Volume 9, Issue 7, July – 2024 International Journal of Innovative Science and Research Technology
ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL1732

Air Quality Matters: A Holistic Strategy and Approach to HVAC System Validation in Pharmaceuticals

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Abstract:- Heating, ventilation, and air conditioning (HVAC) systems plays a critical role in pharmaceutical manufacturing facilities by ensuring the integrity of product quality, safety, and compliance with regulatory requirements. HVAC validation is an essential process that verifies and documents the performance and effectiveness of these systems. This review paper explores various strategies and approaches to HVAC validation in pharmaceutical manufacturing facilities, including regulatory considerations, validation methodologies, risk assessment, and ongoing monitoring. The paper also discusses the challenges associated with HVAC validation and presents best practices to improve the effectiveness of the validation process.

Keywords:- *Heating, Ventilation, and Air Conditioning (HVAC), Validation.*

I. INTRODUCTION

The validation of HVAC systems is critical to ensure they meet regulatory requirements and maintain environmental conditions crucial for pharmaceutical manufacturing. This paper explores strategies, regulatory guidelines, and best practices for HVAC validation, including risk assessment and methodologies. It addresses challenges and emphasizes continuous improvement, preventive maintenance, and calibration. Real-world examples illustrate successful validation implementations. Recommendations for improvement and future trends are discussed. Effective HVAC validation ensures product quality, regulatory compliance, and safe pharmaceutical production.

A. Importance of HVAC Systems in Pharmaceutical Manufacturing

➢ *Product Quality:*

- *Temperature and Humidity Control:*

HVAC systems ensure that pharmaceutical manufacturing areas maintain precise temperature and humidity levels, which are critical for the stability and efficacy of pharmaceutical products.

- *Cleanroom Environment:*

HVAC systems provide high-efficiency particulate air (HEPA) filtration and control the airflow patterns, preventing the introduction of contaminants and maintaining a sterile environment necessary for the production of drugs with stringent quality requirements.

- *Airborne Particle Control:*

HVAC systems help to remove airborne particles, such as dust, bacteria, and other contaminants, minimizing the risk of cross-contamination and ensuring product purity

➢ *Regulatory Compliance:*

- *GMP Requirements:*

HVAC systems are essential for complying with Good Manufacturing Practices (GMP) regulations, which mandate controlled environmental conditions to prevent product contamination, ensure batch-to-batch consistency, and protect patient safety.

- *Validation and Documentation:*

HVAC systems require thorough validation to demonstrate their performance and compliance with regulatory guidelines. Proper documentation of HVAC system design, installation, qualification, and maintenance is crucial for regulatory inspections and audits.

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ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL1732

➢ *Employee Safety and Comfort:*

- Indoor air quality:

HVAC systems improve the indoor air quality by controlling ventilation rates, filtering pollutants, and removing harmful airborne substances, protecting employees from respiratory issues and occupational hazards.

- *Temperature Control:*

HVAC systems maintain comfortable working temperatures, ensuring employee productivity, well-being, and safety.

- *Adequate Airflow:*

Proper ventilation and airflow management prevent the accumulation of airborne contaminants, odours, and hazardous substances, promoting a healthier and safer working environment.

➢ *Energy Efficiency and Cost Savings*

- *Energy Consumption:*

HVAC systems can consume a significant amount of energy in pharmaceutical manufacturing facilities. Energy-efficient design, equipment selection, and control strategies can help minimize energy usage, reduce operational costs, and support sustainability goals.

- *Demand-Based Control:*

Implementing HVAC systems with demand-based control strategies, such as variable air volume (VAV) systems and occupancy sensors, optimizes energy usage by adjusting ventilation and cooling requirements based on real-time needs.

B. Regulatory Considerations

Overview of relevant regulatory guidelines (e.g., FDA, EMA, WHO); Regulatory guidelines play a crucial role in ensuring the safety, efficacy, and quality of pharmaceutical products. Here is an overview of some relevant regulatory guidelines from key regulatory authorities:

➢ *U.S. Food and Drug Administration (FDA):*

- *Current Good Manufacturing Practice (cGMP) regulations:*

FDA's cGMP regulations outline the requirements for the design, operation, and control of pharmaceutical manufacturing facilities, including HVAC systems. Title 21 of the Code of Federal Regulations (CFR) Part 211 covers cGMP regulations for finished pharmaceuticals, while Part 210 covers general cGMP requirements.

