HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

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GUIDANCE NOTES ON HEATING, VENTILATION AND AIR-CONDITIONING (HVAC) SYSTEMS FOR MANUFACTURERS OF ORAL SOLID DOSAGE FORMS

HSA
Health Sciences Authority

Introduction

Heating, Ventilation and Air-Conditioning (HVAC) plays an important role in supporting the manufacture of quality pharmaceutical products. A well designed HVAC system will also provide operator comfort. This guideline mainly focuses on recommendations for systems for manufacturers of oral solid dosage forms. Reference in this guideline is also made to other systems or components which are not relevant to solid dosage form manufacturing plants as these references may assist in providing a comparison between the requirements for different facilities.

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 provide guidance to pharmaceutical manufacturers on the design, installation, qualification and maintenance of HVAC systems.

2. GLOSSARY:

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

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

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

Air Handling Unit (AHU)
Air handling unit which 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 and MAL = Material airlock).

Alert limit
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.

API
Active pharmaceutical ingredient

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

ASHRAE
American Society of Heating, Refrigeration and Air Conditioning Engineers.

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) *
An area (or room) 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.

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.

* 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 in order to define and classify the different manufacturing environments.

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.

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

Cross-contamination
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 to determine the performance requirements of an engineered system.

Design qualification (DQ)
DQ is the documented check of planning documents and technical specifications for design conformity 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 lifecycle to deliver appropriate, cost-effective solutions.

HEPA filter
High Efficiency Particulate Air filter.

HVAC
Heating Ventilation and Air-Conditioning

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.

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

ISO 14644-1
International standard relating to the classification of clean environments. It is set to replace all existing national standards such as the US Fed. Std. 209, BSS5295, EEC and DIN. This guideline will make reference to the ISO classifications. A comparison between the various existing standards is given in Chapter 8.

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
Normal operating range is 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)
OQ 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.

OSD
Oral solid dosage – usually referring 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.

Pressure cascade
A process whereby air flows from one area, which is maintained at the highest 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. equipment operation, 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.

ULPA filter
Ultra-Low Penetration Air filter (not applicable to normal pharmaceutical installations, but given for background information).

Unidirectional airflow
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).

3. LIST OF ABBREVIATIONS USED

AHU - Air Handling Unit
API - Active pharmaceutical ingredient
ASHRAE - American Society of Heating, Refrigeration and Air Conditioning Engineers.

BAS - Building automation system
BMS - Building management system
C - Celsius

DQ - Design qualification

GEP - Good Engineering Practice
GMP - Good Manufacturing Practices

HEPA - High Efficiency Particulate Air
HVAC- Heating Ventilation and Air-Conditioning

IQ - Installation qualification
ISPE - International Society for Pharmaceutical Engineering
MAL - Material airlock

OQ - Operational qualification
OSD - Oral solid dosage

PAL - Personnel airlock
PQ - Performance qualification

RH- Relative humidity

SCADA - System control and data acquisition
SOP - Standard Operating Procedure

UDAF - Unidirectional airflow
ULPA - Ultra-Low Penetration Air

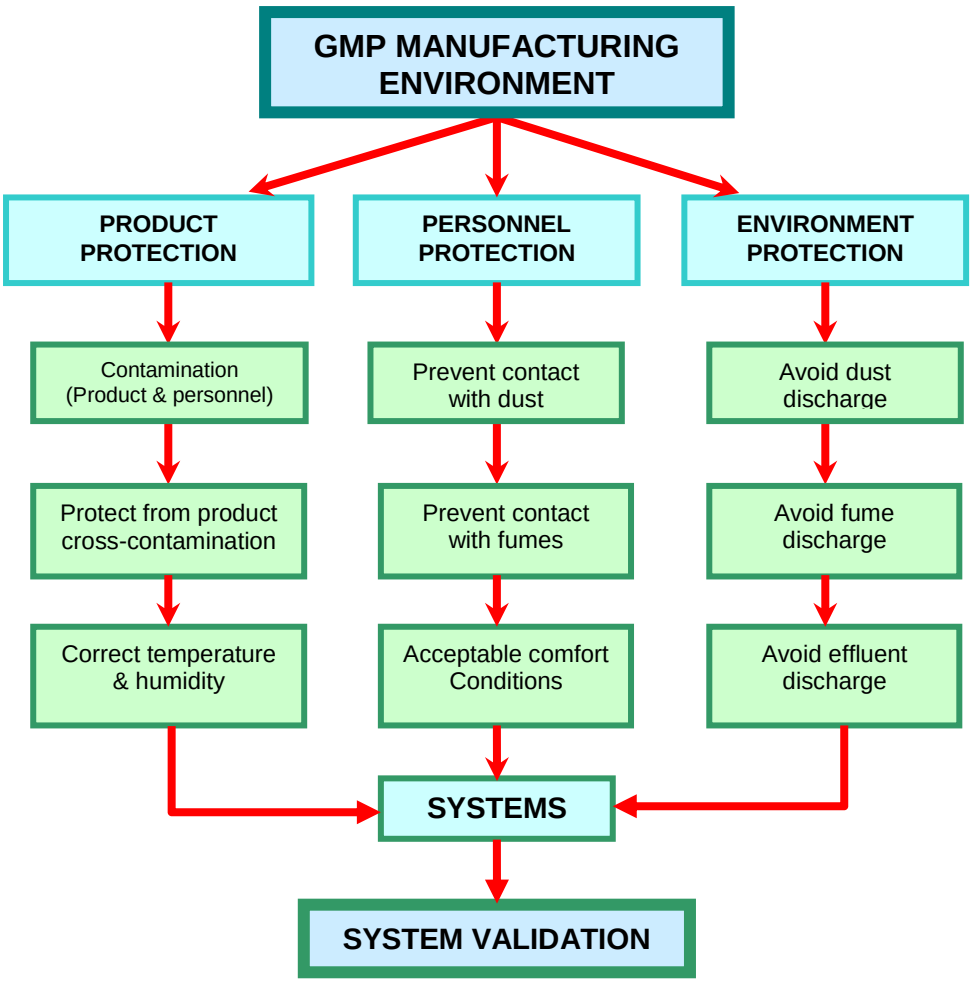
VMP - Validation Master Plan

4. SCOPE

The guideline focuses primarily on the design and GMP requirements for HVAC systems for oral solid dosage form facilities. Most of the system design principles for solid dosage manufacturing facilities will also apply to other facilities such as liquids, creams and ointments. This guideline does not cover

requirements for manufacturing facilities for the production of sterile dosage products.

Many manufacturers have their own engineering design and qualification standards and requirements may vary from one manufacturer to the next. Design parameters should, therefore, be realistically set for each project, with a view to creating a cost-effective design, 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. These aspects are represented in **Figure 1**.



5. PROTECTION

5.1 Product and Personnel

5.1.1 Pharmaceutical manufacturing areas where pharmaceutical starting materials, intermediates, in-process materials and products, product contact utensils and equipment are exposed to the environment, should be classified as “clean areas”.

5.1.2 The achievement of a particular clean area classification depends on a number of criteria which should be addressed at the design stage and qualification. There should be a balance between the different criteria in order to create an efficient clean area.

5.1.3 Some of the basic criteria to be considered should include:

- Building finishes and structure
- Air filtration
- Air change rate or flushing rate
- Room pressure and pressure differentials
- Location of air terminals and directional airflow
- Temperature
- Humidity
- Material flow
- Personnel flow
- Equipment movement
- Process being carried out

- Outside air conditions
- Occupancy

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

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

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

- 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

5.1.7 Each clean area class should be specified as achieving the clean area classification under “as-built”, “at-rest” or “operational” conditions.

Figure 2. "As-built" condition

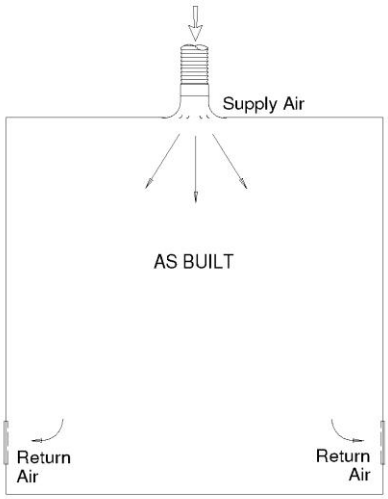


Figure 3. "At-rest" condition

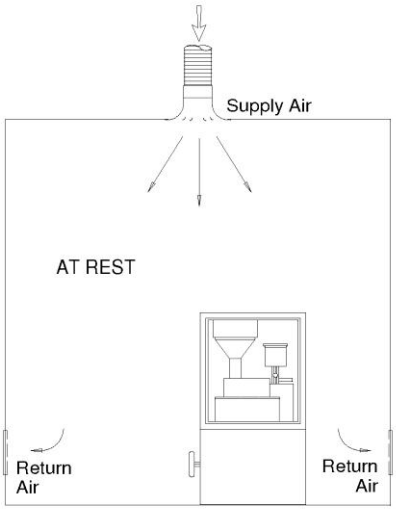
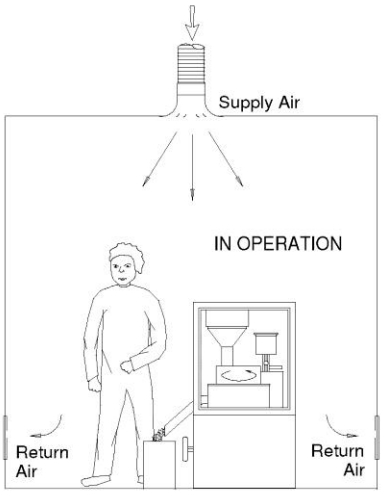


Figure 4. "Operational" Condition



5.1.8 The “as-built” condition should relate to carrying out room classification tests on the bare room, without any equipment or personnel.

