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"Exploring HVAC System Validation and Qualifications in Pharmaceutical Quality Assurance"

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ABSTRACT
The quality of the air flow in the pharmaceutical industry has a big effect on the safety of the workers and the effectiveness of the materials, such as raw materials, things in progress, final products, and machines. HVAC stands for "Heating, Ventilation, and Air Conditioning." This system makes sure that the air quality is just right, as required by government rules. Validating the HVAC system within a certain amount of time is one way to find out how well it works. There are three levels of validation for an HVAC system: installation qualification (IQ), operating qualification (OQ), and performance qualification (PQ). Each level requires proof that the results it produces are correct. The HVAC system's functional specifications are organized and put together in the form of design drawings, plans, and specifications. This is followed by a validation master plan that includes testing, adjusting, and balancing (TAB), and finally, the starting reports. Some of the things that are looked at are air flow speed, air flow pattern, air changes per hour, particle count, valid tracking, filter integrity test, pressure difference, temperature and humidity recovery test, temperature and humidity consistency test, and fresh air determination.

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

INTRODUCTION

In its definition, the Indian Society of Heating, Refrigerating and Air-Conditioning Engineers (ISHRAE) says that an air HVAC system must handle four things at the same time: the temperature, the humidity, the flow, and the quality of the air. The goal of HVAC technology is to keep rooms at a comfortable temperature and with good air quality. The creation of HVAC systems is a branch of mechanical engineering that uses thermodynamics, fluid physics, and heat movement to explain how things work. It is very important to take care of the HVAC system because it helps keep the grade of the drugs high. Its main job is to help keep the working areas at the right temperature and with the right amount of air flow and cooling. The design of the HVAC system has a direct effect on keeping the workplace clean and preventing and controlling cross-contamination. For pharmaceuticals that need to be kept at a certain temperature, like injectable drugs, bulk drugs, etc., the HVAC system is very important. Temperature and air flow conditions stay the same while different drug chemicals and drug products are being processed, manufactured, and stored, which affects their quality in the end. Air conditioning is more than just cooling the air. It also controls the temperature and humidity, brings in outside air for airflow, filters out particles in the air, and moves air around in the area that people are in.
In the pharmaceutical industry, validation is necessary to make sure that results are accurate, consistent, and repeatable by finding the best way for systems to work at different levels. Keeping the standard of the items high is very important if you want to give a good product to the customer. This is especially true in the area of medicine, which deals with drugs that have direct effects on the body2.
Reasons for having an HVAC system3,4
Because of the following, the HVAC systems should be part of the building design:
The tools and delivery parts of the HVAC system are big and take up a lot of floor room and/or building volume.

A big part of the budget goes to HVAC systems.
How well or how poorly thermal comfort efforts work depends a lot on how well a building's HVAC systems are working when passive systems are not used.
The pharmaceutical business has to worry about the health of its workers and the effectiveness of its raw materials, goods that are still being made, finished goods, and machines.
Particulate air with high performance
High efficiency particulate air (HEPA) screens are used to keep the store and quarantine room clean. In addition, they keep the job place clean and germ-free. Leak tests must be done on a regular basis to make sure that the filters in this system are still working well and aren't broken. These are the HEPA screens