- *Guidance for Industry Sterile Drug Products Produced by Aseptic Processing*

Current Good Manufacturing Practice: This guidance document provides recommendations for HVAC systems in sterile pharmaceutical manufacturing facilities, addressing topics such as air filtration, temperature control, and environmental monitoring.

➢ *European Medicines Agency (EMA):*

- *EU GMP Annex 1*

Manufacture of Sterile Medicinal Products: Annex 1 provides guidelines for the manufacture of sterile medicinal products, including requirements for cleanrooms, HVAC systems, and environmental monitoring. It covers aspects such as air quality, particle control, and contamination prevention.

- *EU GMP Chapter 3*

Premises and Equipment: Chapter 3 of the EU GMP guidelines addresses the requirements for premises and equipment, including HVAC systems, in pharmaceutical manufacturing facilities. It covers aspects such as facility design, control of environmental conditions, and qualification/validation of HVAC systems.

➢ *World Health Organization (WHO):*

- *WHO Good Manufacturing Practices (GMP) for Pharmaceutical Products*

The WHO GMP guidelines provide a global standard for the manufacturing of pharmaceutical products. Chapter 3 of these guidelines covers premises and equipment requirements, including HVAC systems. It addresses aspects such as facility design, cleanliness, air handling, and environmental control.

- *WHO Technical Report Series, No. 961: Annex 5*

Supplementary guidelines on good manufacturing practices for HVAC systems for non-sterile pharmaceutical dosage forms: This WHO publication provides detailed guidance on HVAC systems for non-sterile pharmaceutical manufacturing facilities. It covers topics such as ventilation principles, air quality, filtration, and monitoring.

- *Guidelines on Heating, Ventilation and Air-Conditioning Systems for Non-Sterile Pharmaceutical Product*

Annex 8: provides guidelines for sterile pharmaceutical production, covering requirements for clean area design, clean air devices, environmental monitoring, validation, and maintenance. It emphasizes ensuring the quality and sterility of pharmaceutical products through proper facility design and operational practices.

II. MATERIAL AND METHOD

❖ *Material*

Relevant internal Procedures of Pharmaceutical industries are referred like Standard Operating Procedures (SOPs) ,Validation Protocols and reports , Preventive maintenance records of Equipment , Calibration records of instruments and external documents include book references, peer-reviewed journals, supplier reports, published papers (review and research papers), and more. In addition, Regulatory guidelines were followed.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL1732

❖ *Method*

To initiate work on this project, I first visited the pharmaceutical industry site to thoroughly review the standard operating procedures and guidelines specific to HVAC systems, focusing on validation strategies I then observed activities related to the HVAC system within the Production area ,noting the challenges that arise in maintaining optimal conditions during the manufacturing of dosage forms. Additionally, I examined the relevant documentation pertaining to HVAC systems, ensuring compliance and performance standards were met.

➢ *HVAC Validation Steps*

- *Installation Qualification (IQ)*
- *Operational Qualification (OQ)*
- *Performance Qualification (PQ)*
- *Validation protocols and documentation requirements*

➢ *HVAC Validation Steps:*

- Installation Qualification (IQ): Verify correct installation according to specifications and regulatory requirements.
- Operational Qualification (OQ): Test system components and functionalities under normal conditions.
- Performance Qualification (PQ): Demonstrate consistent maintenance of required environmental conditions.
- Risk Assessment: Identify and mitigate risks associated with HVAC system.
- Continuous Monitoring and Maintenance: Ensure ongoing performance and compliance through monitoring and maintenance.

✓ Routine monitoring of critical parameters, preventive maintenance activities, calibration of sensors and instruments, and periodic revalidation are essential components of maintaining the validated state of the HVAC system.

- Van type Anemometer, Hot wire anemometer and Capture Hood
- PAO (Poly alpha olefin) Aerosol generator
- Photometer
- Air borne particulate counter
- Camera-Based Recording of Airflow Patterns from Smoke Generators
- Calibrated Air borne particle counter
- Thermometers and Hygrometers
- Magnehelic Gauge

Following methods I have examined during the project-

A. Air Velocity / Air Changes By Hot Wire/Vane Type Anemometer:

➢ *Objective:*

Evaluate the performance of the HVAC system to ensure it meets specified requirements for air velocity, airflow volumes, and the necessary number of air changes.

