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Review Article

Validation and Various Qualifications in HVAC System - A Review from Pharmaceutical Quality Assurance Prospect

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ABSTRACT
The safety of personnel and efficacy of the material including raw ingredients, in-process goods and finished products as well as machineries in the pharmaceutical industry is majorly impacted by the air ventilation quality within the industry. HVAC system stands for Heating, Ventilation and Air Conditioning system, which ensures the optimum quality of air environment as directed by regulatory authorities. The performance of HVAC system is ascertained by conducting validation of this system within specified duration. Validation of HVAC system is achieved at three levels such as installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ); Which is subject to provide documented evidence about the accuracy of results produced by it. The validation of HVAC system involves systemized and assembled documents of its functional specifications such as design drawings, plans, and specifications; followed by validation master plan involving testing, adjusting, and balancing (TAB); and finally, the startup reports. The parameters analyzed are air flow velocity, air flow pattern, air changes per hour, filter leak test, particle count, viable monitoring, filter integrity test, pressure difference, recovery test for temperature and humidity, temperature and humidity uniformity, and fresh air determination.

Keywords: Validation, Installation qualification, Operational qualification and performance qualification.

INTRODUCTION

The Indian Society of Heating, Refrigerating and Air-Conditioning Engineers (ISHRAE) defines air HVAC system as "A system that must accomplish four objectives simultaneously, namely; control of air temperature; control of air humidity; control of air circulation; and control of air quality". HVAC technology aims to provide thermal comfort and acceptable indoor air quality. HVAC system design is a sub discipline of mechanical engineering, based on the principles of thermodynamics, fluid mechanics, and heat transfer[1]. The HVAC system is an extremely vital concern, which aids to enhance and maintain the quality of drug products. It mainly helps in achieving an optimal temperature, ventilation, and air conditioning in the production areas. The HVAC system design directly impacts prevention and control of cross contamination; and maintains hygienic condition at the work place. Certain pharmaceutical products such as parenteral, bulk drug, etc. that are temperature sensitive, HVAC system plays pivotal role. Temperature and ventilation parameters perpetuates during the processing, manufacturing and storage of the various drug substances and drug products, which ultimately influence their quality. Air conditioning implies not only to cooling of air but also maintenance of temperature, humidity, supply of outside air for ventilation, filtration of airborne particles, and air movement in the occupied space.

Validation is mandatory in the field of pharmaceutical industries as it ensured the accuracy, precession and reproducibility of results by ascertaining the optimal systems performance at different levels. Maintenance of quality of products is of great importance in order to deliver a quality product to the customer. Especially in the field of pharmacy which deals with drugs that directly affect the human body[2].

Rationalities of HVAC system[3,4]

The HVAC systems should be included in the architectural design for the following reasons:

The HVAC system's equipment and distribution elements are large size and consume substantial floor space and/or building volume.

HVAC systems constitute a major budget item.

The success or failure of thermal comfort efforts is influence greatly by the working condition of a building's HVAC systems; when passive systems are not used.

Health of personnel and efficacy of the material including raw ingredients, in-process goods and finished products as well as machineries in the pharmaceutical industry.

High efficiency particulate air

In order to achieve a proper cleanliness in the storage and quarantine area, High efficiency particulate air (HEPA) filters are used. They also maintain the aseptic condition in the working area. The efficiency and integrity of the filters that are used in this system must be checked at regular intervals by performing leak test. HEPA filters are the

