HVAC System Validation in the Pharmaceutical Sector: Strategies for Ensuring Regulatory Compliance and Operational Efficiency

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ABSTRACT

Heating Ventilation and Air Conditioning (HVAC) systems are designed to provide buildings with a controlled atmosphere, maintaining a comfortable and secure space for occupants. This paper introduces an HVAC system. Validation studies assess the test methods used, ensuring their accuracy, sensitivity, specificity, and reproducibility. These studies are carried out following a predefined protocol. HVAC systems are essential for maintaining appropriate temperatures and ensuring a consistent airflow, which helps to prevent contamination and creates optimal conditions within the premises. The HVAC qualification process includes design, installation, operational, and performance qualifications. The evaluation assesses airflow, filtration, contamination control, pressure, temperature, humidity, and environmental uniformity.

Keywords: HVAC system, Validation, Qualification.

INTRODUCTION

HVAC systems are used to heat or cool residential, commercial, and industrial buildings. Enhancing HVAC controls can reduce energy consumption without incurring additional costs. The main objective of an HVAC system is to maintain optimal indoor comfort through responsive heating and cooling. In pharmaceutical industry, a high-quality product relies on effective HVAC systems. Heating systems raise indoor temperatures to counteract heat loss to the external environment. Ventilation systems introduce fresh air into a space while removing contaminated air. Cooling systems, on the other hand, reduce temperatures in areas experiencing heat build-up from occupants, equipment, or sunlight, which may otherwise cause discomfort. HVAC system designs also impact architectural features like the placement of airlocks, doors, and lobbies. Therefore, it is crucial to ensure appropriate levels of temperature, relative humidity and ventilation [1].

The core functions of an HVAC system include:

1) Prevent airborne contamination of products: HVAC systems address this by filtering the air, effectively removing these contaminants to create a clean and controlled environment for production processes.

2) Regulate room temperature: Fluctuating room temperatures can degrade product quality and encourage microbial growth. To prevent this, HVAC systems ensure consistent temperature control.

3) Maintain room humidity/moisture (RH): Proper humidity control is crucial during drug manufacturing to ensure stability. The HVAC system regulates relative humidity (RH) levels to create optimal conditions and preserve the quality of the drugs.

4) Control room pressure differential (ΔP): Maintaining a higher pressure in clean rooms than in adjacent areas helps prevent cross-contamination. HVAC systems achieve

this by maintaining a higher airflow rate in clean rooms than in black areas, ensuring a controlled and safe environment.

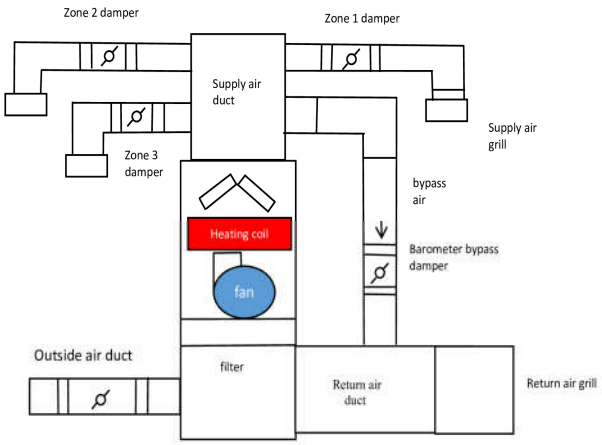

Figure no 1: Schematic Diagram of HVAC system

High-performance air purification system

Storage and quarantine areas incorporate High Efficiency Particulate Air (HEPA) filters, which deliver an impressive 99.995% filtration efficiency, to ensure a clean environment. These filters also ensure aseptic conditions in workspace. It is necessary to conduct regular leak testing to ensure the efficiency and integrity of these filters. HEPA filters play a crucial role in the Air Handling Unit (AHU) system. AHU pulls in outside air, blends it with recirculated air from cubicles, and distributes the treated air throughout laboratory spaces. Meanwhile, a portion of laboratory air is expelled outside via an exhaust fan, while the remainder is recirculated back to the AHU. At this stage, the air passes through prefilters and medium filters to remove particulate matter. After filtration, the air is conditioned to control humidity and temperature, and then supplied to various areas, including laboratories, via a pressurized supply fan. Positioned at the entry points of clean rooms, HEPA filters act as terminal filters, delivering a high level of air purification[2].

