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Execution & Qualification of Heating, Ventilation and Air Conditioning System

Himmat Singh*, Jatin Vidja, Mohit Agrawal, Rakesh Kr Sharma and S.Pathak
School of Pharmacy, SGVU

Abstract: Qualification is an integral part of quality assurance. Qualification is systematic approach to gathering and analyzing sufficient data that will give reasonable assurance (documented evidence), based on scientific judgment that a system when operating within specified parameters will give accepted results. There should be proper preparation and planning before qualification is performed. There should be a specific programme for qualification activities. Qualification should be performed in a structured way according to the documented procedures and protocols. Qualification should be performed for new premises, equipment, utilities and systems, at periodic intervals, when major changes have been made. Qualification establishes and provides documentary evidence that:

(a) The premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP (Design Qualification).
(b) The premises, supporting utilities and equipment have been built and installed in compliance with their design specifications (Installation Qualification).
(c) The premises, supporting utilities and equipment operate in accordance with their design specifications (Operational Qualification).
(d) A specific process will consistently produce a product meeting its predetermined specifications and quality attributes (Performance Qualification).

This industrial aspect includes importance, benefit, Operational stage and control variables and sampling plan related to HVAC system.

Key Words: Qualification, GMP, HVAC system & Control Variables.

Introduction

Qualification is the planning, carrying out and recording of tests on equipment and a system, which forms part of the validated process, to demonstrate that it will perform as intended. In accordance with Good Manufacturing Practices, each pharmaceutical company should identify what qualification work is required to prove that the critical aspects of their particular operation are controlled. The key elements of a qualification and validation programme of a company should be clearly defined and documented.[1]

The Basic Principles for Qualification: Equipment is correctly installed in accordance with an installation plan. Requirements for calibration, maintenance and cleaning are covered in approved SOP's. Tests are conducted to assure that equipment is operating correctly, under normal and "worst case" conditions. Operator training requirements pertaining to new equipment should be conducted and documented. Any aspect of operation, including significant changes to the premises, facilities, equipment or processes, which may affect the quality of the product, directly or indirectly, should be qualified and validated.[2]

For new utility, following activities carried out to demonstrate the compliance of equipment to design, characteristics and capabilities to meet the intended purpose.

