, air should be exhausted from a low level in rooms to help provide a flushing effect.

4.3 Unidirectional airflow

4.3.1 Unidirectional airflow (UDAF) should be used where appropriate to provide product protection by supplying a clean air supply over the product, minimizing the ingress of contaminants from surrounding areas.

Figure 9. Induction diffuser (not recommended)

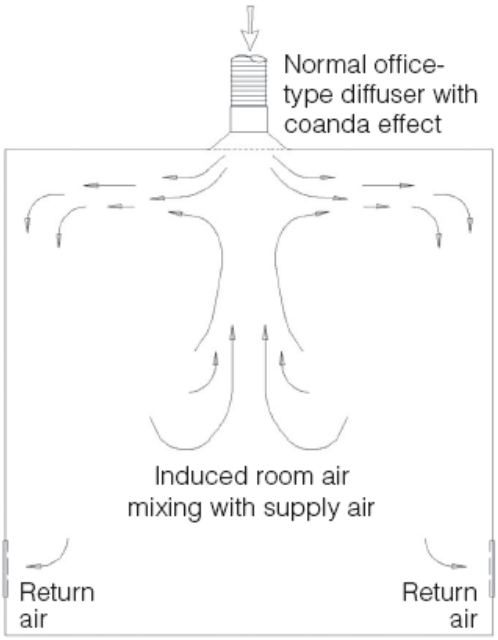

Figure 10. Perforated plate diffuser

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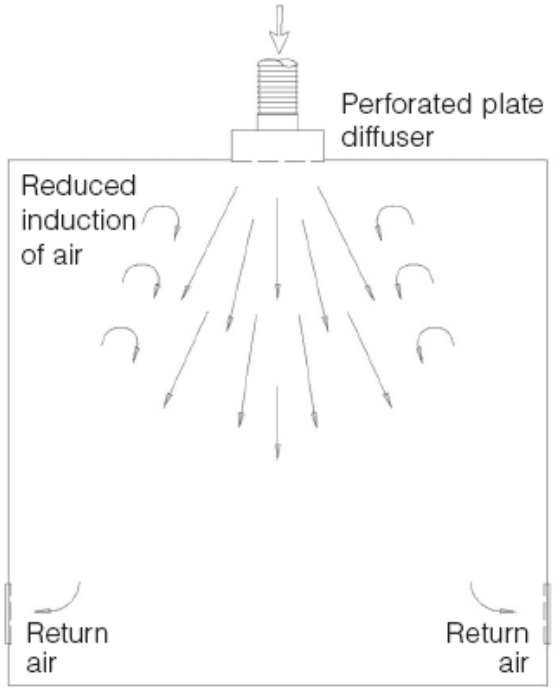
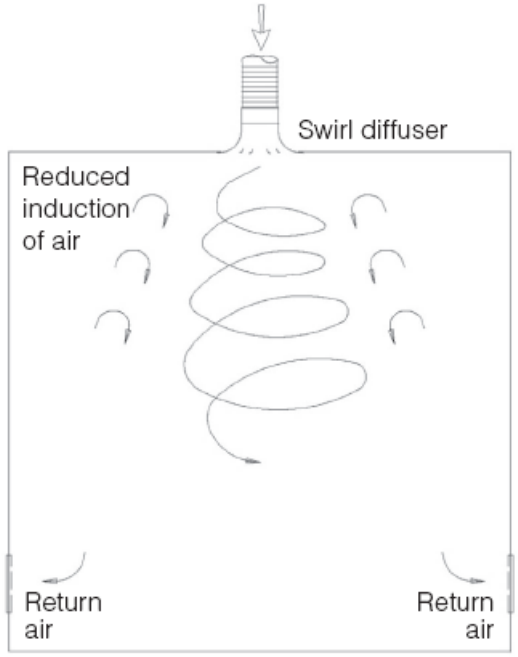


(recommended)

Figure 11. Swirl diffuser (recommended)



4.3.2 Where appropriate, the unidirectional airflow should also provide protection to the operator from contamination by the product.

4.3.3 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.

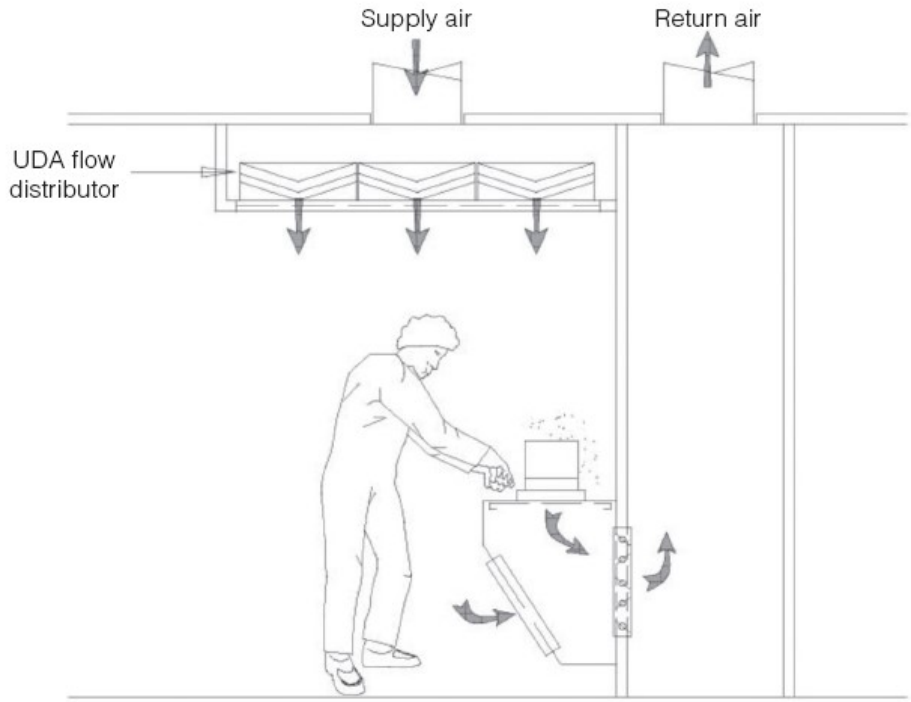
4.3.4 In a weighing booth situation, the aim of the design using UDAF should be to provide dust containment.

4.3.5 A dispensary or weighing booth should be provided with unidirectional airflow for protection of the product and operator.

4.3.6 The source of the dust and the position in which the operator normally stands should be determined before deciding on the direction of unidirectional flow.

Example: In Fig. 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.

Figure 12. Operator protection at weighing station



UDA, Unidirectional air.

4.3.7 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.

4.3.8 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 (Fig. 13).

4.3.9 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.

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

Fig. 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.

Fig. 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.

Fig. 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.

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

4.4 Infiltration

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

4.4.2 Manufacturing facilities should 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 to prevent the escape of harmful products to the outside (such as penicillin and hormones), special precautions should be taken.

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.