Qualification of HVAC system

1. **Design Qualification (DQ)**
   This process involves conducting and documenting design reviews to demonstrate that all quality aspects have been thoroughly addressed during the design phase. Its purpose is to ensure that all requirements for the final system are clearly defined from the outset. DQ must align with Good Manufacturing Practices (GMPs) and other regulatory standards. Qualification of HVAC system shown in Figure 2.

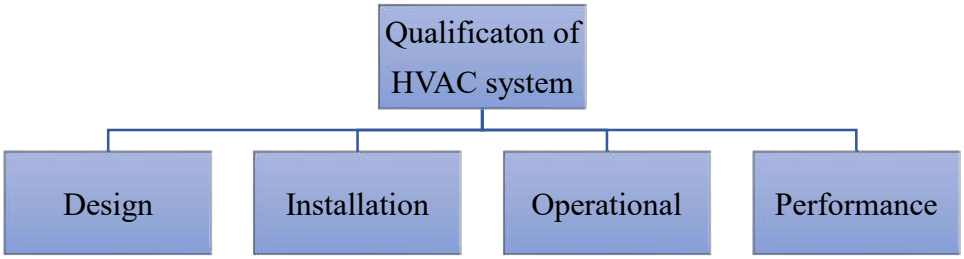

Figure no 2: Qualification of HVAC system

2. Installation Qualification (IQ)

The IQ report provides documented evidence that the installation's critical components align with the manufacturer's guidelines, relevant codes, and the qualified design specifications. IQ aims to confirm and document the conformity of the HVAC system's components to the requirements outlined in the functional specifications and Validation Master Plans, ensuring their quality and integrity. In simpler terms, equipment can only be installed if it successfully passes the IQ test, ensuring it is qualified for installation.

3. Operational Qualification (OQ)

The purpose of OQ is to confirm through documentation that a system or subsystem meets its performance specifications and operates as expected under all specified operating conditions. To ensure optimal performance and safety, equipment should only be operated after passing the OQ test. The equipment is tested under a variety of operating conditions, including normal, extreme, and worst-case scenarios, to assess its ability to perform under different circumstances. Operational components, such as controls, alarms, switches, and displays, must undergo thorough testing. OQ provides verified documentation that utility systems, equipment, and all their components function as per operational specifications without load[3].

4. Performance Qualification (PQ)

The objective of PQ is to confirm through documentation that HVAC systems provide effective control and consistent performance when operating under full-load conditions. The sequence of qualification activities culminates in PQ, following the successful execution of IQ and OQ. The ultimate challenge for environmental control and HVAC systems lies in supporting the processes performed within the areas they serve. When new approved conditions are determined, any required system changes must be implemented, revalidated, and verified before commencing PQ activities.

Vaidation Parameter

1. Non-living particle count
2. Air circulation pattern
3. Air velocity measurement
4. Pressure gradients
5. Recovery test
6. Filter leakage assessment
7. particle count
8. Temperature and moisture levels
9. Filter integrity testing (HEPA leak test)
10. Sound level test
11. Microbial count
12. Fresh Air Assessment

1. Non-living particle count

Non-living particles may act as vectors for viable particles, but they do not contain live microorganisms. The monitoring process for non-living particles entails collecting a specific volume of air and analysing it with a particle counter. The particle counter features a specially designed dark chamber or sensor that utilizes a laser, mirrors, and optics to detect particles, accompanied by a pump that facilitates air sample passage through the sensor[4]. Acceptance criteria for non-living particle are shown in Table no 1.