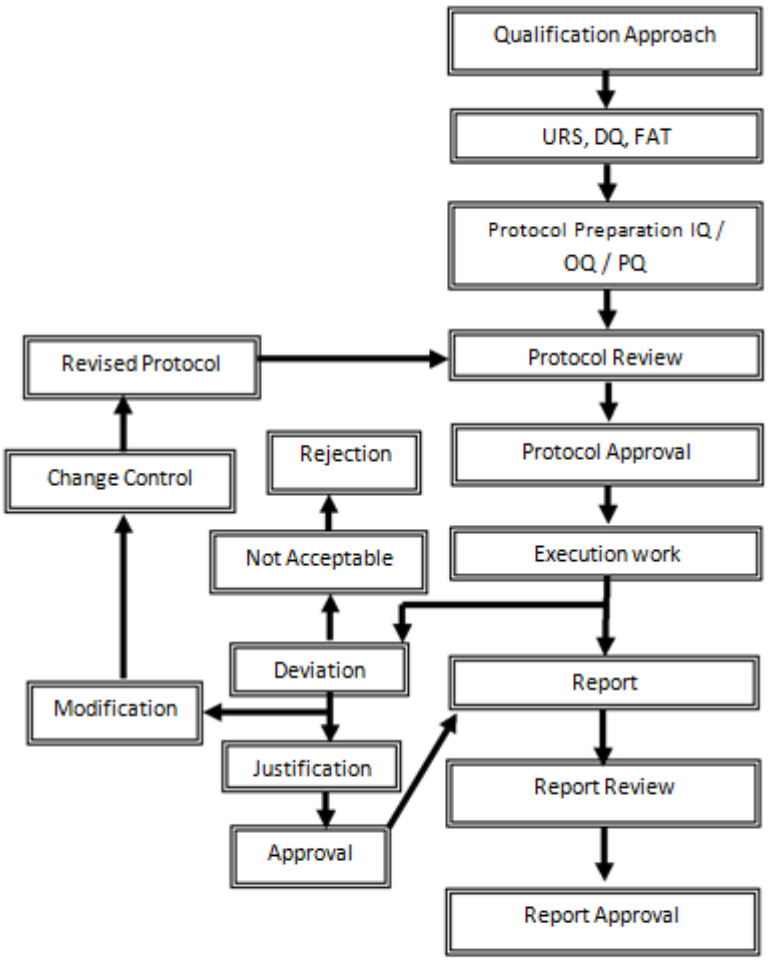

Figure -1: Qualification Approach

Heating, Ventilation and Air-Conditioning (HVAC) system

Heating, Ventilation and Air-Conditioning (HVAC) system is one of the most widely used systems in the pharmaceutical industries. HVAC system plays an important role in ensuring the manufacture of good quality pharmaceutical products. A well designed HVAC system will also provide comfortable condition for operators and prevent microbial contamination of sterile products and clean areas. It prevents spreading and contamination of virus and pathogens used in the manufacturing of pharmaceuticals. The intent of this HVAC system qualification is to provide a written plan for establishing documented evidence of the suitability of facility and consistency of system. Incorporating a properly defined and validated HVAC system will benefit pharmaceutical companies through quality control, by reducing capital costs, lifetime maintenance costs and monitoring costs. The manufacture of pharmaceuticals products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.

2. HVAC System Description:

High Side System: High Side system consists of following components

1. Chilled water system
2. Chilled water distribution
3. Hot water generation system
4. Hot water Distribution

1. Air Handling Unit
2. Air Distribution
3. Duct components
    A) Air Dampers
    B) Fire Dampers
    C) Diffuser and Grill
    D) Return Air Riser
    E) Duct Insulation
4. Piping Details
    A) Butterfly valves
    B) Control Valves
    C) Ball Valves
    D) Strainers
    E) Piping insulation
5. Electrical Details

    A) Electrical Panels
    B) Cabling & Cable Tray
    C) Building Management System

3. Importance of Qualification:

First, and certainly foremost, among the reasons for qualification is that it is a regulatory requirement for virtually every process in the global health care industry-for pharmaceuticals, biologics, and medical devices. The continuing trend toward harmonization of requirements will eventually result in a common level of expectation for qualification worldwide. The emphasis placed on compliance as a rationale has reduced the visibility of the other advantages a firm gleans from having a sound qualification program.

4. Benefits of Qualification

Quality:

- Customer satisfaction.
- It has been built into the equipment.

Understanding equipment, systems, process:

- Process improvement related equipment qualification, rapid failure investigations.
- Improve employee awareness and increased outputs.
- Easier maintenance of the equipment.
- Fewer complaints about process related failures.
- More rapid and reliable startup of new equipment.
- More rapid automation.

Regulatory benefits:

- Successful inspections.
- Approved products.

5. Stage of Qualification

There are different stages of qualification. These include:

Design Qualification

Design qualification should provide documented evidence that the design specifications were met or quality is built into the design of facilities and operations.

Installation Qualification

Installation qualification should provide documented evidence that the installation was complete and satisfactory. The purchase specifications, drawings, and vendor details should be verified during installation qualification.

Operational Qualification

Operational qualification 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 operation over the normal operating range as well as at the limits of its operating conditions (e.g. including worst case conditions).

Performance Qualification

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

6. Methodology for HVAC Qualification

6.1 Methodology of execution:

- Qualification exercise was performed by the external service provider and by validation team (where appropriate).
- The instruments/ equipments used for performing the tests were under a valid calibration period.
- The qualification activities were performed according to the plan and approved protocol.
- The activities were performed in the presence of representatives from engineering department to witness the activity and verified by the representatives from QA.
- After completion of respective activities, the raw data reviewed by the QA to ensure compliance with the acceptance criteria. A copy of the raw data is retained by the QA.
- After completion of the review process, QA compiles the obtained certificates and prepare a conclusion report for the activities performed.