Figure 13. Operator protection by horizontal airflow

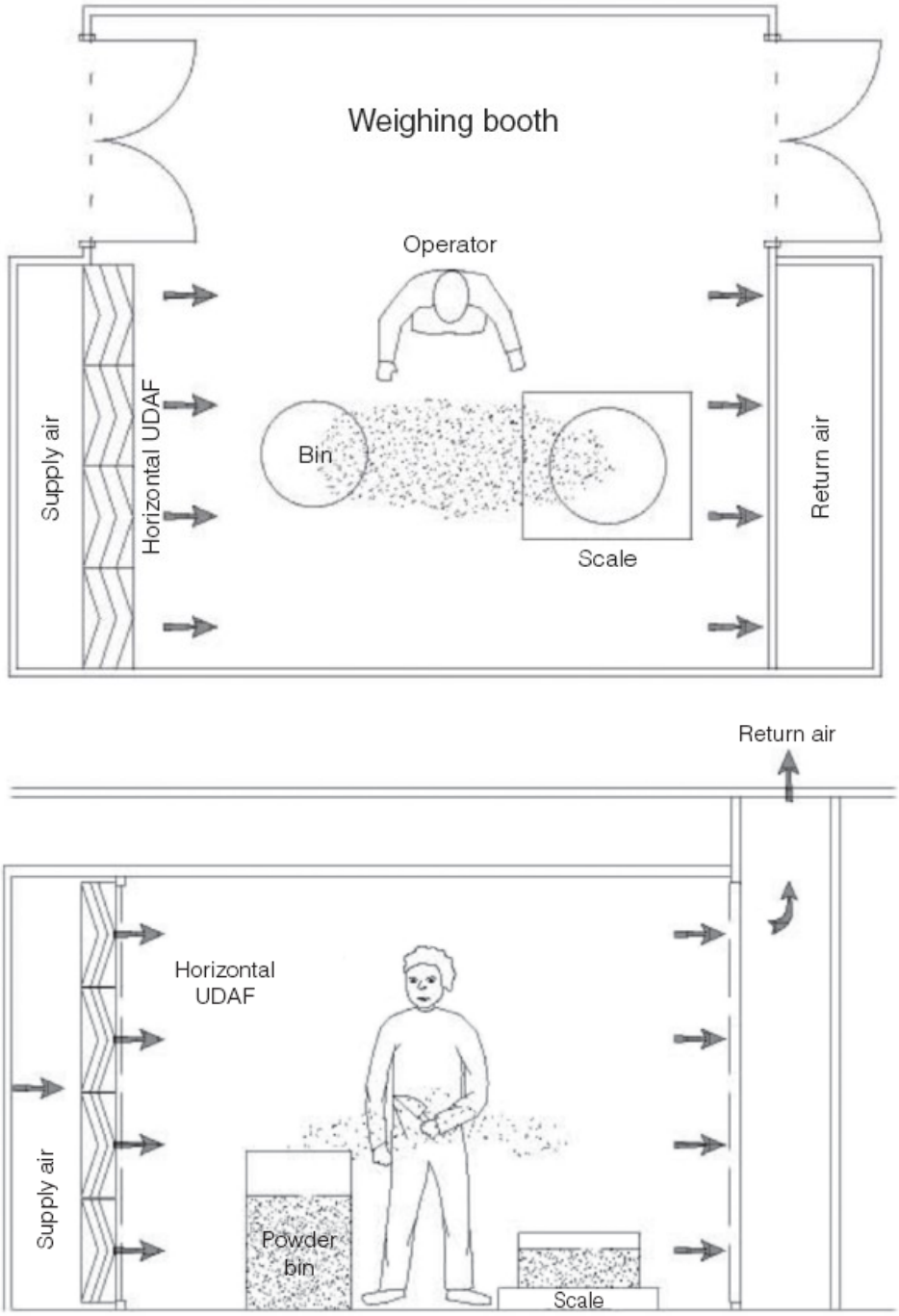
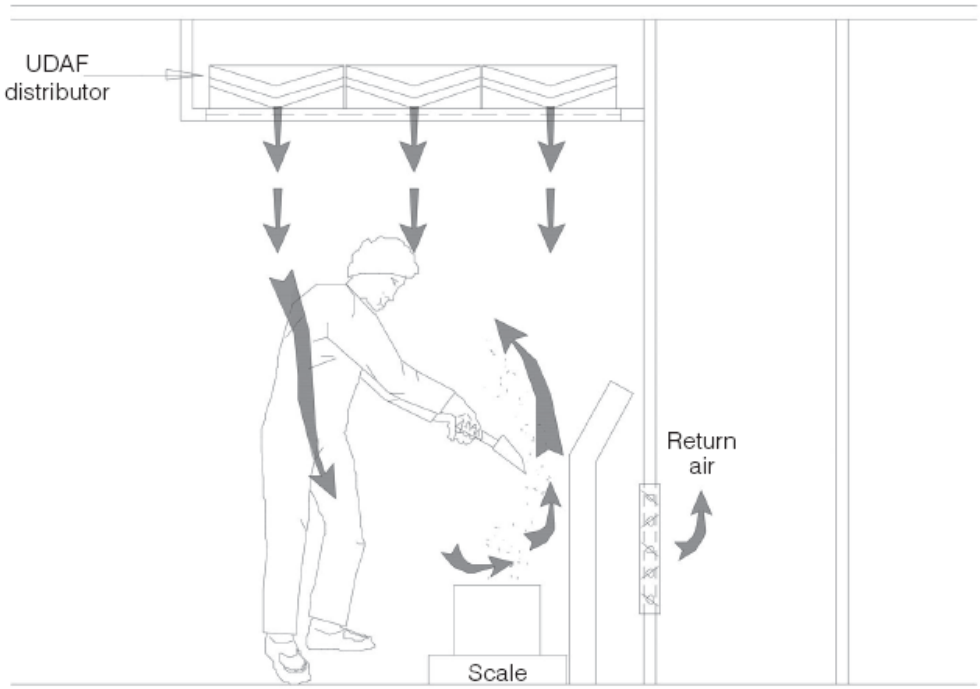


Figure 14. Operator subject to powder inhalation due to obstruction



UDAF, Unidirectional airflow.

