

Annex 8

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

Background

The World Health Organization (WHO) published the first edition of the *WHO Guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* in 2006 (1). After a revision, the second edition of the document was published in 2011 (2). Consideration of various comments and questions related to good manufacturing practices (GMP) for heating, ventilation and air-conditioning (HVAC) systems led to the proposal to revise the document. After wide public consultation, and taking into account comments received, the document and comments were discussed during an informal consultation in Geneva in April 2017.

During this informal consultation the proposed changes based on comments received as well as additional suggestions made during the consultation, were discussed. It was agreed that the guidelines be amended to comprise two documents: one that would consist of guidelines containing recommendations for GMP for HVAC systems for non-sterile products and a second document that would contain examples and drawings that would clarify some of the recommendations made in the first document.

Therefore, the previous version of the *WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* as published in 2011 (2) should be amended according to these new guidelines.

Summary of main changes

In accordance with the recommendation made during the informal consultation in April 2017, the guidelines have been rewritten in two parts. The present document is the first part and contains the recommendations that are to be considered as good practices in design, management, control and qualification over the life cycle of HVAC systems.

The second part will contain non-binding examples, clarifications and drawings in support of the guidelines in the present document and is currently being drafted.

No summary of changes is provided here, as the content of the previous guidelines has been reorganized taking into account all the comments received during the last comment period.

The illustrative guidance and explanations (second part) will be published separately.

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1. Introduction

Heating, ventilation and air-conditioning (HVAC) play an important role in ensuring the manufacture of quality pharmaceutical products. The good manufacturing practice (GMP) requirements for the prevention of contamination and cross-contamination are an essential design consideration of an HVAC system. A well-designed HVAC system also provides for protection of the environment and the operators as well as comfortable working conditions.

These guidelines mainly focus on recommendations for HVAC systems used in facilities for the manufacture of non-sterile dosage forms, which include tablets, capsules, powders, liquids, creams and ointments. The general HVAC system design principles contained in these guidelines may, however, also be applied to other dosage forms.

HVAC system design influences architectural building design and layout, for example, with regard to airlock positions, doorways and lobbies. These in turn have an effect on room pressure, pressure differentials, pressure cascades, contamination and cross-contamination control. Therefore, the design of the HVAC system should be considered at the initial 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 and instruments.

A comprehensive science- and risk-based approach should be followed throughout the life-cycle of an HVAC system, including its design, qualification and maintenance. Risk assessment is, however, not a substitute for GMP (3).

2. Scope

These guidelines focus primarily on GMP for the design, qualification, management and maintenance of HVAC systems in facilities for the manufacture of non-sterile dosage forms. They are intended to complement the guidelines on GMP for pharmaceutical products and should be read in conjunction with the parent guide. The additional standards addressed in these guidelines should therefore be considered supplementary to the general requirements set out in the main principles guide (4).

Most of the system principles described in these guidelines may also be considered in facilities manufacturing other dosage forms and products, and finishing processing steps for active pharmaceutical ingredients (APIs). Additional, specific requirements may apply for air-handling systems for pharmaceutical products containing hazardous substances, sterile products and

biological products. These are covered in separate WHO guidelines (3, 5) and working document WHO/BS/2015.2253, intended to replace (6), respectively.

3. Glossary

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

acceptance criteria. Numerical limits, ranges or other suitable measures for acceptance of test results.

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 flow rate of air supplied to a room, in m³/hour, divided by the room volume, in m³.

air-handling unit (AHU). The AHU serves to condition the air and provide the required airflow 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, for example, 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 various stages during 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 procedures and environmental parameters, including viable and non-viable particles, are defined, controlled and monitored to prevent degradation, contamination or cross-contamination of the product.

controlled not classified. An area where some environmental conditions or other attributes (such as temperature) are controlled, 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 the changing 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. 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. 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 refers to air that is returned to the air-handling unit and exhaust air is air that is vented to the 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. 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. 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 (ISO) has developed a set of standards for the classification and testing of cleanrooms. Where ISO 14644 is referenced it implies the latest revision and all its separate parts.

no-impact system. 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.

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

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

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

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

oral solid dosage form. Usually refers to solid dosage forms of 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 while maintaining the pressure cascade and segregation between two controlled zones. A passive pass-through hatch (PTH) has no air supply or air extraction. A dynamic PTH has an air supply into the chamber.

performance qualification. 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 point located so that it effectively captures dust near its source.

