Validation of Heating Ventilation Air Conditioning (HVAC) System

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Heating Ventilation and Air Conditioning System

• HVAC or “aitch-vak” systems are mechanical arrangement that treat outside air to produced cleaned (from dust and microbes) and conditioned air (temp. & Humidity) for use in controlled and critical areas within the Pharmaceutical manufacturing space.

• The systems normally consist of filtration, heating, cooling, dehumidification, and humidification steps.

• It is the technology of indoor environmental control and/or comfort.
Heating Ventilation and Air Conditioning

- The most important utility in the manufacture of drug products.
- Controls the environmental conditions in the manufacturing space, which may affect product quality, safety, and Efficacy (temperature and Humidity).
- Control the cleanliness of the manufacturing space (Room classification-particulate number both viable and non viable) which may affect purity.
- Prevent cross contamination (relative pressurization between spaces) which may affect purity and identity.
Regulatory Imperatives

• Control Temperature, Humidity, Pressure, Dust (Particulate), and Microbial load (21 CFR 211.46)

• The need to filter the air coming into manufacturing space (21 CFR 211.46)

• Protect product from extraneous contamination by microorganisms or their byproducts. Most intermediates and materials used in the industry are excellent promoters of microbial growth.

• The need to ensure that the product is not cross contaminated by other products being processed in adjacent space.
FDA Guidance To Industry
January 2011

Process Validation: General Principles and Practices

- Guidance to industry issued by the FDA January 2011.
- Outlines the life cycle approach to validation.
- Inline with the principles advanced in ICH Q8, ICH Q9, ICH Q10 and in ASTM E2500.
- Defines **PROCESS VALIDATION** as the collection and evaluation of data, from the process design stage throughout commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products.
FDA Guidance On Process Validation
January 2011

• Three Stages of Process Validation
  – Process Design Stage (process is defined based on development and scale-up)
  – Process Qualification Stage (Design is confirmed as being capable of reproducible production)
  – Continued Verification and improvement (Continuously gaining assurance the process remains in a state of control)
Stage 1: Process Design

- Understanding the science
- Understanding the risk
- Building Quality into the process
- Establishing Control Strategy
Stage 2: Implementation and Process Performance Qualification

• Implement the process and Facility
• Qualification of utilities and equipment
• Performance qualification and PPQ protocol
• Protocol execution and report
Stage 3: Continued Process Verification

• Monitoring appropriate parameters to ensure process in a validated state of control.
• Ensure proper maintenance of the facility, utilities, and process equipment
• Use CAPA, PAT and Change control as well as data collected in monitoring to continually improve the process.
HVAC System Consists of

1. Air Handling Unit (AHU)
   - Air filtration and conditioning.
   - Pump and meter the air into the distribution system.

2. Air Distribution System – Duct Work
   - Distribute the air to the various areas.
   - Temperature, humidity and smoke detection controls
   - Final filtration and heating if necessary.
   - Returning or exhausting the air.

3. Use Areas
   - Manufacturing spaces
   - Support spaces
Typical HVAC System for a Biotech Facility (Schematic)
Schematic of Biotech Facility
(Air flow pattern for cleanliness and cross contamination control)
Schematic of Biotech Facility
(Typical Room Classification)

Typical Layout

Air Flow/Relative Pressure

Packaging & Shipping
- Class 100
- Class 10,000
- RH 50% +/- 10%

Fill & Finish
- Gown/Degown

Corridor
- Class 100,000

Cold Room

Gown & Degown

Buffer & Media Prep
- Wash room

Fermentation Class 100,000

Purification
- Class 100,000

Isolation
- Class 100,000
Development & Design; Stage-1

- User requirements
- Define risk issues and assessment
- Functional specification
- Design control strategy and how to control conditions.
Design Stage

• User requirements:
  – Defines, temperature, humidity, cleanliness requirements for the product as defined by the design organization and others.

• Risk assessment:
  – Identifies issues associated with maintaining the user requirements such as required levels of cleanliness and air flow parameters.
  – Relative importance (based on risk to product quality) of the various conditions and whether or not there is a need to control all of them.
Design Stage

• Functional specifications:
  – Identify how conditions can be reached using the appropriate technology and technical knowledge.

• Design specifications:
  – Defines the design specifications and the appropriate design space that would allow reaching the required conditions. Defines CQA and their relationship to the CPP.