Figure 15. Operator subject to powder contamination due to airflow reversal in bin

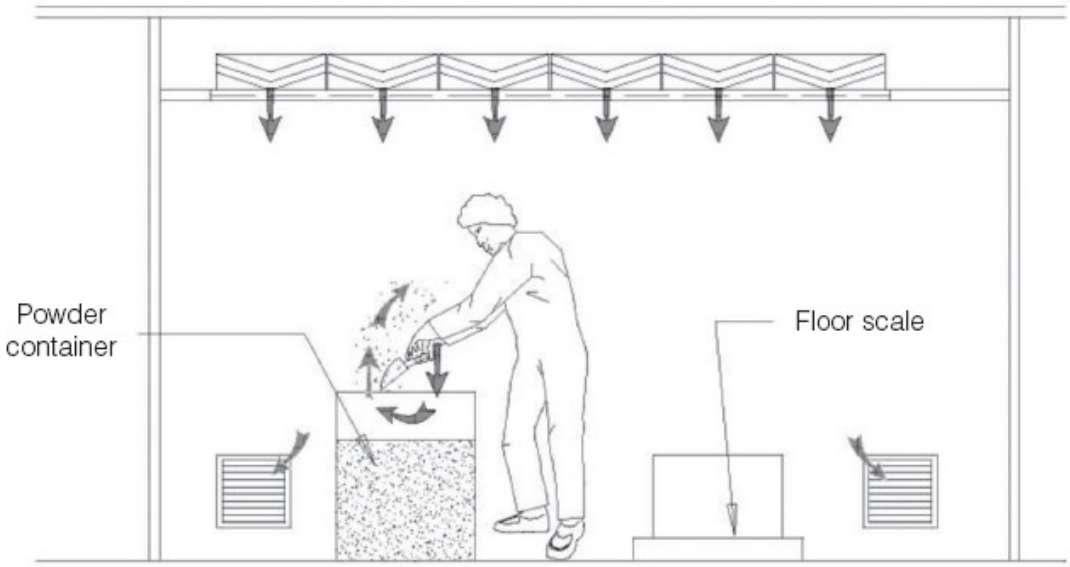
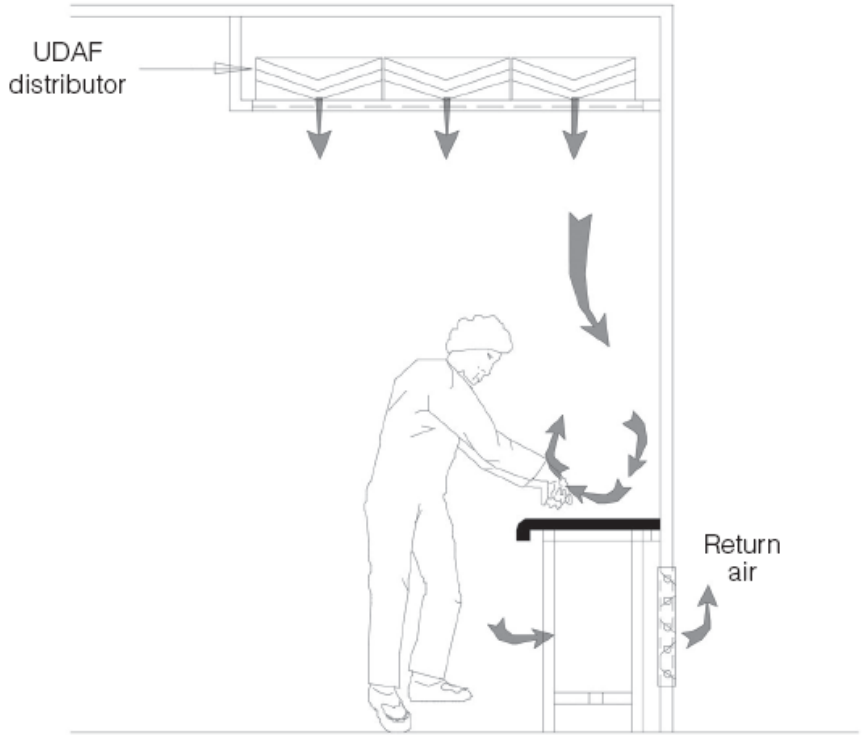
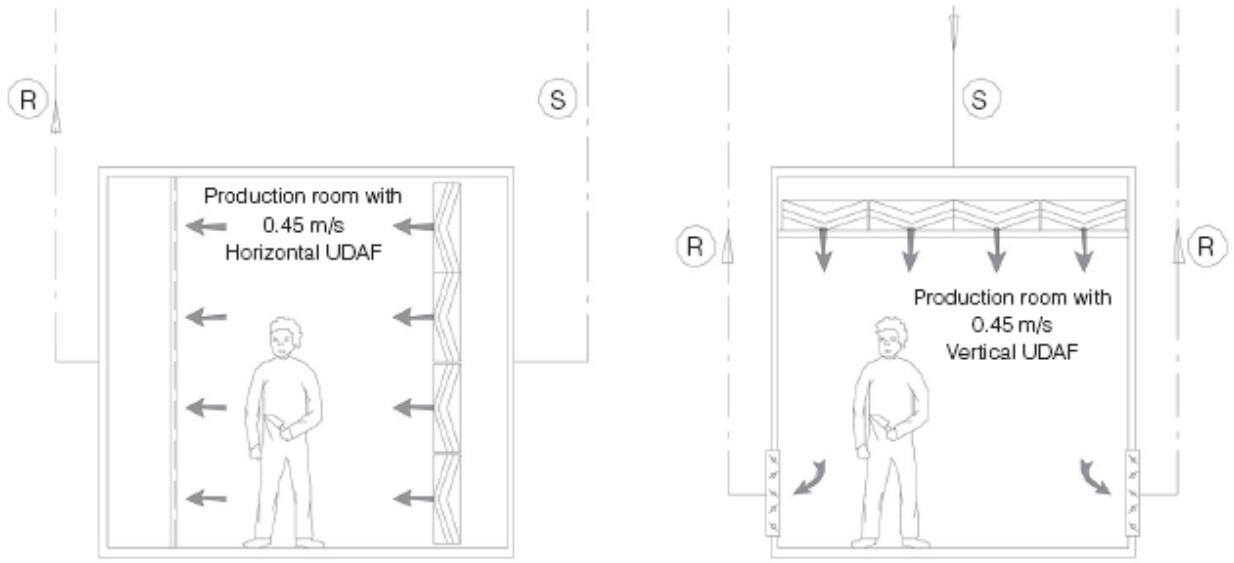


Figure 16. Operator subject to powder inhalation due to worktop obstruction



UDAF, Unidirectional airflow.

Figure 17. Diagram indicating horizontal and vertical unidirectional flow



UDAF, Unidirectional airflow.

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.

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 Airtight ceilings and walls, close fitting doors and sealed light fittings should be in place.

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 should ideally be applied in production processes where large amounts of dust are generated.

4.5.10 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.

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

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

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.

4.5.13 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.

4.5.14 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.

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

Note: The most widely accepted pressure differential for achieving containment between two adjacent zones is 15 Pa, 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 the upper and lower tolerances on containment should be evaluated.