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. 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 that 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 (for example 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 air 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. A rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (see also **turbulent air 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. A high-level document that 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 a master qualification plan).

4. Premises

- 4.1 The manufacture of non-sterile pharmaceutical products should take place in a controlled environment, as defined by the manufacturer.
- 4.2 The design of the HVAC system should be closely coordinated with the architectural design of the building.
- 4.3 Infiltration of unfiltered air into a manufacturing facility should be prevented as this can be a source of contamination.
- 4.4 Manufacturing facilities should normally be maintained at a positive pressure relative to the outside, to prevent the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to the outside, special precautions should be taken to mitigate any risks (see (3)).
- 4.5 Areas for the manufacture of products, especially where materials and products are exposed to the environment, should be of an appropriate level of cleanliness. The level of air cleanliness for different areas should be determined according to, but not limited to, the products manufactured, the process used and the products' susceptibility to degradation.

Where a clean room classification is specified, the manufacturer should state whether the classification is rated for the "as-built", "at-rest" or "operational" condition.

- 4.6 HVAC systems should ensure that the specified room conditions are attained, for example through heating, cooling, air filtration, air distribution, airflow rates and air exchange rates.

- 4.7 Any area where pharmaceutical starting materials, products, primary packing materials, utensils and equipment are exposed to the environment should have the same level of cleanliness or classification as the area in which the products are produced.
- 4.8 Appropriate design and controls for the premises and HVAC systems should be in place to achieve containment, cleanliness and the appropriate levels of protection of the product, personnel and the environment.

Note: For facilities where the highest level of containment is a requirement, refer to the guidance in *WHO good manufacturing practices for pharmaceutical products containing hazardous substances* (3).

- 4.9 Containment, cleanliness and protection may be facilitated through, for example:
- correct building layout;
 - building finishes;
 - the use of airlocks such as personnel airlocks (PAL) and/or material airlocks (MAL);
 - pass-through hatches (PTH);
 - change rooms and passages;
 - sufficient pressure differentials.
- 4.10 Detailed schematic diagrams should be maintained, indicating, for example, air supply and air return, room pressure differentials and airflow directions.
- 4.11 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. Where this is unavoidable, risks should be identified and controlled.
- 4.12 The final change room should be at the same cleanliness level (at rest) as the area into which it leads.
- 4.13 Where appropriate, such as where the simultaneous opening of airlock doors might lead to a cross-contamination risk, airlock doors should not be opened at the same time. In such cases, controls such as interlocking systems, warning systems and procedures should be implemented.
- 4.14 Swing doors should normally open to the high-pressure side and be provided with self-closers. Exceptions to the door swing direction should be justified and may include for fire escapes or other health and safety measures. In these cases, door closer mechanisms should be carefully controlled and other controls should be in place to prevent any risk.

- 4.15 Sampling, weighing and dispensing areas should be appropriately designed to provide the required levels of containment, operator protection and product protection.
- 4.16 Sampling, weighing and dispensing should be performed under the same environmental conditions as specified in the areas for the next stage of processing of the product.
- 4.17 Factors such as airflow should not disrupt the accuracy of balances.
- 4.18 The position of the operator, equipment and containers should not obstruct airflow patterns and result in risks.
- 4.19 Once an area is qualified with a specific layout for operators, equipment and processes, this configuration should be ensured during routine activity.
- 4.20 Return and exhaust filters and grilles selected and installed should be appropriate and their design should facilitate cleaning and maintenance.
- 4.21 The impact and risk to the HVAC system should be considered when changes are planned to an existing facility. This includes upgrades and retrofitting of facilities.

5. Design of HVAC systems and components

HVAC systems should be appropriately designed and managed throughout their life cycle. Documentation such as schematic drawings should be maintained to reflect the current situation.

- 5.1 Risk management principles should be applied for HVAC systems. This includes, but is not limited to, appropriate design, operation and monitoring, control of the climatic conditions and the prevention of contamination and cross-contamination.
- 5.2 The HVAC system capacity should be sufficient to ensure that the required performance is maintained during normal use by taking into consideration, for example, room leakage, duct leakage and filter conditions.
- 5.3 Materials for constructing the components of an HVAC system should not become a source of contamination.
- 5.4 Where possible, ducting, piping, fittings, sensors and other components should be clearly marked or labelled for ease of identification, indicating location and direction of flow as appropriate.

