REVIEW ARTICLE

Demand of pharmaceutical facility functionality: Validation and qualification of HVAC system

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Heating, ventilation, and air system encompasses heating, ventilation, and air conditioning, which is integral component of pharmaceutical facility functionality. The system is needed for maintenance of a suitable temperature, for continuous flow of air, which ultimately prevents cross-contamination and accumulation of air and to ensure the cooling of air in the premises. The three core facets of HVAC system validation comprises of installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). Validation of HVAC system is an essential subject to provide documented evidence about the accuracy of results produced by it. The validation of HVAC system involves systemized and assembled documents of functional specifications; design drawings, plans, and specifications; validation master plan; testing, adjusting, and balancing (TAB); and startup reports. The various parameters to be evaluated for the validation of HVAC system include air flow pattern, air flow velocity, 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.

Key words: *Heating, qualification, validation, ventilation and air conditioning*

INTRODUCTION

Validation is a very vast topic in the field of pharmaceutical sciences. It ensures about the accuracy of results being produced by any system. Maintenance of quality of products is of great importance, especially in the field of pharmacy as this field deals with drugs which directly affect the human body.[1]

The heating, ventilation, and air conditioning (HVAC) system is an extremely vital concern, which aids to enhance and maintain the quality of drug products. It assists in achieving an adequate temperature, ventilation, and air conditioning in the premises. The HVAC system design has an immense impact on the prevention and control of cross contamination and for the achievement of a hygienic condition at the work place. Temperature and ventilation are very important parameters to be perpetuated during the processing as well as storage of the various drug substances and drug products, which ultimately influence their standard. Air conditioning not only mean cooling of air but also embrace temperature, moisture in the air (humidity), supply of outside air for ventilation, filtration of airborne particles, and air movement in the occupied space.

The American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) 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".[2]

IMPORTANCE OF HVAC SYSTEM

HVAC systems are of great importance to architectural design efforts for four main reasons. Firstly, these systems often require substantial floor space and/or building volume for equipment and distribution elements that must be accommodated during the design process. Secondly, HVAC systems constitute a

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major budget item for numerous common building types. Thirdly, the success or failure of thermal comfort efforts is usually directly related to the success or failure of a building's HVAC systems (when passive systems are not used), even though the HVAC systems should be viewed as part of the larger architectural system. Last, but not least, maintaining appropriate thermal conditions through HVAC system operation is a major driver of building energy consumption.[3]

High-efficiency particulate air

To achieve an appropriate cleanliness in the premises, High-efficiency particulate air (HEPA) filters are used. The HEPA filters are employed to ensure the aseptic condition. The integrity of the filters should be checked at regular intervals by performing leak test. HEPA filters are a part of the air handling unit (AHU).

In the AHU, the outside fresh air, combined with the return air from the cubicles, is treated by AHU and supplied 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 recirculated to the AHU as return air by a return fan. The air entering into the AHU is filtered by prefilters and medium filters and then air conditioned for humidity and temperature control, and is supplied to the laboratory area by a supply fan at desired pressure. The supply air is terminal filtered by HEPA filers at the entrance to the clean rooms [Figure 1].[4,5]

VALIDATION OF EQUIPMENT

Equipment is one of the basic components of the pharma processing and hence, a critical validation issue also. If one wants a pharmaceutical process to be validated then the equipment used plays a very major role in the whole process. The equipment validation process generally covers the following steps:

1. Customer requirements or user requirement specification (URS)
2. Preparation of design qualification (DQ) and its certification
3. Installation qualification (IQ)
4. Operational qualification (OQ)
5. Performance qualification (PQ).

User requirement specifications

Customer of the equipment has certain expectations about the equipment which he wants to use. Some of the general requirements may be stated in the form of certain parameters like:

1. Size of the equipment
2. Speed of the equipment
3. Effectiveness of the equipment
4. Availability of spares, change parts, and prompt services at reasonable cost
5. Ease of operation, cleaning, and maintenance
6. Low dust and sound generation
7. Lesser breakdowns

