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May 2016
Draft document for comment

World Health Organization

SUPPLEMENTARY GUIDELINES ON GOOD MANUFACTURING PRACTICES FOR HEATING, VENTILATION AND AIR-CONDITIONING SYSTEMS FOR NON-STERILE PHARMACEUTICAL DOSAGE FORMS (May 2016)

REVISED DRAFT FOR COMMENT

Should you have any comments on the attached text, please send these to Dr S. Kopp, Group Lead, Medicines Quality Assurance, Technologies, Standards and Norms (kopps@who.int) with a copy to Ms Marie Gaspard (gaspardm@who.int) by **12 July 2016**.

Medicines Quality Assurance working documents will be sent out electronically only and will also be placed on the Medicines website for comment under "Current projects". If you do not already receive our draft working documents please let us have your email address (to bonnyw@who.int) and we will add it to our electronic mailing list.

SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/15.639

SUPPLEMENTARY GUIDELINES ON GOOD MANUFACTURING PRACTICES FOR HEATING, VENTILATION AND AIR-CONDITIONING SYSTEMS FOR NON-STERILE PHARMACEUTICAL DOSAGE FORMS.

PROPOSAL FOR REVISION

Discussion of proposed need for revision in view of the current trends in engineering and experience gained during the implementation of this guidance in inspection during *informal consultation on data management, bioequivalence, GMP and medicines' inspection*	29 June– 1 July 2015
Preparation of draft proposal for revision by Mr D. Smith, consultant to the Medicines Quality Assurance group and Prequalification Team (PQT)-Inspections, based on the feedback received during the meeting and from PQT-Inspections	July–August 2015
Circulation of revised working document for public consultation	September 2015
Consolidation of comments received and review of feedback	10 October 2015
Presentation to the fiftieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations	12–16 October 2015
Consolidation of comments received and review of feedback	January–March 2016
Discussion at the informal consultation on good practices for health products manufacture and inspection, Geneva,	4–6 April 2016
Preparation of revision by Mr D. Smith, based on comments provided by Mr A. Kupferman and Dr A.J. Van Zyl, both participants at the above-mentioned consultation.	May 2016
Circulation of revised working document for public consultation	May 2016

Consolidation of comments received and review of feedback	August–September 2016
Presentation to the fifty-first meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations	17–21 October 2016
Any other follow-up action as required	…

BACKGROUND

During the *consultation on data management, bioequivalence, GMP and medicines' inspection held in 2015* the possible revision of the guidance for (WHO Technical Report Series, No. 961, Annex 5, 2011) was discussed with the inspectors. It was suggested that in light of the new developments a draft for revision be prepared. This new proposal for revision was drafted based on the feedback received, the new, current trends in engineering and the experience gained during the implementation of this guidance in inspection.

At the same time, the opportunity was used to improve the graphic images and make them more readable in e-version as well as in print.

Summary of main changes

Below is a list of the main changes that have been made to the WHO Technical Report Series, No. 961, 2011, Annex 5: *Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms*.

1. The *Premises* section has been moved towards the beginning of the document due to its important impact on HVAC designs. In addition the text has been expanded and a number of sample layouts have been included.

2. The *HVAC* sections have been re-arranged into a more logical sequence.

3. The *Commissioning, Qualification and Validation (C, Q & V*) section has been aligned with the proposed revisions to the Supplementary GMP Validation TRS, No. 937, Annex 4 guidelines.

4. Significant notes were added under the new *Supplementary notes on test procedures* section.

5. The *Maintenance* section has been separated out of the C, Q & V section.

6. All the diagrams have been revised (mainly to achieve better clarity).

7. Throughout the document additional notes have been added and text revised to provide better understanding and avoid ambiguity.

Contents

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 non-sterile dosage forms, and include tablets, capsules, powders, liquids, creams, ointments, etc. The HVAC design principles contained in the guidelines may be applied to other dosage forms.

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 this guide should, therefore, be considered supplementary to the general requirements set out in the main principles guide (WHO Technical Report Series, No. 961, Annex 3)

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 facilities manufacturing other dosage forms (such as liquids, cream, ointments) and other classes of products including biological products, herbal medicines, complementary medicines and finishing process steps for APIs.

Non-sterile forms typically include:

- products with low water activity (less subject to microbial contamination), e.g. oral solid dosage forms, suppositories;
- products with high water activity (more subject to microbial contamination, depending on the formulation), e.g. liquids, drops, syrups, ointments and creams.

Additional specific requirements apply for air-handling systems of pharmaceutical sterile products and hazardous products. Guidelines for hazardous, sterile and biological product facilities are covered in separate WHO guidelines (WHO Technical Report Series, No. 957, Annex 3; WHO Technical Report Series, No. 961, Annex 6; and working document WHO/BS/2015.2253, intended to replace WHO Technical Report Series, No. 822, Annex 1, 1992, respectively).

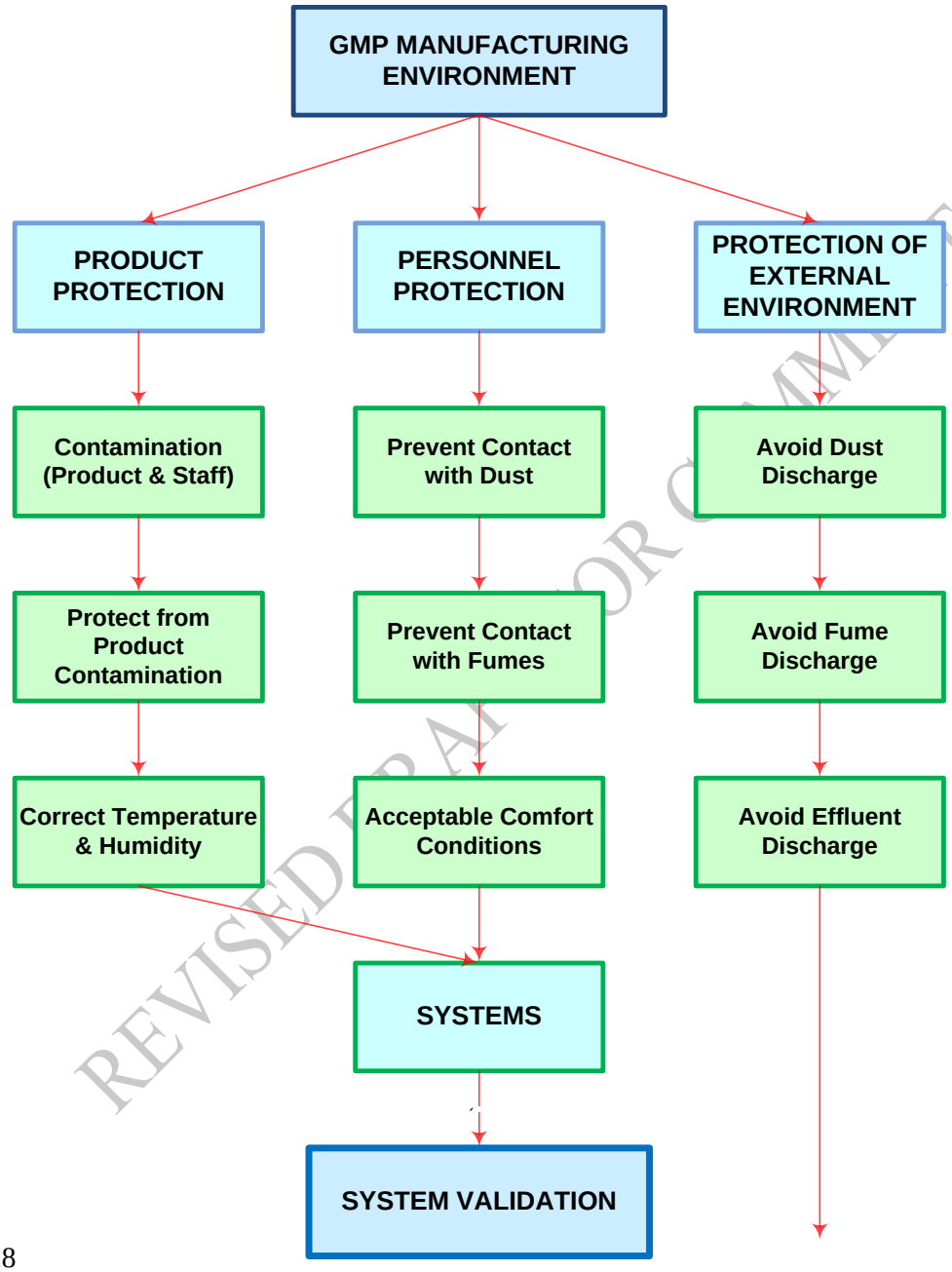
These guidelines are not intended to be prescriptive in specifying requirements and design parameters. There are many parameters affecting a clean area condition and it is, therefore, difficult to lay down the specific requirements for one particular parameter in isolation.

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

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

Risk assessment studies should be an integral part of the facility design and implementation, from the user requirement specification stage right through to validation, as indicated in the diagram below (Figure 2). Validation protocols and criteria should be justified by links to a written risk assessment.

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



220 Figure 2. GMP compliance sequence diagram

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3. GLOSSARY

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

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

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

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

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

airflow protection booth. A booth or chamber, typically for purposes of carrying out sampling or weighing, in order to provide product containment and operator protection.

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 (personnel airlock (PAL); material airlock (MAL)).

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

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

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

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

change control. A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that

would ensure that the system is maintained in a validated state.

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

clean-up (see **recovery**)

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

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

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

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

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

controlled not classified. An area where some environmental conditions are controlled (such as temperature), but the area has no cleanroom classification.

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

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

cross-contamination. Contamination of a starting material, intermediate product or finished product with another starting material or

product during production.

cross-over-bench. Cross-over or step-over bench in change room to demarcate the barrier between different garment change procedures.

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

differential pressure. The difference in pressure between two points such as the pressure difference between an enclosed space and an independent reference point, or the pressure difference between two enclosed spaces.

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 and, in addition, are subject to qualification practices.

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

extract air. Air leaving a space, which could be either return air or exhaust air. Return air means that the air is returned to the air-handling unit and exhaust air means that the air is vented to atmosphere.

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

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

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

HEPA filter. High efficiency particulate air filter.

HVAC. Heating, ventilation and air-conditioning. Also referred to as Environmental control systems.

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 good engineering practice only.

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

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

ISO 14644. The International Standards Organization has developed a set of standards for the classification and testing of cleanrooms. The standard comprises 12 separate parts. Where ISO 14644 is referenced it implies the latest revision.

NLT. Not less than.

NMT. Not more than.

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 good engineering practice only.

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

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

OOS. Out of specification. In relation to HVAC systems this could refer to any of the environmental conditions being OOS, i.e. falling outside of alert or action limits.

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 specific room.

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

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

pass-through-hatch or **pass box.** A cabinet with two or more doors for passing equipment, material or product, whilst maintaining the pressure cascade and segregation between two controlled zones. A passive pass-through-hatch (PTH) has no air supply or extract. A dynamic PTH has an air supply into the chamber.

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

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

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

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

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

recovery. Room recovery or clean-up tests are performed to determine whether the installation is capable of returning to a specified cleanliness level within a finite time, after being exposed briefly to a source of airborne particulate challenge.

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. 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 standard operating procedures may be used to supplement product-specific master and batch production documentation.

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

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

4. PREMISES

4.1. There is a close relationship between architectural design and HVAC design, as they both have an impact on the functionality of the other. HVAC system design influences architectural layouts with regard to items such as airlock positions, doorways and lobbies. The architectural layouts and building 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, and the design should be closely coordinated with the architectural designers. The above design considerations should also be applicable to facility upgrades or the retrofitting of facilities.

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

4.2.1. Adequate airlocks, such as personnel airlocks (PAL) and/or material airlocks (MAL), pass-through hatches (PTH), change rooms and passages should be provided to limit air transfer between different cleanliness zones, and may be provided to limit cross-contamination within the same cleanliness zone. These should have supply and extract air systems as appropriate.

4.2.2. Areas such as airlocks, change rooms and passages should be designed so that the required pressure cascades can be achieved.

4.2.3. Detailed diagrams depicting pressure cascades, air flow directions and flow routes for personnel and materials should be prepared and maintained.

4.2.4. Where possible, personnel and materials should not move from a higher cleanliness zone to a lower cleanliness zone and back to a higher cleanliness zone (if moving from a lower cleanliness zone to a higher cleanliness zone, changing/decontamination procedures should be followed).

4.2.5. The final change room should be the same good manufacturing practices (GMP) classification grade (at rest) as the area into which it leads.

4.2.6. Door gaps around the door perimeter have a marked impact on the pressure differential across the doorway. The fit of the doors should be agreed upon between the architect and the HVAC designer to ensure that the correct leakages are allowed for. Likewise the maintenance of doors is a critical factor in room pressure control (a poorly fitting door can severely compromise a room pressure differential).

4.2.7. Where the opening and closing of airlock doors could lead to cross-contamination, these airlock doors should not be opened simultaneously. An interlocking system and/or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.

4.2.8. Doors should be carefully designed to avoid un-cleanable recesses. Swing doors should open to the high-pressure side and be provided with self-closers. Exceptions are permitted based on site environmental, fire, health and safety containment requirements. Cognizance should be taken of possible room pressure changes due to fan failure and the impact on ease of opening doors for escape purposes.

4.2.9. The choice of building finishes and materials also has an impact on air conditioning performance and air cleanliness. Materials should be selected that will provide a well-sealed building to facilitate room pressure control. Materials and paint finishes should also be non-dust and particle liberating as this impacts on room cleanliness. Finishes should be easy to clean and non-absorbent. To reduce the accumulation of dust and to facilitate cleaning, there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment.

The following diagrams are examples of room and suite layouts with their associated room pressures. These are purely examples and other factors may dictate different room arrangements and room pressures.

Room pressure differentials could be lower or higher depending on the specific design and operations. The purpose of a pressure differential is to enhance the separation between areas with different levels of cleanliness and also to provide containment to prevent cross-contamination. Where there is no difference in cleanliness level, and no potential for cross contamination, a zero pressure differential can be applied.