- 5.5 Air intake and exhaust air terminals should be positioned in a manner in relation to one another that assists in preventing cross-contamination.
- 5.6 Air-handling units (AHUs) should be provided with adequately designed drains to remove any condensate that may form in them.
- 5.7 Conditions and limits for parameters such as temperature, relative humidity and air cleanliness should be specified and achieved, as needed, for the materials and products handled, as well as for process risk.
- 5.8 Where appropriate, recovery rates should be specified and achieved to demonstrate that the HVAC system is capable of returning an area to a specified level of cleanliness or classification, temperature, relative humidity, room pressure and microbial limits within the specified time.
- 5.9 Failure mode and effect of critical components should be analysed. The analysis should include possible room pressure changes due to fan failure and possible impact of partial system shutdown on ease of opening doors for escape purposes.
- 5.10 The air distribution and airflow patterns should be appropriate and effective.
- 5.11 Air supply and extract grilles should be appropriately located to provide effective room flushing and to prevent zones of stagnant air.
- 5.12 The performance of HVAC systems should be controlled and monitored to ensure continuous compliance with defined parameters, and records should be maintained. Limits defined should be justified.
- 5.13 Where automated monitoring systems are used, these should be capable of indicating any out-of-limit condition by means of an alarm or similar system. Where these systems are identified as GXP systems, they should be appropriately validated.
- 5.14 Appropriate alarm systems should be in place to alert personnel in case of failure of a critical component of the system, for example, a fan.
- 5.15 The effect of fan failure on building and HVAC components should be assessed. Where appropriate, provision should be made for a fan interlock failure matrix.
- 5.16 Periodic switching off of AHUs, for example, overnight or at weekends, or reducing supply air volumes during non-production hours, should be avoided so that material or product quality is not compromised. Where

AHUs are switched off, there should be appropriate justification and no risk to materials or products. The procedure and its acceptability should be proven and documented.

- 5.17 Procedures should be in place and records maintained for the startup and shutdown sequence of AHUs.

6. Full fresh air systems and recirculation systems

- 6.1 Full fresh air or recirculation type HVAC systems may be used. Fresh air should be adequately filtered to remove contaminants. Where recirculation systems are used, there should be no risk of contamination or cross-contamination.
- 6.2 HEPA filters may be installed (in the supply air stream or return air stream) to remove contaminants and thus prevent cross-contamination. The HEPA filters in such an application should have an EN 1822 classification of at least H13 or equivalent.
- 6.3 HEPA filters may not be required to control cross-contamination where evidence that cross-contamination would not be possible has been obtained by other robust technical means, or where the air-handling system is serving a single product facility.
- 6.4 The amount of fresh air intake required should be determined. As a minimum, the following criteria should be considered:
- sufficient volume of fresh air to compensate for leakage from the facility and loss through exhaust air systems;
 - operator occupancy;
 - regional or national legislation.
- 6.5 Air that might be contaminated with organic solvents or highly hazardous materials should normally not be recirculated.
- 6.6 The need for and the degree of filtration of the exhaust air should be considered based on risk, exhaust air contaminants and local environmental regulations.
- 6.7 Where energy-recovery wheels are used in multiproduct facilities, controls should be in place to ensure that these do not become a source of cross-contamination.

7. Air filtration, airflow direction and pressure differentials

- 7.1 Where different products are manufactured at the same time, i.e. in different areas or rooms in a multiproduct manufacturing site, measures should be taken to ensure that dust cannot move from one room to another. Facility design and layout, appropriate levels of filtration, airflow direction and pressure differentials can assist in preventing cross-contamination.
- 7.2 Filters selected should be appropriate for their intended use and classified according to the current international classification system (see Table A8.1).
- 7.3 Airflow directions should be appropriate, taking operator and equipment locations into consideration.
- 7.4 The pressure differential between areas in a facility should be individually assessed according to the products handled and level of protection required. The pressure differential and the direction of airflow should be appropriate to the product and processing method used, and should also provide protection for the operator and the environment.
- 7.5 The pressure differential should be designed so that the direction of airflow is from the clean area, resulting in dust containment, for example, from the corridor to the cubicle.
- 7.6 The limits for the pressure differential between adjacent areas should be such that there is no risk of overlap in the defined dynamic operating ranges.
- 7.7 Normally, for rooms where dust is liberated, the corridor should be maintained at a higher pressure than the rooms and the rooms at a higher pressure than atmospheric pressure. (For negative pressure facilities refer to *WHO good practices for pharmaceutical products containing hazardous substances* (3), for guidelines and design conditions.)