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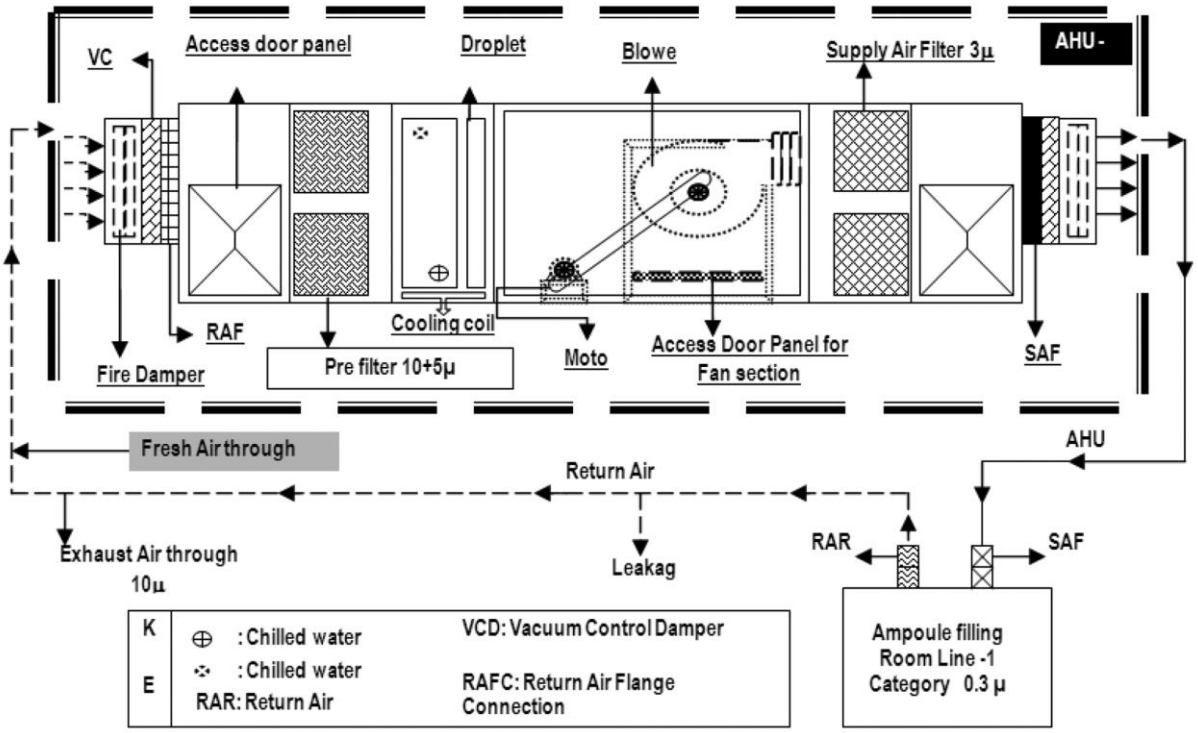

Figure 1: Construction and functioning of AHU.

Table 1: Air Classification as per WHO/EU/PICS GMP guidelines [9, 10]

Maximum permitted number of particles per m^3 greater than or equal to the tabulated size				
GRADE	AT REST [a]		IN OPERATION [be]	
	0.5 µm	5.0 µm	0.5 µm	5.0 µm
A	3,520	20	3,520	20
B	35,200	29	3,52,000	2,930
C	3,52,000	2930	35,20,000	29,300
D	35,20,000	29,300	Not Defined	Not Defined

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

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.

Table 2: Airflow velocity test and ACPH.

Grill/Filter ID no	Measured supply air velocity (cu ft/min)	Total air flow rate (cu ft/min)	Room Volume	ACPH
A06A/S-029/S-01	638			
A06A/S-029/S-02	649			
A06A/S-029/S-03	654	3326	2474	81
A06A/S-029/S-04	687			
A06A/S-029/S-05	698			

main part of the air handling unit (AHU). The AHU collects the outside fresh air and combines it with the air returning from the cubicles and then supplied the treated air back to the laboratory area. A part of the air exiting from the laboratory rooms is directly exhausted into the atmosphere by an exhaust fan, while the remaining air is directed to the AHU where it is filtered by passing through prefilters which is attached to the medium filters, to remove any entrapped particles and then the same air is conditioned for humidity and temperature control, and this filtered air is passed to the laboratory and other areas by a supply fan at desired pressure. HEPA filers are terminal filter which is attached at the entrance to the clean rooms (Fig. 1)[4,5].

Validation process of HVAC system

The validation process of HVAC system usually involves documented evidence with respect to various aspects of HVAC system such as:

functional specifications (the conceptual design)
Validation master plans
Startup reports
IQ
OQ
PQ

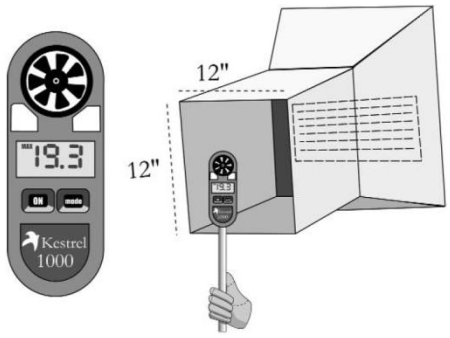

Figure 2: A velometer and method of measuring air velocity.