563 Figure 3. Example of a weigh booth layout
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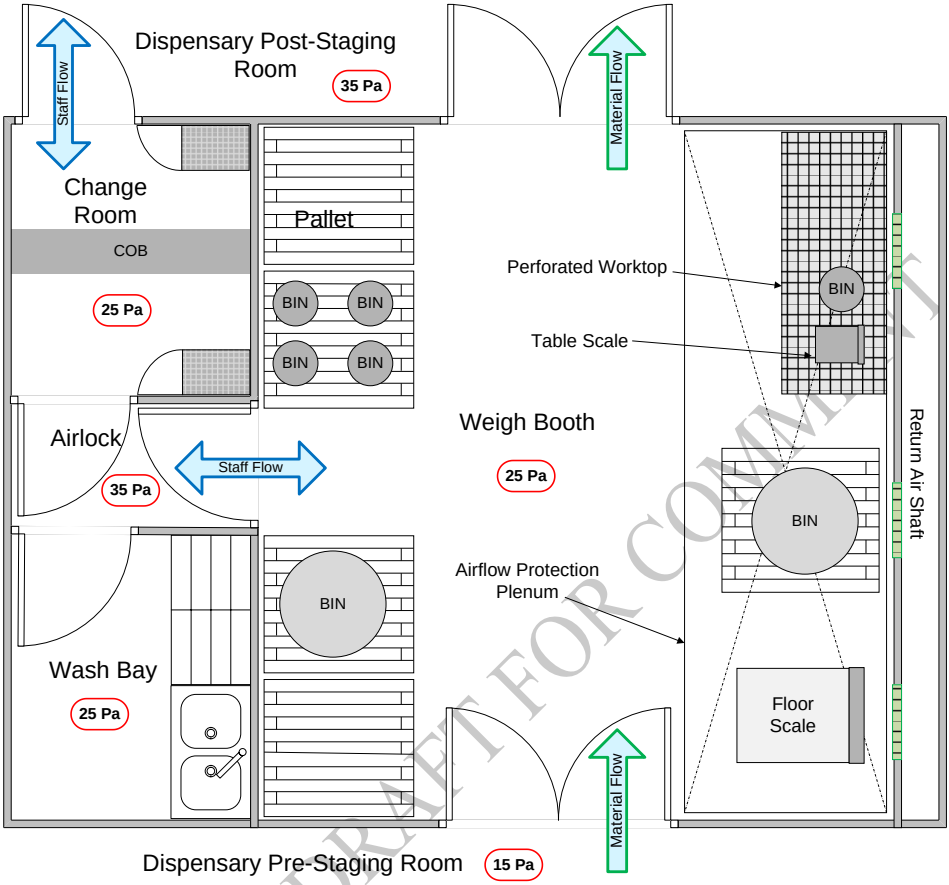

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566 *Note: Similar air handling and product protection principles apply to*
567 *sampling suites.*

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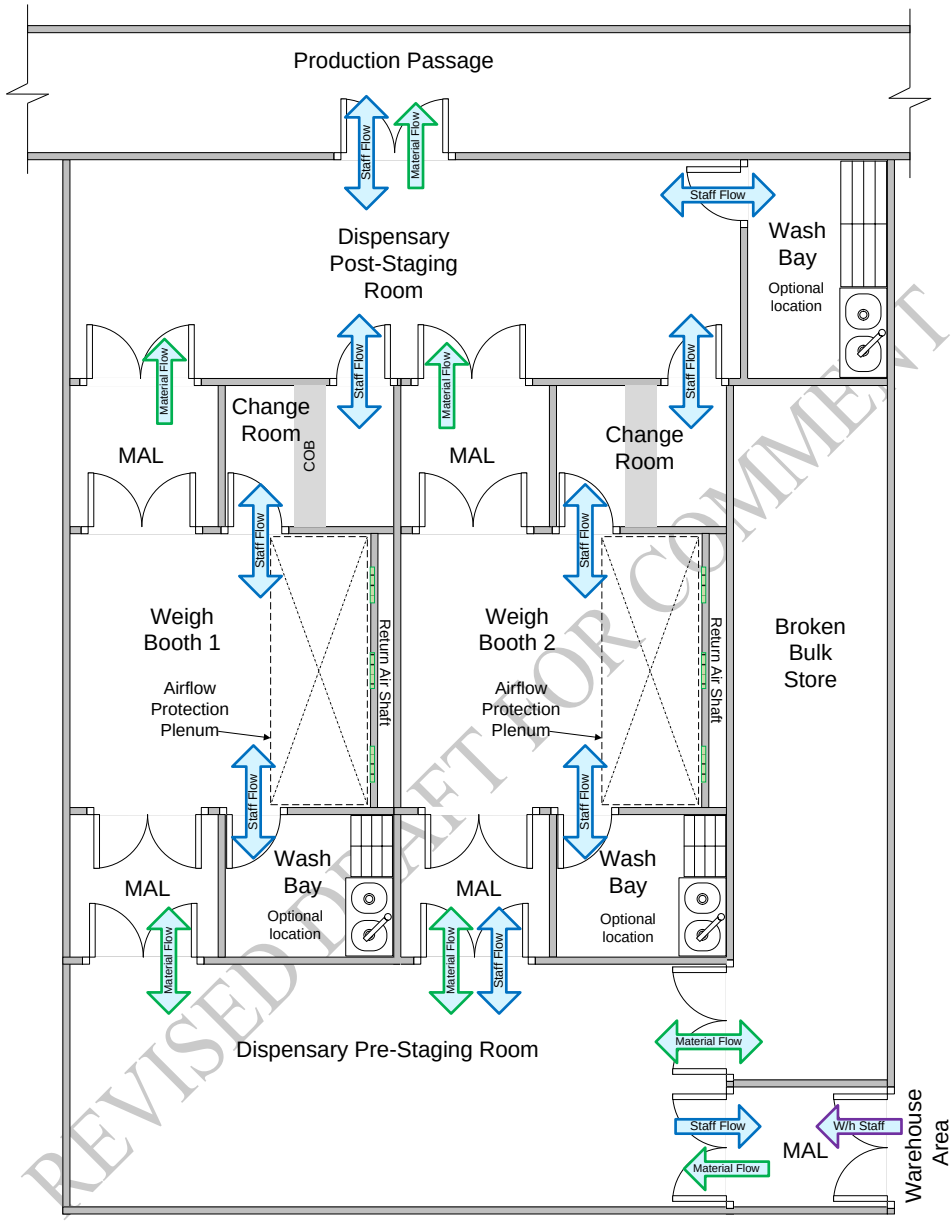
Figure 4. Example of a dispensary suite



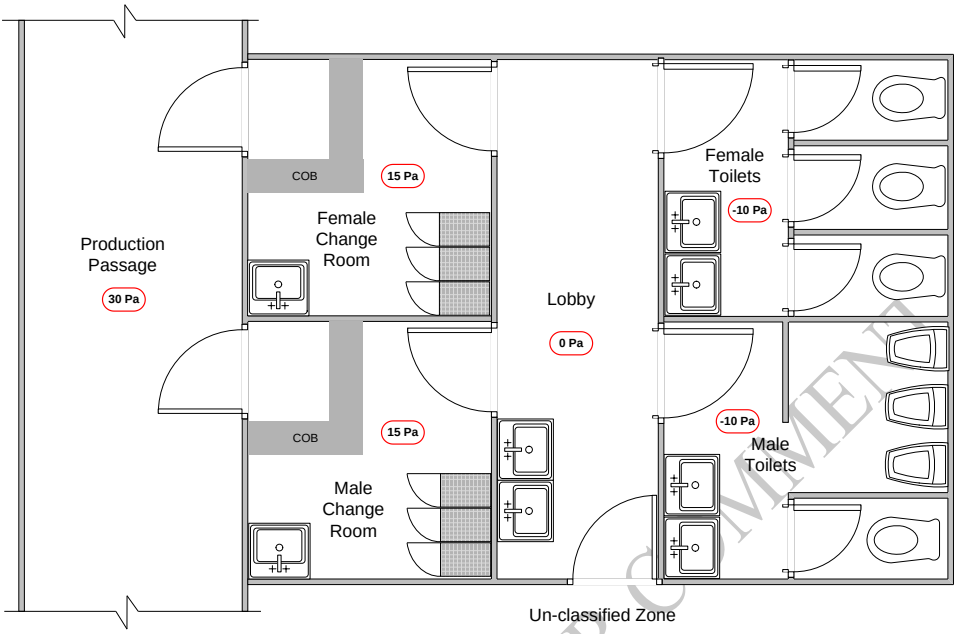
Notes:

1. Two alternative locations are indicated for the wash bays.

2. The broken bulk store is optional. Alternatively partially used containers can be returned to the warehouse.

3. The inclusion of MALs at entrance and exit to weigh booths depend on containment risks and the pressure cascade design.

580 Figure 5. Change rooms and washing area layouts



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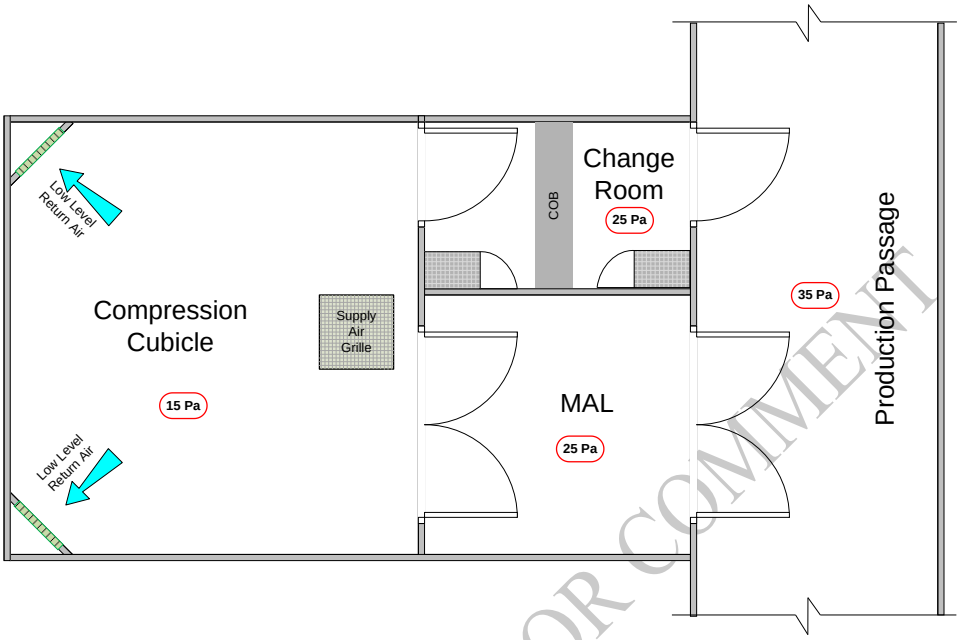
583 Figure 6. Example of a compression cubicle with change room and MAL,
584 for higher risk materials.



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586 *Note: The inclusion of the PAL and MAL is dependent on product risk,*
587 *range of products handled in adjacent cubicles, pressure cascade and open*
588 *vs closed manufacturing processes.*
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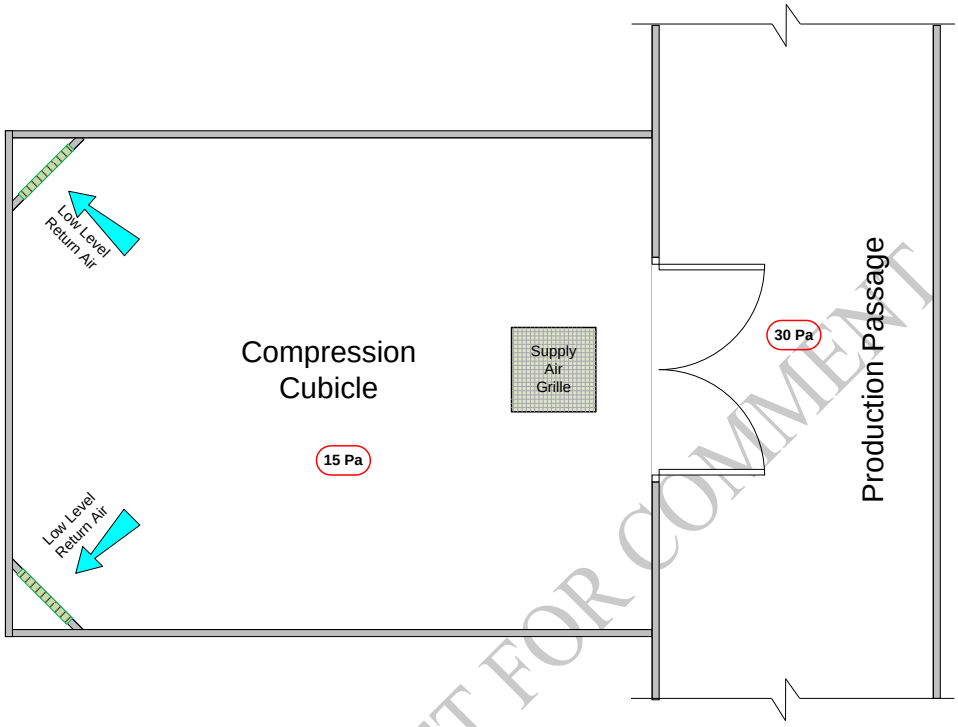
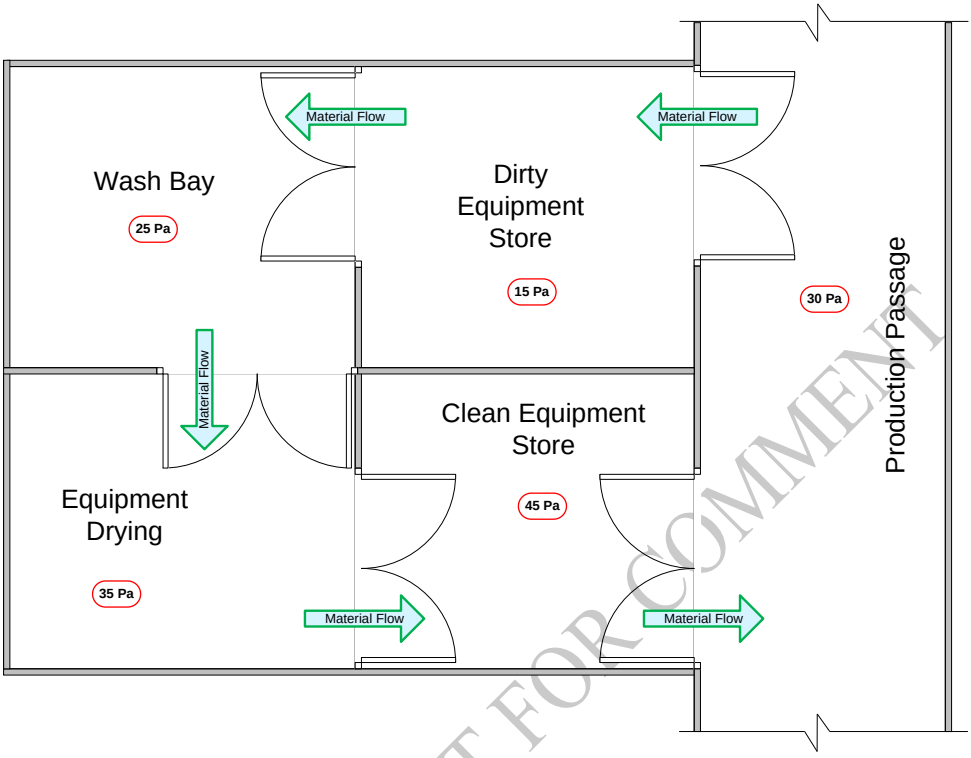
Figure 7. Example of compression cubicle without change room and MAL, for lower risk materials (inclusion of airlocks dependant on risk assessment)



Note the supply air from the ceiling towards the front of the cubicle and air extract at low level at the back corners of the cubicle.