5.1.9 The “at-rest” condition should relate to carrying out room classification tests with the normal production equipment in the room, but without any operators. Due to the amounts of dust usually generated in a solid dosage facility most clean area classifications are rated for the “at-rest” condition.

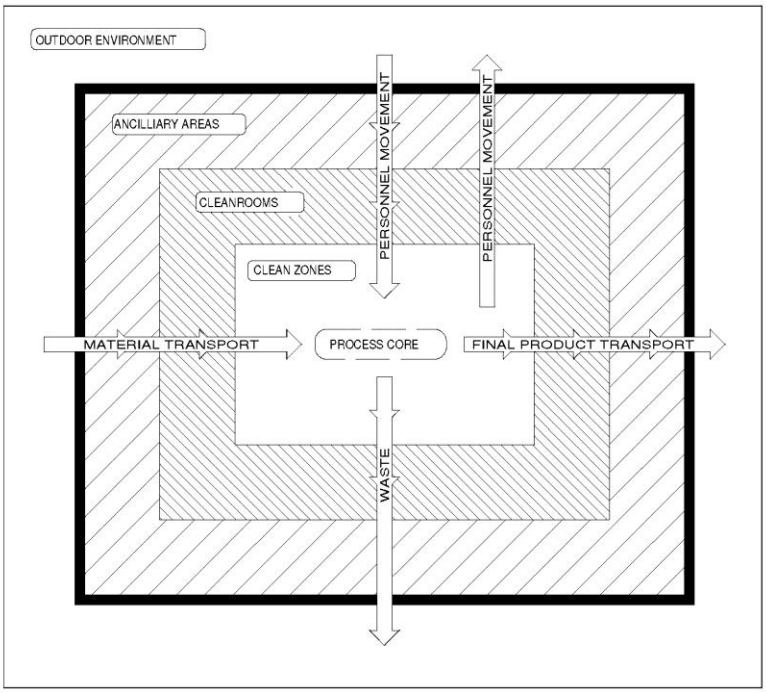
5.1.10 The “operational” condition should relate to carrying out room classification tests with the normal production process with equipment operating, and the normal number of personnel present in the room. Generally a room that is tested for an “operational” condition should be able to clean up to the “at-rest” clean area classification, after a short clean-up time. The clean-up time should be determined through validation and may typically be in the order of 20 minutes.

5.1.11 Materials and products should be protected from contamination and cross-contamination through all stages of manufacture (See also section 5.5 for cross-contamination control). Note: Contaminants may result from inappropriate premises (e.g. design, layout, finishing), poor cleaning procedures, personnel, and a poor HVAC system.

5.1.12 Contaminants should be removed through effective ventilation.

5.1.13 External contaminants should be removed by effective filtration of the supply air (See Figure 5; 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.

5.1.14 Internal contaminants by dilution and flushing of contaminants in the room, or by displacement airflow (See Figs 6 and 7; Examples of airborne contaminant flushing methods).

Figure 6. Turbulent dilution of dirty air

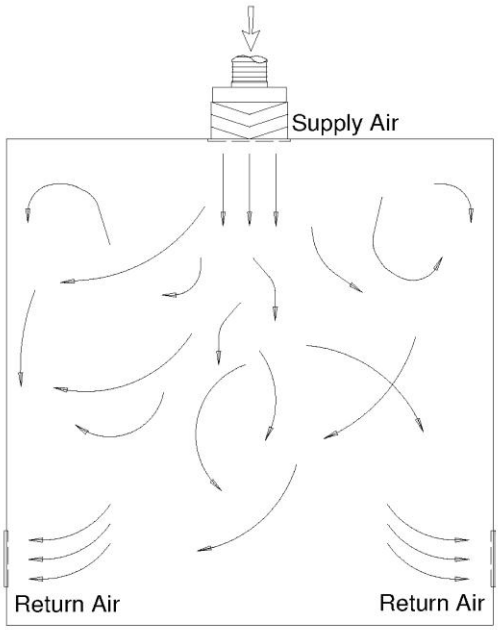
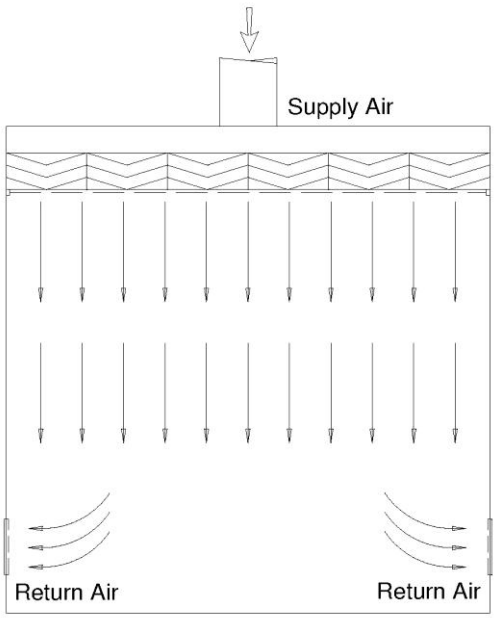


Figure 7. Unidirectional displacement of dirty air



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

5.1.16 The level of protection and air cleanliness for different areas should be evaluated based on the product being manufactured, the process and the product's susceptibility to degradation.

Table 1. Examples of levels of protection include:

Level	Condition	Example of area
Level 1	General	An area with normal housekeeping and maintenance e.g. Warehousing, Secondary Packing
Level 2	Protected	An 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, etc.
Level 3	Controlled	An area in which specific environmental conditions are defined, controlled and monitored to prevent contamination or degradation of the pharmaceutical starting material or product.

5.2 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.

5.2.1 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. The table below gives the recommended filtration levels for different levels of protection in a pharmaceutical facility. Manufacturers should determine and prove the appropriate use of filters.

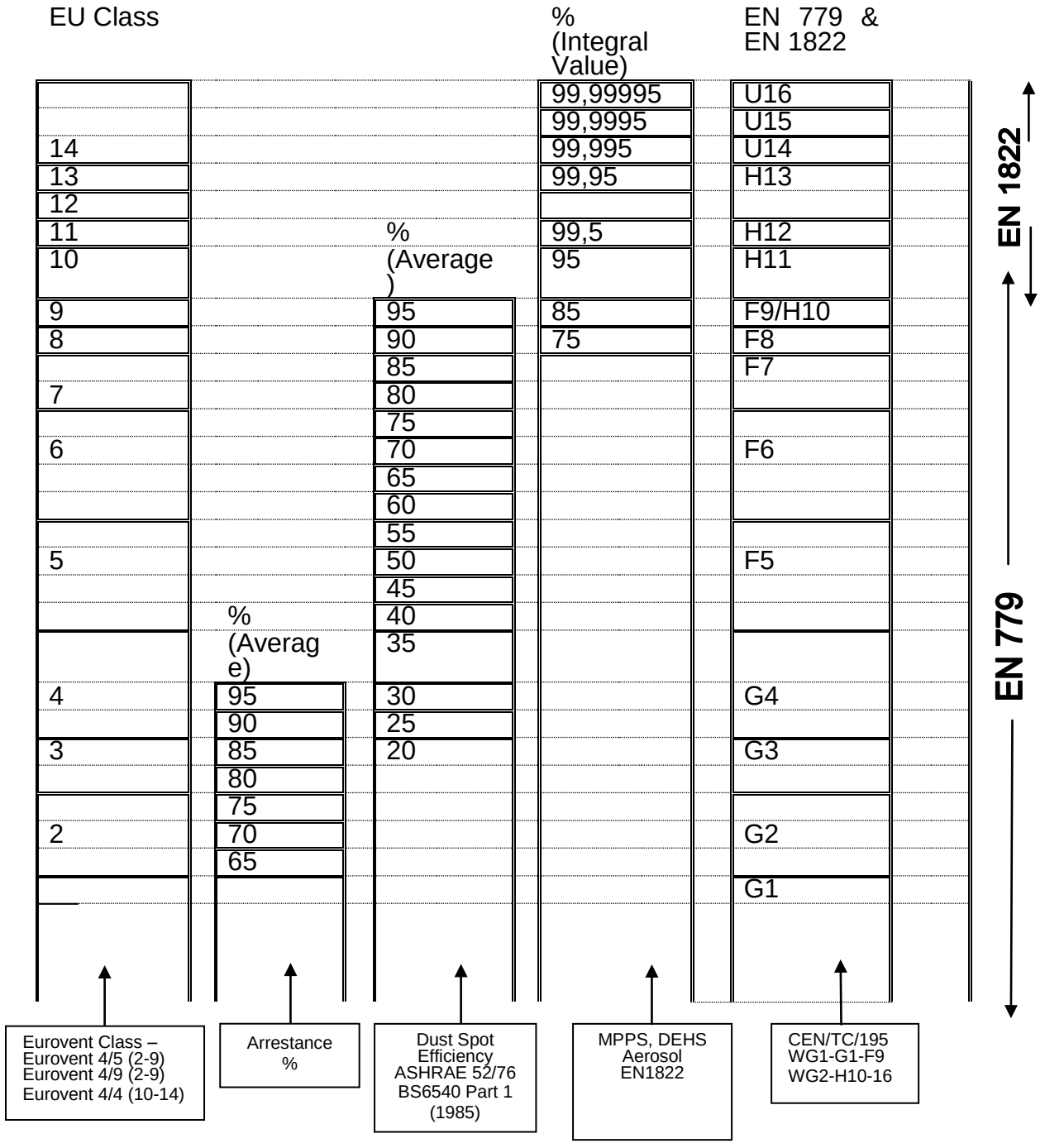
Table 2. Levels of protection and recommended filtration