- The conclusion reports reviewed by engineering team, and authorized by Head –QA.

6.2 Methodology for Installation Qualification

Installation qualification consist of following check point

- Reason for installation qualification
- Brief overview of the equipment / instrument / system
- Equipment details
- Physical verification on receipt
- Physical verification of the area
- Verification of material of construction and surface finish
- Identification of major components and accessories
- Verification of specifications of major components
- Identification of instruments requiring calibration or testing
- Verification of required change parts
- Identification and verification of supporting utilities
- Identification of standard operating procedures
- Deficiency and corrective action report

6.3 Methodology for Operational Qualification

The objective of the operational qualification was to establish documented evidence that the Air Handling Unit was operated within tolerances and limits. This operational qualification is applicable to Air Handling Unit and also covers equipment operation, objective, scope, responsibility, operational test, safety feature, acceptance criteria, equipment description, and calibration of equipments, functional test plan at rest.

Operational Qualification consists of the following check points and test:

1. Calibration of instruments
2. Electrical panel testing

3. Verification of Motor operation in no load / load condition when belt was disconnected
4. Verification of all the key functionalities of the control panel
5. Verification of safety features of the system

6. AHU Panel leak test
7. AHU drains verification
8. AHU blow down and leak test
9. System Balancing

6.4 Methodology for Performance Qualification

6.4.1 Air flow velocity test and calculation of Air changes per hour[8, 15]

Objective:

The purpose of this test was to measure air flow velocity and its uniformity across the filter, and supply air flow rate in clean room & clean zones. Measurement of supply air flow rate was carried out to ascertain the air volume supplied to the clean installation per unit of time, and this value was used to determine the air changes per unit of time.

Instrument used	Acceptance criteria	Frequency	
		ISO 5 & 7 areas	ISO 8 areas
1. Van type anemometer. 2. Thermal (Hot wire) anemometer.	For ACPH: NLT 40 in class 100A & Class 100B (1000) NLT 30 in Class 10,000 NLT 20 in Class 100,000	6 months ± 20 days -Replacement of HEPA filters -Any modifications in the AHU - As required on case to case basis	12 months ± 20 days - Replacement of HEPA filters - Any modifications in the AHU - As required on

			case to case basis

Procedure: For plenum HEPA

- Readings were taken in a plane perpendicular at a distance of approximately 75-150 mm from the HEPA filter face.
- The air velocity of the unit was measured in FPM.
- Measured the air flow velocity from the four corners and center of filter (as indicated in figure-III) and obtain an average reading. Obtain the average velocity of all the HEPA filters of the plenum in FPM and calculate the total no of CFM supplied by the unit using the following formula.

Total CFM = Average velocity in FPM x No. of filters x surface area of the filters (in ft^2)

For terminal HEPA filters & diffusers:

- Readings were taken in a plane perpendicular to and at a distance of approx. 50-100 mm downstream of the HEPA parallel face.
- Air velocity of the unit was measured in FPM.
- Measured the air flow velocity from the four corners and centre of the filter (as in figure-III) and calculate the average velocity in FPM.
- Determined the CFM of air flowing out of each filter by using the formula.

  Air flow in CFM = Average velocity in FPM x Surface area of the filter (in ft^2)

- Calculate the total air flow in CFM from all the supply filters available in the room by adding the CFM values obtained from supply grills.
- Calculate the no. of air changes per hour inside each room by using the formula,

$$\text{No. of air changes/hour} = \frac{\text{Total CFM x 60}}{\text{Room volume in ft}^3}$$

Or

$$\text{No. of air changes/hour} = \frac{\text{Total CFM x 1.7}}{\text{Room volume in m}^3}$$

6.4.2 Filter integrity test[15]

Objective:

This test was performed to confirm that the filter system was properly installed and the leaks have not developed during use. The test verifies the absence of leakages, relevant to the cleanliness performance of the installation. This test was applicable for HEPA filters having efficiency of 99.97% and above only.