Figure 8. Example of wash-bay suite



5. DESIGN OF HVAC SYSTEMS AND COMPONENTS

5.1. General

5.1.1. The required degree of air cleanliness in most non-sterile dosage form manufacturing facilities can normally be achieved without the use of high-efficiency particulate air (HEPA) filters, provided the air is not recirculated or in the case of a single-product facility. Many open product zones of non-sterile dosage form facilities are capable of meeting ISO 14644-1 Class 8 or Grade D, “at-rest” condition, measured against particle sizes of 0.5 µm and 5 µm, but cleanliness may not necessarily be classified as such by manufacturers.

Grade D conditions usually have a maximum viable particle concentration of 200 cfu/m^3. Alternative microbiological levels as per the table below could be used depending on risk assessments.

Table 1. Microbiological air quality in production premises for the manufacture of non-sterile medicinal products

Area	Limits in operation		Limits at rest	Routine monitoring frequency of testing
Manufacture of nonsterile, semi-solid[4] and liquid dosage forms[2]	Alert limit (cfu[1]/m3)	Action limit (cfu/m3)	(cfu/m3)	
	250	500	100	Weekly
Manufacture of tablets, capsules and coated tablets[3]	500	800	400	Monthly

[1] Colony-forming unit.
[2] In analogy to WHO GMP guidelines, this area can also be classified as grade E.
[3] In analogy to WHO GMP guidelines, this area can also be classified as grade F.
4 Depending on the product properties it may be necessary to define stricter limits for water-based semi-solid dosage.

5.1.2. A risk assessment should be carried out to determine the room cleanliness conditions required and the extent of validation required. Once room cleanliness and environmental conditions have been determined, qualification of these conditions should be carried out.

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

- sufficient fresh air to compensate for leakage from the facility and loss through exhaust air systems;
- sufficient fresh air to comply with national building regulations *(depends on occupant density)*;
- sufficient fresh air for odour control;
- sufficient fresh air to provide the required building pressurization.

5.1.4. Where automated monitoring systems are used, these should be capable of indicating any out-of-specification (OOS) condition by means of an alarm or similar system. Sophisticated computer-based data monitoring systems may be installed, which can aide with planning of preventive maintenance and can also provide trend logging.

(This type of system is commonly referred to as a building management system (BMS), building automation system (BAS) or system control and data acquisition (SCADA) system. If these systems are used for critical decision-making, they should be validated. If the BMS is not validated in full (or in part for these critical parameters), an independent validated environmental monitoring system (EMS) should be provided, specifically for recording and alarming critical parameters. The EMS for monitoring of critical parameters could be a computerized system or a more manual means of recording data. Critical parameters could include, for example, room temperature in production areas, humidity, differential pressures, fan failure alarms, etc.)

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

5.1.6. Appropriate alarm systems should be in place to alert personnel if a critical fan fails. Critical alarms should be easily identifiable and visible and/or audible to relevant personnel. There should be an action plan for such alarms i.e. stop production, close up open product, move product, etc., and may include corrective and preventive action (CAPA).

5.1.7. Based on a risk assessment a fan interlock failure matrix should be set up, such that if a fan serving a high pressure zone fails, then any fans serving surrounding lower pressure areas should automatically stop, to prevent an airflow reversal and possible cross-contamination. This fan stop-start matrix should apply to the switching on and switching off of systems to ensure that there is no flow reversal causing cross-contamination. The effect of fan failure on building and HVAC components should also be assessed. A failure of one fan could cause excessive positive or negative pressures resulting in damage such as structural failure of components.

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

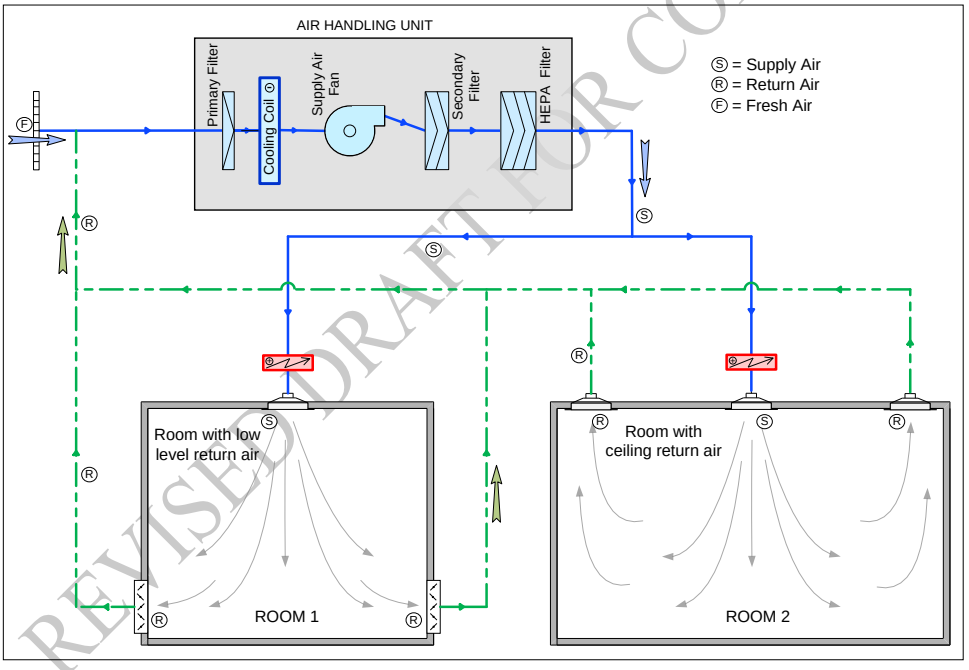
5.1.9. Where possible ventilation dampers, filters and other services should be designed and positioned so that they are accessible from *outside* the manufacturing areas (service voids or service corridors) for maintenance purposes.

5.2. Air distribution

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

5.2.2. There may be alternative locations for return air leaving the room. For example, referring to Figure 9, room 1 (low-level return air) and room 2 (ceiling return air).

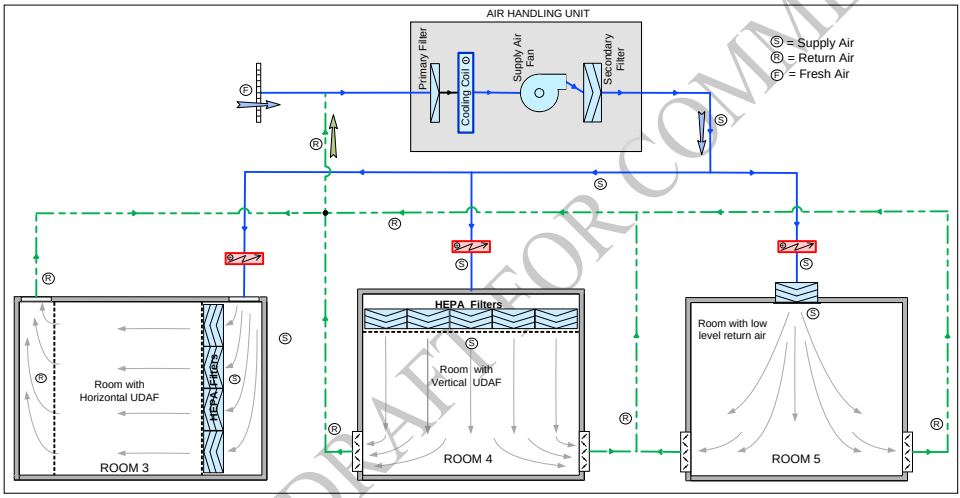
Figure 9. Air-handling system with high-efficiency particulate air filters in air-handling unit



The airflow schematics of the two systems (Figures 9 and 10) indicate air-handling units with return air or recirculated air, having a percentage of fresh air added. Depending on product characteristics and dust loading it is sometimes preferable to fit filters on return air outlets or in return air ducting.

Figure 10 is a schematic diagram of an air-handling system serving rooms with horizontal unidirectional flow, vertical unidirectional flow and turbulent flow, for rooms 3, 4 and 5, respectively. In this case the HEPA filters are terminally mounted at the rooms and not in the AHU. Terminally mounted supply air HEPA filters can assist with preventing cross-contamination from room to room in the event of a fan failure condition. The decision whether to install terminal HEPA filters should be based on a risk-assessment study.

Figure 10. Horizontal unidirectional flow, vertical unidirectional flow and turbulent flow



5.3. **Recirculation system**

5.3.1. The risk of contamination and/or cross-contamination (including by fumes and volatiles) due to recirculation of air should be evaluated to determine if recirculation of air is acceptable.

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

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

5.3.4. Recirculation of air in areas where pharmaceutical dust is not

generated such as secondary packing, may not require HEPA filters in the system.

5.3.5. HEPA filters may be located in the air-handling unit or placed terminally. Where HEPA filters are terminally mounted they should preferably not be connected to the ducting by means of flexible ducting. Due to the high air pressure required for the terminal filter, this connection should preferably be a rigid duct connection. Where flexible ducting is used, it should be as short as possible and properly fixed to withstand duct pressure.

When HEPA filters are terminally mounted, it should be possible to carry out filter integrity tests from within the room. The filter housings will therefore require ports for measuring appropriate upstream concentration (refer to ISO 14644.3) and penetration concentration from within the room. In addition it should be possible to measure the filter pressure drop in individual HEPA filters by means of test ports provided.

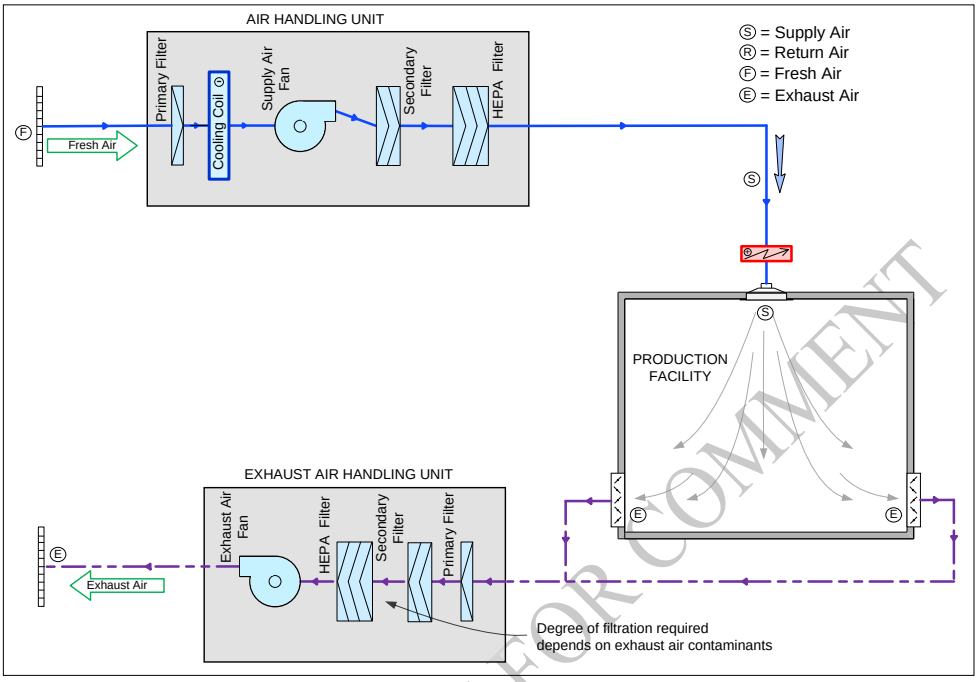
5.3.6. Air containing solvents or flammable vapours should **not** be recirculated to the HVAC system. Air containing dust from highly toxic processes should only be recirculated if risk assessments shows adequate protection and special precautions are in place (e.g. triple HEPA filtration).

5.4. Full fresh-air systems

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

Figure 11 indicates a system operating on 100% fresh air and would normally be used in a facility dealing with toxic products or solvents, where recirculation of air with contaminants should be avoided.

Figure 11. Full fresh-air system

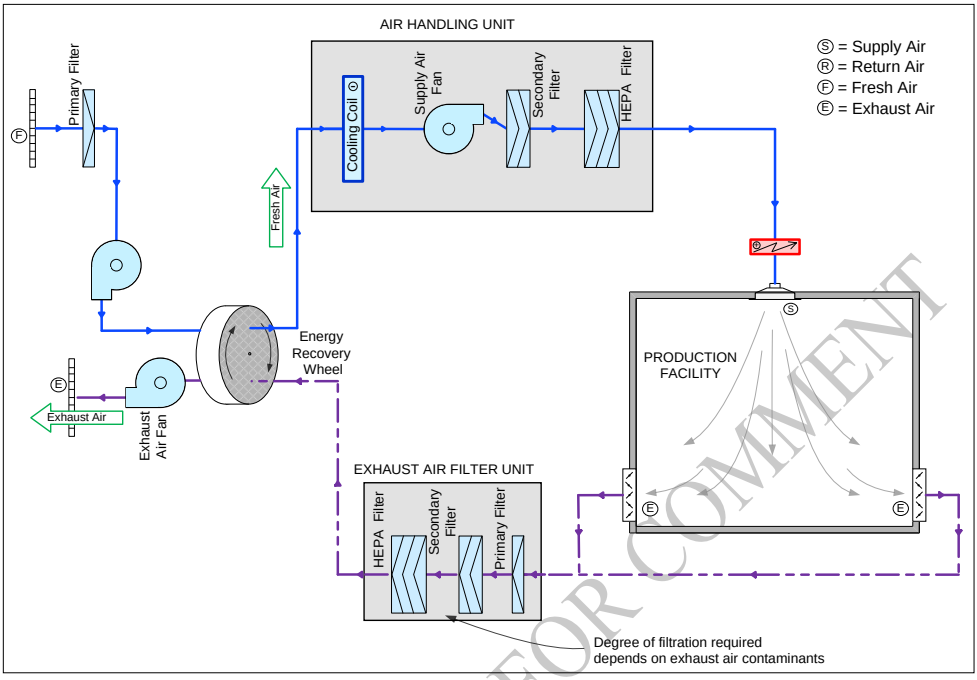


Note: A HEPA filter on supply air is optional for a full fresh-air system. A HEPA filter on the exhaust air is dependent on type of contaminants in the exhaust leaving the room.