Level of Protection	Recommended filtration
Level 1	Primary filters only (E.g. EN779 G4 filters)
Level 2 & 3	Production facility operating on 100% outside air: Primary plus secondary filters (E.g. EN779 G4 plus F8 filters)
Level 2 & 3	Production facility operating on re-circulated 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).

5.2.2 Filter classes should always be linked to the standard test method as referring to actual filter efficiencies can be very misleading (due to different test methods each resulting in a different value for the same filter).

Figure 8. Comparison of filter test standards



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

5.2.4 Materials for components of an HVAC system should be selected with care so as not to 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.

5.2.5 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.

5.2.6 Personnel should not be a source of contamination.

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

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

5.2.9 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. Air diffusers should be of the non-induction type, introducing air with the least amount of induction so as to maximize the flushing effect.

5.2.10 Whenever possible, air should be exhausted from a low level in rooms.

Figure 9. Induction diffuser (not recommended)

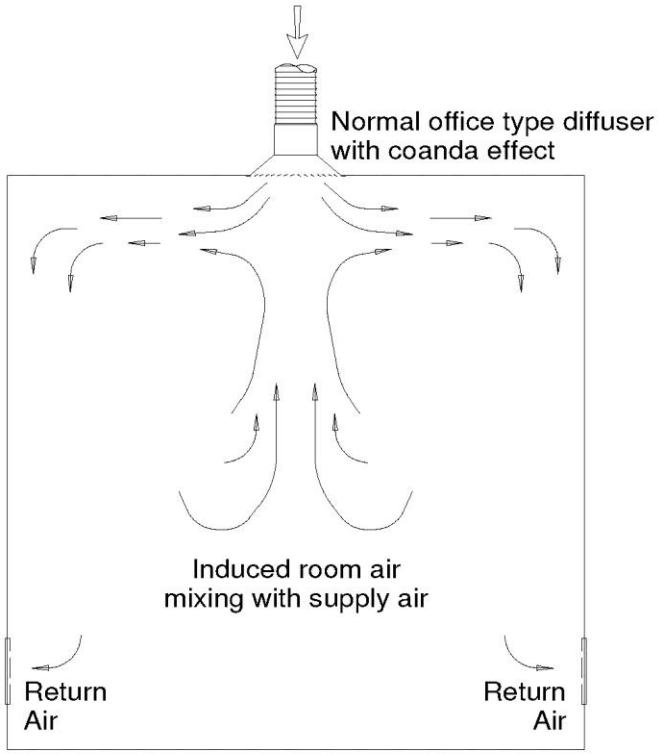


Figure 10. Perforated plate diffuser (recommended)

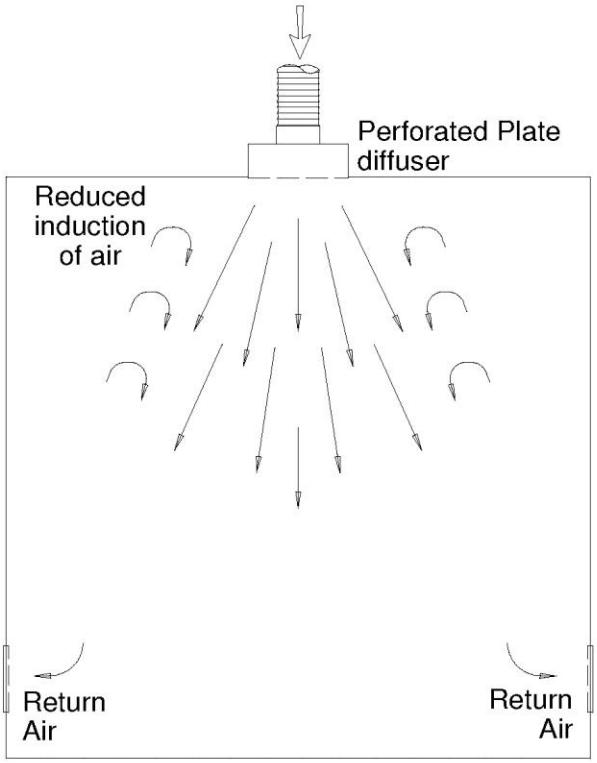
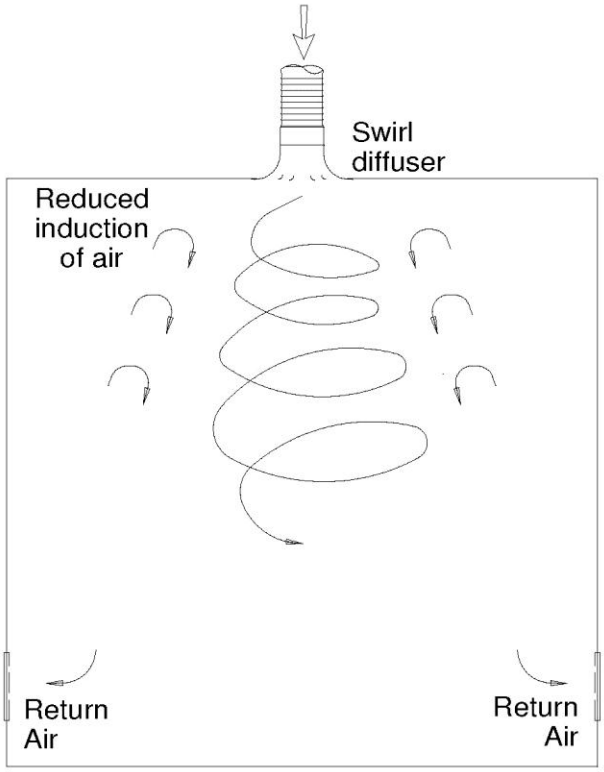


Figure 11. Swirl diffuser (recommended)



5.3 Unidirectional airflow (UDAF)

5.3.1 Unidirectional airflow 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.

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

5.3.3 Sampling should be carried out in the same environmental condition that is required for the further processing of the product. In some cases, sampling cubicles located in warehouses are used. These cubicles should normally provide a unidirectional airflow screen to ensure that clean air is flowing over the container when it is opened. (Note: Unidirectional flow normally provides a Class A (ISO Class 5, operational, 0.5 μm) environment, but for a sampling cubicle this degree of protection may not be required).

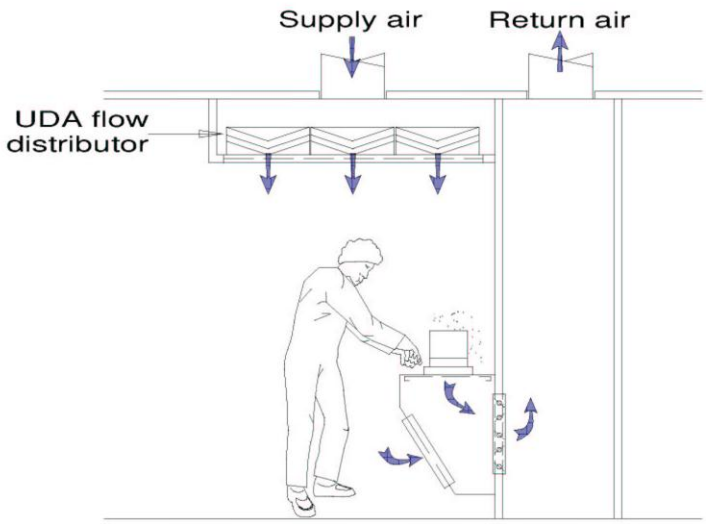
5.3.4 In a weighing booth situation, the aim should be to provide dust containment.