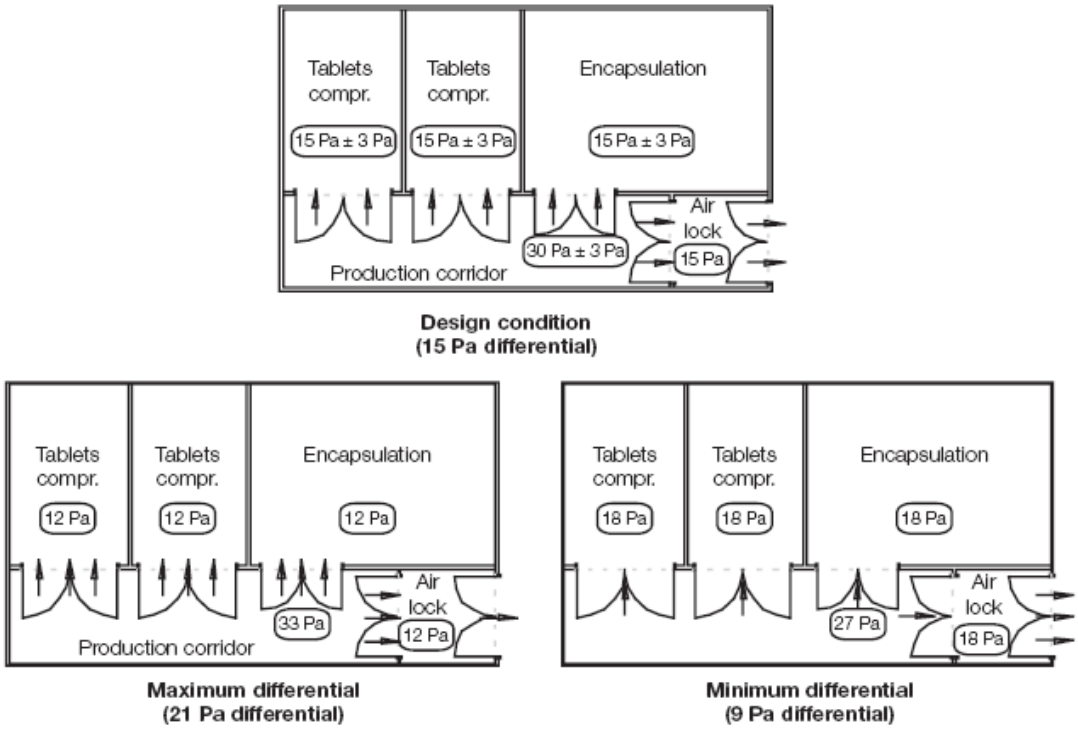
4.5.16 The pressure differential between adjacent rooms could be considered a critical parameter, depending on the outcome of risk analysis. The limits for the pressure differential between adjacent areas should be such that there is no risk of overlap, e.g. 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in no pressure cascade, if the first room is at the maximum tol- erance and the second room is at the minimum tolerance.

4.5.17 Low pressure differentials may be acceptable when airlocks (pressure sinks or pressure bubbles) are used.

4.5.18 The effect of room pressure tolerances are illustrated in Fig. 18.

4.5.19 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.

Figure 18. Examples of pressure cascades



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

4.5.21 Airlocks can be important components in setting up and maintaining pressure cascade systems.

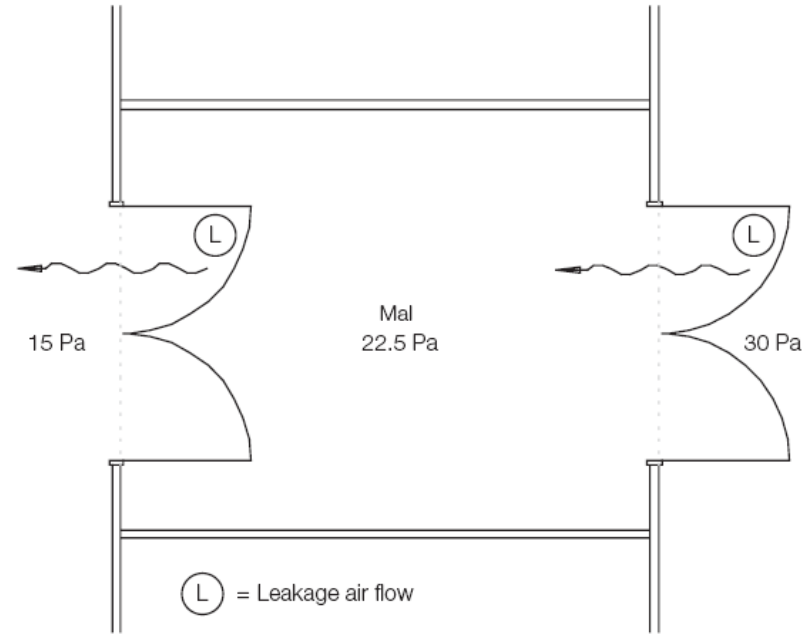
4.5.22 Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock (Figs 19–21).

- Cascade airlock: high pressure on one side of the airlock and low pressure on the other.
- Sink airlock: low pressure inside the airlock and high pressure on both outer sides.
- Bubble airlock: high pressure inside the airlock and low pressure on both outer sides.

4.5.23 Doors should open to the high pressure side, and be provided with self- closers. Door closer springs, if used, should be designed to hold the door closed and prevent the pressure differential from pushing the door open. Sliding doors are not recommended.

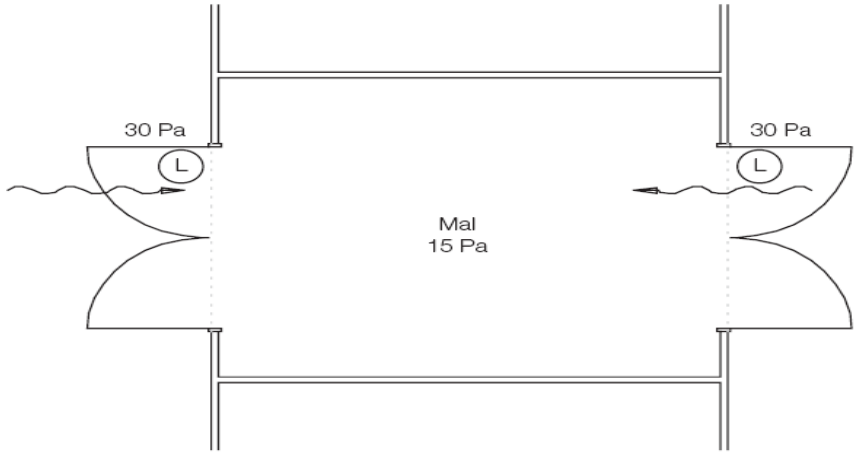
4.5.24 Central dust extraction systems should be interlocked with the appropriate air handling systems, to ensure that they operate simultaneously.