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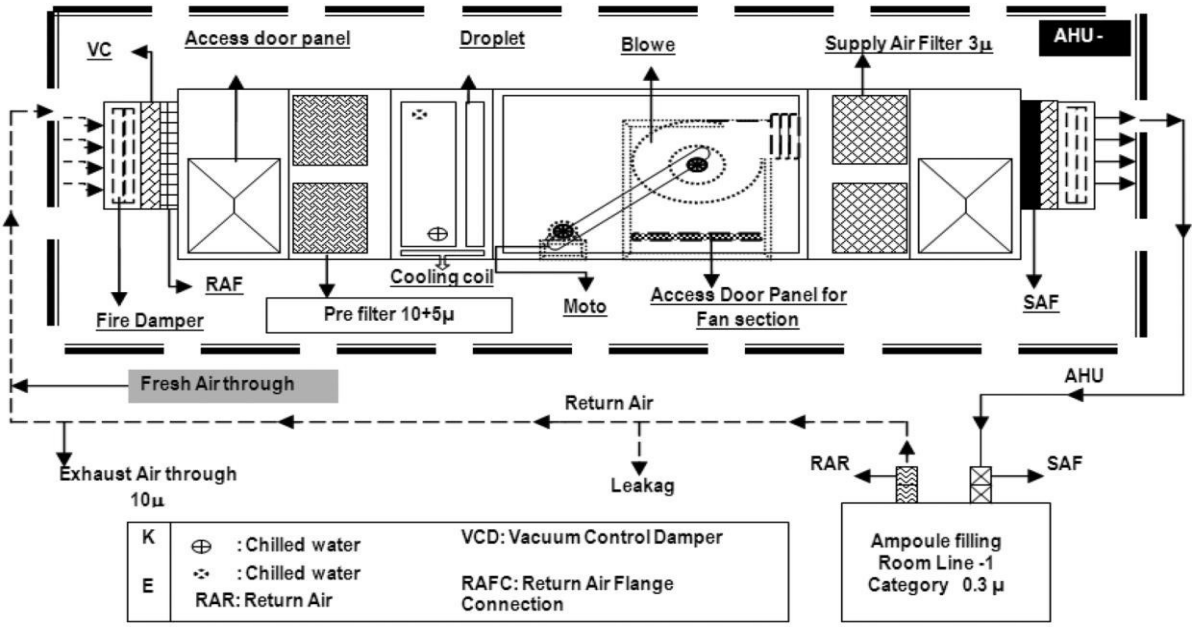

Figure 1: Construction and functioning of AHU.

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			

The air handling unit's (AHU) main part. The AHU takes in fresh air from the outside and mixes it with air coming back from the cells. The cleaned air is then sent back to the lab area. An exhaust fan sends some of the air leaving the lab rooms directly into the air outside. The rest of the air is sent to the AHU and filtered by prefilters that are attached to the medium filters to get rid of any particles that got caught. The air is then conditioned to control the humidity and temperature, and a supply fan sends the filtered air to the lab and other areas at the right pressure. HEPA cleaners are done for good.

There is a screen at the door to the clean rooms (Fig. 1)4,

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

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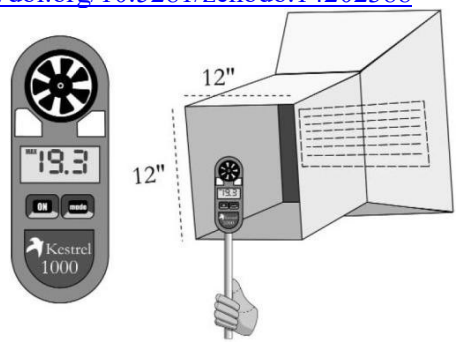

Figure 2: A velometer and method of measuring air velocity.

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)

Design drawings, system plans, and specs are all part of it.6. A design plan that shows the size of the equipment, how well it works, where to get extra parts, and how quickly and cheaply it can be serviced. The manufacturer's specific goals are written in the system plans. These goals include operation, cleaning, upkeep, and making as little noise and dust as possible. Specifications in which the maker describes the equipment's quality and quantity; Master plans for validation

It includes a paper from the provider that is very specific to the needs of the maker. It involves visual and physical testing, as well as tuning and balancing (TAB), and it is generally done with the seller present6.

Reports on startups

The report is made up of ordering reports, which show how the validation processes and procedures were carried out at different levels, like IQ, OQ, and PQ6.

The IQ report is a "documented confirmation about all key aspects of the installation complying with manufacturer's recommendations, meeting relevant codes, and meeting approved design qualifications." The purpose of IQ is to check and record the quality of installation and the stability of the HVAC system's parts, as described in the initial design and validation master plans. Installation procedures are made with the help of design papers and books. It is important to adjust measure and control tools. IQ shows proof that the work was finished and met expectations.6. The simple meaning of this sentence is that the equipment can be put in place when it is

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

qualified for installation, that is, when it passes the IQ test[7,8].
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

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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;

$T = A \times V$

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

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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

Following all the tests, it was seen that the design criteria for all the needed rooms were met, as well as the performance qualification goal for the HVAC system in the whole area. This means that the system is ready for regular use by qualified personnel, as shown by the results of the tests comparing the system to the acceptance criteria (limits).

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