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HVAC for non-sterile Pharmaceutical Products: Design, Qualification and Maintenance

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Abstract

Heating, ventilation and air-conditioning (HVAC) system plays an important role to ensure the manufacture of quality pharmaceutical products. In this article, design consideration, qualification requirements and maintenance of HVAC has been discussed. Regulatory guidelines and risk-based approaches are considered. Pharmaceutical company should design HVAC, qualify and managed the HVAC system based on risk assessment.

Keywords: HVAC, non-sterile pharmaceutical facility, air handling unit, AHU

Introduction

Heating, ventilation and air-conditioning (HVAC) system of a pharmaceutical factory is crucial to the production of safe and effective medicines. An HVAC system must be designed with good manufacturing practice (GMP) criteria for contamination and cross-contamination avoidance in mind. Along with ensuring the safety of the workers and the surrounding area, a well-designed HVAC system also ensures pleasant working conditions.

The manufacturing of non-sterile dosage forms, such as tablets, capsules, powders, liquids, creams, and ointments, is the primary emphasis of this article, with specific requirement of HVAC systems utilized in pharmaceutical facilities. The design of an HVAC system affects the design and layout of a building, such as where airlocks, doors, and lobbies are placed.

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Room pressure, pressure differentials, pressure cascades, contamination, and cross-contamination control are all affected by these elements. As such, the HVAC system design should be addressed right from the start when planning a pharmaceutical production facility.

Manufacturing and storing of pharmaceuticals should take place in conditions where temperature, relative humidity, and ventilation are acceptable and do not compromise product quality or the efficacy of machinery and instruments.

All phases of an HVAC system—from design to qualification to maintenance—should adhere to a systematic, scientific and risk-based approach. In this article, we will discuss design, qualification and maintenance of HVAC system.

Consideration for HVAC Design

Below mentioned points should be considered for HVAC design of non-sterile pharmaceutical facilities[1]:

I. The HVAC system design should be integrated closely with the building's architectural design.
II. As this can be a source of contamination, unfiltered air should not be allowed to enter a production plant.
III. Typically, manufacturing facilities should be maintained at a positive pressure relative to the exterior in order to avoid the introduction of contaminants. When facilities are to be maintained under negative pressures relative to the outside environment, additional steps must be taken to mitigate any potential risks.
IV. Areas where products are manufactured, especially where materials and products are exposed to the environment, should be clean enough. The level of clean air in different areas should be based on, but not limited to, the products manufactured, the process used, and the product’s susceptibility to degradation. When a clean room classification is given, the manufacturer should mention if the rating is for the room "as-built," "at-rest," or "operational."

V. HVAC systems should make sure that the room is at the right temperature and humidity. They do this by heating, cooling, filtering, distributing, and exchanging air.

VI. Any area where pharmaceutical raw materials, products, primary packaging materials, tools, and equipment are exposed to the environment should have the same level of cleanliness or classification as the area where the products are manufactured.

VII. The building and HVAC systems should have the right design and controls for containment, cleanliness, and the right level of protection for the product, the people who work there, and the environment.

VIII. 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.

IX. Maintaining detailed schematic diagrams depicting, for example, air supply and air return, room pressure differentials, and airflow directions is required.

X. Personnel and materials should avoid moving from a higher cleanliness zone to a lower cleanliness zone and back to a higher cleanliness zone whenever possible. Where this cannot be avoided, risks must be identified and managed.

XI. The final change room should be at the same cleanliness level (at rest) as the area into which it leads.

XII. Where appropriate, such as in situations where the simultaneous opening of airlock doors could provide a risk of cross-contamination, airlock doors should not be opened simultaneously. In such situations, it is necessary to install controls such as interlocking systems, warning systems, and processes.

XIII. Typically, swinging doors should open to the high-pressure side and be equipped with automatic closers. Exceptions to the door swing direction must be justifiable, such as for fire escapes or other health and safety measures. In these situations, door closer mechanisms and other controls should be closely monitored to prevent any potential risk.

XIV. The sampling, weighing, and dispensing areas should be built to ensure the required levels of containment, operator safety, and product safety.

XV. Sampling, weighing, and dispensing should be carried out under the same environmental conditions as those required for the subsequent stage of product processing.

XVI. Airflow should not interfere with the accuracy of balances.

XVII. The position of the operator, equipment, and containers must not restrict airflow patterns and create risks.

XVIII. After an area has been qualified with a particular layout for personnel, equipment, and processes, this configuration must be maintained during ordinary operations.

XIX. Return and exhaust filters and grilles should be properly selected and installed, with a design that facilitates cleaning and maintenance.

XX. When planning alterations to an existing building, the impact and risk to the HVAC system should be evaluated. This comprises facility renovations and retrofits.

Design of HVAC

HVAC systems should be designed and managed effectively throughout their lifetime. Maintaining documentation such as schematic drawings to reflect the existing situation is essential. Following are the design requirements as per regulatory guidelines[1,2]:

I. The ideas of risk management should be applied to HVAC systems. This includes, but is not limited to, suitable design, operation, and monitoring, climate control, and contamination and cross-contamination prevention.