5.3.5 A dispensary or weighing weigh booth should be provided with unidirectional airflow for product and operator protection.

5.3.6 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 Figure12 (see Appendix) the dust generated at the weighing station is immediately extracted via the perforated work-top, 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.

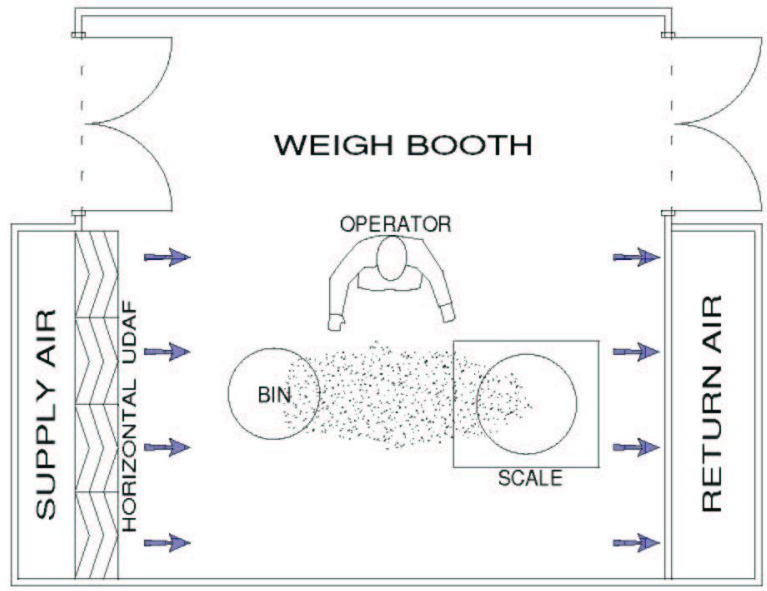
Figure 12. Operator protection at weighing station

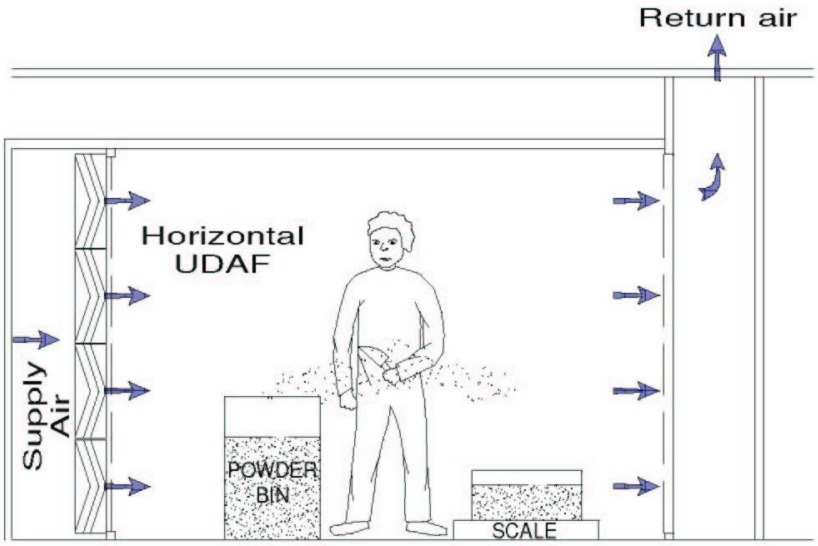


5.3.7 The unidirectional flow velocity should not disrupt the sensitivity of balances in weighing areas. Where necessary the velocity may be reduced to prevent scale inaccuracies, provided that sufficient airflow is maintained to provide containment.

5.3.8 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.

Figure 13. Operator protection by horizontal airflow





5.3.9 Once the system has been designed and qualified with a specific operator and process layout, this should be maintained in accordance with an SOP.

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

Figure 14 (see Appendix) indicates the incorrect use of a scale which has a solid back. The back of the scale should not block the return air path, causing air to rise up vertically, resulting in a hazardous situation for the operator.

Figure 14. Operator subject to powder inhalation due to obstruction

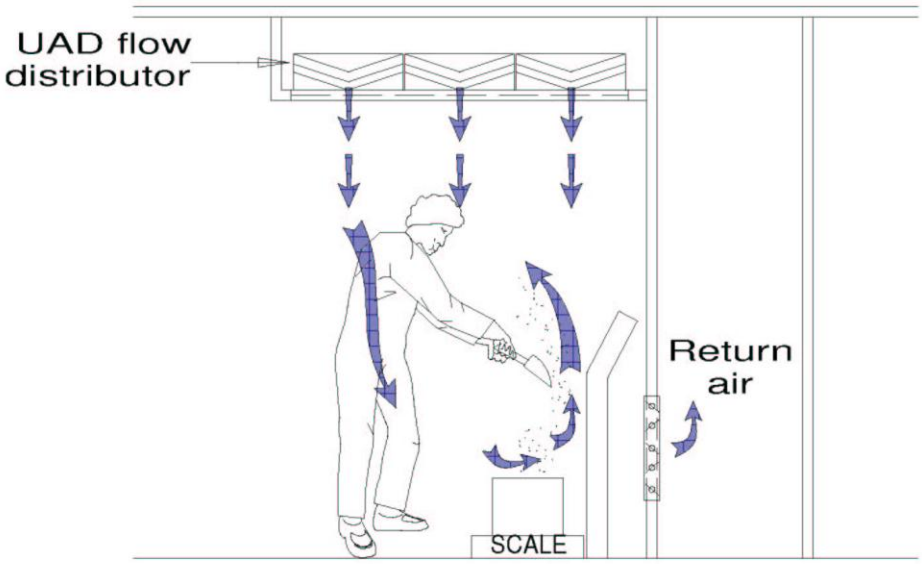


Figure 15 (see Appendix) indicates a situation where an open bin is placed below a vertical unidirectional flow distributor. The downward airflow should be prevented from entering the bin, and then being forced to rise up again, carrying dust up towards the operator's face.

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

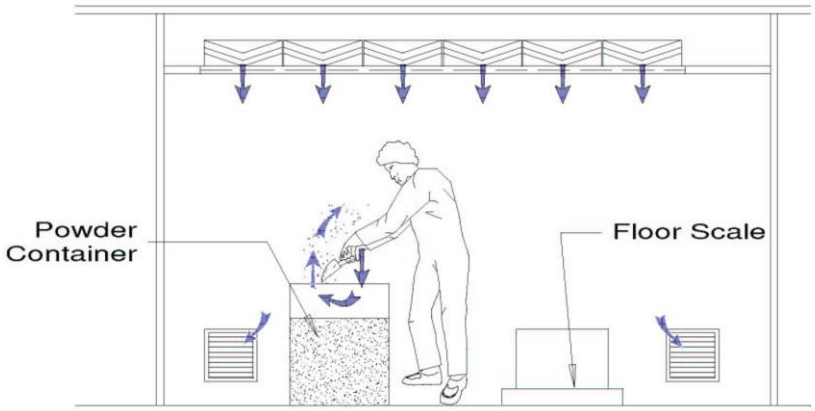
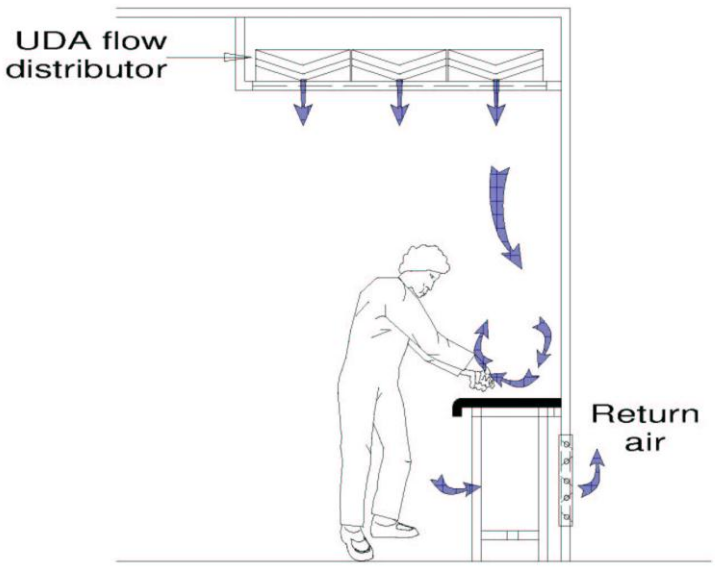
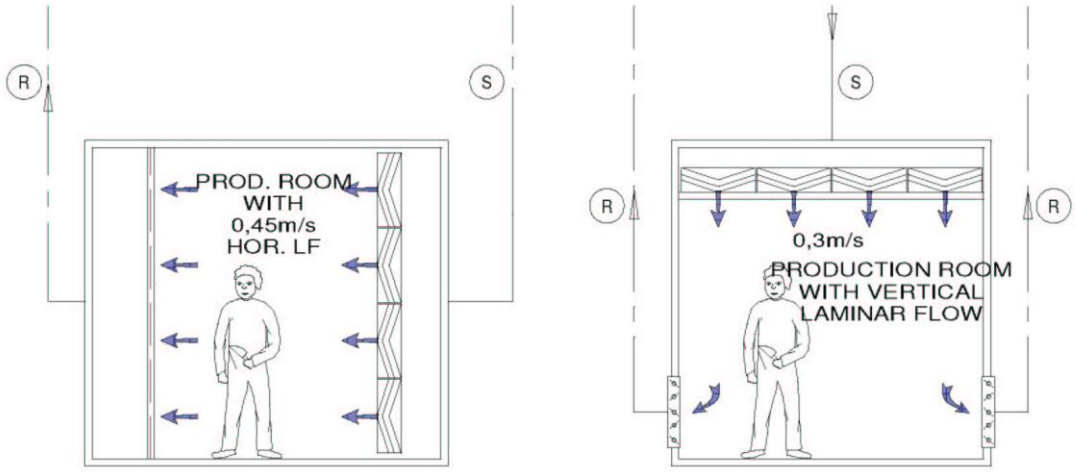