5.4.2. Energy-recovery wheels if used in multiproduct facilities should have been subjected to a risk assessment to determine if there is any risk of cross-contamination. When such wheels are used they should not become a source of possible contamination (see Figure 12).

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 12. Full fresh-air system with energy recovery

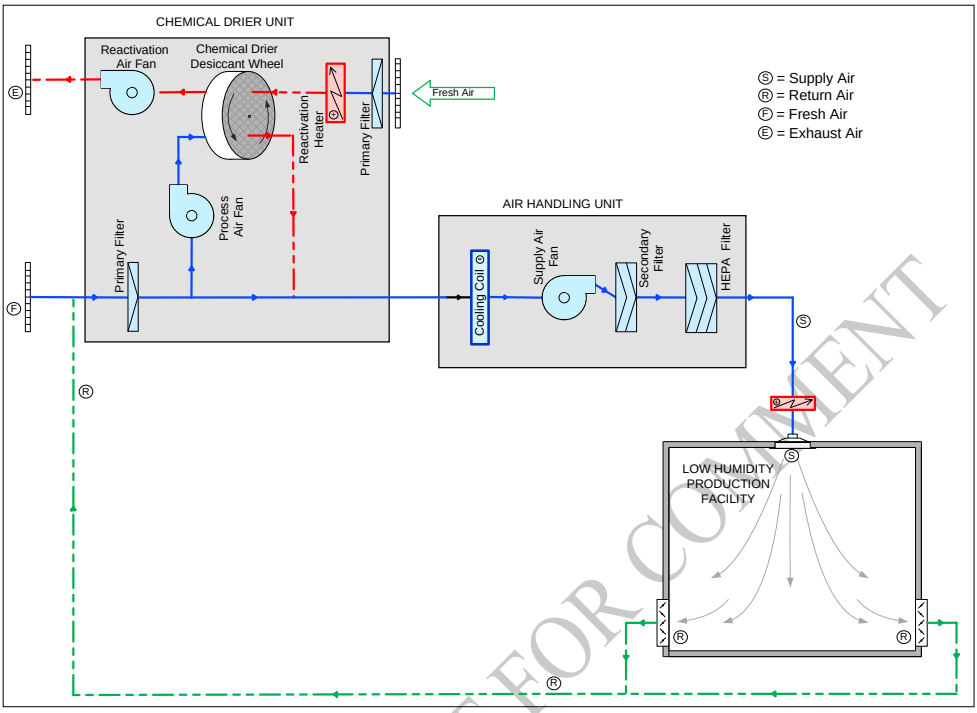


5.4.3. The potential for air leakage between the supply air and exhaust air as it passes through the wheel should be prevented. The relative pressures between supply and exhaust air systems should be such that the exhaust air system operates at a lower pressure than the supply system.

5.5. **Additional system components**

5.5.1. A schematic diagram of the airflow for a typical system serving a low relative humidity suite is represented in Figure 13. Air can be dried with a chemical drier (e.g. a rotating desiccant wheel which is continuously regenerated by means of passing hot air through one segment of the wheel). Alternative methods of drying air are also available.

Figure 13. Air-handling system with chemical drying



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

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

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

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

- snow eliminators to prevent snow entering air inlets and blocking airflow;
- dust eliminators on air inlets in arid and dusty locations;
- moisture eliminators in humid areas with high rainfall;
- fresh air precooling coils for very hot or humid climates.
- Air-handling units should be provided with adequate drains to remove condensate.

6. PROTECTION

6.1. Products and personnel

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

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

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

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

6.1.4. Air filtration and air change rates should be set to ensure that the defined room conditions are attained.

6.1.5. The air change rates should be determined by the manufacturer and designer, taking into account the various critical parameters using a risk-based approach with due consideration of capital and running costs and energy usage. Primarily the air change rate should be set to a level that will achieve the required room condition.

6.1.6. Air change rates are normally determined by the following considerations (could normally vary between 10 and 20 air changes per hour):

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

6.1.7. If a cleanroom classification is specified, the manufacturer should state if the classification is rated for the "as-built" (Figure 14), "at-rest" (Figure 15) or "operational" (Figure 16) conditions.

6.1.8. Room classification tests in the "as-built" condition should be carried out on the bare room, in the absence of any equipment if feasible. Due to equipment size the rooms are constructed around the equipment and therefore the equipment is included in the "as-built" condition.

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

6.1.10. Room classification tests in the "operational" condition are normally carried out during the normal production process with equipment operating and the normal number of personnel present in the room. When qualifying for the operational condition details of the process operating, number and positions of staff should be stipulated for each room, to enable future qualifications to duplicate the same conditions.

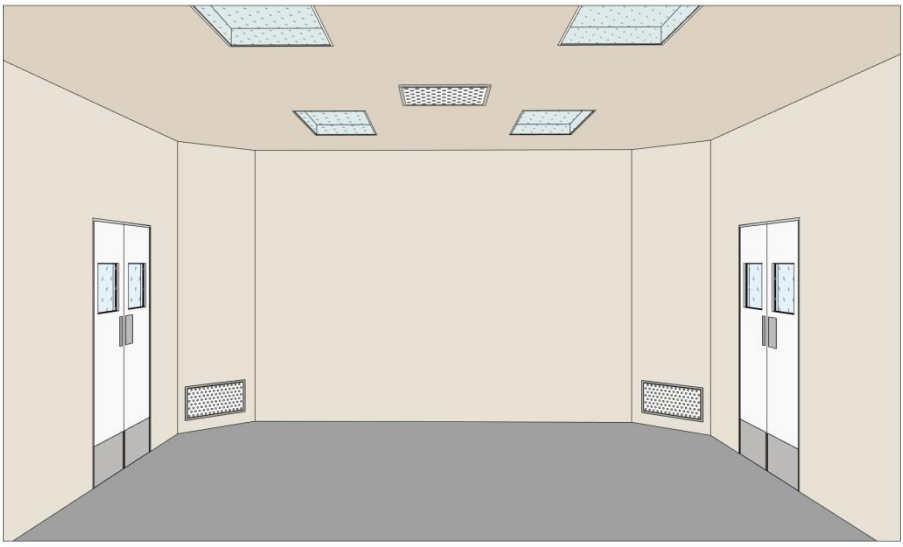
6.1.11. Room recovery tests are performed to determine whether the installation is capable of returning to a specified cleanliness level, temperature, humidity, microbial limits, room pressure, etc. where appropriate, within a finite time. This test is carried out after the above room conditions have reached an OOS state after the HVAC system has been switched off. Room recovery tests should demonstrate a reduction in particle concentration by a factor of 100 within the prescribed time (as per ISO 14644-3 clause B.12) (3). The guidance time period for recovery is about 15 to 20 minutes.

In some instances it is not possible to increase the particle concentration by a factor of 100 (such as for an ISO 14644 Class 8 condition) as the high particle concentration can damage the particle counter. In this instance the particle decay method can be used as per ISO 14644-3 clause B.12.3.2. Risk assessments should be carried out to determine which rooms should be subject to recovery tests. Recovery tests are also required to determine how long it takes for specified conditions to be achieved after power failure or system start up.

6.1.12. Materials and products should be protected from contamination and cross-contamination during all stages of manufacture (see also section 6.5 for cross-contamination control).

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

967 Figure 14. "As-built" condition



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971 Figure 15. "At-rest" condition

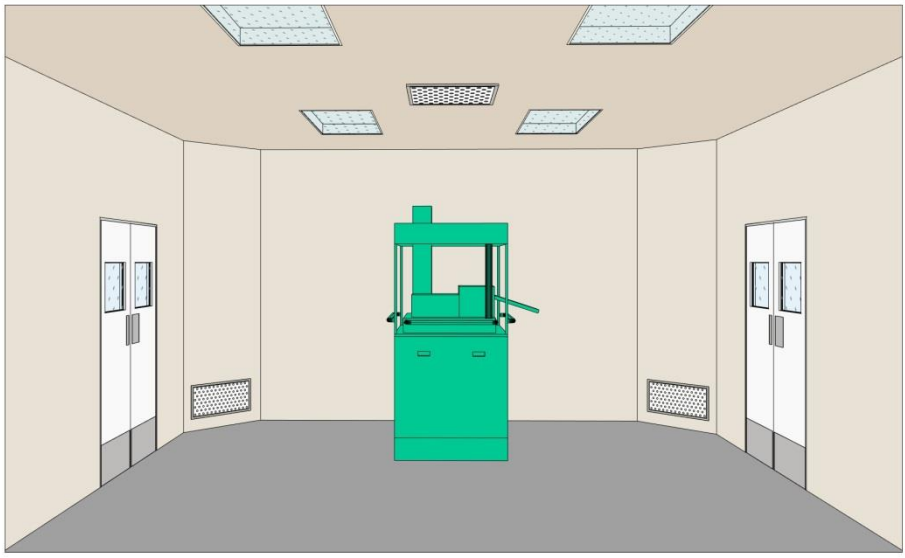

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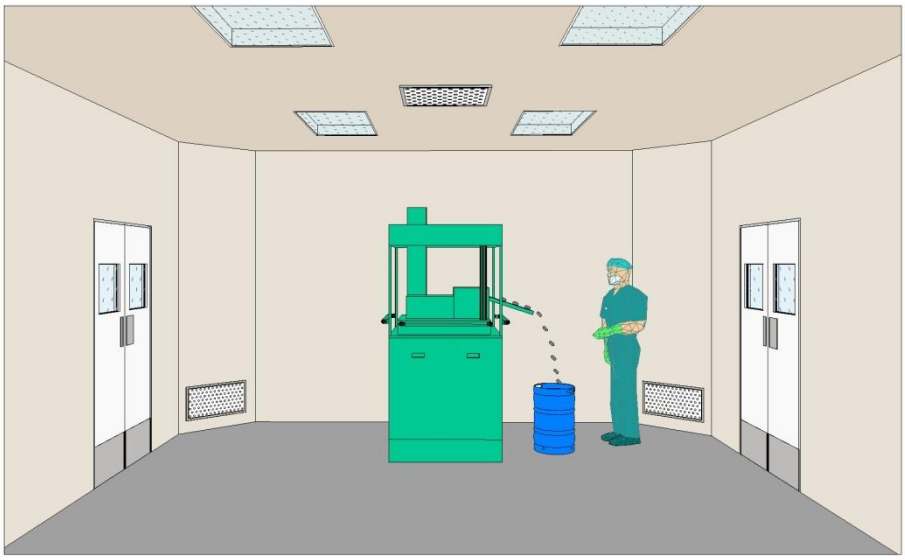
Figure 16. “Operational” condition



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

6.1.14. External contaminants should be removed by effective filtration of the supply air.

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

6.1.16. Internal contaminants should be controlled by dilution and flushing of contaminants in the room, or by displacement airflow (see Figures 10, 17 and 21 for examples of methods for the flushing of airborne contaminants).

6.1.17. The level of protection and air cleanliness for different areas should be determined according to the product being manufactured, the process being used and the product’s susceptibility to degradation (Table 3).

6.2. Air filtration and air patterns

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

6.2.1. The type of filters required for different applications depends on the quality of the ambient air and the return air (where applicable) and also on the air change rates. Table 4 gives the recommended filtration levels for different levels of protection in a pharmaceutical facility. Manufacturers should determine and prove the appropriate use of filters.

6.2.2. 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 efficiency value for the same filter). (Referring to filter classifications such as an 85% filter or a 5 µm filter are not valid classifications and should not be used, as this can lead to the incorrect filter being installed. Only the EN 779 and EN 1822 or ISO 29463 classifications, or ASHRAE Merv classifications, as per Tables 1 and 2, should be used.)

Table 2. Comparison of filter test standards

Eurovent 4/5 rating	ASHRAE 52.2	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	EN 779 & EN 1822			ISO 29463
(superseded)	Merv rating	Average arrestance Am (%)	Average dust spot efficiency Em (%)	MPPS integral overall efficiency (%)	EN rating		
				99.999995	U17	EN 1822: 2009	75E
				99.99995	U16		65E
EU 14				99.9995	U15		55E
EU 13	Merv 18			99.995	H14		45E
EU 12	Merv 17			99.95	H13		35E
EU 11				99.5	E12		25E
EU 10				95	E11		15E
EU 9	Merv 16		>95	85	E10		
EU 9	Merv 15		95	MPPS = most penetrating particle size	F9	EN 779: 2012	
EU 8	Merv 14		90		F8		
	Merv 13	>98	85		F7		
EU 7		>98	80				
	Merv 12	>95	75				
EU 6		>95	70		M6		
	Merv 11	>95	65				
		>95	60				
	Merv 10	>95	55				
EU 5	Merv 9	>95	50		M5		
	Merv 8	>95	45				
		>95	40				
	Merv 7	>90	35				
EU 4		>90	30		G4		
	Merv 6	90	25				
EU 3	Merv 5	85	20		G3		
		80	<20				
	Merv 4	75					
EU 2	Merv 3	70			G2		
	Merv 2	65					
EU 1	Merv 1	<65			G1		

Note: The filter classifications referred to above relate to the EN 1822:2009 and EN 779: 2012 test standards (EN 779 relates to filter

classes G1 to F9 and EN 1822 relates to filter classes E10 to U17).