GRADE	At rest		In operation	
	0.5 µm	5.0 µm	0.5 µm	5.0 µm
A	3520	20	3520	20
B	35200	29	352000	2930
C	352000	2930	3520000	29300
D	3520000	29300	Not defined	Not defined

Table no 1: Acceptance criteria

2. Air circulation pattern

In cleanroom design, airflow patterns are categorized into three main types: laminar flow (unidirectional), turbulent flow (non-unidirectional), and mixed flow patterns. To achieve the desired airflow, the AHU supply to each location must be calibrated to meet the specified design flow rates and tolerances[5]. To ensure optimal airflow distribution, this adjustment is essential, and the room must also maintain a minimum air exchange rate of 20 changes per hour. Acceptance criteria for Airflow pattern shown in Table no 2.

Classification of Cleanrooms	**Air Exchange Rate per Hour**
Cleanroom Class 100	Not Less Than 250
Cleanroom Class 10000	60 with a tolerance of ±10%
Cleanroom Class 100000	40 with a tolerance of ±10%

Table no 2: Airflow pattern

3. Air flow measurement

The speed at which air moves, known as airflow velocity, is usually measured in feet per minute. This term describes the circulation of air between different spaces. The flow of air is driven by pressure gradients, with air naturally moving from high-pressure zones to low-pressure zones, behaving similarly to a fluid.

Acceptance criteria: The specified air circulation parameters are 20 air changes per hour and an average velocity of 90 ft/min, with an acceptable deviation of ±20%[6].

4. Pressure gradients

This test is designed to determine the HVAC system's efficiency in maintaining the specified pressure gradients between the facility, adjacent areas, and individual rooms within the facility. The pressure gradients is measured using a manometer mounted on the walls of adjoining areas and is typically maintained within a range of 5 to 20 mm/Hg.

Acceptance criteria:

The pressure difference between the classified area and adjacent areas with lower levels of contamination should be at least 10Pa.

The pressure difference between the classified and unclassified areas should be at least 15Pa.

5. Recovery test

The recovery performance test evaluates how effectively the HVAC system can restore controlled conditions within a specified time frame, typically 15 minutes. The process involves the following steps:

1. The HVAC system is deactivated, and the initial humidity and temperature levels in the control zone are measured and recorded.
2. The test parameters are then set to a humidity level of 75% and a temperature of 400°C.
3. The HVAC system is then enabled, initiating the recovery sequence.
4. The time taken for the humidity and temperature to stabilize to their desired levels is recorded.

This recovery test ensures that airborne particles are efficiently flushed out and that temperature and humidity conditions are restored promptly, demonstrating compliance with European Union Good Manufacturing Practice (EUGMP) standards, as evidenced by the results in Table 3.

Test Parameter	No of Particles ≥ 0.5µm/m^3	Acceptance Limit	Recovery Time (mins)
Initial Reading	15110	NMT 15 mins	8
Worst Case	11028210		
Reading Final Reading	1310		

Table no 3: Recovery test

6. Filter leakage assessment

The purpose of this test is to validate the proper installation and integrity of the HEPA filter system.

1. An anemometer (velometer) is placed upstream of the AHU system.
2. Measurements of air velocity are taken from each corner, recorded, and displayed on a digital monitor.
3. The measured air velocity must fall within the accepted upper limit for the HEPA filter.

If the air velocity exceeds the permissible upper limit, **silicon gas cut** is applied to reduce leakage, ensuring proper functionality of the filter system.

7. Particle count Measurement

The objective of this test is to ensure the cleanliness of clean rooms by evaluating the concentration of viable particles, which provide an indication of microbial load. The procedure involves:

1. The concentration of particles is assessed using a particle counter.
2. Taking measurements in both pre-operational and operational conditions.
3. The results are evaluated in accordance with the established standards for cleanroom areas classified as Grade A, B, C, and D.