➢ *Acceptance Criteria:*

Ensure that the Air Change per Hour (ACPH) of all HVAC systems meets the designated Design Qualification standards. Specifically, it should adhere to the following requirements:

- Grade D areas should have a minimum of 20 air changes per hour.
- Grade C areas, including Non-Sterile and Sterile Manufacturing areas, Microbiology Labs, etc., should maintain a minimum of 50 air changes per hour.
- Grade B and A areas within Sterile Manufacturing and Sterility testing areas should maintain a minimum of 100 air changes per hour.

B. Integrity Test of Hepa Filters:

➢ Objective: To Confirm the effectiveness and reliability of HEPA filters.

➢ Test Apparatus: PAO (Poly alpha olefin) Aerosol generator, Photometer

Table 1 Different Types of Leakages and their Respective Corrective Actions are Mentioned in the Following Table:

Type of Leakage	Corrective Action
Airborne leaks through HEPA filters	Replace or repair HEPA filters as necessary
Seals around ductwork or access panels	Apply silicone sealant to seal leaks
Cracks or gaps in ductwork	Patch or repair using appropriate materials
Leaks at connection points or joints	Tighten connections or replace gaskets as needed
Leaks around windows or doors	Apply weatherstripping or caulking to seal gaps
Leakage due to damaged insulation	Repair or replace insulation to eliminate leaks

➢ Acceptance Criteria: Leakage should be NMT 0.01%

C. Air Borne Non-Viable Particle Monitoring:

➢ Objective: To verify that airborne particle levels at various locations within the core process areas consistently remain below the specified threshold for particles measuring 0.5 microns or larger per cubic meter of air.

➢ Test Apparatus - Air borne particulate counter.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL1732

Table 2 Acceptance Criteria:

ISO Classification Number	Specify the maximum concentration limits for particles per cubic meter of air, focusing on particles equal to or larger than the considered sizes.	
	0.5 µm	5µm
ISO 7	352,000	2930
ISO 8	35,20,000	29,300

D. Smoke Test (Air Flow Direction):

- Objective: To visualize the airflow patterns within the process area to ensure that there is no cross-contamination between different zones.
- Test Equipment: Utilize a camera to capture the airflow pattern generated by the smoke generator.
- Acceptance Criteria:
- Ensure uniform diffusion of smoke/fog at supply grill/risers and passage through return terminals.
- Verify absence of airflow short-circuiting, dead pockets, and confirm unidirectional airflow from supply to return.
- Validate the movement of smoke/fog from areas under positive pressure to those under negative pressure.

E. Recovery Test (Or Decontamination Time):

- Objective: To evaluate the capability of the core process area to return to its specified cleanliness class within a predetermined time period.
- Test Apparatus:
- Calibrated Air borne particle counter
- Thermometers and Hygrometers
- Magnehelic Gauge
- Acceptance criteria:
- The recovery time (or decontamination time) must not exceed 15-20 minutes.

F. Pressure Differential, Temperature And Relative Humidity Test:

- *Objective: To confirm that the HVAC system can consistently control and maintain the specified levels of differential pressure, temperature, and relative humidity across different rooms.*
- *Test Apparatus: Magnehelic Gauge, Thermometers and Hygrometers.*

G. Air Borne Viable Particle Monitoring By Settle Plate:

- *Objective: To assess the concentration of viable particles in a controlled environment through the use of settle plates.*
- *Test Instrument/Sampling aids: Media plates*

Table 3 Acceptance Criteria

Plates	Alert Limits	Action Limit
Total Bacterial Count (TBC)	NMT 60 cfu / plate	NMT 100 cfu / plate
Total Fungal Count (TFC)	Less than 1 cfu / plate	Less than 1 cfu / plate

III. DISCUSSION

Validating HVAC systems in pharmaceutical manufacturing involves a complex process that demands meticulous planning, implementation, and ongoing enhancement. By adhering to regulatory guidelines like WHO , EU US FDA ISO etc, implementing best practices, and embracing technological advancements, pharmaceutical companies can ensure their HVAC systems effectively support product quality and regulatory compliance. This review underscores the importance of HVAC validation as a cornerstone of pharmaceutical manufacturing, highlighting the need for ongoing efforts to optimize system performance and safeguard public health.

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ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL1732

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