Most penetrating particle size (MPPS) is a means of determining HEPA and ultra low penetration air (ULPA filter efficiencies). The MPPS is the particle size with the highest penetration for a defined filter medium. (MPPS integral overall efficiency is the efficiency, averaged over the whole superficial face area of a filter element under a given operating conditions of the filter. MPPS local efficiency is the efficiency, at a specific point of the filter element under given operating conditions of the filter). Note: ULPA filters are not applicable to pharmaceutical installations.

6.2.3. 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.

6.2.4. Filters have an impact on the cleanroom class or level of protection. The different levels of protection and recommended filters grades are given in Tables 3 and 4 below.

Table 3. Examples of levels of protection (based on ISPE oral solid dosage (OSD) guideline criteria)

Level	**Condition**	**Example of area**
Level 1	General	Area with normal housekeeping and maintenance where there is no potential for product contamination, e.g. warehousing.
Level 2	Protected	Area in which steps are taken to protect the pharmaceutical starting material or product from direct or indirect contamination or degradation, e.g. secondary packing, warehousing, first stage change rooms.

Level 3	Controlled	Area in which specific environmental conditions are defined, controlled and monitored to prevent contamination or degradation of the pharmaceutical starting material or product, e.g. where product, starting materials and components are exposed to the room environment; plus equipment wash and storage areas for equipment product contact parts.

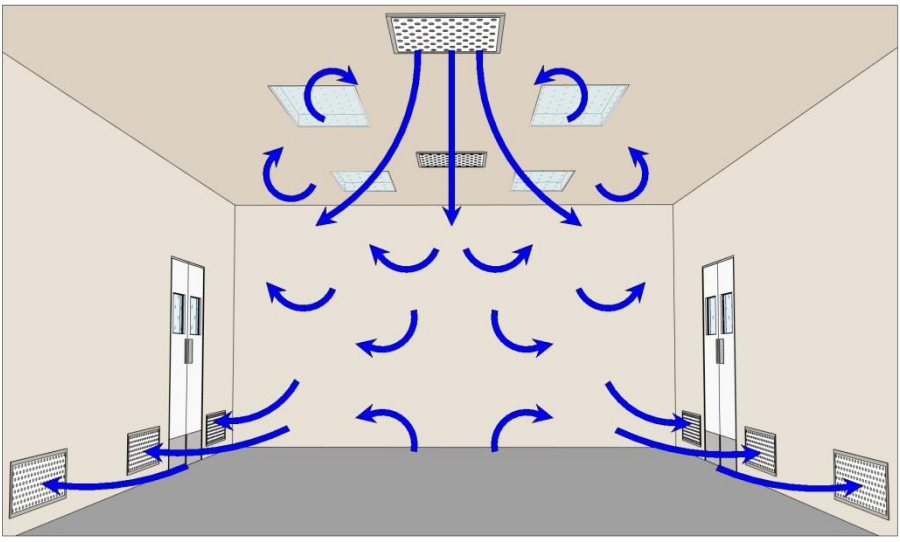
Table 4. Levels of protection and recommended filtration

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

6.2.5. Directional airflow within production or primary packing areas should assist in preventing contamination. Airflows should be planned in conjunction with operator locations, so as to minimize contamination of the product by the operator and also to protect the operator from dust inhalation. An example of flushing effect with turbulent airflow and low level extract is indicated in Figure 17 below.

6.2.6. At airlocks and change rooms supply air and extract air terminals should be positioned such that air flows from the clean side of the room to the less clean side, to enhance the separation between the two adjoining rooms.

Figure 17. Turbulent dilution of dirty air



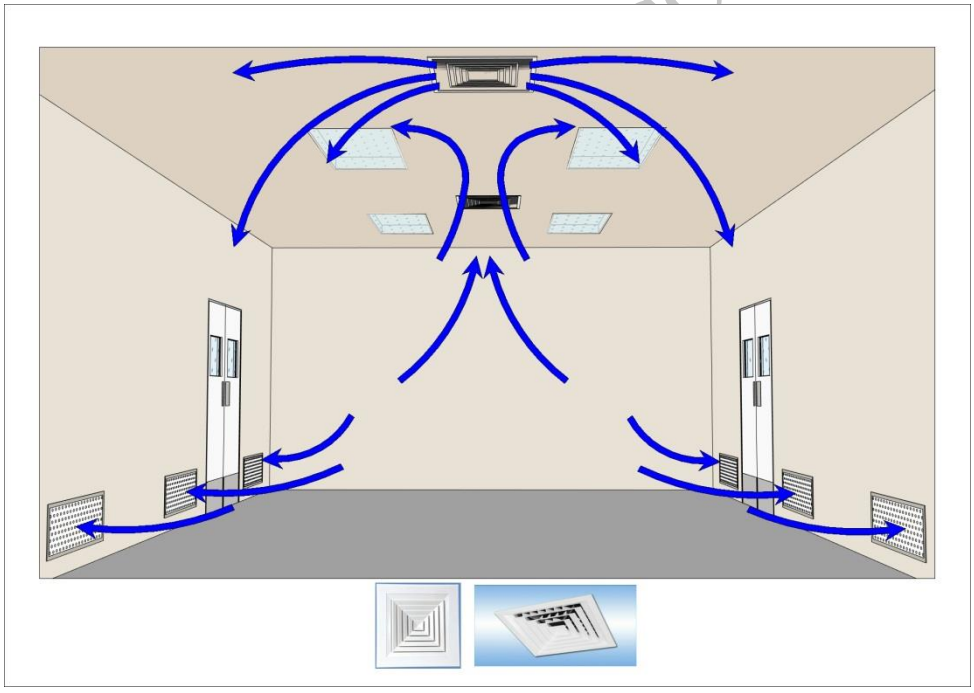
Low-level extract is ideal for dust suppression purposes, but is not essential where no dust is liberated. (Low-level extract is essential for Grade C classified areas – for information only.)

6.2.7. Supply air diffusers should be selected with care taking consideration of, e.g. room requirements and positions of equipment and operators in the room. Supply air diffusers of the high induction type (e.g. those typically used for office-type air-conditioning) should where possible not be used in clean areas where dust is liberated. Air diffusers should be of the non-induction type, introducing air with the least amount of induction so as to maximize the flushing effect. In rooms where the process results in high dust liberation; perforated plates or low induction swirl diffusers with low level extract or return should be used (to contain the dust at the lower level of the room) (see Figures 18–20 for illustrations of the three types of diffuser). Although ceiling returns are generally avoided in cases where dust liberation is low, ceiling return air grilles may be acceptable.

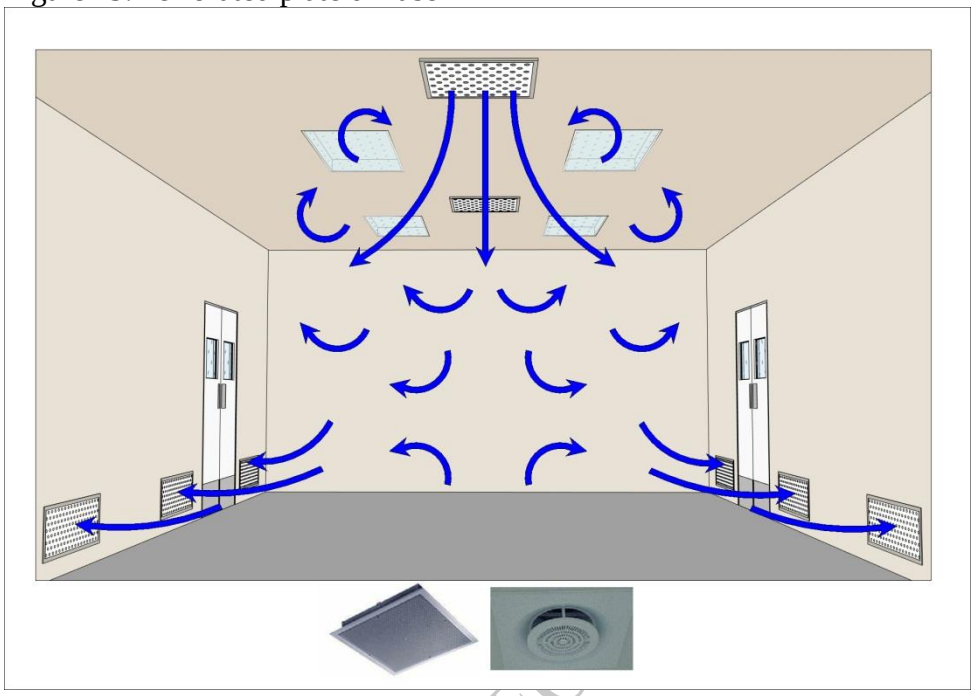
6.2.8. The type of diffusers used for each room should be carefully selected considering their air flow patterns and the amount of dust liberated in the room. Induction and certain swirl diffusers create good dilution of room air and may be used where dust liberation is minimal. If used in rooms where significant dust is generated, their use may draw dust up into the air stream and spread it throughout the room, presenting increased hazards to containment and to operators. Some swirl type diffusers have less induction (as indicated in Figure 20)

6.2.9. Airflow patterns for different diffuser types are indicated in Figures 18, 19 and 20 below.

Figure 18. Induction diffuser



1108 Figure 19. Perforated plate diffuser



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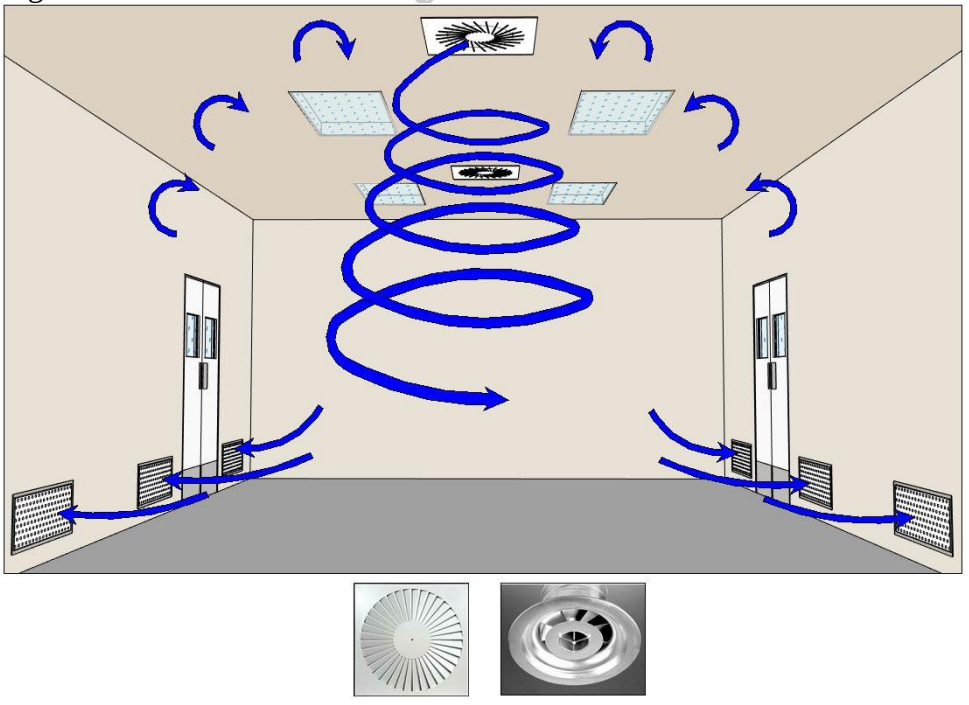
1111 Figure 20. Swirl diffuser



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6.3. Unidirectional airflow

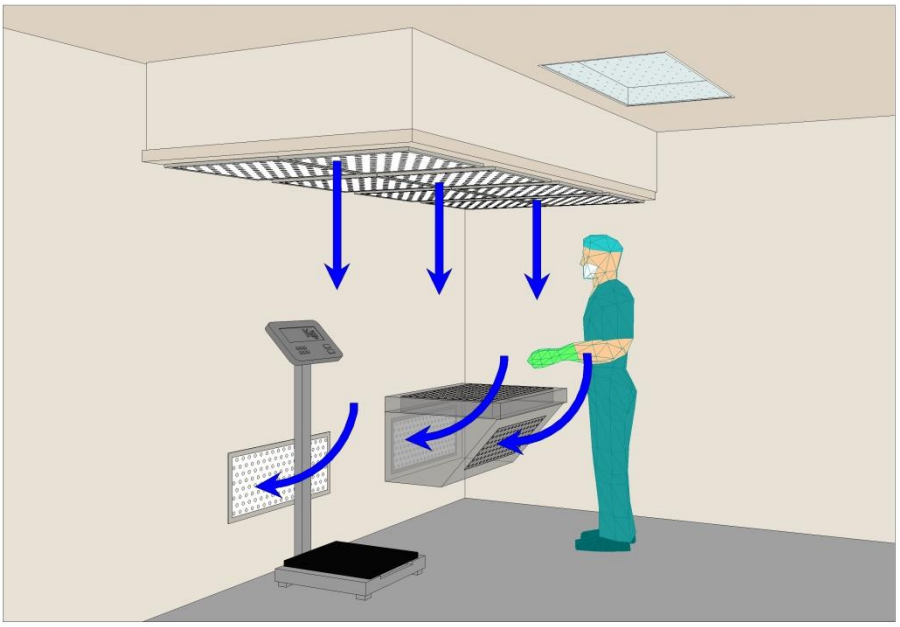
6.3.1. Unidirectional airflow (UDAF) should be used for weighing booths or sampling booths to provide operator and product protection and should also have a slight air in-flow from the room to enhance containment. Dust containment at the weigh booth should be demonstrated by smoke airflow pattern tests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

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

6.3.3. In a weighing booth situation, the aim of the UDAF is to provide dust containment and operator protection. The weigh booth and dispensary should have the same environmental conditions that are required for the further processing of the product.

Example: in Figure 21 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.