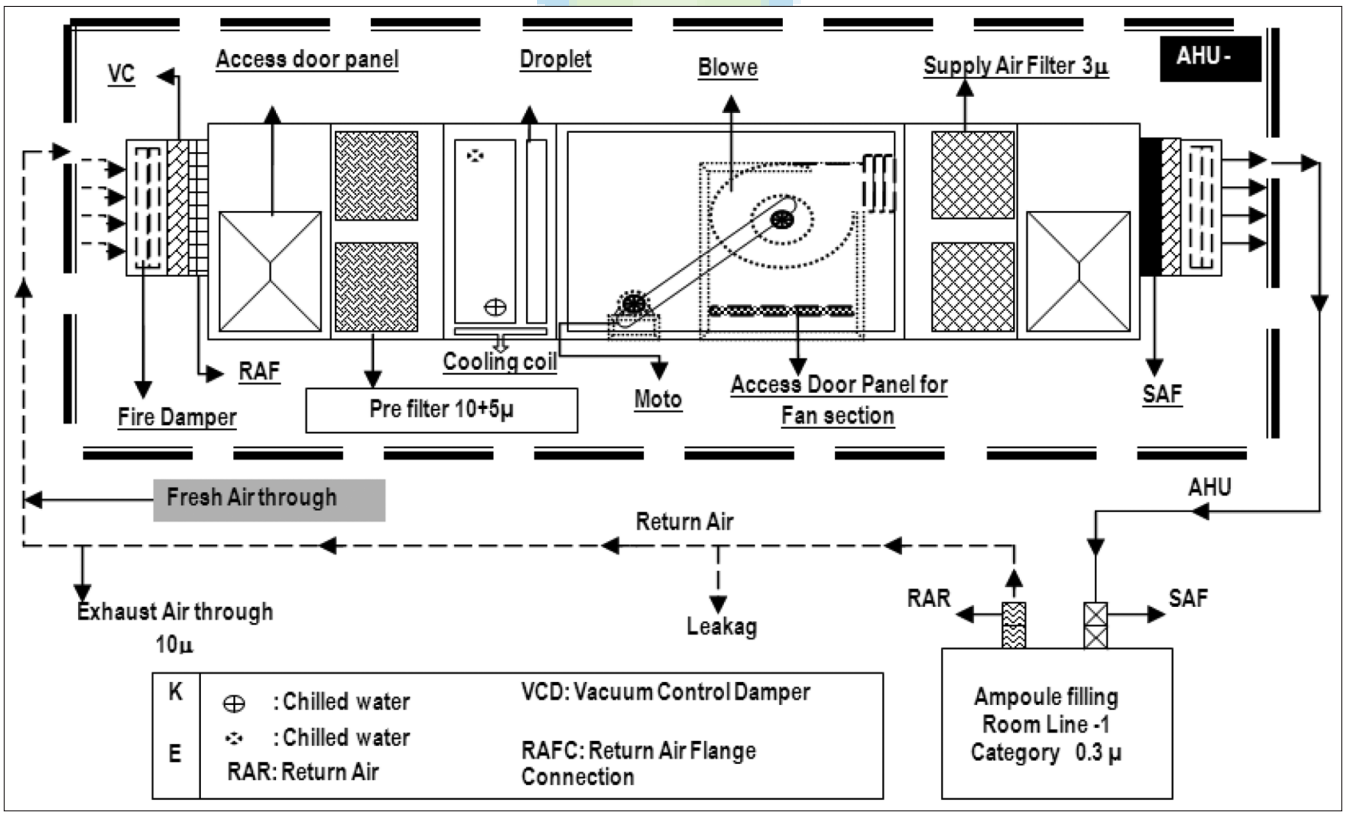

Figure 1: Diagram representing the construction and functioning of air handling unit

8. Materials of construction
9. Autocontrol system
10. Easy change over
11. Overall good construction and workmanship, etc.

These requirements are generally discussed with the equipment manufacturer or supplier and based on that discussion; the selection of the equipment is done. In case of standard items, user accepts the standard specifications of the manufacturer.[6]

Preparation of DQ and its certification

If particular equipment is to be fabricated as per the user requirements, then it is very essential to design detailed qualification document. It is advisable to work out the detailed equipment specification by sitting together with the manufacturer. Once this is ready, it should be agreeable to both the parties, that is, the purchaser and manufacturer.

At this stage it may be advisable to identify the stages during the fabrication of the equipment, where visual, instrumental, or even physicochemical testing may be performed in the presence of the purchaser. Generally, the factory acceptance test (FAT) is performed at the manufacturer's premises before dispatch of the equipment to the purchaser.

DQ should provide documented evidence that the design specifications were met.[4,6]

Installation qualification

It may be defined as: "Documented verification that all key aspects of the installation adhere to manufacturer's recommendation, appropriate codes, and approved design qualification".[7]

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.