The particle count must meet the required criteria to ensure compliance[7.] For specifics on

the acceptance criteria, you can refer to Table 4: Acceptance Criteria for Particle Count

Classification of Cleanrooms	Particles per cubic foot	Colony-forming units per cubic foot
100	100	Less than 0.1
10000	10000	Less than 0.5
100000	100000	Less than 2.5

Table no 4 : Particle count range

8. Temperature and moisture levels

The relative humidity of air indicates its water vapor content, which is influenced by changes in temperature. As air temperature increases, the air can hold more water vapor, causing relative humidity to decrease. A decrease in temperature is accompanied by an increase in relative humidity. The test evaluates the HVAC system's capacity to regulate temperature and relative humidity levels within a predetermined range.

Acceptance criteria:

Temperature should range from 21°C to 25°C, with a maximum limit of 27°C.

Humidity levels should range from 40% to 50%, with a maximum limit of 55%.

9. DOP/PAO filter leak test

To test the integrity of HEPA filters, a Poly alpha olefin (PAO) aerosol is generated using an aerosol generator. The aerosol is directed upward, and the receptor probe of the HEPA filter detects the amount of aerosol that is not captured. This amount must be below the HEPA filter's established upper limit. Dioctyl phthalate (DOP) was once used for this test, but concerns over its carcinogenic effects led to its replacement with PAO, the now-preferred testing agent.

10. Sound level test

To verify that the clean room area meets the required noise standards, a sound level test is performed, utilizing a sound level meter to measure the sound levels[8]. The equipment must be properly calibrated, with calibration traceable to national or international standards. Acceptance criteria for Sound level test shown in Table no 5.

Table no 5: Acceptance criteria

S.no	Classification of Cleanrooms	Sound Level Threshold (dB)
1	Class 100/ISO 5	Not More Than 60
2	Class 10000/ISO 7	Not More Than 80
3	Class 100000/ISO 8	Not More Than 60

11. Microbial Count

Soya bean Casein Digest Agar is a suitable solid growth medium for identifying bacterial and fungal contaminants. The ideal dimensions for settle plates and contact plates are 90 mm and 55 mm in diameter, respectively. This media is used to monitor airborne microbial contamination levels in critical areas. For detailed acceptance criteria, refer to Table no 7.

Table no 6: Acceptance criteria

TESTS	Alert Level	Alert Level
1. Settle Plate Test: Colony-Forming Units (CFU) per 90 mm Plate over 4 Hours		
Under dispensing and sampling booth Alternate Location	Not More Than 1	Not More Than 1
	Not More Than 75	Not More Than 100
2.Active Air Sampling: Colony-Forming Units per Cubic Meter of Air (CFU/m^3)		
Within the Dispensing and Sampling Booth Alternate location	Not More Than 1	Not More Than 5
	Not More Than 100	Not More Than 200
3.Sampling: Colony-Forming Units per 55 mm Plate (CFU)		
Within the Dispensing and Sampling Booth Other location	Not More Than 10	Not More Than 25
	Not More Than 25	Not More Than 50

12. Fresh Air Assessment

The fresh air intake is monitored at the inlet of the fresh air damper, and the total air changes are calculated. To determine the fresh air intake percentage for each cycle in individual rooms, the fresh air intake is divided by the room's total air changes, and the result is then multiplied by 100 to obtain the percentage.

CONCLUSION

This article emphasizes the importance of thorough validation and qualification of HVAC systems in pharmaceutical facilities to ensure compliance with product quality standards HVAC systems are critical in creating and maintaining the precise environmental conditions required for producing high-quality products, emphasizing the importance of their validation. This article outlines the key parameters for validating HVAC systems, the procedures for qualifying them, and the acceptance criteria that must be met, all of which are consistent with established guidelines. Additionally, the HVAC system demonstrated its ability to achieve performance qualification objectives, proving its suitability

for routine use as confirmed through intended experiments.

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