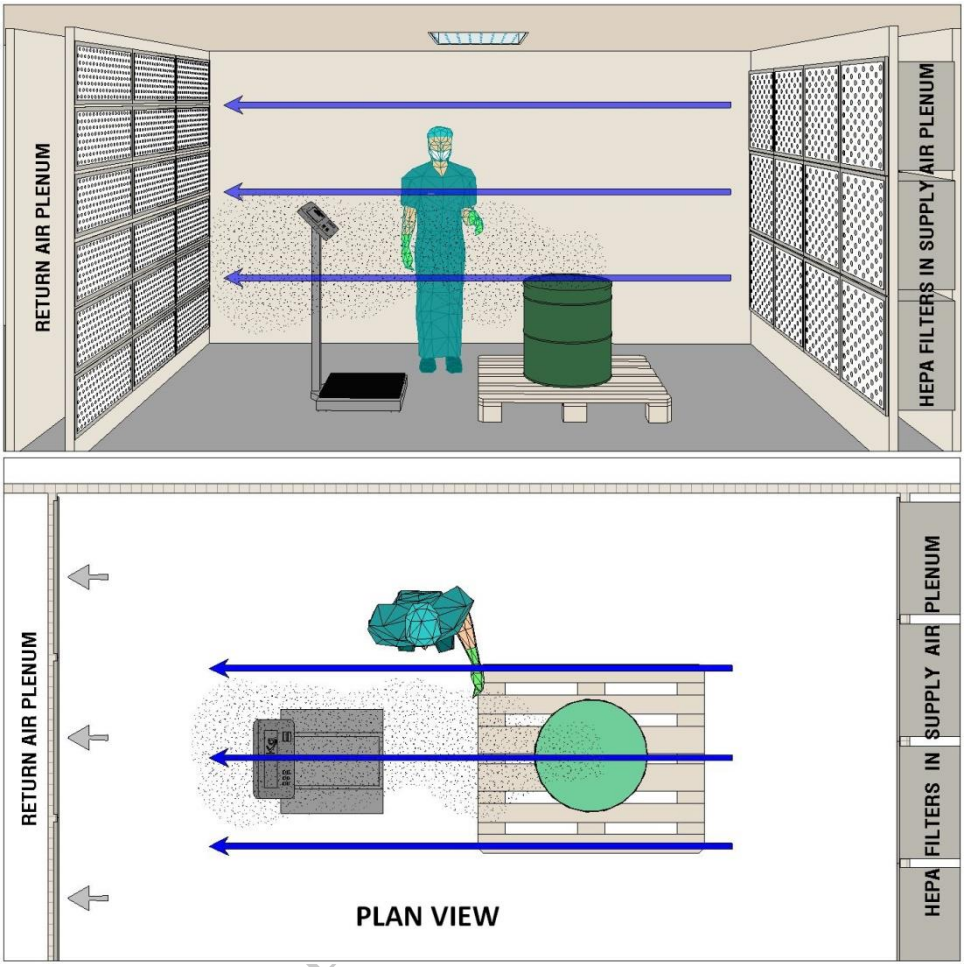
Figure 21. Operator protection at weighing station



6.3.4 The unidirectional flow velocity should be such that it does not disrupt the sensitivity of balances in weighing areas. However, the airflow velocity and directional flow should be appropriate to ensure product containment and operator protection. For this type of application it is sometimes better to refer to the unit as an airflow protection booth (APB) rather than a UDAF, in order to avoid confusion, with a Grade A requirement. To assist with containment for weighing and sampling operations there should be a slight inflow of air into the UDAF protected zone from the surrounding room in order to prevent dust escaping. Thus the amount of air extracted from below the UDAF/APB should exceed the amount of air supplied.

6.3.5 The position in which the operator stands relative to the source of dust liberation and airflow should be determined to ensure that the operator is not in the path of an airflow that could lead to contamination of the product (Figure 22).

Figure 22. Operator protection by horizontal airflow



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

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

Figure 23 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 obstructs the airflow and causes air to rise vertically carrying dust, resulting in a hazardous situation for the operator.

Figure 24 illustrates a situation where an open bin is placed below a vertical unidirectional airflow distributor. The downward airflow should be prevented from entering the bin, and then being forced to rise again, as this

would carry light dust up towards the operator's face. In such an occurrence it may be necessary to add a partial cover over the bin to limit the entry of air. Point extraction could also be used but this can result in the excessive loss of product.

Figure 25 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, or have a perforated worktop with extraction below..

Figure 23. Operator subject to powder inhalation due to obstruction

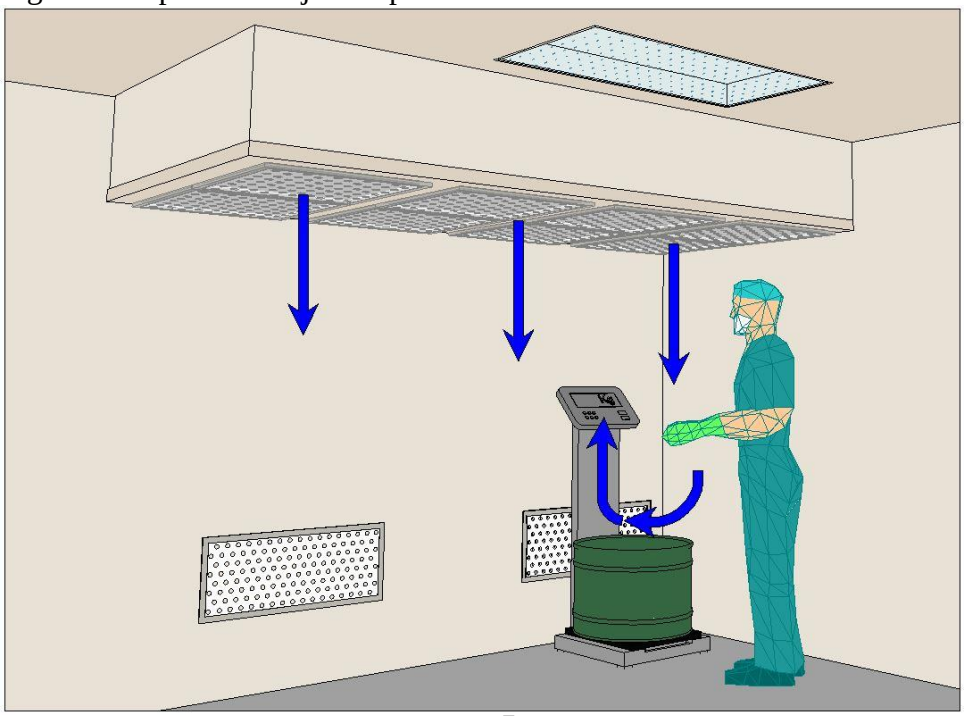
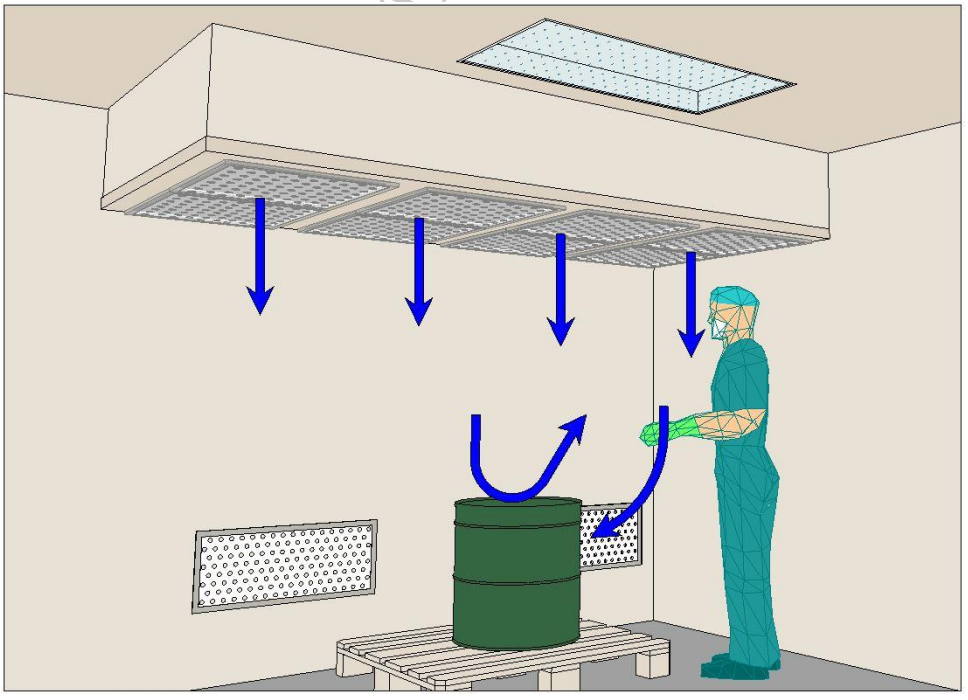


Figure 24. Operator subject to powder contamination due to airflow reversal in bin



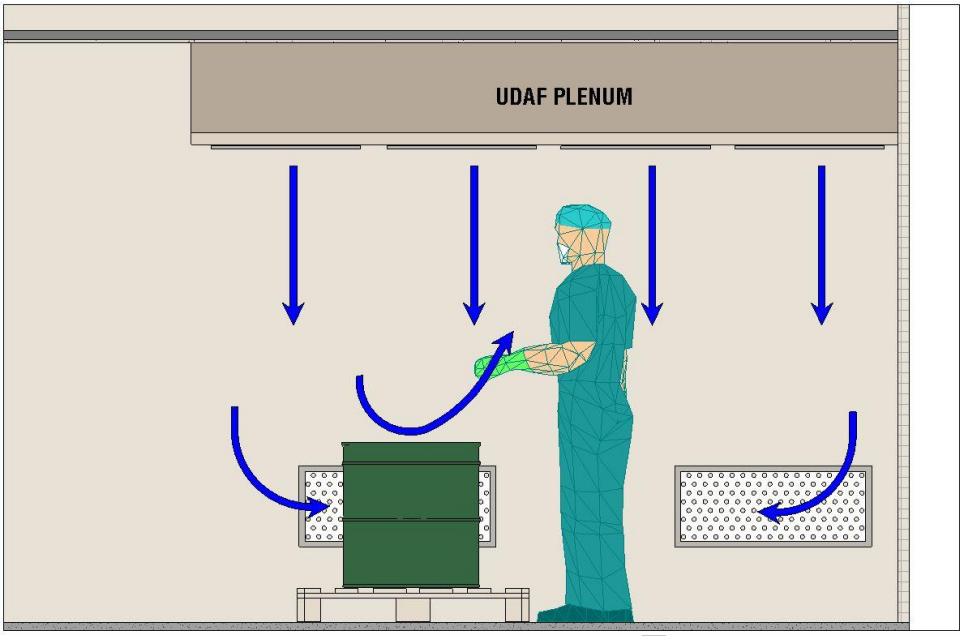
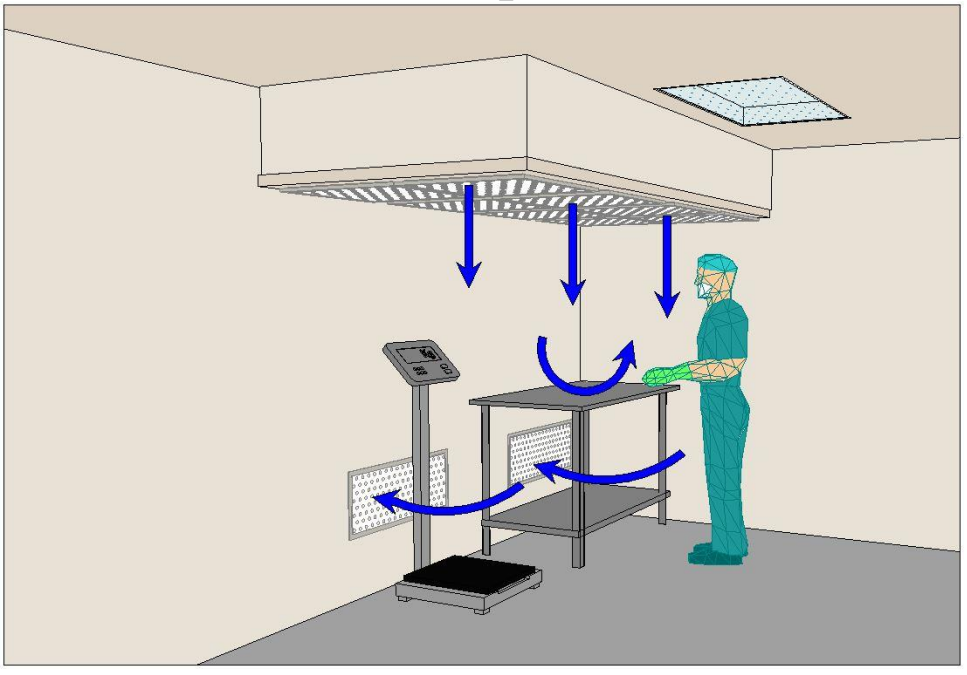


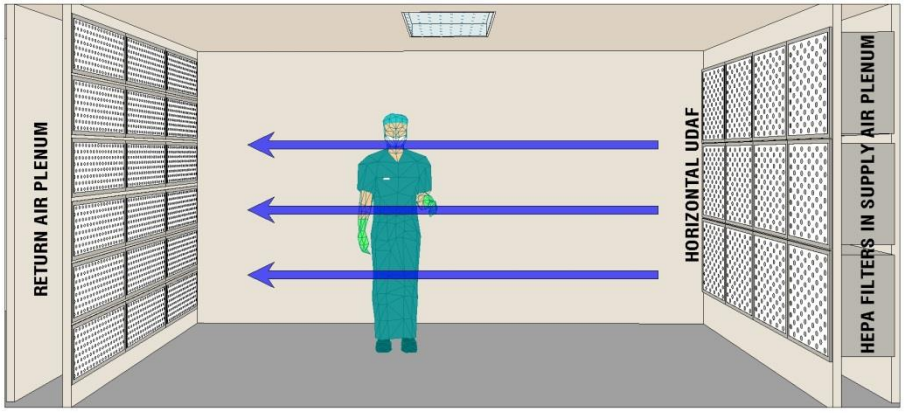
Figure 25. Operator subject to powder inhalation due to worktop obstruction

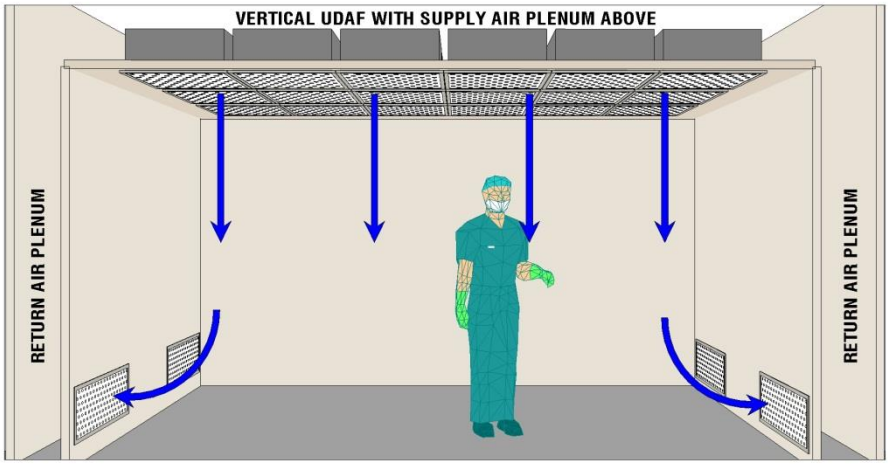


6.3.8 The manufacturer should select either vertical or horizontal unidirectional airflow (Figure 26), and an appropriate airflow pattern to

provide the best protection for the particular application.

