GUIDELINES ON
HEATING, VENTILATION AND AIR-CONDITIONING
SYSTEMS FOR NON-STERILE PHARMACEUTICAL
PRODUCTS

(June 2017)

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 finnertvk@who.int by 15 September 2017.

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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 WHO Technical Report Series, No. 937, 2006. After a revision, the second edition of the document was published in WHO Technical Report Series, No. 961, 2011. Having considered various comments and questions related to good manufacturing practices (GMP) for heating, ventilation and air-conditioning (HVAC) systems, the document was opened for revision. After wide public consultation over the recent years (see history of the process and timelines above), and considering comments received from (but not limited to) various organizations, industry and individuals, the document and comments were considered during an informal consultation in Geneva in April 2017.

During this informal consultation the proposed changes based on comments received as well as additional comments made during the consultation, were discussed. It was agreed that the guidelines be amended to make provision for two documents. It was recommended that the one document should consist of guidelines that contain recommendations for GMP for HVAC systems for non-sterile products, while a second document should contain examples and drawings that will clarify some of the recommendations included 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 was published in WHO Technical Report Series, No. 961, Annex 5, 2011 is proposed to be amended accordingly as set out in this draft guideline.

Summary of main changes

In accordance with the recommendation made during the informal consultation in April 2017, the guidelines have been rewritten into two parts. This is the first part of the guidelines and this part contains the recommendations that are to be considered as good practices in the 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 Part one and is currently under preparation.

Due to the rewriting of the guidelines, a summary of changes is not provided here, as the content in the previous guideline has been reorganized. In addition, all the comments received during the last comment period were considered in rewriting the guidelines.

The illustrative guidance and explanations (Second part) will be published at a later stage.
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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 of the prevention of contamination and cross-contamination are an essential design consideration of an HVAC system. A well designed HVAC system also provides environmental protection, operator protection as well as comfortable working conditions for operators.

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 the guidelines may, however, also be applied to other dosage forms.

HVAC system design influences architectural building design and layouts with regard to, e.g. airlock positions, doorways and lobbies. These in turn have an effect on room pressure, pressure differential cascades, contamination and cross-contamination control. In view of these aspects, 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 lifecycle of an HVAC system, including its design, qualification and maintenance. Risk management principles should be applied throughout the life cycle. Risk assessment is however not a substitute for GMP (WHO Technical Report Series, No. 957, Annex 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.

These guidelines are intended to complement those provided for in GMP for pharmaceutical products and should be read in conjunction with the parent guide. The additional standards addressed in 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).

Most of the system principles described in these guidelines may also be considered in facilities manufacturing other dosage forms and products, including biological products, herbal medicines, complimentary medicines and finishing processing steps for active

3. GLOSSARY

The definitions given below apply to terms used in this document. 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 flow rate of air supplied to a room, in m³/hr, divided by the room volume, in m³.

**air-handling unit.** The air-handling unit 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, 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 various stages during the 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 onto 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 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. Where ISO 14644 is referenced it implies the latest revision and all the separate parts thereof.

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.

out-of-specification (OOS). 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 oral solid dosage 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 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. 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. 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 WHO Technical Report Series, No. 957, Annex 3).

4.5. Areas for the manufacture of products, or where open equipment is exposed, should be of an appropriate level of cleanliness. The level of protection and air cleanliness for different areas should be determined according to, but not limited to, the products manufactured, the process used and product 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, e.g. 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 that in which the products are produced.

4.8. Appropriate design and controls for the premises and HVAC systems should be in place to achieve the required containment, cleanliness and the appropriate levels of product, personnel and environmental protection. (Note: For facilities where the highest level of containment is a requirement refer to the WHO Technical Report Series, No. 957, Annex 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 cascades.

4.10. Detailed schematic diagrams should be maintained, indicating pressure cascades, airflow directions and flow routes for personnel and materials.

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, e.g. fire escapes or other health and safety constraints. 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 with 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 further 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.

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, including but not limited to, air supply and extraction, air handling units, room pressure cascades, air flow direction, personnel and material movement, and waste removal.

5.1. Risk management principles should be applied during the design of an HVAC system. This includes, but is not limited to, appropriate controls 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.

5.3. Materials of construction for 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, 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 assist in preventing cross-contamination.

5.6. Air-handling units (AHUs) should be provided with adequate drains to remove condensate that may form in the AHU.
5.7. Conditions and limits for parameters such as temperature, relative humidity, air cleanliness and recovery times should be specified and achieved, as needed, for the materials and products handled, as well as process risks.

5.8. Room recovery rates should 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, as appropriate, within the specified time.