Figure 19. Example of cascade airlock



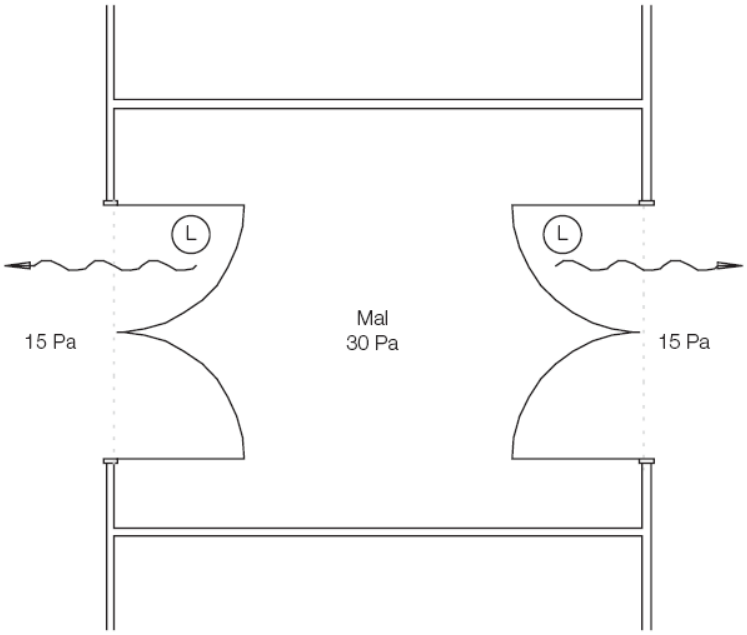
MAL, Material airlock.

Figure 20. Example of sink airlock



MAL, Material airlock.

Figure 21. Example of bubble airlock



MAL, Material airlock.

4.5.25 Room pressure imbalance between adjacent cubicles which are linked by common dust extraction ducting should be prevented.

4.5.26 Air should not flow from the room with the higher pressure to the room with the lower pressure, via the dust extract ducting (this would normally occur only if the dust extraction system was inoperative).

Physical barrier concept

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

4.5.28 Spot ventilation or capture hoods may be used as appropriate.

4.6 Temperature and relative humidity

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

4.6.2 Maximum and minimum room temperatures and relative humidity should be appropriate.

4.6.3 Temperature conditions should be adjusted to suit the needs of the operators while wearing their protective clothing.

4.6.4 The operating band, or tolerance, between the acceptable minimum and maximum temperatures should not be made too close.

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

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

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

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

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

4.6.10 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.

4.6.11 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.

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

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

4.6.14 Duct material in the vicinity of the humidifier should not add contaminants to air that will not be filtered downstream.

4.6.15 Air filters should not be installed immediately downstream of humidifiers.

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

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

4.6.18 Chemical driers using silica gel or lithium chloride are acceptable, pro- vided that they do not become sources of contamination.

5. Dust control

5.1 Wherever possible, the 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.

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.

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 so that the operator is not put at risk by the product.

Figure 22. Protective garments

5.6 Dust-related hazards to which the operators may be subjected should be assessed. An analysis of the type of dust and toxicity thereof should be done and the airflow direction determined accordingly.

5.7 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.

5.8 Typically, in a room operating with turbulent airflow, the air should be introduced from ceiling diffusers and extracted from the room at low level to help give a flushing effect in the room.

5.9 The low-level extraction should assist in drawing air downwards and away from the operator's face. The extract grilles should be positioned strategically to draw air away from the operator, but at the same time to prevent the operator from contaminating the product.

5.10 When planning the system for the extraction of 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.

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

5.12 When working with exposed products such as hormones or highly potent products, operators should wear totally enclosed garments, as indicated in Fig. 22. Operators should also be equipped with an air-breathing system that provides a supply of filtered and conditioned air. The air supply to this type of breathing apparatus should normally be through an air compressor. Filtration, temperature and humidity need to be controlled to ensure operator safety and comfort.

5.13 The rates at which fresh air is supplied to the facility should comply with national, regional and/or international regulations, to provide operators with an acceptable level of comfort and safety and also to remove odours or fumes.

5.14 The rate of fresh airflow should also be determined by leakage from the building, for pressure control purposes.

6. Protection of the environment

6.1 Dust in exhaust air

6.1.1 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.

6.1.2 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 EN779 filter standards.

6.1.3 Where harmful substances such as penicillin, hormones, toxic powders and enzymes are manufactured, the final filters on the dust exhaust system should be HEPA filters with at least an H12 classification according to EN1822 filter standards, as appropriate.

6.1.4 For exhaust systems where the discharge contaminant is considered particularly hazardous, it may be necessary to install two banks of HEPA filters in series, to provide additional protection should the first filter fail.

6.1.5 When handling hazardous compounds, safe-change filter housings, also called “bag-in-bag-out” filters, should be used.

6.1.6 All filter banks should be provided with pressure differential indication gauges to indicate the filter dust loading.

6.1.7 Filter pressure gauges should be marked with the clean filter resistance and the change-out filter resistance.

6.1.8 Exhaust filters should be monitored regularly to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in contamination of the ambient air.

6.1.9 Sophisticated computer-based data monitoring systems may be installed, with which preventive maintenance is planned by 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.)

6.1.10 An automated monitoring system should be capable of indicating any out-of-specification condition without delay by means of an alarm or similar system.

6.1.11 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.

6.1.12 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.

6.1.13 Mechanical-shaker dust collectors should not be used for applications where continuous airflow is required.

6.1.14 When wet scrubbers are used, the dust-slurry should be removed by a suitable drainage system.

6.1.15 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.

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

6.2 Fume removal

6.2.1 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.

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

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

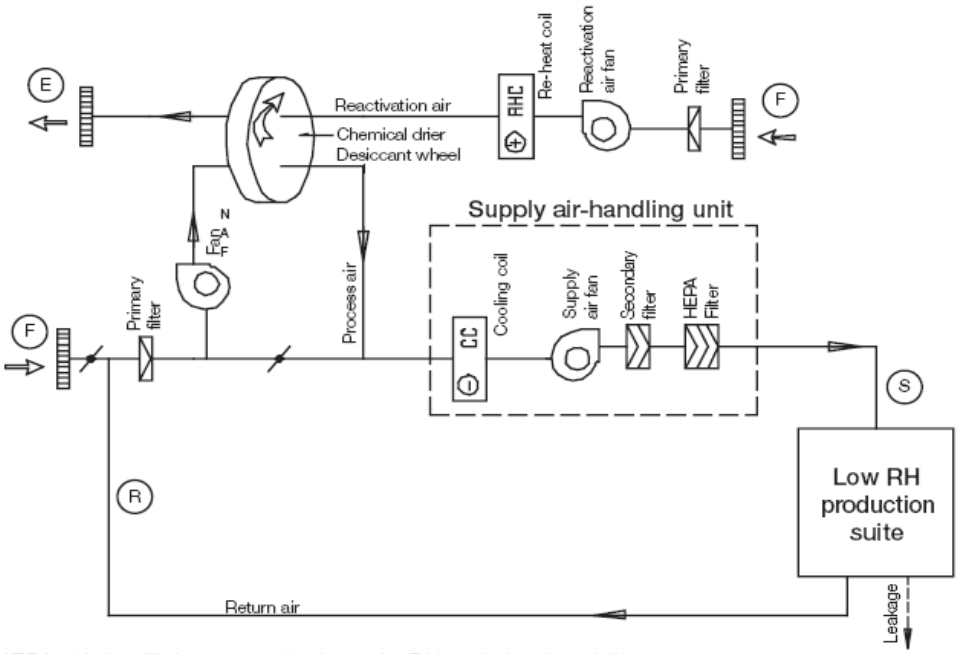
6.2.4 Deep-bed scrubbers should be designed with activated carbon filters or granular chemical adsorption media. The chemical media for deep-bed scrubbers should be specific to the effluent being treated.