Figure 26. Diagram indicating horizontal and vertical unidirectional flow





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

6.4. Infiltration

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

6.4.2. Manufacturing facilities should normally be maintained at a positive pressure relative to the outside, to limit the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to the ambient pressure, special precautions should be taken. Refer to the WHO guidelines for hazardous products, for further guidance on negative pressure facilities.

6.4.3. 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.

6.4.4. 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.

6.5. Cross-contamination and contamination

6.5.1. 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.

6.5.2. 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.

6.5.3. For cubicles where dust is liberated, the corridor should be maintained at a higher pressure than the cubicles and the cubicles at a higher pressure than atmospheric pressure. (For negative pressure facilities

refer to WHO Technical Report Series, No. 957, Annex 3 for hazardous products guidelines and design conditions.)

6.5.4. Containment can normally be achieved by application of the pressure differential concept (high pressure differential, low airflow), or the displacement concept (low pressure differential, high airflow), or the physical barrier concept, as described in ISO 14644-4. However, the "low pressure differential, high airflow" method is no longer used as a means of room segregation.

6.5.5. The pressure cascade for each facility should be individually assessed according to the product handled and level of protection required. The pressure cascade regime and the direction of airflow should be appropriate to the product and processing method used, and should also provide operator and environmental protection.

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

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

6.6. **Pressure differential concept** (high pressure differential, low airflow)

Note: The pressure differential concept may be used alone or in combination with other containment control techniques and concepts, such as a double door airlock.

6.6.1. The high pressure differential between the clean and less clean zones should be generated by balancing the supply and extract air quantities in the two adjoining rooms, thus resulting in the pressure gradient. Leakage through the cracks around the door, as a result of the pressure differential, is acceptable.

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

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

6.6.4. A pressure differential of 15 Pa is often used for achieving containment between two adjacent zones, but pressure differentials of

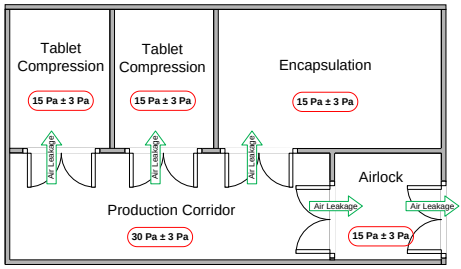
between 5 Pa and 20 Pa may be acceptable. Where the design pressure differential is too low and tolerances are at opposite extremities, a flow reversal can take place. For example, where a control tolerance of ± 3 Pa is specified, the implications of adjacent rooms being operated at the upper and lower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

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

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

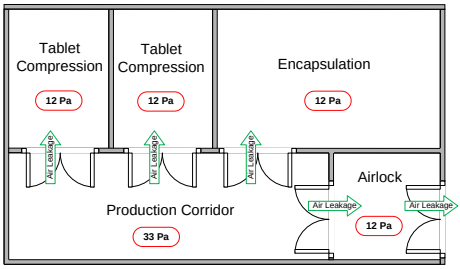
6.6.7. The effect of room pressure tolerances are illustrated in Figure 27. If one room is at the higher side of the tolerance and the other at the lower side of the tolerance, it could result in either a high or a low pressure differential. When setting tolerances it is also important to specify if the tolerance is applicable to the absolute room pressures or the pressure differentials. In the diagram below the tolerances have been based on a ± 3 Pa tolerance on absolute room pressures, resulting in pressure differential variances of between 21 and 9 Pa. For a room pressure differential of 15 Pa and a tolerance based on ± 3 Pa of **differential** pressure, then the resultant variances would only be between 12 and 18 Pa.

Figure 27. Examples of pressure cascades

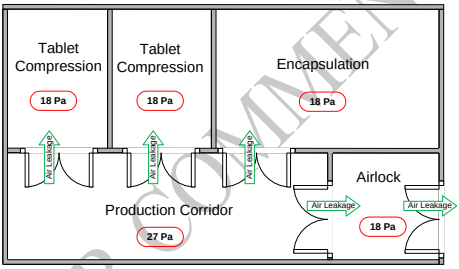


Design Condition (15 Pa Pressure Differential)

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



Maximum Differential (21 Pa Pressure Differential)



Minimum Differential (9 Pa Pressure Differential)

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

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

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

6.6.11. Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock (Figures 28–30):

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

Figure 28. Example of cascade airlock

(In most cases the internal pressure of the airlock is not critical. The pressure differential between the two outer sides is the important criteria.)

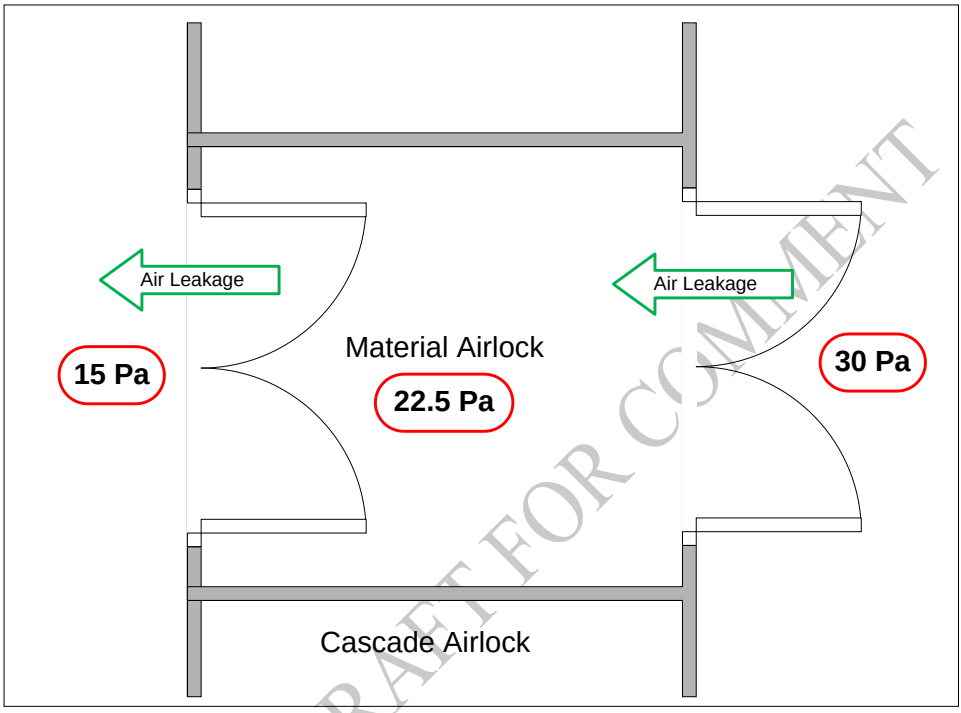


Figure 29. Example of sink airlock

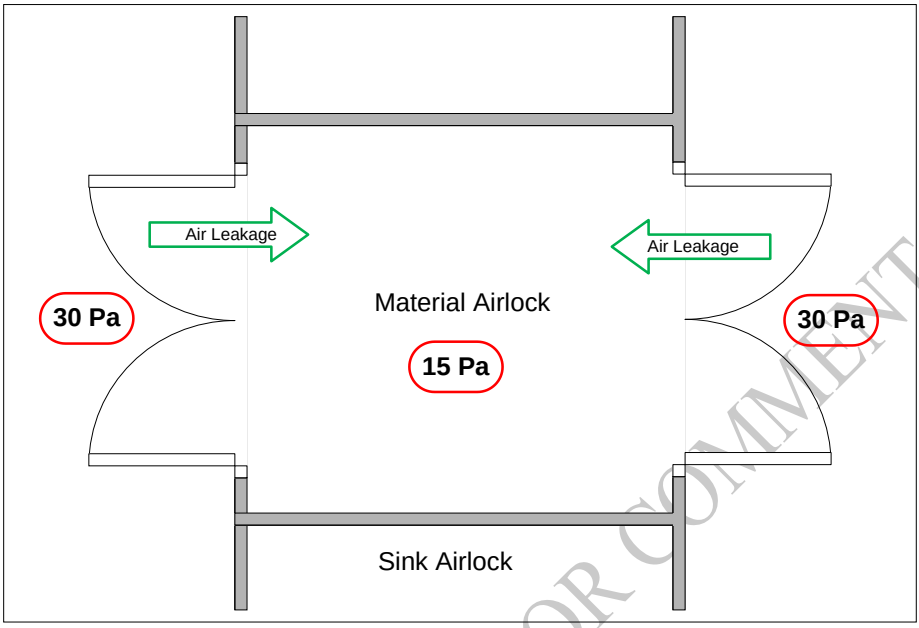
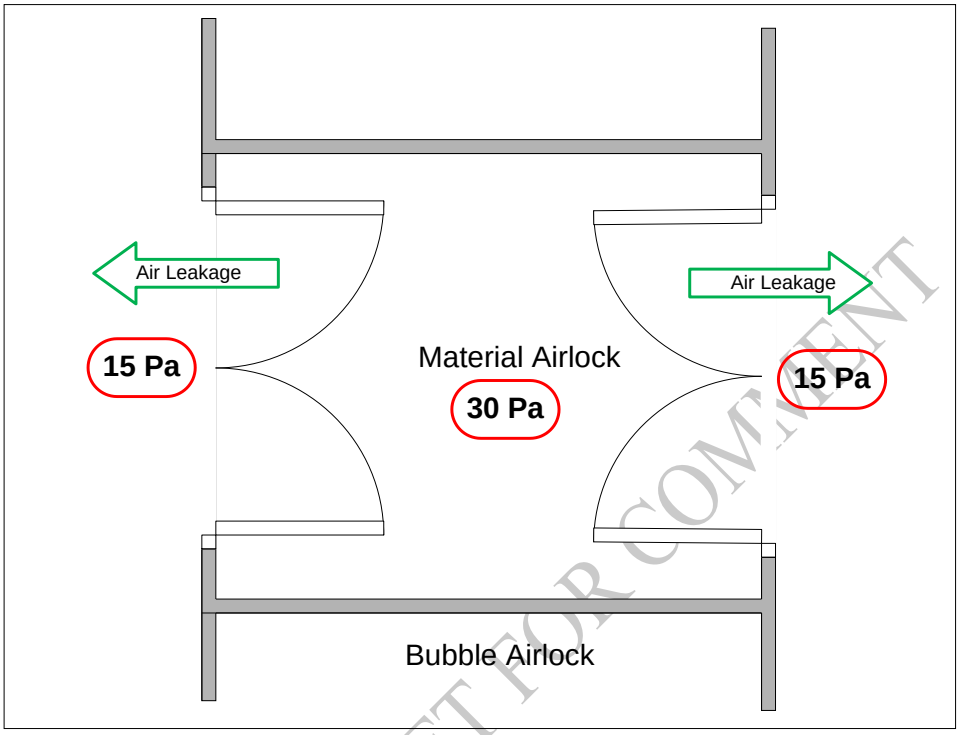


Figure 30. Example of bubble airlock



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

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

6.6.13. Risk assessment should be done to determine whether dust extraction systems should be interlocked to the appropriate air-handling systems. Failure to interlock fans could result in pressure cascade imbalances.

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

6.6.15. Adequate room pressure differential indication should be provided so that each critical room pressure can be traced back to ambient pressure (by summation of the room pressure differentials), in order to determine the room actual absolute pressure. A pressure gauge installed to indicate the pressure differential from a central corridor to ambient could serve to trace pressures to ambient.

6.6.16. Room pressure indication gauges should have a range and graduation scale which enables the reading to an appropriate accuracy. Normal operating range, alert and action limits should be defined and displayed at the point of indication. A colour coding of these limits on the gauge may be helpful.

Room pressure indication may be either analogue or digital, and may be represented as either pressure differentials or absolute pressures. Whichever system is used any out-of-specification (OOS) condition should be easily identifiable. Zero setting of gauges should be frequently checked (such as, weekly) and zero setting should preferably be tamper proof.

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

6.6.18. Room pressure differential tolerances should always be set with a maximum and minimum tolerance. Setting tolerances as NMT or NLT can easily lead to an OOS condition.

6.7. Physical barrier concept

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

6.8. Temperature and relative humidity

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

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

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

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

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

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

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

6.8.8. 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 purified water or clean steam is required for the purposes of humidification.

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

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

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

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

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

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

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

7. DUST CONTROL

7.1. Wherever possible, dust or vapour contamination should be removed at source. Point-of-use extraction, i.e. as close as possible to the point where the dust is generated, should be employed. Spot ventilation or capture hoods may be used as appropriate. The HVAC system should not serve as the primary mechanism of dust control.

7.2. 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. Care should be taken in the design and positioning of dust extract points to prevent cross-contamination by powders dropping down from the extract point.

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

7.4. 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).

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

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

7.7. Typically, in a room operating with turbulent airflow, the air should be introduced from ceiling diffusers, located at the door entry side of the room and extracted from the rear of the room at low level to help give a

flushing effect in the room. Correct flushing of the rooms may be verified by airflow visualization smoke tests.

7.8. When dealing with particularly harmful products, additional steps, such as handling the products in glove boxes or using barrier isolator technology, should be used (refer to WHO Technical Report Series, No. 957, Annex 3 for additional guidance on handling hazardous products).

8. PROTECTION OF THE ENVIRONMENT

8.1. General

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

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

8.2. Dust in exhaust air

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

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

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

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

8.2.5. Mechanical-shaker dust collectors should not be used for applications where continuous airflow is required, in order to avoid unacceptable

fluctuations in room pressures, except in the case where room pressures are automatically controlled.