Instrument used	**Acceptance criteria**	**Frequency**	
		ISO 5 & 7 areas	**ISO 8 areas**
Aerosol generator & Linear Aerosol Photometer	PAO (Poly Alpha Olefin) penetration from the downstream air of the HEPA filters should not be more than 0.01% of the upstream challenge aerosol	6 months ± 20 days - Replacement of HEPA filters -Any modifications in the AHU	24 months ± 30 days - Replacement of HEPA filters -Any modifications in the AHU

	concentration.	- As required on case to case basis	- As required on case to case basis

Procedure:

- AHU was started which filter integrity was to be checked. Ensure the power supply of photometer.
- The test was performed after the completion of air flow velocity test.
- The compressed air/Nitrogen gas was started to generate the test aerosol.
- The test aerosol was directed at the return air point or fresh air intake of the AHU.
- Put the photometer selector switch on upstream mode.
- Connected the tube of photometer to the upstream port of HEPA housing. Wait until the photometer displays 100% upstream concentration.
- Removed the tube of photometer and close the upstream port of HEPA housing and ensure for Zero Leakage. Put the photometer selector switch on downstream mode. Wait until photometer displays '0' (zero). Measure the downstream concentration.
- Observed the percentage of leakage directly on the photometer. If any leakages observed through the sealing of the filter inform respective department and get things done, tighten the filter nuts and check again for any leakage.

Following precautions were taken during the test:

1 The scanning probe was held at a distance of approx. 3 cm from the downstream filter face. Scanning rate should not exceed 5 cm/sec.

2 Scanning was done using slightly overlapping strokes and performed over the entire face of each filter, the perimeter of each filter, the seal between the filter frame & the grid structure including joints.

3 Observe the penetration of PAO particles across the HEPA filter on the display of photometer and record the value. Carry out the same for each HEPA filters of AHU system.

4 If the display shows value greater than the 0.01% considers it as leakages. Sealing of the leakages shall be carried out with sealant. If leakage is more than 1% of the total filter areas, replace the filter with new filter.

6.4.3 Air flow visualization test[1, 15]

Objective:

The purpose of airflow direction test and visualization was to confirm that the airflow direction and its uniformity confirm to the design and performance specification.

Instrument used	Acceptance criteria	Frequency
1. For the use of dry ice smoke generating device (Jacketed container for hot water, connecting pipe). 2. For Titanium Tetra chloride: A long stick with cotton wool embedded at one end.	1. A unidirectional flow of the smoke should be observed without any turbulence, from the supply to the return/exhaust grill inside the clean room. 2. Clean areas maintained at different pressure differential values shall have appropriate air flow patterns, where in, the air flow shall be from a region of higher Pressure differential to lower Pressure differential.	Once in 24 Months ±30 days or after any modification.

Procedure: Air handling unit of the room was in operation mode. Before performing this test system must be balanced and differential pressure among the rooms was maintained.

A] For test through Titanium Tetrachloride

- A suitable glass stick was used with one end covered with cotton wool. End of the wool dipped in a bottle Containing Titanium Tetrachloride.
- All the personal working in the area have suitable nose mask and goggles as Titanium Tetrachloride is corrosive in nature.
- The bottle was closed immediately after the stick has been removed.
- Placed the stick dipped with Titanium Tetrachloride at supply air stream or at a point where air flow visualization is to be observed.
- Allow the smoke to flow and check the air flow direction. Observe the air flow pattern.
- The fumes take the path of the airflow.