IQ should provide documented evidence that the installation was complete and satisfactory. The purchase specifications, drawings, manuals, spare parts lists, and vendor details should be verified during IQ. Control and measuring devices should be calibrated.

Operational qualification

It may be defined as: "Documented verification that the system or subsystem performs as intended throughout all specified operating range". The equipment should be operated only when it passes the OQ Test.

OQ should provide documented evidence that utilities, systems, or equipment and all its components operate in accordance with operational specifications. Tests should be designed to demonstrate satisfactory operation over the normal operating range as well as at the limits of its operating conditions (including worst case conditions). Operation controls, alarms, switches, displays, and other operational components should be tested. Measurements made in accordance with a statistical approach should be fully described.[4,7]

Performance qualification

PQ is considered by many as synonymous with OQ. Some experts consider OQ as verification of performance of the system or subsystem without load and PQ is the same with load. However, these two terms always go hand in hand and no water tight distinction can be made.

PQ should provide documented evidence that utilities, systems or equipment and all its components can consistently perform in accordance with the specifications under routine use. Test results should be collected over a suitable period of time to prove consistency.[8]

VALIDATION OF HVAC SYSTEM

The validation of HVAC system usually involves the compilation of the documents like functional specifications (the conceptual design); design drawing, plans, and specifications; validation master plans; contractor documents; testing, adjusting, and balancing (TAB); startup reports; commissioning reports (the actual execution of validation protocols); and validation (IQ, OQ, and PQ).[9,10]

IQ may be defined as: "Documented verification that all key aspects of the installation adhere to manufacturer's recommendation, appropriate codes, and approved design qualification". The goal of IQ is to verify and document the quality, installation, and integrity of HVAC system components. Design documents and literatures are used to design installation protocols.

OQ may be defined as: "Documented verification that the system or subsystem performs as intended throughout all specified operating range". The equipment should be operated only when it passes the OQ Test.

PQ should provide documented evidence that utilities, systems, or equipment and all its components can consistently perform in accordance with the specifications under routine use. Test results should be collected over a suitable period of time to prove consistency.

In general the various parameters to be evaluated for the validation of HVAC system comprise of air flow pattern or smoke pattern, air flow velocity and changes per hour, filter leak test, particle count, viable monitoring, filter integrity test (dioctyl phthalate (DOP)/polyalphaolefin (PAO) test), pressure difference, recovery test (temperature and humidity), temperature and humidity uniformity test, and fresh air determination.[11,12]

METHODOLOGY

The methodology for the validation of the HVAC system embrace:

Air flow or smoke pattern

For the evaluation of this parameter, a titanium tetrachloride stick is taken and burnt and the burning stick is placed in front of the AHU. The distribution of smoke is observed. It should be uniform.

Air flow velocity and changes per hour

For this test, the area of HVAC is divided into four hypothetical grids and the air velocity is measured at each grid and then the average air velocity (V) is calculated. The area of the HEPA filter inlet (A) is calculated in feet and the total air volume (T) is then calculated by multiplying the average velocity of air and the area of the inlet ($T = A \times V$). After this, the volume of the room is calculated and the air changes per hour are obtained by dividing the total air change by the volume of the room.

Filter leak test

For the leak test of the HEPA filter, a velometer is placed at the front of the AHU system and the air velocity is checked at all the corners. The air velocity should 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.

Particle count

A particle counter is used to conduct the test. Particle count is taken before the operation as well as 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 is performed on daily basis by employing 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 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 taken.

Filter integrity test (DOP/PAO test)

The HEPA filter integrity is tested by generating a PAO aerosol by an aerosol generator and allowing the upward flow of the aerosol. The 100% upward flow of the aerosol is ensured and then the receptor probe of the HEPA is monitored to know the amount of the aerosol reversed. It should not exceed the higher limit of the HEPA filter. Earlier to carry out this test, DOP was used. But nowadays, it is replaced by the PAO taking into consideration the carcinogenicity of the DOP.

Pressure difference

It 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 mmHg pressure.

Recovery test

The recovery of temperature and humidity is checked. For this, the humidity and temperature are checked at the off position of the HVAC system. Then the humidity is increased to 75% and temperature to 400°C and again the temperature and humidity are measured after switching on the HVAC system, and the time required to stabilize the temperature and humidity is noted.

Temperature and humidity uniformity test

The uniformity of temperature and humidity are monitored by employing a calibrated thermometer and manometer, respectively. The two parameters are monitored on daily basis, documented in the format and stabilization is ensured within the specified limit.

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 all the individual rooms.[13-15]

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