6.2.5 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.

1. HVAC systems and components

Note: 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 re-circulated. Many open product zones of OSD form facilities are capable of meeting ISO 14644-1 Class 8, “at-rest” condition, measured against particle sizes of 0.5 □m and 5 cm, but cleanliness may not be classified as such by manufacturers.

Figure 23. Air-handling system with chemical drying



HEPA, high-efficiency particulate air; RH, relative humidity.

ANNEX 6: HEATING, VENTILATION AND AIR-CONDITIONING SYSTEMS FOR NON-STERILE PHARMACEUTICAL DOSAGE FORMS

7.1 General

7.1.1 There should be no failure of a supply air fan, return air fan, exhaust air fan or dust extract system fan. Failure can cause a system imbalance, resulting in a pressure cascade malfunction with a resultant airflow reversal.

7.1.2 A schematic diagram of the airflow for a typical system serving a low humidity suite is represented in Fig. 23.

7.1.3 Air should 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).

7.1.4 The figure illustrates the chemical drier handling part of the fresh air/ return air mixture on a by-pass flow. The location of the chemical drier should be considered in the design phase. Examples of appropriate locations include:

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

7.1.5 Possible additional components that may be required 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;
- 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; and
- fresh air pre-cooling coils for very hot or humid climates.

7.1.6 Appropriate alarm systems should be in place to alert personnel if a critical fan fails.

7.1.7 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 classification, e.g. where ceiling return air grilles are used.

7.1.8 There may be alternative locations for return air. For example, referring to Fig. 24, room D (low-level return air) and room E (ceiling return air).

The airflow schematics of the two systems (Figs 24 and 25) indicate air-handling unit with return air or re-circulated air, having a percentage of fresh air added. Fig. 25 is a schematic diagram of an air-handling system serving rooms with horizontal unidirectional flow, vertical unidirectional flow and turbulent flow, for rooms A, B and C, respectively.

The airflow diagram in Fig. 24 is an example of a typical system with a lower clean area classification.

Note: 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).

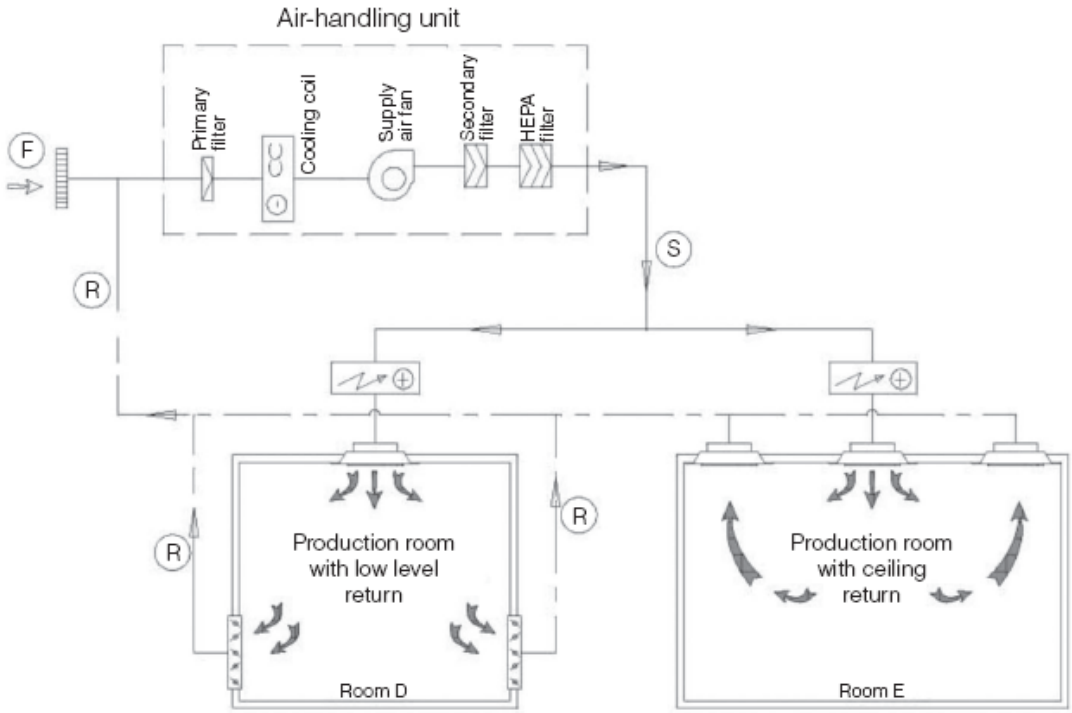
7.2 Recirculation system

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

7.2.2 Depending on the airborne contaminants in the return-air system it may be acceptable to use re-circulated air, provided that HEPA filters are installed in the supply air stream to remove contaminants and thus prevent cross-contamination. The HEPA filters for this application should have an EN1822 classification of H13.

ANNEX 6: HEATING, VENTILATION AND AIR-CONDITIONING SYSTEMS FOR NON-STERILE PHARMACEUTICAL DOSAGE FORMS

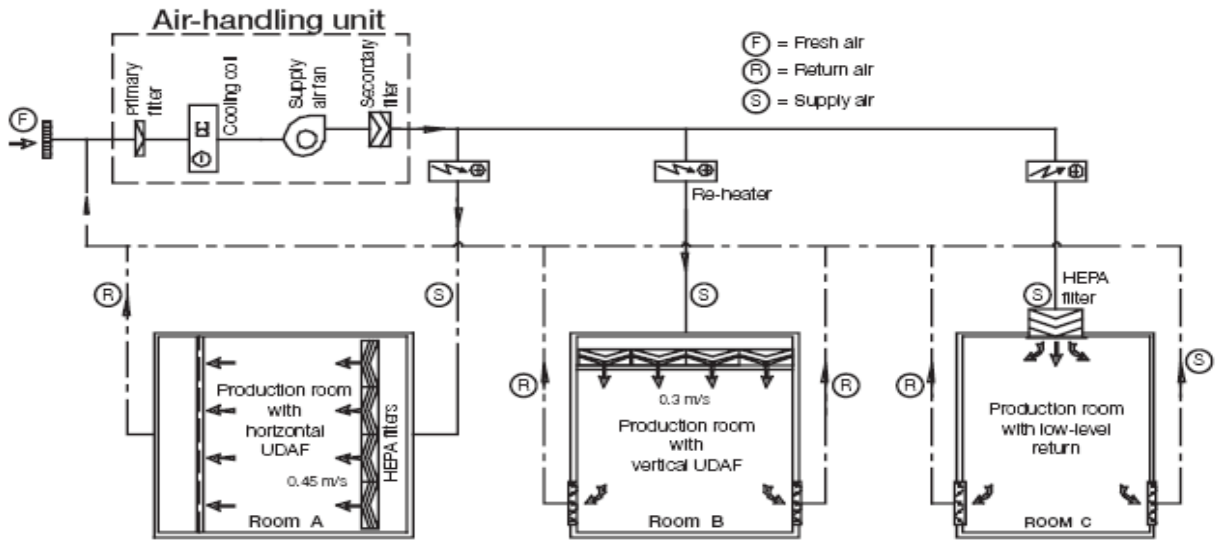
Figure 24. Air-handling system with high-efficiency particulate air filters in air-handling unit