Figure 16 (see Appendix) shows that sometimes a solid worktop can cause deflection of the vertical unidirectional airflow resulting in a flow reversal. A possible alternative solution would be to have a 100 mm gap at the back of the table, with the air being extracted here.



5.3.11 The manufacturer should select either vertical or horizontal unidirectional flow and an appropriate air flow pattern that provides the best protection for the particular application.

Figure 17. Diagram indicating horizontal and vertical unidirectional flow



5.4 Infiltration

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

5.4.2 Manufacturing facilities should be maintained at a positive pressure relative to the outside, in order to limit the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to ambient, in order to prevent the escape of harmful actives to the outside (such as penicillin and hormones), then special precautions should be taken.

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

5.4.4 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.

5.5 Cross-contamination

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

5.5.2 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 air flow is from the clean corridor into the cubicles, resulting in dust containment.

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

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

5.5.5 The choice of pressure cascade regime and choice of airflow direction should be considered in relation to the product and processing method used).

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

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

5.5.8 Building structure should be given special attention because of the pressure cascade design.

5.5.9 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 doorway velocities is difficult. This concept should ideally be used in production processes where large amounts of dust are generated.

5.5.10 With this concept the air should be supplied to the corridor, flow through the doorway, and should 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.

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

5.5.12 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 there is little or no dust being generated. It may be used alone or in combination with other containment control techniques and concepts, such as a double door airlock.

5.5.13 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.

5.5.14 The pressure differential should be of sufficient magnitude to ensure containment and prevention of flow reversal, but should not be too high so as to create turbulence problems.

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

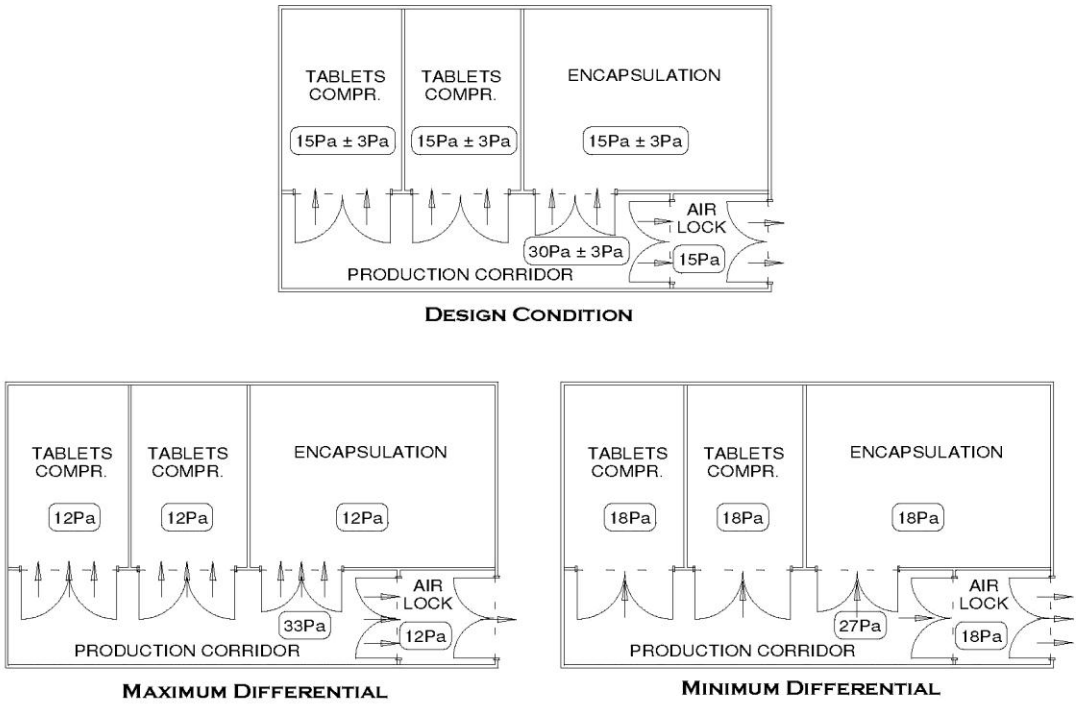
Note: The most widely accepted pressure differential to achieve containment between the two adjacent zones is 15 Pa, but pressure differentials of between 5 Pa and 20 Pa could be acceptable. Where the design pressure differential is too low and tolerances are at opposite extremities, a flow reversal can take place. E.g. where a control tolerance of ±3 Pa is specified, the implications of the upper and lower tolerances on containment should be evaluated.

5.5.16 The pressure differential between adjacent rooms could be considered a critical parameter, depending on 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, 15 Pa to 30 Pa, resulting in no pressure cascade.

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

5.5.18 The effect of room pressure tolerances are illustrated in Figure 18 (see Appendix).

Figure 18. Examples of pressure cascades



5.5.19 Pressure control and monitoring devices used should be calibrated and qualified. Compliance with specifications should be verified and recorded on a regular basis. Based on a risk analysis, pressure control devices should be linked to an alarm system. Generally, the pressure differential and the duration of excursion are considered when triggering audio/ visual alarms. Production operators and other users of the premises must be notified of the alarms in a timely manner in order to take corrective/ mitigating actions.

5.5.20 Where manual control systems are used, these should be set up during air balancing activities during commissioning and should not change unless other system conditions change.

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

5.5.22 Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock. (See Figures 19 to 21 (see Appendix).

Figure 19. Example of cascade airlock

Figure 20. Example of sink airlock

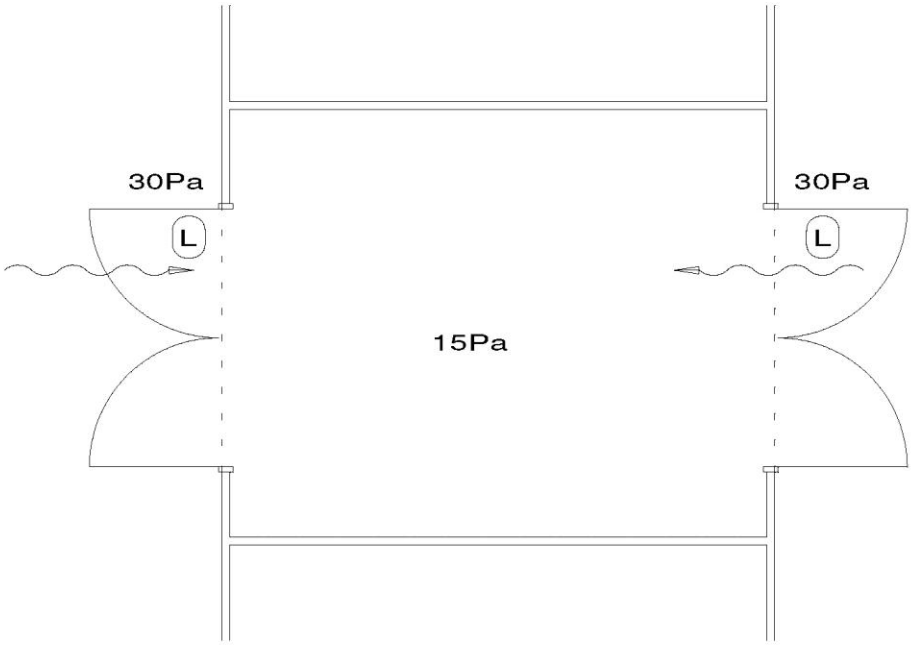
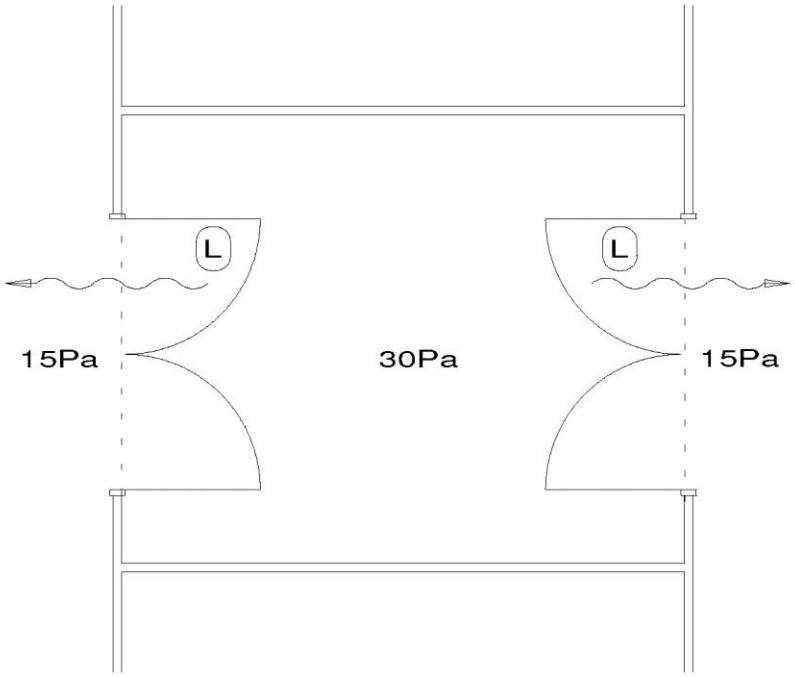