B] For test through dry ice (Solid Carbon Dioxide)

- Purified water was put into jacketed container and filled the volume inside the container to 2/3rd of its capacity.
- The power supply was connected with the hot water-jacket and allow the water to boil.
- Dry ice was manually put into the water and observed for the dense smoke to come out of the pipe.
- The pipe was hold at supply air stream or at a point where air flow visualization is to be observed.
- The flow (passage) of the smoke was observed and also observed the air flow pattern.

6.4.4 Temperature, %RH monitoring test.

Objective:

The purpose of this test was to demonstrate the capability of the installed air-handling system to maintain the air temperature, %RH within the acceptance criteria

Instrument used		Acceptance criteria	Frequency
Temperature, % RH	Psychrometer/ Hygrometer	The temperature of specified locations shall be 23±2 ° C	1. This test is performed only for the new installation or any modifications done to t he existing installations at the define frequency 2. This test is not a part of periodical validation exercise.

Test Procedure:

1. HVAC system was run for 24 hours before the test to stabilize the room and all the doors were properly closed.
2. The temperature and relative humidity were measured with the help of sling psychrometer.
3. Reading were recorded for a period of eight hours with interval of every one hour for 3 days at rest condition and & 7 days for at working condition.

6.4.5 Room differential pressure checks test:

Objective:

To check that the differential pressures between room and atmosphere and to verify that the readings are within designed values.

Instrument used		Acceptance criteria	Frequency
Differential Pressure	Magnehelic gauge / Manometer	The Relative Humidity in each room/area shall be 50±5%	1. This test is performed only for the new installation or any modifications done to the existing installations at the define frequency 2. This test is not a part of periodical validation exercise.

Acceptance criteria:

The relative room differential pressures between room and atmosphere shall be lass then 30 Pa of the designed values.

Test Procedure:

1. An air-handling unit was continuously operated.
2. Unexpected changes in air pressure was avoid to establish a baseline, all doors in the facility were closed and no man movement to be allowed during observations.
3. The differential pressure of the room was recorded from the Magnehelic gauge.
4. Readings were taken for a period of eight hours with an interval of every one hour for 3 days at rest condition and 7 days for at working condition.

6.4.6 Non-viable air borne particle count monitoring
Objective:

To verify the cleanliness classification of the installation (under test) with respect to the presence of non-viable air borne particles and to assure that, the installation cleanliness was maintained in accordance with the acceptance criteria.

4, 14, 15

Instrument used	Acceptance criteria			Frequency	
	Particle count at rest			**ISO 5 & 7 areas**	**ISO 8 areas**
	Cleanliness classification	**0.5µm (in m^3)**	**5.0 µm (in m^3)**		
Light scattering discrete particle counter (Having a sampling capacity of either 1 CFM or 1.77 CFM of air)	100A	3520	20	6 months ± 20 days -Replacement of HEPA filters -Any modification in the AHU -As required	6 months ± 20 days, - Replacement of HEPA filters -Any modification in the AHU -As required
	100B	3520	29		
	10,000	352000	2900		
	100,000	3520,000	29000		
	Particle count at operation				
	Cleanliness classification	**0.5µm (in m^3)**	**5.0 µm (in m^3)**		
	100A	3520	20		
	100B	352000	2900		

	10,000	3520,000	29000	on case to	on case to
	100,000	Not defined	Not defined	case basis	case basis

Procedure:

- Measurements of particle count ensure the cleanliness of the area. Also ensure that the area was in rest condition for at rest condition.
- The measurements were performed at a height of 1.5 m above floor level.
- The minimum volume of air required per sample can be calculated using the following formula:

Volume = 20 particles/class limit (particles/volume)

- Calculate the no. of location to be monitored for particle counts using following formula: No. of location N = $\sqrt{A}$ (In sq. meter)

Where, N = is the minimum no. of sampling points location from the above equation (Rounded up to a whole number)

A = is the area of the clean room or clean zone in sq. meter.