HEPA, high-efficiency particulate air

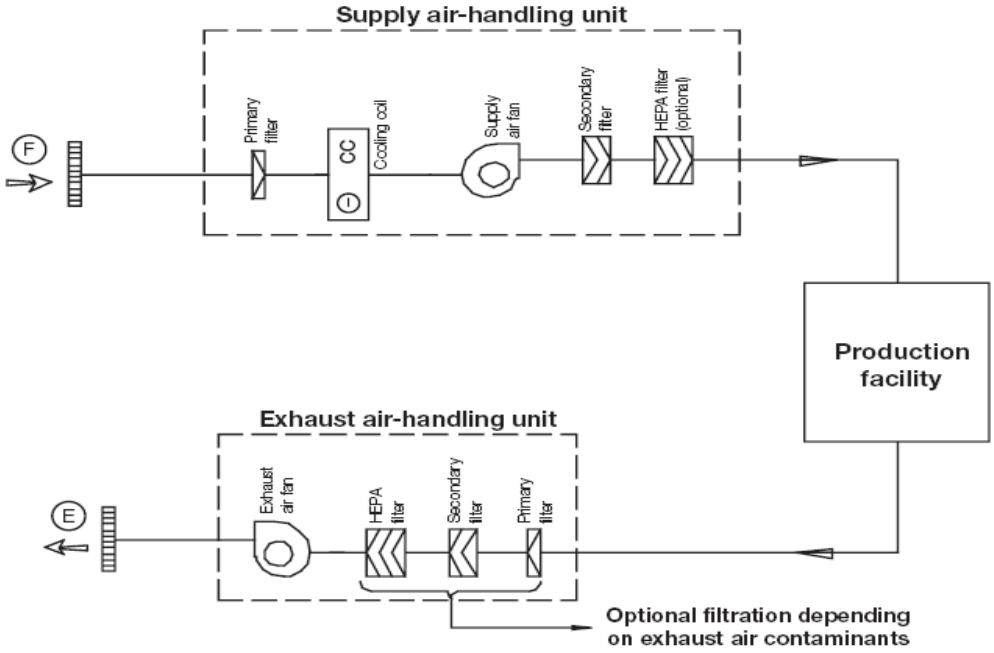
ANNEX 6: HEATING, VENTILATION AND AIR-CONDITIONING SYSTEMS FOR NON-STERILE PHARMACEUTICAL DOSAGE FORMS

Figure 25. Horizontal unidirectional flow, vertical unidirectional flow and turbulent flow



UDAF, unidirectional airflow; HEPA, high-efficiency particulate air.

Figure 26. Full fresh-air system



7.2.3 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.

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

7.2.5 HEPA filters may be located in the air-handling unit or placed terminally.

7.2.6 Air containing dust from highly toxic processes should never be re-circulated to the HVAC system.

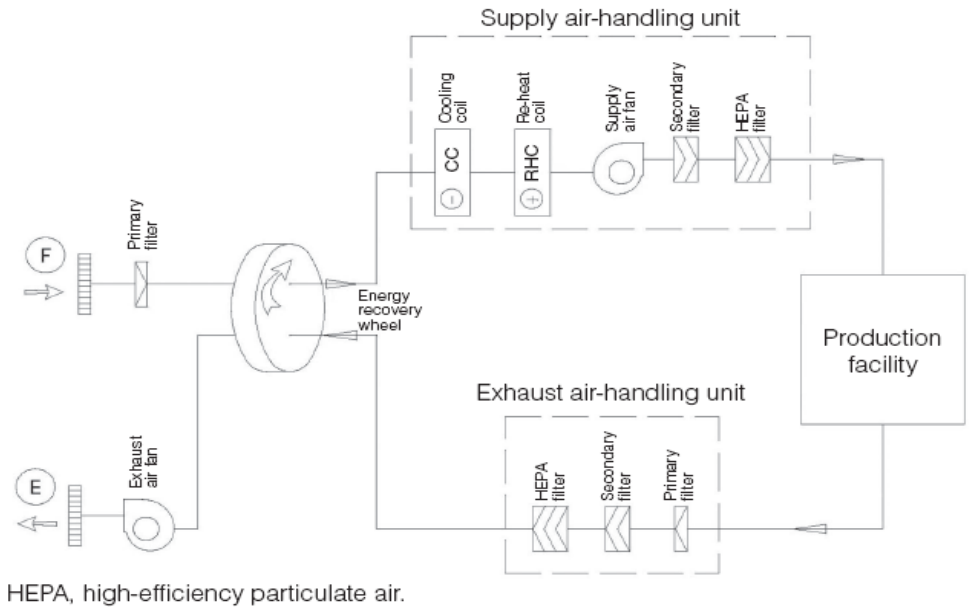
7.3 Full fresh-air systems

Fig. 26 indicates a system operating on 100% fresh air and would normally be used in a facility dealing with toxic products, where recirculation of air with contaminants should be avoided.

7.3.1 The required degree of filtration of the exhaust air depends on the exhaust air contaminants and local environmental regulations.

7.3.2 Energy-recovery wheels should normally not be used in multiproduct facilities. When such wheels are used they should not become a source of possible contamination (see Fig. 27). Note: Alternatives to the energy-recovery wheels, such as crossover plate heat exchangers and water-coil heat exchangers, may be used in multiproduct facilities.

Figure 27. Full fresh-air system with energy recovery



7.3.3 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.