Figure 21. Example of bubble airlock



Cascade airlock - high pressure on one side of the airlock and low pressure on the other side.

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.

5.5.23 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. Use of interlocks on doors ensures that pressure differentials designed are achieved within airlock areas before doors leading to clean areas and corridors are opened. Audio/ visual alarms within the airlocks may be used. Pressure differential data may also be captured by the building management system.

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

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

5.5.26 Air should not flow from the room with the higher pressure to the room with the lower pressure, via the dust extract ducting.

Physical barrier concept

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

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

5.6 Temperature and relative humidity

5.6.1 Temperature and relative humidity should be controlled, monitored and recorded where relevant, in order to ensure compliance with materials and product requirements, and to provide operator comfort where necessary.

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

5.6.3 Temperature conditions should be adjusted to suit the protective clothing worn by the operators.

5.6.4 The operating band or tolerance between the acceptable minimum and maximum temperatures should not be made too close. Temperature and humidity excursions and the duration of excursion are considered when triggering audio/ visual alarms. Production operators and other users of the premises must be notified of the alarms in a timely manner in order to take corrective/ mitigating actions. Temperature and humidity data may also be captured by the building management system.

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

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

5.6.7 Humidity control should include removing moisture from the air, or adding moisture to the air, as relevant.

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

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

5.6.10 Humidifiers should be avoided if possible as these 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 humidification purposes.

5.6.11 No chemicals (such as corrosion inhibitors/chelating agents) which could have a detrimental effect on the product steam humidifiers used should be added to the boiler system.

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

5.6.13 Other humidification appliances such as evaporative systems, atomizers and water mist sprays, should not be used due to the possible microbial contamination risk

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

5.6.15 Final air filters should not be installed immediately downstream of humidifiers.

5.6.16 There should be insulation of cold surfaces in order to prevent condensation within the clean area or on air-handling components, where high humidity is required.

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

5.6.18 Chemical driers may be used to achieve conditions lower than 45% RH at a temperature of 22°C. Chemical driers or dehumidifiers employing a desiccant, such as silica gel or lithium chloride to remove the moisture from the air, should have desiccant wheels of the non-shedding type and should not support microbial growth. Appropriate air filters are to be used

downstream to prevent desiccant particulates from entering the productions premises.

6. DUST CONTROL

6.1 Wherever possible, the dust or vapour contamination should be removed at source. Point extraction, as close as possible to the point where dust is generated, should be employed.

6.2 Point extraction known commonly as 'elephant trunks', 'fish tails', etc should be either in the form of a fixed high velocity extraction point or an articulated arm with movable hood or a fixed extract hood.

6.3 Dust extraction ducting should be designed so as to have sufficient transfer velocity to ensure that dust is carried away, and does not settle in the ducting. Risk during product changeovers must be assessed and periodic cleaning of the dust extraction ducting is to be carried out.

6.4 The required transfer velocity should be determined as 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).

6.5 Airflow should be carefully planned, to ensure that the operator does not contaminate the product, and so that the operator is not put at risk by the product.

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

6.7 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.

6.8 Typically in a room operating with turbulent airflow the air should be introduced from ceiling diffusers and extracted from the room at low level.

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

6.10 When dealing with the extraction of vapours the density of the vapour should be taken into account. If the vapour is lighter than air, then the extract grilles should be at high level, or possibly at high and low level.

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

6.12 For products such as hormones or highly potent products, operators should wear totally enclosed garments, as indicated in Figure 22. In this instance a portable of fixed tubing air-breathing system should provide a supply of HEPA filtered and conditioned air to the operator. 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. Re-usable pressurized air suits must be checked for leakages as this could lead to contamination of the production environment.

Figure 22. Protective garments

6.13 Fresh air rates supplied to the facility should comply with national, regional and or international regulations, to provide operator comfort and safety and also to provide odour or fume removal.

6.14 Fresh air rate should also be determined by leakage from the building, for pressure control purposes.

7. PROTECTION OF THE ENVIRONMENT

7.1 Exhaust air dust

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

7.1.2 Where the powders are not highly potent, final filters on a dust exhaust system should be fine dust filters having a filter classification of F9 according to EN779 filter standards.

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

7.1.4 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.

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

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

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

7.1.8 Monitoring of filters should be done at regular intervals in order to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in ambient contamination.

7.1.9 More sophisticated computer-based data monitoring systems may be installed, with preventive maintenance plans 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).

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

7.1.11 Where reverse pulse dust collectors are used for removing dust from dust extract systems, these should usually be equipped with cartridge filters containing a compressed air lance, and be able to operate continuously without interrupting the airflow.

7.1.12 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 for cross contamination. There should be no disruption of airflow during a production run as the loss of airflow could disrupt the pressure cascade.

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

7.1.14 When wet scrubbers are used, the dust-slurry should be passed to a suitable drainage system.

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

7.1.16 Where necessary, additional filtration may be required downstream of the dust collector. In the event of power failure, 'fail-safe' systems should be in place to prevent backflow of residues from the ductwork.

7.2 Fume removal

7.2.1 Fume, dust and effluent control should be designed, installed and operated in a manner that these 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.

7.2.2 Removal of fumes should be by means of wet scrubbers or dry chemical scrubbers (deep bed scrubbers).

7.2.3 Wet scrubbers for fume removal should normally have various chemicals added to the water to increase the adsorption efficiency.

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

7.2.5 The type and quantity of the vapours to be treated should be known, to select the type of filter media as well as the volume of media required.

8. HVAC SYSTEMS AND COMPONENTS

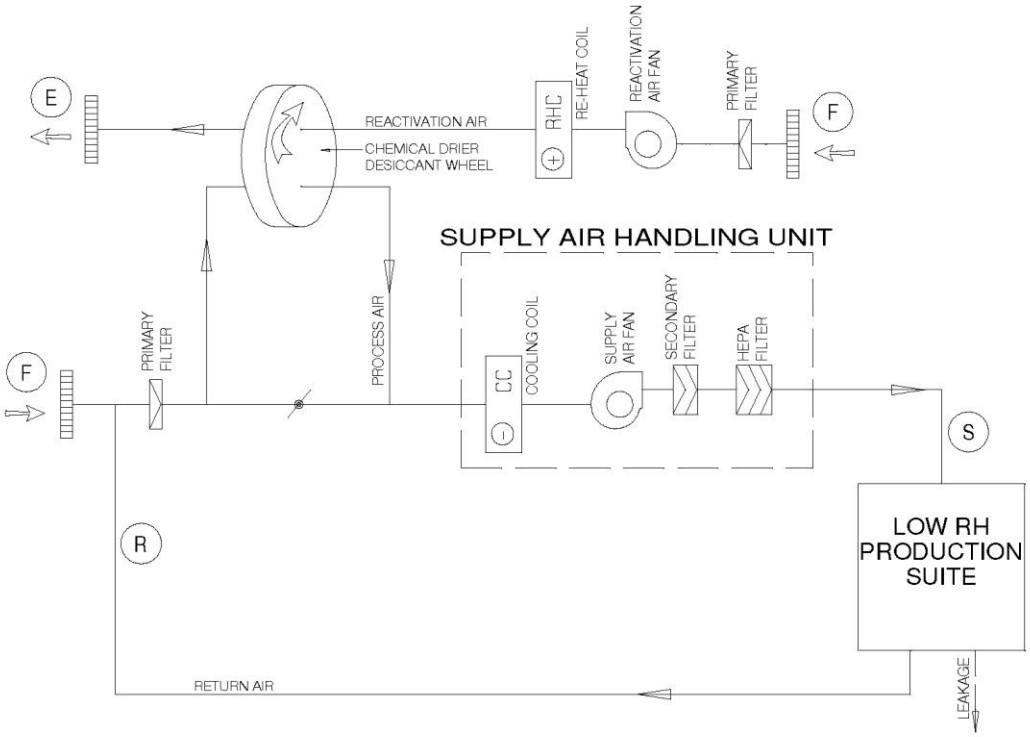
Note: The required degree of air cleanliness in most OSD manufacturing facilities can normally be achieved without the use of HEPA filters. Many open product zones of oral solid dosage form facilities are capable of meeting ISO 14644-1 Class 8, "at-rest" condition, measured against particle sizes of 0,5 μm and 5 μm, but may not be classified as such by manufacturers.