5.9. Possible room pressure changes due to fan failure and partial system shut down with an impact on ease of opening of doors for escape purposes should be considered.

5.10. The effectiveness of the air distribution and air flow patterns should be appropriate and effective.

5.11. Air supply and extract grilles should be appropriately located to provide effective room flushing and prevent zones of stagnant air.

5.12. The performance of HVAC systems should be controlled and monitored to ensure ongoing compliance with defined parameters. 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-specification (OOS) 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 a critical component of the system fails, e.g. 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. Switching off of AHUs at intervals such as overnight or weekends, or reducing supply air volumes during non-production hours, should not compromise product quality. Where this is done, there should be appropriate justification and no risk to materials or products. The procedure and acceptability should be proven through validation and qualification.

5.17. There should be procedures and records maintained for the start up and shut down sequence of air handling units.

6. **FULL FRESH AIR SYSTEMS AND RECIRCULATION SYSTEMS**

6.1. Full fresh air, or recirculation type HVAC systems may be used. Where recirculation systems are used, there should be no risk of contaminants in the return-air system. The
recirculated air should be adequately filtered.

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 there is evidence that cross-contamination would not be possible due to 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 required 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, such as in different areas or cubicles in a multiproduct manufacturing site, measures should be taken to ensure that dust cannot move from one cubicle to another. Appropriate levels of filtration, airflow direction and a pressure cascade systems can assist in preventing cross-contamination.

7.2. Filters selected should be appropriate for their intended use and classified according to current international classification (see Table 1 below).

7.3. Airflow directions should be appropriate, taking operator and equipment locations into consideration.

7.4. The pressure cascade for areas in a facility should be individually assessed according to the products 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.

7.5. The pressure cascade should be such that the direction of airflow is from the clean area, resulting in dust containment, e.g. 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 operating ranges.

7.7. Normally, 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.)

Room pressure differential indication should be provided. The pressure indication gauges should have a range and graduation scale which enables the reading to an appropriate accuracy. The normal operating range, alert and action limits should be defined and displayed at the point of indication.

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

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 cascade regimes selected should be appropriate. In considering room pressure differentials, transient variations, such as machine extract systems and their impact, should be taken into consideration.
### Table 1. Comparison of filter test standards*

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<th>Eurovent 4/5 rating</th>
<th>ASHRAE 52.2</th>
<th>Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1</th>
<th>Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1</th>
<th>EN 779 &amp; EN 1822</th>
<th>Merv rating</th>
<th>Average arrestance Am (%) (superseded)</th>
<th>Average dust spot efficiency Em (%) (superseded)</th>
<th>MPPS integral overall efficiency (%)</th>
<th>EN rating</th>
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*Ensure that the classification is current.

**Note:** The filter classifications referred to above relate to the EN1822:2009 and EN779: 2012 test standards (EN779 relates to filter classes G1 to F9 and EN1822 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. Alert and action limits should be set appropriate to material and product requirements, and to inhibit increased microbial loading.

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 which does 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 location of discharge exhaust points relative to air inlet points should be carefully considered to prevent contamination and cross-contamination.

9.1. Dust, vapours and fumes could be possible sources of contamination and should be appropriately controlled. Wherever possible, these should be removed at source. The HVAC system should normally not serve as the primary mechanism of dust control.

9.2. Dust extraction systems should be appropriately designed and installed. Dust should not flow back in the opposite direction, e.g. 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 positioning of dust extraction points should be appropriate 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 the dust in the ducting.

9.6. Dust extraction systems should be interlocked, where appropriate, to the relevant air-handling unit to avoid any risk and 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 carry dust loads, adequate filtration should be provided to prevent contamination of the ambient air.

10.1. Waste from wet and dry scrubbers should be disposed of in an appropriate manner.

10.2. Dust-slurry should be removed by suitable means, e.g. a drainage system or waste removal contractor.

11. **COMMISSIONING**

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 Guideline on Validation.*


12.1. HVAC systems, including recirculation and full fresh air systems, should be qualified to ensure continued performance in accordance with specifications and achieving 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 the conduct of tests should be in accordance with the appropriate parts as mentioned in ISO 14644 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 for the HVAC system should
be determined by means of a risk assessment.

12.7. Acceptable tolerances for system parameters, where appropriate, should be specified prior to 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 air flow 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, e.g. 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 considered 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, containing 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:
13.4. There should be a planned preventive maintenance programme for the HVAC system. The details of the maintenance 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, e.g. 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 followed by installed filter leakage testing.

13.7. Records should be kept for a sufficient period of time.

REFERENCES AND FURTHER READING


3. ICH Harmonised Tripartite Guideline on Quality Risk Management (Q9), 2005.


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Revised draft for comments...