Figure 3: Laser Particle Counter[9].

Table 3: Particle Count Test.

Class	At rest		In operation	
	0.5 particles/m^3	5 particles/m^3	0.5 particles/m^3	5 particles/m^3
Grade "A"	3520	20	3520	20
Grade "B"	3520	29	352000	29
Grade "C"	352000	2900	3520000	2900
Grade "D"	3520000	29000	Not defined	29000

Functional specifications (the conceptual design)

It involves design drawing, system plans and specifications[6].

Design drawing which is relates to the dimension of the equipment, effectiveness of the equipment, availability of spares parts, and prompt services at reasonable cost,

System Plans explains the specific objectives that the manufacturer intents such as operation, cleaning, and maintenance, Low dust and sound generation.

Specifications wherein the manufacturer explains qualitative and quantitative aspects of the equipment;

Validation master plans

It consisting of contractor's document which is very specific to the manufacturer's requirements. It includes testing in-terms of visual and physicochemical, adjusting, and balancing (TAB) and which is usually performed in presence of vendor[6].

Startup reports

The report consists of commissioning reports which is the actual execution of validation protocols and validation procedure at different levels such as IQ, OQ, and PQ[6].

IQ report is a "Documented verification about all key aspects of the installation adhering to manufacturer's recommendation, bearing appropriate codes, and approved design qualification". The goal of IQ is to verify and document the quality of installation and integrity of HVAC system's components which is mentioned in functional specifications (the conceptual design) and Validation master plans. Design documents and literatures are used to design installation protocols. Control and measuring devices should be calibrated. IQ provides documented evidence that the installation was complete and satisfactory[6]. The simple meaning of this statement is that the equipment in question can be installed when it is qualified for installation, that is, when it passes the IQ test[7,8].

Figure 4: PAO Aerosol Generator and method of performing test [11]

OQ defines "Documented verification that the system or subsystem performs as intended throughout all specified operating range". It is recommended that the equipment should be operated only after it has passed the OQ Test.

OQ Test is performed by operating the equipment at normal range, at the higher range condition mentioned and including worst case conditions. The result should indicate the safety, optimum performance and forecast the

Table 4: Recovery test.

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

problems associated with the equipment. Operation controls, alarms, switches, displays, and other operational components should be tested. Measurements made in accordance with a statistical approach should be fully described. OQ provides documented evidence that utilities systems, or equipment and all its components operate in accordance with operational specifications without load[7,8]. *PQ* provides documented evidence about the consistent perform of the utilities, systems or equipment and all its components which are in accordance with the specifications under routine use with load. Test results should be performed over a suitable period of time to prove the consistency[7,8].

Validation test procedures

In general, various parameters to be evaluated and analyzed for the validation of HVAC system comprise of

Air flow pattern or smoke pattern,
Air flow velocity and Air changes per hour,
Filter leak test,
Particle count,
Viable monitoring,
Filter integrity test (Dioctyl phthalate (DOP)/ polyalphaolefin (PAO),
Pressure difference,
Recovery test (temperature and humidity),
Temperature and humidity uniformity test, and
Fresh air determination.

Air flow or smoke pattern:

The air flow parameter is evaluated by burning a titanium tetrachloride stick and then placing the burning stick in front of the AHU. The distribution of smoke is observed. It should be uniform[9]. An example is illustrated in Table 1.

Air flow velocity and Air changes per hour (ACPH)

The purpose of this test is to measure airflow velocity in terms of uniformity and supply airflow rate in clean zones of unidirectional airflow systems. The data given in the Table 2 is an example to shows the method to document the results of Airflow Volume Test and ACPH[11]. The values given are in the acceptable range as per the specification by regulatory authorities.

The test is performed by dividing the area of HVAC into four hypothetical grids and then air velocity is measured at each grid. The average air velocity (V) is calculated. Total air volume (T) is calculated by using the following equation;

$T = A \times \mathrm{V}$

Where; A = Area of the HEPA filter inlet (ft)

Later, the volume of the room is calculated and ACPH is obtained by dividing the total air change by the volume of the room.

Filter leak test

The objective of this test is to confirm that the filter system is properly installed and that leaks have not developed during installation.