8.1 General

8.1.1 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.

8.1.2 An airflow schematic diagram for a typical system serving a low humidity suite is represented in Figure 23 (see Appendix).

Figure 23. Air handling system with chemical drying



8.1.3 Drying of air should be done 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).

8.1.4 The figure indicates the chemical drier handling part of the fresh air/return air mixture on a by-pass flow. The chemical drier should be appropriately located as considered in the design phase, e.g. in:

- Full flow of fresh/return air
- Partial handling of fresh/return air (by-pass airflow)
- Return air only
- Fresh air only
- Pre-cooled air with any of the above alternatives

8.1.5 Additional components that may be required on a system 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
- Fresh air precooling coils for very hot climates

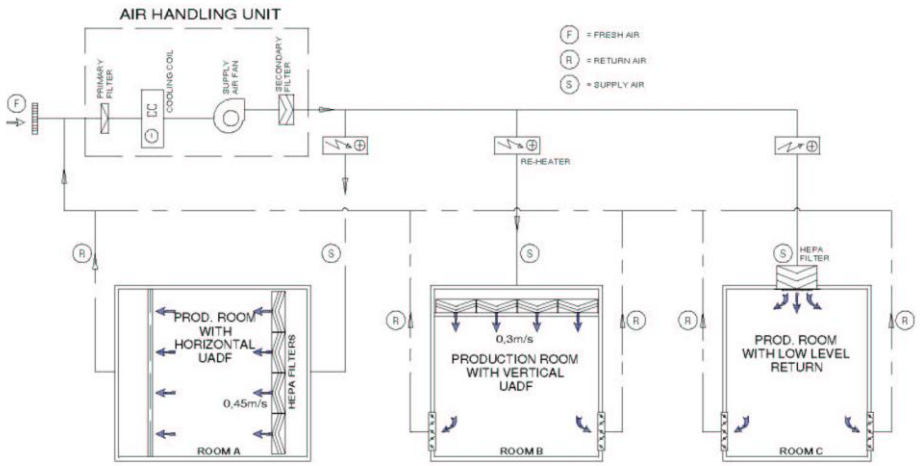
8.1.6 Appropriate alarm systems should be in place to alert personnel if failure of a critical fan occurs.

8.1.7 Low level return or exhaust air grilles are always preferred. However, where this is not possible, a higher air change rate to achieve a specified clean area classification may be required, e.g. where ceiling return air grilles are used.

8.1.8 There may be alternative locations for return air, e.g. room D (low-level return air) and room E (ceiling return air).

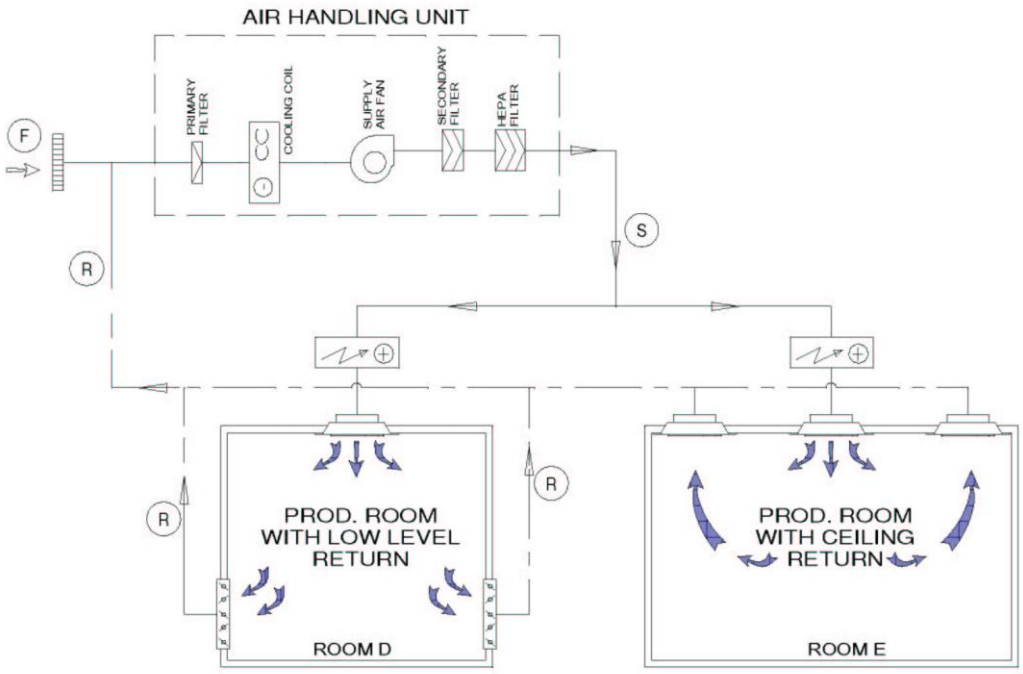
The airflow schematics of the two systems (Figures 24 and 25) indicate air handling units with return air or recirculated air, having a percentage of fresh air make-up. Figure 24 indicates a schematic diagram of an air handling system serving rooms with horizontal unidirectional flow, vertical unidirectional flow and turbulent flow respectively for rooms A, B and C.

Figure 24. Horizontal unidirectional flow, Vertical unidirectional flow and Turbulent flow



The airflow diagram Figure 25 (see Appendix) reflects and example of a typical system with a lower clean area classification.

Figure 25. Air handling system with HEPA filters in AHU



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).

8.2 Recirculation system

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

8.2.2 Depending on the airborne contaminants in the return air system it may usually be acceptable to use recirculated 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.

8.2.3 HEPA filters may not be required where the air handling system is serving a single product facility and there is evidence that there is no possibility of cross-contamination.

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

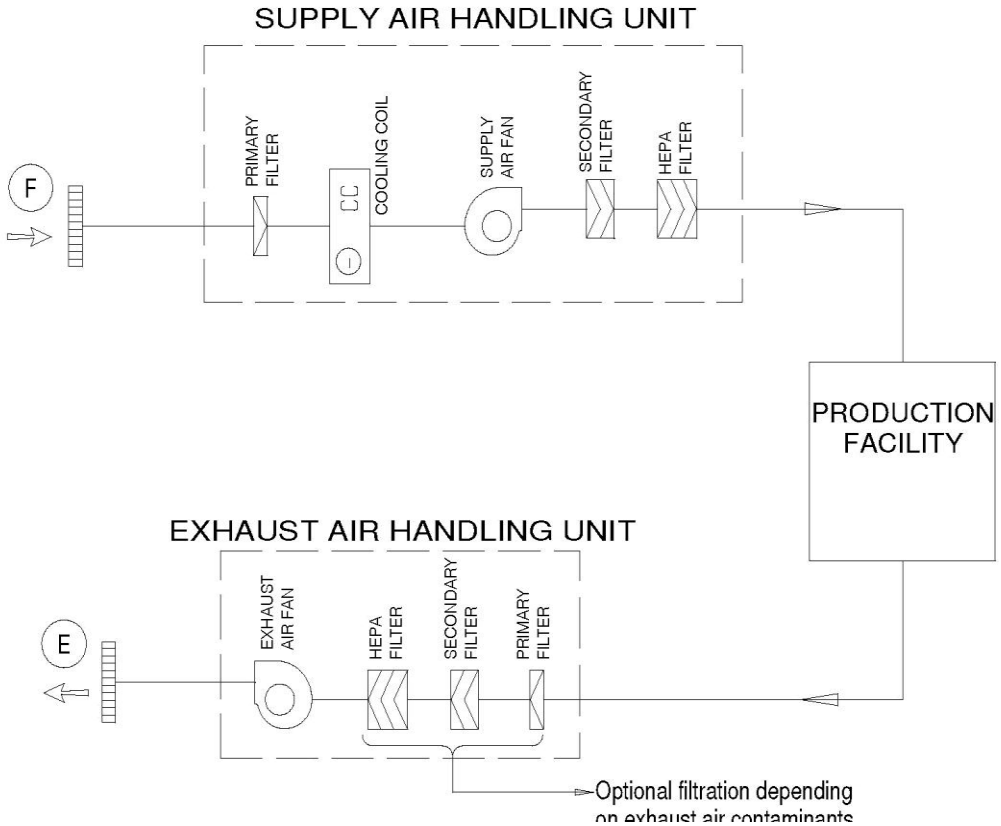
8.2.5 HEPA filters may be located in the air handling unit or placed terminally.