Room pressure differential indication should be provided. This may be by pressure gauges or suitable electronic systems such as EMS or BMS. Where pressure indication gauges are provided, these should have a range and graduation scale that enables them to be read to an appropriate accuracy. The normal operating range, alert and action limits should be defined and displayed at the point of indication or EMS/BMS.

Room pressure should be traced back to representative ambient pressure (by summation of the room pressure differentials), in order to determine the actual absolute pressure in the room.

- 7.8 The pressure control and monitoring devices used should be calibrated. Compliance with specifications should be regularly verified and the results recorded.
- 7.9 Pressure control devices should be linked to an alarm system which is set according to the levels determined by a risk analysis and justified dead times.
- 7.10 Zero setting of gauges should be tamper proof. Zero setting should be checked at regular intervals.
- 7.11 Where airlocks are used, the pressure differentials selected should be appropriate. When selecting room pressure differentials, transient variations, such as machine extract systems and their impact, should be taken into consideration.

Table A8.1
Comparison of filter test standards – approximate equivalencies^a

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	Average dust spot efficiency Em (%) (superseded)	EN 779 & EN 1822		ISO 29463
					MPPS integral overall efficiency (%)	EN rating	
(superseded)	Merv rating	Average arrestance Am (%) (superseded)	Average dust spot efficiency Em (%) (superseded)		99.999995	U17	75E
					99.999995	U16	65E
EU 14					99.9995	U15	55E
EU 13					99.995	H14	45E
EU 12					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			F9	
EU 8	Merv 14		90			F8	
	Merv 13	>98	85			F7	
EU 7		>98	80				

Table A8.1 continued

Eurovent 4/5 rating (superseded)	ASHRAE 52.2 Merv rating	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1 Average airresistance Am (%) (superseded)	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1 Average dust spot efficiency Em (%) (superseded)	EN 779 & EN 1822		ISO 29463
				MPPS integral overall efficiency (%)	EN rating	
EU 6	Merv 12	>95	75		M6	EN 779: 2012
		>95	70			
EU 5	Merv 11	>95	65			
		>95	60			
	Merv 10	>95	55			
		>95	50			
EU 4	Merv 9	>95	45		M5	
		>95	40			
	Merv 7	>90	35			
		>90	30			
EU 3	Merv 6	90	25		G4	
		85	20			
	Merv 5	80	<20		G3	

Table A8.1 continued

Eurovent 4/5 rating (superseded)	ASHRAE 52.2	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	Average dust spot efficiency Em (%) (superseded)	MPPS integral overall efficiency (%)	EN 779 & EN 1822		ISO 29463
						Average arrestance Am (%) (superseded)	EN rating	
	Merv 4	75				EN 779: 2012		
EU 2	Merv 3	70				G2		
	Merv 2	65						
EU 1	Merv 1	<65				G1		

^a Ensure that the classification is current.

MPPS: most penetrating particle size.

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).

8. Temperature and relative humidity

- 8.1 Where appropriate, temperature and relative humidity should be controlled, monitored and recorded to ensure that the conditions are maintained pertinent to the materials and products as required, and provide a comfortable environment for the operators.
- 8.2 Limits for minimum and maximum room temperatures and relative humidity should be appropriate taking into consideration, for example, materials and products.
- 8.3 Where steam or humidity is present, controls should be in place to ensure that the HVAC system will remain effective. Precautions should be taken to prevent moisture migration that may increase an uncontrolled load on the HVAC system.

Where humidification or dehumidification is required, this should be achieved by appropriate means that will not become a source of contamination.
- 8.4 Dehumidification and cooling systems should be well drained. Condensate should not accumulate in air-handling systems and should not become a source of contamination.

9. Dust, vapour and fume control

The discharge location of dust, vapours and fumes should be carefully considered to prevent contamination and cross-contamination.