II. The HVAC system's capacity should be adequate to guarantee that the required performance is maintained during normal operation, taking into account factors such as room leakage, duct leakage, and filter conditions.

III. Components of a heating, ventilation, and air conditioning system should not become a contaminant due to their construction materials.

IV. Whenever possible, ducting, piping, fittings, sensors, and other components should be clearly marked or labeled for identification purposes, indicating location and flow direction as needed.

V. The air intake and exhaust air terminals should be positioned in a manner that aids in the prevention of cross-contamination.

VI. Air-handling units (AHUs) must be equipped with condensate-removing drains of suitable design.

VII. Conditions and limits for parameters such as temperature, relative humidity, and air cleanliness should be established and met, as required, for the materials and products being handled and for process risk.

VIII. When applicable, recovery rates should be defined and attained to indicate that the HVAC system is capable of returning a space to the specified cleanliness or classification, temperature, relative humidity, room pressure, and microbiological limits within the specified time.

IX. Failure mode and effect of critical components must be analyzed. The analysis should consider the potential for a change in room pressure in the event of a failed fan, as well as the influence of a partial system shutdown on the ease of opening doors for escape purposes.

X. The air distribution and airflow patterns must be efficient and appropriate.

XI. Air supply and extract grilles should be positioned suitably for effective room flushing and to prevent stagnant air zones.

XII. The performance of HVAC systems must be controlled and monitored to assure continual compliance with predetermined parameters, and records must be kept. Justification is necessary for establishing limits.

XIII. When automated monitoring systems are utilized, they must be able to signal any out-of-limit condition via an alarm or similar mechanism. Where these systems are identified as GXP systems, they must be validated accordingly.

XIV. Alarm systems should be in place to let people know if a critical part of the system, like a fan, stops working.

XV. Assess the impact of fan failure on the building and HVAC systems. Where appropriate, a fan interlock failure matrix should be specified.

XVI. To ensure that material or product quality is not affected, periodic AHU shutdowns, such as overnight or on weekends, or reductions in supply air volume during non-production hours should be avoided. When air handling units are turned off, there must be a valid reason and no risk to materials or products. The procedure and its acceptability must be demonstrated and recorded.

XVII. The start-up and shut-down sequence of AHUs should be governed by procedures and recorded.

Full Fresh Air Systems and Recirculation Systems

Full fresh air or recirculation HVAC systems are acceptable options. Air should be filtered appropriately to remove contaminants. There should be no risk of contamination or cross-contamination in areas where recirculation systems are utilized. To eliminate contaminants and prevent cross-contamination, HEPA filters may be installed in the supply air stream or return air stream. In such an application, the HEPA filters must have an EN 1822 classification of at least H13 or its equivalent[1]. HEPA filters may not be necessary to prevent cross-contamination if other robust technical measures have demonstrated that cross-contamination is not conceivable, or if the air-handling system serves a single-product plant.

The appropriate amount of fresh air intake must be determined. The following parameters should be considered as a bare minimum:

- sufficient amount of fresh air to compensate for leakage from the facility and loss through exhaust air systems
- operator occupancy
- The following parameters should be considered as a bare minimum:

Typically, air that may be contaminated with organic solvents or extremely hazardous substances should not be recirculated. The necessity and degree of exhaust air filtering must be determined depending on risk, exhaust air contaminants, and local environmental regulations.

When energy-recovery wheels are utilized in multi-product facilities, precautions must be taken to prevent them from becoming a source of cross-contamination.

Applicable Cleanliness Grade for Non-Sterile Pharmaceutical Facility

Applicable cleanliness grade for non-sterile pharmaceutical facility included in below table. WHO and equivalent ISO cleanliness is also mentioned[3,4].

Cleanliness Grade	Typical Applications
WHO Grade C ISO Class 7	Critical areas in the manufacturing and primary packaging of drug products, including inhalation products (e.g. nasal spray), and topical products (other than rectal products) for use on injured skin (e.g. creams, ointments)
WHO Grade D ISO Class 8	- Background environment for cleanliness grade C/ ISO class 7 - Critical areas in the manufacturing and primary packaging of oral, rectal products including products for use on the uninjured skin - Non aqueous preparation for oral use, aqueous preparations for oral use, preparations for oromucosal, gingival, cutaneous, nasal, auricular, vaginal use, preparation for rectal use - Storage of the in-process products
CNC (Controlled Not Classified)	- Secondary and final packaging / visual inspection activities - Ancillary production rooms in which product is not handled in open containers and not exposed to the surrounding environment - Corridors - Technical rooms inside production areas - Warehouses
UC (Uncontrolled)	-Offices, infrastructure, etc.