- The sampling location was evenly distributed throughout the area of the clean room or clean zone and positioned at the height of the work activity.
- Isokinetic probe was placed at the specified location in the area.
- Particle counter was rune to collects the sample an amount of 1CFM of air per sampling location in class 100,000 areas. For areas having cleanliness classification of 100A and 100B, a minimum equivalent sample volume of $1m^3$ of air shall be taken per sample location.
- Set cycle to be completed.
- Recorded the count of 0.5 µm and 5.0 µm (per m^3) in report.

- Particle counter was set up the according to appropriate test equipment operating procedures at the first sample point. Monitored the particles daily for 3 days at rest condition and & 3 days at working condition.

6.4.7 Area recovery test (Restoration test) [15]

Objective: This test was performed to determine the ability of the installation to eliminate airborne particles. Cleanliness recovery performance after a particle generation event was one of the most important abilities of the installation.

Instrument used	Acceptance criteria	Frequency
Light –scattering discrete-particle counter (The Particle Counter should have a sampling capacity of either 1 CFM or 1.77 CFM of air.)	Shall not be more than 15 minutes.	24 months ±30 days

Procedure:

- Particle counter was set and check apparatus calibration certificate.
- The single sample volume was adjusted to the same values used for the determining the cleanliness class.
- Particle counter was placed in the clean room at the location, where the non-viable particle count concentration found to be maximum.
- The clean room area to be examined should be contaminated with an aerosol while the air handling units are in operation or stop the air handling unit.
- Raise the initial particle concentration to 100 times or more the target cleanliness level.
- Commence measurements at 1 minute intervals. Note the reading when the particle concentration reaches the 100 x target concentration.
- The time was recorded when the particle concentration reaches the approximately the target cleanliness level.

6.4.8 Viable particle count monitoring test:

Objective: To verify the cleanliness classification of the installation (under test) with respect to the presence of viable particles and to assure that, the installation cleanliness was maintained in accordance with the acceptance criteria.

Material used: Soybean Casein Digest Agar (SCDA) media.

Acceptance criteria: Settle plate (diameter 90mm), 50 CFU/ 4 hr.

Frequency: Viable particle count test was performed consecutively 3 days.

Procedure:

- Prepared and pre-incubate the required number of Soybean Casein Digest Agar (SCDA) plates.
- Marked the plates with location of plate exposure and plate number.
- Media name & plate number was recorded.
- Cleaned the SS dish carrier with 70% IPA and double wrap the plates in sterile aluminium foil then transfer the pre-incubated SCDA plates for exposure in clean area.
- Keep monitoring aids in the dynamic pass box for exposure in clean area.
- Removed the lid of plate and put it on the sterilized piece of aluminium foil in invert position and put the base plate on it in titled position.
- The plate was exposed for 4 four at the specified location.
- Completion of exposure time closes the lid and collects the plates in the SS Petri dish carrier and brings the plates to the microbiology laboratory.

Incubation condition:

- The SCDA plates were incubated at temperature 20 -25 ºC for 3 day followed by 30-35 ºC for 2 days in incubator room of microbiology laboratory.
- Once pre-incubated SCDA plates taken along with other plate in clean area & don't expose & incubate as above procedure. This is treated as negative control.
- Incubation period was completed then count the no. of bacteria and recorded.

Precautions:

- During the environment monitoring, if any plate has fallen down in respective area mark the plate and consider the plate as invalid.
- Expose a new pre incubated SCDA plate in place of invalid plate at the same time and same location.

7. Conclusion:

Qualification of HVAC system has been carried out as per approved qualification plan. All the equipments and instruments used for the testing of the performance qualification are calibrated qualified. On assessment of data it was found that uniformity is observed. It can be concluded that obtained values found meeting the acceptance criteria specified in the plan. Based on the results of qualification data for HVAC system, it is concluded that system consistently producing air are meeting its predetermined specifications and quality attributes. Hence the HVAC system is considered to be qualified and can be routinely used.

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