The leak test on HEPA filter is conducted by placing a velometer in the front of the AHU system and documenting the air velocity from all the corners that is being displayed on the digital screen (Fig. 2). The air velocity is accepted to be within the higher limit of the HEPA filter. In case it is found to exceed the upper limit, a gas cut (silicon) is used to decrease the leakage[12].

Particle count

The purpose of this test is to provide overall cleanliness of the environment with respect to the concentration of viable particles and thus providing an indication of microbial load of the clean rooms. The data given in the Table 3, shows particle count test results confirms to EUGMP Grade "B"[13,14].

This test is performed using a particle counter (Fig. 3). Particle count is taken before and during the working condition. The particle count should be within the range as per the standards of Grade A, B, C, and D area.

Viable monitoring

Viable monitoring should be done every day by the swab test and using nutrient agar medium for the incubation of microorganisms. The different media plates are exposed in every manufacturing section including the reverse air duct of the HEPA filter located at the back of the cubicle. The microorganism count should be within the range and if it is found out of specification for consecutive two times, an effective corrective and preventive action is initiated[14].

Filter integrity test (DOP/PAO test)

The filter integrity test is performed on HEPA filters this is done preparing a PAO aerosol using an aerosol generator and allowing an upward flow of the aerosol (Fig. 4). The receptor probe of the HEPA is monitored to know the amount of the aerosol reversed. Total amount of reversed aerosol should not exceed the higher limit of the HEPA filter. Previously DOP was employed to perform this test but because of the carcinogenicity of the DOP, it is being prohibited and replaced by the PAO, which is currently used[13,14].

Pressure difference

The test aims at verifying the capability of HVAC system and to maintain the specified pressure difference between the installation and its surrounding areas and also between the separate rooms within the installation. Pressure difference is calculated by making use of the manometer attached at the walls of the adjacent area. The pressure difference is generally kept between 5 and 20 mm/hg pressure[13,14].

Recovery test

Recovery performance is evaluated upon the time frame of 15 minutes, the recovery test indicates the time required to flush of the airborne particles accumulated inside the control zone, during the period when AHU is put off. The recovery of temperature and humidity is recorded (Table

Table 5: Temperature and Humidity Mapping.

Location ID of data logger	Temperature in °C			Relative humidity in % RH		
	Minimum	Maximum	Average	Minimum	Maximum	Average
T1	20.27	23.50	21.88	58.88	63.93	62.64
T2	20.29	24.49	22.39	59.11	64.62	62.58
T3	21.15	22.45	21.80	59.18	63.60	62.40
T4	20.31	24.45	22.38	58.48	62.72	61.88
T5	22.33	23.54	22.93	55.96	60.83	60.09
T6	20.16	24.37	22.26	58.50	62.92	61.98
T7	22.43	24.59	23.01	58.38	62.86	61.81
T8	20.95	24.52	22.73	58.88	63.93	62.64
T9	20.09	24.29	22.19	59.88	64.84	62.56
T10	20.27	23.48	21.87	59.29	63.84	62.67

4). For this purpose the humidity and temperature are checked at the off position of the HVAC system. Followed by increasing the humidity to 75% and temperature to 400°C and again the temperature and humidity are recorded after switching on the HVAC system, and the time required for temperature and humidity to stabilize the is recorded. The data given in the Table no 4. shows recovery test results confirms to EUGMP[13,14].

Temperature and humidity uniformity test

The objective of this test is to demonstrate the capability of the clean room air handling system to maintain air temperature and relative humidity within the desired limits over specified time period. The uniformity of temperature and humidity are monitored by employing a calibrated thermometer and manometer, respectively. The two parameters are monitored on daily basis, the data given in the Table 5 is an example of temperature and humidity mapping test results confirms which are within the specified limit[14].

Fresh air determination

The fresh air intake is observed at the inlet on the fresh air dumper. The total air change is calculated. The intake fresh air is divided by the total air change in the room and multiplied by 100 to obtain the percent fresh air intake on each cycle by the HVAC system in the entire individual rooms[13,14].

CONCLUSION

After all the test it has been observed that the design criteria for all the required rooms is achieved and objective of performance qualification is met with the HVAC system of all the area and is suitable for routine intended use as established by carrying out intended experiments and comparing the results with the predetermined acceptance criteria (limits) after which the HVAC system is ready for routine use by qualified personnel.

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