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

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

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

8.3. Vapour and fume removal

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

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

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

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

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

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

9. COMMISSIONING, QUALIFICATION AND VALIDATION

9.1. General

9.1.1. The HVAC system plays an important role in the protection of the product, the personnel and the environment.

9.1.2. For all HVAC installation components, subsystems or parameters, critical parameters and non-critical parameters should be determined.

9.2. **Commissioning**

9.2.1. 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. The commissioning plan should start at the early stages of a project so that it can be integrated with qualification and verification procedures.

9.2.2. Acceptable tolerances for all system parameters should be specified and agreed by the user prior to commencing the physical installation. These tolerances should be specified in the user requirement specifications

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

9.2.4. System installation records should provide documented evidence of all measured capacities of the system.

9.2.5. The installation records should include items such as the design and measured figures for airflows, water flows, system pressures electrical amperages, etc. These should be contained in the operating and maintenance manuals (O & M manuals). The installation records of the system should provide documented evidence of all measured capacities of the system.

9.2.6. Typical information that should be contained in the O&M manuals is the following:

- system description;
- operating instructions;
- trouble shooting;
- commissioning data schedules;
- maintenance instructions;
- list of equipment suppliers;
- spare parts lists;
- equipment capacity and data schedules;
- supplier's literature;

- control system operation;
- electrical drawings;
- as-built drawings;
- maintenance records.

9.2.7. O & M manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system. As-built drawings should be available and should be kept up to date with all the latest system changes. Any changes from the originally approved system should be covered by change control documentation and risk assessment studies where deemed necessary.

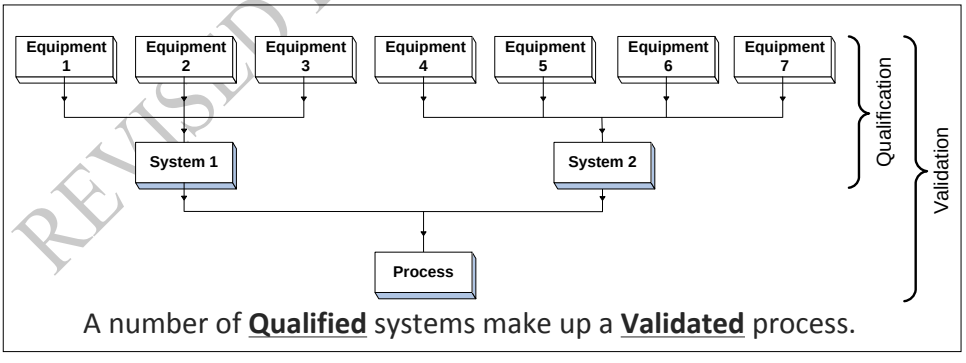
9.2.8. Training should be provided to personnel after installation of the system, and should include how to perform operation and maintenance.

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

9.3. Qualification

9.3.1. Manufacturers should qualify HVAC systems using a risk-based approach. The basic concepts of qualification of HVAC systems are set out in Figure 31 below.

Figure 31. Qualification is a part of validation



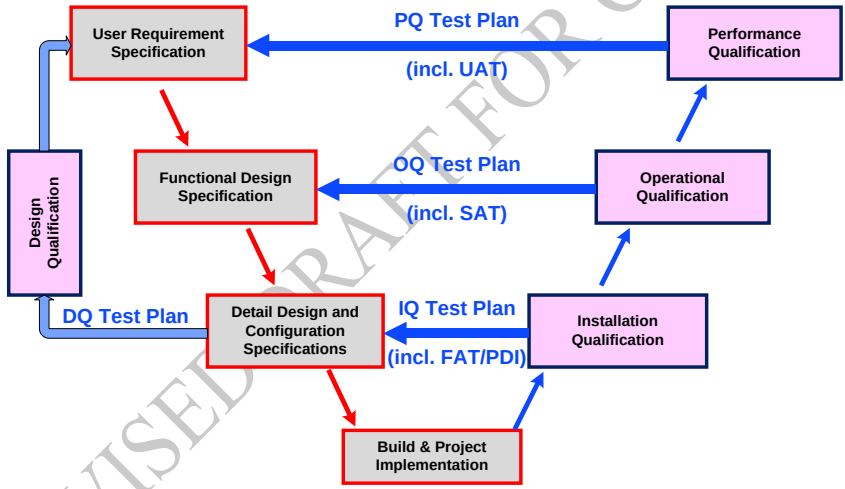
9.3.2. The qualification of the HVAC system should be described in a validation master plan (VMP), or a subsection of the VMP.

9.3.3. The VMP should define the nature and extent of testing and the test procedures and protocols to be followed.

9.3.4. Stages of the qualification of the HVAC system should include design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). The relationship between the development stage of a project (user requirement specification, functional design specification, detail design and configuration specifications, build & project implementation) and the qualification stages are given in the V-diagram (Figure 32) below. The V-model is one example of an approach to qualification and validation.

Figure 32.

V-Model for Direct Impact Systems



UAT=user acceptance tests; FAT=factory acceptance tests; SAT=site acceptance tests; PDI=pre-delivery inspections.

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

9.3.6. Any parameter that may affect the quality of the pharmaceutical product should be considered a critical parameter.

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

Note: A realistic approach to differentiating between critical and noncritical parameters, systems or components 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. Components or equipment such as 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 high-efficiency particulate air (HEPA) filters should be considered critical parameters and components, and therefore require qualification. Components such as the fan generating the airflow and the primary and secondary filters are considered non-critical components, and may not require operational qualification.*

9.3.8. Non-critical systems and components should be subject to verification by good engineering practice and may not necessarily require full qualification.

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

9.3.10. The design condition, normal operating ranges, operating range and alert and action limits should be defined and be realistic. Alert limits should be based on system capability.

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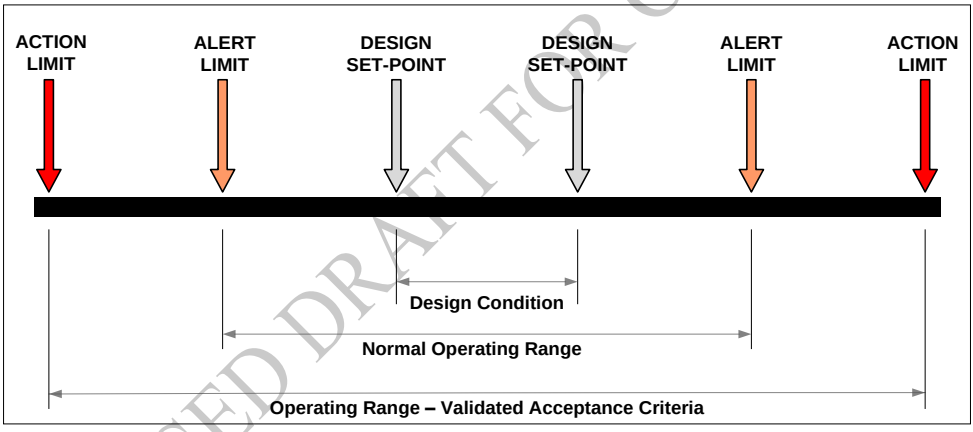
9.3.11. All parameters should fall within the design condition range during system operational qualification. Conditions may go out of the design condition range during normal operating procedures but they should remain within the operating range.

9.3.12. OOS results (e.g. alert or action limit deviations) should be recorded and form part of the batch manufacturing records, and their impact should be investigated. Such incidents should be handled in accordance with a deviation procedure.

9.3.13. The relationships between design conditions, operating range and qualified acceptance criteria are given in Figure 33. There should be SOPs to determine action to be taken when alert and action limits are reached.

Figure 33. System operating ranges



9.3.14. 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.

9.3.15. Some of the typical HVAC system parameters, based on a quality risk assessment, that should be qualified for a pharmaceutical facility 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 recovery rate tests;
- duct leakage tests;
- materials of construction;
- microbiological air and surface counts where appropriate;
- operation of de-dusting;
- warning/alarm systems where applicable.

9.3.16. The maximum time interval between tests and requalification should be defined by the manufacturer. The type of facility under test and the product level of protection should be considered.

Note: Table 5 gives intervals for reference purposes only. The actual test periods may be more or less frequent, depending on the product and process and subject to risk assessment.

Table 5. Strategic tests to demonstrate continued compliance
(Time intervals given for requalification are for reference purposes only. The actual tests required will depend on specific facility requirements)

Test parameter	**Example of time intervals between tests** (all classes)	**Test procedure**
Particle count test (verification of cleanliness)	6 months (≤ ISO 5) 12 months (> ISO 5) *ISO 5 not applicable to non-steriles*	Dust particle counts to be carried out and result printouts produced. No. of readings and positions of tests to be in accordance with ISO 14644-1 A.3

Air pressure difference (to verify absence of cross-contamination)	12 months	Log of pressure differential readings to be produced – critical plants should be logged daily, preferably continuously. In accordance with ISO 14644-3 Annex B.5
Airflow volume (to verify air change rates)	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 B.4
Airflow velocity (to verify unidirectional flow or containment conditions)	12 months	Air velocities for containment systems and unidirectional flow protection systems to be measured. In accordance with ISO 14644-3 Annex B.4
HEPA filter leakage tests (to verify filter integrity)	12 months	Filter penetration tests to be carried out by a competent person to demonstrate filter media, filter seal and filter frame integrity. In accordance with ISO 14644-3 Annex B.6
Containment leakage (to verify absence of cross-contamination)	12 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 B.13
Recovery	12 months	Test to establish time that a cleanroom takes to recover from a contaminated condition to the specified cleanroom condition. In accordance with ISO 14644-3 Annex B.12

Room temperatures (to verify temperature tolerance adherence)	12 months	Demonstrate that room temperatures at determined locations comply with specified tolerances. In accordance with ISO 14644-3 Annex B.8.2
Warehouse and store temperatures (to verify temperature mapping conditions)	36 months	Demonstrate that store temperatures are uniform within specified tolerances In accordance with WHO Technical Report Series, No. 961, Annex 9 and WHO Technical Report Series, No. 992, Annex 5 plus Supplements 1 to 16
Room Humidities (To verify humidity tolerance adherence)	12 months	Demonstrate that room humidities at determined locations comply with specified tolerances. In accordance with ISO 14644-3 Annex B.9.2

9.3.17. Any change to the HVAC system should be handled according to change procedure, and requalification should be considered. Risk assessments should be performed with such changes that affect system performance and documented with specific change controls. Justification and rationale should also be captured if no requalification is performed.

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

These precautionary measures should be based on a risk assessment to ensure that there is no negative impact on the quality of the product. Qualification tests should be carried out to demonstrate that there are no flow reversals, loss of room pressurization cascade, temperature, humidity excursions, etc.

Additional documents that should be included in the qualification

manuals should include system airflow schematics, room pressure cascade drawings, zone concept drawings, air-handling system allocation drawings, particle count mapping drawings, airflow direction diagrams, man, material and waste flow routes, etc.

9.4. Supplementary notes on test procedures

9.4.1. General

9.4.1.1. Tests should be carried as described in ISO 14644-3. However below are some supplementary notes and aspects that provide additional guidance.

9.4.2. Airflow measurements

9.4.2.1. The ISO 14644-3 method - "B.4.3.3 Supply airflow rate calculated from filter face velocity" – should not be used to measure the airflow at diffuser outlets. The diffuser air directional blades or swirl outlets result in highly inaccurate measurements.

9.4.2.2. The cone and anemometer method is more accurate. Other methods can be used such as volume flow regulators with built in orifice and pressure differential ports, whereby airflow can be read off a graph from the corresponding pressure differentials.

9.4.3. Non-viable air particle counts

9.4.3.1. Particle count test results should be calculated using the UCL (upper confidence level) formulas as described in ISO 14644-3, if there are up to nine locations. The practice of using the average value of all particle count readings as the pass criteria is not acceptable.

9.4.3.2. Ensure that the test certificate states the condition under which the test was taken i.e. “as built”, “at-rest” or “operational”. The operational condition should be clearly defined for each room. (*For example: number of staff, staff locations, manner of equipment operating, etc.)*

9.4.3.3. The number of test sample location is determined based on the area of the room as per Table A1in ISO 14644-1 2015. The sampling locations should be chosen representatively, meaning that features such as

cleanroom or clean zone layout, equipment positions and airflow systems should be considered when selecting sampling locations

9.4.3.4. In addition to determining the number of the sampling locations based on the area of the clean room, a risk assessment should determine if additional sample locations are warranted. Consider aspects such as personnel and/or production activities and air flow dead spots.

9.4.3.5. Where a UDAF is located within a room the UDAF and its background environment should be considered separately in terms of sampling location calculations, and should be individually certified.

9.4.3.6. The mapping drawing indicating test location should be included with the test certificate, and the same mapping locations should be used for future tests for comparative purposes.

9.4.4. **HEPA filter integrity tests**

9.4.4.1. Filter media, frame and seal should be tested for each filter and results for media, frame and seal penetration reflected separately on the test certificates.

9.4.4.2. When HEPA filters are terminally mounted at the room, it should be possible to carry out filter integrity tests from within the room. The filter housings will therefore require ports for measuring appropriate upstream concentration and penetration concentration from within the room. In addition it should be possible to measure the filter pressure drop in individual HEPA filters, also preferably from within the room. These pressure drops should be recorded on the filter test certificate as an indication of the filter life. (The practice of measuring the appropriate upstream concentration from the ceiling void or at the air handling plant-room, and then measuring the filter penetration concentration in the room is unacceptable. The time lag between measuring the upstream concentration and the penetration concentration could mean that by the time the room penetration is measured, the upstream concentration is no longer the required concentration.)

9.4.4.3. The implementation of the tests should not compromise the quality of the product.

10. MAINTENANCE

10.1. Maintenance records, maintenance procedures and O&M manuals should be sufficient to indicate that the company has control over the HVAC systems. There should be a planned preventive maintenance programme, procedures and records for the HVAC system. The details of the maintenance programme should be commensurate with the criticality of the system and components. Records should be kept for a sufficient length of time should they be required for any product defect analysis.

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

10.3. The O&M manuals should typically contain the following information: system description; operating instructions; trouble shooting; commissioning data; maintenance instructions; list of equipment suppliers; spare parts list; equipment data/capacity schedules; supplier's literature; control system description; electrical drawings; and as-built drawings.

10.4. Maintenance personnel should receive appropriate training and training records should be kept.

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

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

10.7. 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.

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