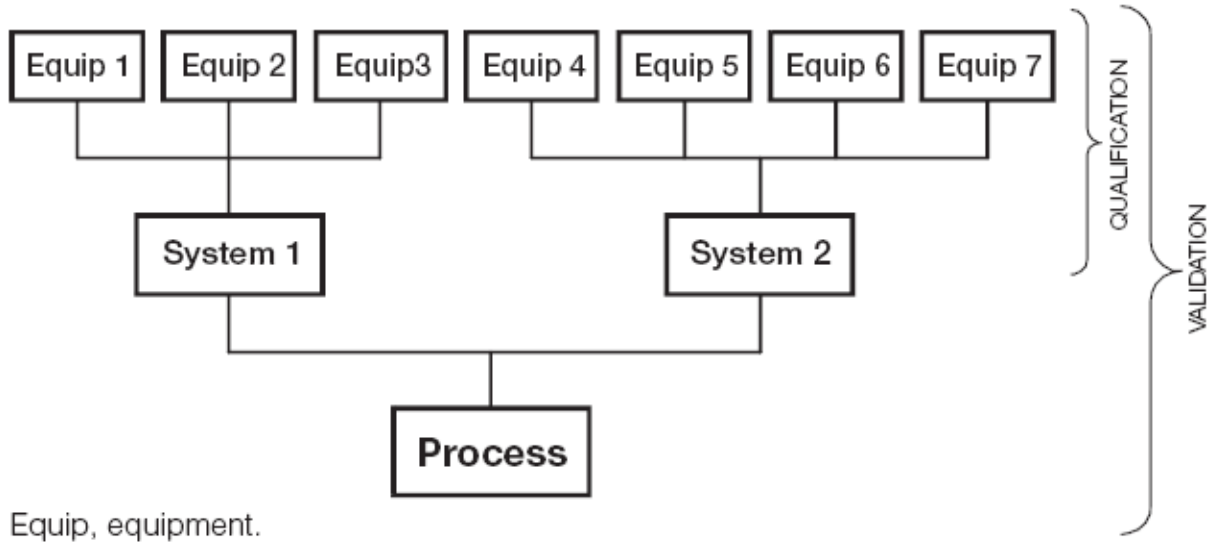
2. Commissioning, qualification and maintenance

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.

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

Figure 28. Qualification is a part of validation



8.1.3 The data should include items such as the design and measurement figures for airflows, water flows, system pressures and electrical amperages. These should be contained in the operating and maintenance manuals (O & M manuals).

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 O & M manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system.

8.1.7 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. Qualification and validation guidelines are included in: Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 937), Annex 4 (see also Fig. 28).

Manufacturers should qualify HVAC systems using a risk-based approach. 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.

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 non-critical parameters is required, to avoid making the validation process unnecessarily complex.

Example:

- *The 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 classification 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 Acceptance criteria and limits should be defined during the design stage.

8.2.11 The manufacturer should define design conditions, normal operating ranges, operating ranges, and alert and action limits.

8.2.12 Design condition and normal operating ranges should be identified and set to realistically achievable parameters.

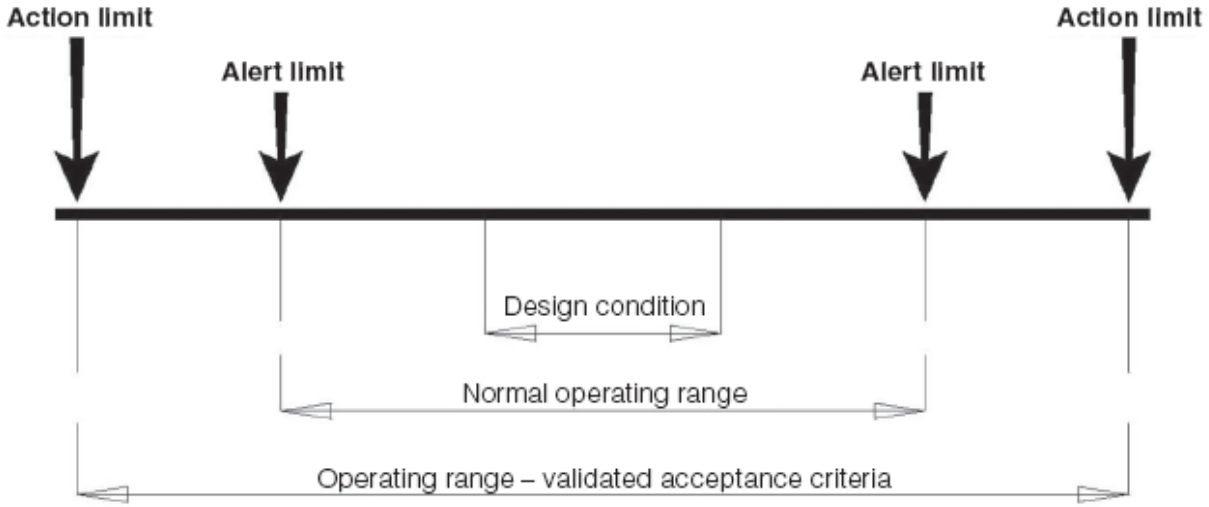
8.2.13 All parameters should fall within the design condition range during system operational qualification. Conditions may go out of the design condition range during normal operating procedures but they should remain within the operating range.

8.2.14 Out-of-limit results (e.g. action limit deviations) should be recorded and form part of the batch manufacturing records.

8.2.15 The relationships between design conditions, operating range and qualified acceptance criteria are given in Fig. 29.

8.2.16 A narrow range of relative humidities coupled with a wide range of temperatures is unacceptable as changes in temperature will automatically give rise to variations in the relative humidity.

Figure 29. System operating ranges



8.2.17 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.

Table 3. Part A: schedule of tests to demonstrate compliance (for reference purposes only)

Schedule of tests to demonstrate continuing compliance			
Test parameter	**Clean room class**	**Max. time interval**	**Test procedure**
Particle count test (Verification of cleanliness)	All classes	6 months	Dust particle counts to be carried out and printouts of results produced. No. of readings and positions of tests to be in accordance with ISO 14644-1 Annex B
Air pressure difference (To verify absence of cross-contamination)	All classes	12 months	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 rioates)	All classes	12 months	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	All Classes	12 Months	Air velocities for containment systems and laminar flow protection

laminar flow or containment conditions)	systems to be measured. In accordance with ISO 14644-3 Annex B4*

8.2.18 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.

Note: Table 3 gives intervals for reference purposes only. The actual test periods may be more frequent or less frequent, depending on the product and process.

8.2.19 Periodic requalification of parameters should be done at regular intervals, e.g. annually.

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

8.2.21 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.

Table 3. Part B: recommended optional strategic tests (ISO 14644)

Schedule of tests to demonstrate continuing compliance			
Test parameter	**Clean room class**	**Max. time interval**	**Test procedure**
Filter leakage tests (To verify filter integrity)	All classes	24 months	Filter penetration tests to be carried out by a recognized authority to demonstrate filter media and filter seal integrity. Only required on

			HEPA filters. In accordance with ISO 14644-3 Annex B6*
Containment leakage (To verify absence of cross-contamination)	All classes	24 months	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)	All classes	24 months	Test to establish time that a clean room takes to return from a contaminated condition to the specified clean room condition. This should not take more than 15 min. In accordance with ISO 14644-3 Annex B13*
Airflow visualization (To verify required airflow patterns)	All Classes	24 months	Tests to demonstrate airflows: • from clean to dirty areas • do not cause cross-contamination • uniformly from laminar flow units. Demonstrated by actual or video-taped smoke tests. In accordance with ISO 14644-3 Annex B7*

8.3 Maintenance

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

8.3.2 Maintenance personnel should receive appropriate training.

8.3.3 HEPA filters should be changed either by a specialist or a trained person.

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

8.3.5 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.