8.2.6 Dust from highly toxic processes should never be recirculated to the HVAC system.

Figure 26 (see Appendix) indicates a system operating on 100% fresh air and normally typically applies to toxic products where recirculation of air with contaminants is not advised.

8.3.1 The degree of filtration on the exhaust air should be determined dependent on the exhaust air contaminants and local environmental regulations.

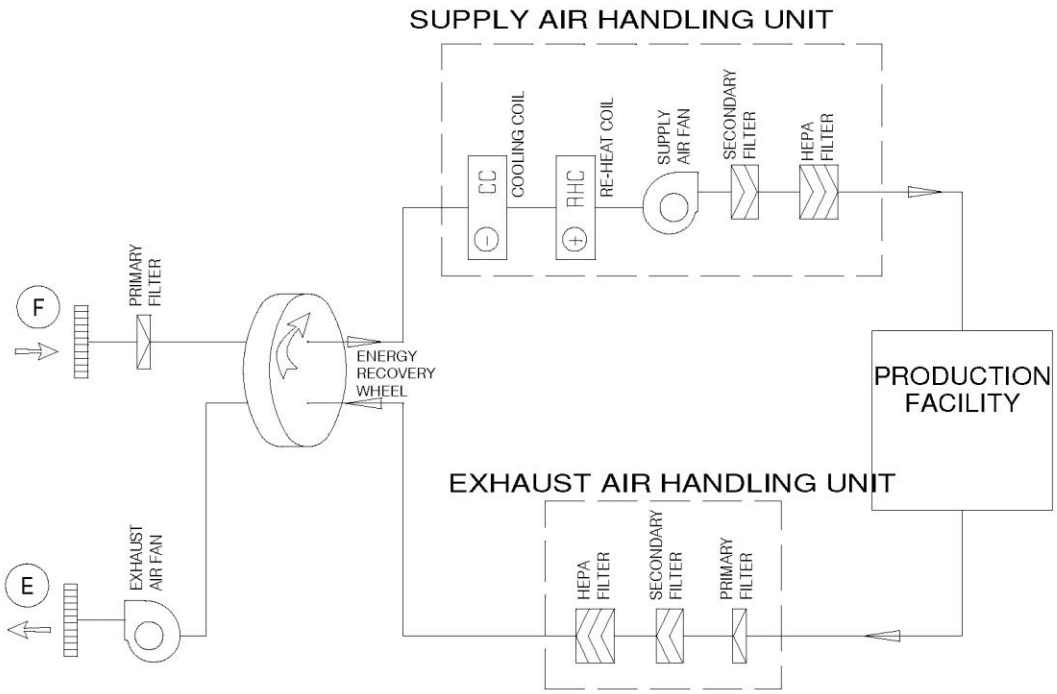
Figure 26. Full fresh air system



8.3.2 Energy recovery wheels should normally not be used in multi-product facilities. When energy wheels are used these should be not become a source of possible contamination. (See Figure 27 (see Appendix). (Note: Alternatives to the energy recovery wheels, such as crossover plate heat exchangers and water coil heat exchangers, should be used).

8.3.3 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.

Figure 27. Full fresh air system with energy recovery



9. COMMISSIONING, QUALIFICATION AND MAINTENANCE

9.1 Commissioning

9.1.1 Commissioning should involve the setting up, balancing, adjustment and testing of the entire HVAC system, to ensure that the system meets all the requirements, as specified in the User Requirement Specification, and capacities as specified by the designer or developer.

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

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

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

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

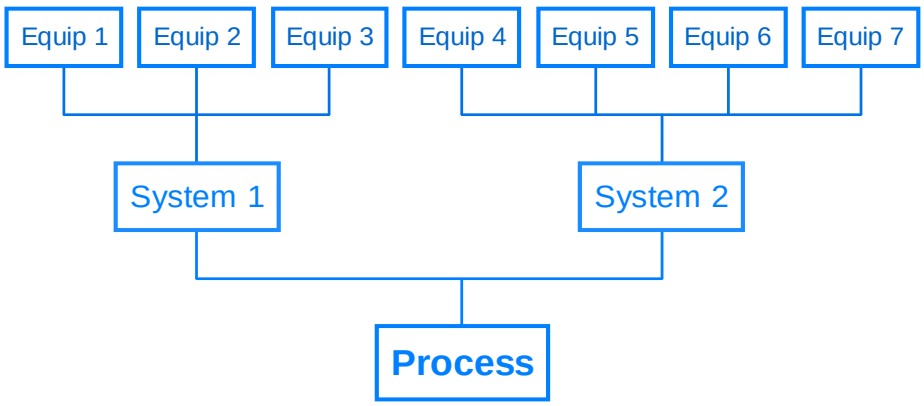
9.1.6 O & M manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system.

9.1.7 Commissioning should be a precursor to system qualification and validation.

9.2.1 Validation is a many-faceted and extensive activity and is beyond the scope of this guideline. Qualification and validation guidelines are included in Annex

Manufacturers should qualify HVAC systems on a risk based approach that addresses different operating modes e.g. operational and non-operational modes. The basic concepts of qualification of HVAC systems are set out below.

Figure 28. Qualification is a part of validation



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

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

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

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

9.2.6 All parameters that may affect the quality of the pharmaceutical product, should be considered to be a critical parameter.

9.2.7 All critical parameters should be included in the qualification process.

Note: A realistic approach to differentiating between critical and non-critical parameters is required, in order not to make the validation process unnecessarily complex. Example:

- The room humidity 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.

9.2.8 Systems and components, which are non-critical, should be subject to GEP and may not necessarily require full qualification.

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

9.2.10 Acceptance criteria and limits should be defined during the design stage.

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

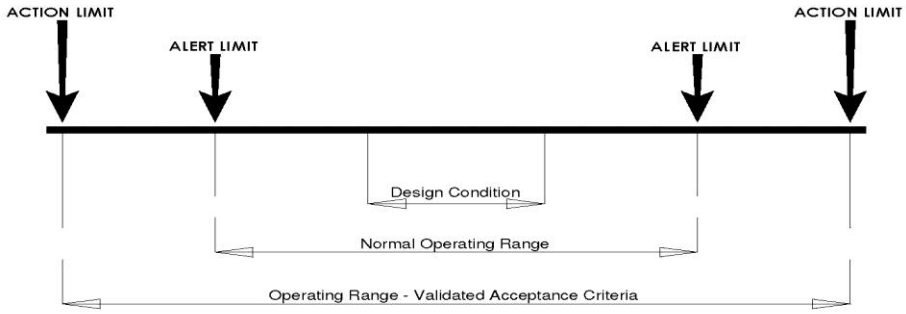
9.2.12 Design condition and normal operating ranges should be set as wide as possible to set realistically achievable parameters.

9.2.13 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.

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

9.2.15 The relationships between design conditions, operating range and qualified acceptance criteria are given in Fig. 29 (see Appendix).

Figure 29. System operating ranges



9.2.16 A very tight relative humidity tolerance, but a wide temperature tolerance, should not be acceptable as variances between the maximum and minimum temperature condition will give an automatic deviation of the humidity condition.

9.2.17 For a pharmaceutical facility 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 dedusting;
- warning/alarm systems where applicable.

9.2.18 Room return or exhaust air is a variable which should be used to set up the room pressure. As room pressure is a more important criteria than the return air, the latter should have a very wide Normal Operating Range.

9.2.19 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 intervals for reference purposes only. The actual test periods may be more frequent or less frequent, depending on the product and process).

Schedule of Tests to Demonstrate Continuing Compliance			
Test Parameter	**Clean area Class**	**Max Time Interval**	**Test Procedure**
Particle Count Test (Verification of Cleanliness)	All classes	6 Months	Dust particle counts to be carried out & result printouts produced. No. of readings and positions of tests to be in accordance with ISO 14644-1 Annex B
Air Pressure Difference (To verify non 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 rates)	All Classes	12 Months	Air flow 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)	All Classes	12 Months	Air velocities for containment systems and unidirectional flow protection systems to be measured. In accordance with ISO 14644-3 Annex B4
HEPA filters (Certification from manufacturers)	All classes	24 months	Filter integrity e.g. DOP testing

Table 3. STRATEGIC TESTS

(Ref: ISO 14644 Standard, given for reference purposes only)

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

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

9.2.22 The table below reflects permissible particle concentrations for various clean area classifications, as well as a comparison between different clean area standards. The ISO 14644 standard has superseded the US and BS standards, but these are given for comparative purposes only. ISO Classes Grades 1 to 4 are not applicable to pharmaceutical facilities, but are included for completeness of the table.

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

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

9.3.2 There should be appropriate training for maintenance personnel.

9.3.3 HEPA filters should be changed only by specialists or trained personnel.

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

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

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