- 9.1 Dust, vapours and fumes could be sources of contamination and should be appropriately controlled. Wherever possible, they should be removed at source. The HVAC system should not normally serve as the primary mechanism of dust control.
- 9.2 Dust extraction systems should be appropriately designed and installed. Dust should not be able to flow back in the opposite direction, for example, in the event of component failure or airflow failure. The transfer velocity should be sufficient to ensure that dust is carried away and does not settle in the ducting.
- 9.3 The dust extraction points should be positioned in such a way as to prevent dust and powders dropping down from the extract point causing contamination or cross-contamination.

- 9.4 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.
- 9.5 Periodic checks should be performed to ensure that there is no build-up of dust in the ducting.
- 9.6 Dust extraction systems should be interlocked, where appropriate, to the relevant AHU to avoid any risk or any impact on pressure cascade imbalances.

10. Protection of the environment

Where exhaust air from equipment such as fluid bed driers, dust extraction systems and facilities carries dust loads, adequate filtration or other control technology should be in place to prevent contamination of the ambient air.

- 10.1 Waste from dust extraction and collection systems should be disposed of in an appropriate manner.
- 10.2 Dust-slurry should be removed by suitable means, for example, a drainage system or waste removal contractor.

11. Commissioning

Note: Commissioning is a precursor to system qualification and validation, and is normally associated with good engineering practice (GEP).

12. Qualification

Note: For general notes on qualification and validation, see *WHO guidelines on validation* (7).

- 12.1 HVAC systems, including recirculation and full fresh air systems, should be qualified to ensure continued performance in accordance with specifications and achievement of the conditions as specified.
- 12.2 The scope and extent of qualification should be determined based on risk management principles.
- 12.3 The qualification of the HVAC system should be described in a master plan. The master plan should define the nature and extent of testing, the test procedures and protocols to be followed.

- 12.4 Where relevant, the procedures followed for conducting the tests should be in accordance with the appropriate parts of the standard as mentioned in ISO 14644 (8) and relevant WHO guidelines.
- 12.5 The design condition, operating ranges, alert and action limits should be defined. Alert limits should be based on system capability.
- 12.6 Performance parameters to be included in qualification of the HVAC system should be determined by means of a risk assessment.
- 12.7 Acceptable tolerances for system parameters, where appropriate, should be specified before commencing the physical installation.
- 12.8 There should be standard operating procedures describing the action to be taken when alert and action limits are reached. This may include, where relevant:
- temperature;
 - relative humidity;
 - supply air quantities;
 - return air or exhaust air quantities;
 - room air-change rates;
 - room pressures and pressure differentials;
 - airflow pattern tests;
 - unidirectional airflow velocities;
 - containment system velocities;
 - HEPA filter penetration tests;
 - room particle count tests;
 - duct leakage tests;
 - materials of construction;
 - microbiological counts;
 - de-dusting and dust extraction systems.
- 12.9 Where routine or periodic revalidation is done, the frequency should be established based on, for example, risk, the type of facility, the level of product protection necessary, performance of the system and the extent of routine ongoing monitoring activities.
- 12.10 Any change to the HVAC system should be handled according to a change control procedure. The extent of qualification or requalification should be decided based on the scope and impact of the change.

13. Maintenance

- 13.1 Operation and maintenance (O&M) manuals, procedures and records should be available and kept up to date with details of any system revisions made.
- 13.2 O&M manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system.
- 13.3 The O&M manuals may typically contain the following information:
 - system description;
 - operating instructions;
 - troubleshooting;
 - commissioning data;
 - maintenance instructions;
 - list of equipment suppliers;
 - spare parts list;
 - equipment data/capacity schedules;
 - supplier's literature;
 - control system description;
 - electrical drawings;
 - as-built drawings.
- 13.4 There should be a planned preventive maintenance programme for the HVAC system. The details of this programme should be commensurate with the criticality of the system and components.
- 13.5 Maintenance activities should not have any negative impact on product quality and should normally be scheduled to take place at appropriate times, for example, outside production hours.

In case of system stoppages, appropriate quality management system procedures should be followed. Where necessary, the root cause and impact should be assessed and appropriate corrective and preventive action taken. Where necessary, qualification or requalification should be considered.
- 13.6 HEPA filters should be changed by a competent person and this should be followed by installed filter leakage testing.
- 13.7 Records should be kept for a sufficient period of time.

References and further reading

References

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Further reading

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