ISO Cleanliness Grade

ISO cleanliness grade has been mentioned below[3]:

ISO classification number (N)	Maximum concentration limits (particles/m^3 of air) for particles equal to and larger than the considered sizes shown below [concentration limits are calculated in accordance with equation (1) in section 3.2 of ISO 14644-1]					
	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1 µm	5 µm
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1 000	237	102	35	8	
ISO Class 4	10 000	2 370	1 020	352	83	
ISO Class 5	100 000	23 700	10 200	3 520	832	29
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO Class 7				352 000	83 200	2 930
ISO Class 8				3 520 000	832 000	29 300
ISO Class 9				35 200 000	8 320 000	293 000
NOTE Uncertainties related to the measurement process require that concentration data with no more than three significant figures be used in determining the classification level						

WHO Cleanliness Grade

WHO cleanliness grade has been mentioned below[4]:

	Maximum permitted number of particles per m^3 greater than or equal to the tabulated size			
	At rest[a]		In operation[b]	
Grade	**0.5 µm**	**5.0 µm**	**0.5 µm**	**5.0 µm**
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

a) The “at rest” state is the 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.

b) The “in operation” state is the condition where the installation is functioning in the defined operating mode and the specified number of personnel is present. The areas and their associated environmental control systems should be designed to achieve both the “at rest” and “in operation” states.

Required Test during Initial Qualification

Following tests should be performed during initial qualification[1,5]:

Tests	WHO Grade C ISO Class 7	WHO Grade D ISO Class 8	CNC (Controlled Not Classified)	UC (Uncontrolled)
Differential pressure on filters(*)	Yes	Yes	Yes	N/A
Room differential pressure	Yes	Yes	N/A	N/A
Airflow velocity / volume & uniformity	Yes	Yes	N/A	N/A
Parallelism for Laminar Flow	Yes	Yes	Yes (if applicable)	N/A
Air flow patterns	Optional	Optional	N/A	N/A
Filter leak test (challenge test)	Yes *	Yes *	N/A	N/A
Recovery **	Yes	Yes	N/A	N/A
Room classification (airborne particle count)	Yes	Yes	N/A	N/A
Temperature	Yes	Yes	N/A***	N/A
Humidity	Yes	Yes	N/A***	N/A

Microbial Contamination Limit	Yes	Yes	N/A	N/A

*: Full leak test in case of H13 or H14 filters

**: For zone transition airlocks and rooms with open product handling. Further rooms based on risk assessment.

***: Temperature and/humidity mapping are required for warehouse.

Limit for Microbiological Contamination as per WHO

Microbial limit of different cleanliness grade included in below table[4]:

Recommended limits for microbial contamination[a]

Grade	Air sample (CFU/m3)	Settle plates (diameter 90 mm) (CFU/4 hours)[b]	Contact plates (diameter 55 mm) (CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

CFU, colony-forming units.
[a] These are average values.
[b] Individual settle plates may be exposed for less than 4 hours.

Routine Requalification

The requirements for room monitoring and routine requalification must be defined. Requalification frequency must be defined based on risk assessment, documented, and approved by QA. All parameters must be considered as an entire entity, and not just be considered on a case by cases basis as an isolated item to determine the combination(s) of tests used for monitoring and periodic requalification. Any requalification failure must be investigated, including performance of a product evaluation and look back. The investigation must include a reevaluation of the requalification frequency. All tests of initial qualification should be considered during routine requalification.

Requalification after Maintenance Shutdown/Breakdown

The tests shown in below table must be performed after HVAC maintenance shutdown.

Tests	WHO Class C ISO Class 7	WHO Class D ISO Class 8	CNC (Controlled Not Classified)	UC (Uncontrolled)
Room differential pressure	CIMA or CI or Yes	CI or Yes	N/A	N/A
Particle count	Optional	N/A	N/A	N/A
Temperature	CI or Yes	CI or Yes	N/A	N/A
Humidity	CI or Yes	CI or Yes	N/A	N/A
Microbial Contamination Limit	Yes if applicable	Yes if applicable	N/A	N/A

CIMA: Continuous indication, monitoring with automatic alarming when out of spec.

CI: Continuous Indication or monitoring

Requalification after Maintenance Work / Filter Replacement /Change Control

All tests of initial qualification must be performed after major preventive maintenance work or replacement of final filters or after any change of initial qualified layout.

Maintenance Requirements

A preventive maintenance program must be established. This program must address in particular:

- All HVAC equipment and controls, including filters
- All environmental monitoring equipment and controls

The maintenance program can either be manual (i.e. log-books) or can be controlled electronically. If an electronic system is used, it must be validated. For either method, records must be easily retrieved and approval steps must be properly documented.

The maintenance program must be documented and approved by QA. Any failures must be investigated, including performance of a product evaluation and look back. The investigation must include a re-evaluation of the preventive maintenance program and frequency of maintenance.

Conclusion

HVAC is a mandatory part of pharmaceutical manufacturing facility. It should be designed, qualified and maintained based on risk assessment. Any breakdown or deviation should be investigated to find out root cause and to remediate the issue and affected material/products/facility should be assessed also.

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