• Control Strategy:
  – How will the conditions be controlled and how will the CPP be manipulated to give the required CQA for the resulting air.
Design Stage

• Documents that would be needed to support the qualification effort:
  – User requirements and design specifications to define the conditions within the space and the critical system components.
  – Control strategy to define what controllers are used and where the monitoring takes place.
  – Mechanical and architectural drawings.
Implementation and Qualification; Stage-2

• In this stage the systems are installed and the installation as well as the operation of the system is verified and its performance qualified (PQ).

• Process Performance Qualification (PPQ) of the process (encompassing facility, utility, and equipment qualification) is conducted, through:
  – Protocol development and defining acceptance criteria
  – Execution of the protocols and certification of the process as being suitable for the intended use and performs as expected.
HVAC: What to Qualify?

• The mechanical system
  – Its installation and operation
  – The controls

• The air distribution system
  – Installation
  – Adequacy
  – Safety issues

• The conditions prevailing in the room.
  – Temperature and humidity
  – Air Changes
  – Relative pressurization
  – Classification if applicable
Documents you need

- User requirements
- Engineering drawings
  - Mechanical drawings (M series)
  - Architectural layout drawings (A series)
- Engineering specifications
- Contractor’s submittals
- O&M Manuals
- Test And Balance (TAB) Report
Qualification Plan For Utilities
(FDA guidance on Process validation)

• Qualification of utilities and equipment can be covered under individual plans or under an overall plan.
• Plan should consider requirements of use and risk management used to prioritize and define extent of activities.
• Plan should define:
  – Studies and tests to be conducted
  – The criteria to assess outcome of studies
  – Timing for qualification
  – Responsibilities for conducting the effort
  – Procedure for documenting and approving the qualification
• Firm’s criteria for evaluating changes
Qualification of the HVAC System

• First step is to confirm that the system has been installed per the design and is capable of operating within the required parameters.

• Second is to verify that the system is capable of providing the needed conditions within the space and maintain them.

• Finally a report summarizing the effort and reaching the conclusion that the system is suitable for the intended use has to be developed.
Installation & Operation Qualification Tests and Acceptance Criteria
IOQ Protocol

Normally the protocol will have the following sections:

• Purpose
• Scope
• Responsibilities
• System description
• References
• Procedures
• Certification records
• Attachments
• Approvals
IOQ or Verification Protocol
Defining Acceptance Criteria

How to Define Acceptance Criteria

• Manufacturer/Vendor Specifications
• Engineering Design Specifications
• Specific Requirements of System (e.g. Temperature homogeneity throughout the space)
• Regulatory Application Requirements (NDA)
• GMP and/or other Regulatory or Compendial Requirements
• Product/Intermediate Characteristics Requirements
Installation Verification

1. List maker, local representative, and maintenance contractor. Include addresses and phone numbers.
2. Confirm completeness of components as per specifications (Fans, Heaters, Humidifiers, Condensers, etc.).
3. Verify existence of Filters and compliance with design specification (Pre-, Terminal, etc.).
4. Document existence of Instrumentation at specified locations (Thermostats, Humidistat, Sensors, Safety devices, etc.) and indicate criticality and frequency of calibration.
5. Verify utilities and connections as per design (electric service to unit, Steam for humidification, Natural gas for heaters, etc.).
6. Ensure control system is installed per the design and verify its components.
7. Confirm the existence of a spare parts list.
8. Confirm that documentation and drawings for the system exist and are accessible.
9. Ensure maintenance, operation, calibration, and training procedures are in place.
Operation Verification

1. Document that all instruments which will be used in the qualification have valid calibration certificates.

2. Test controls, alarms, and interlocks to verify their proper operation.
   1. Start and stop of system
   2. Heating and cooling response
   3. Humidification response
   4. Smoke alarm response

3. Test, Adjust and Balance Report and Room Air Changes Verification
Performance Qualification and PQ Acceptance Criteria
What will the PQ confirm

• Ability of the system to maintain temperature and humidity within the space for extended periods.
• Ability of the system to properly function under normal operating (load) condition of the facility
• Ability of the system to maintain air flow and hence relative pressure between the various spaces.
• Ability of the system to maintain the particulate count levels within the space
• Ability of the system to maintain microbial count within the space
PQ Acceptance Criteria
Product Requirements are the Driving Force

• Temperature and Humidity in the space should not negatively impact the product.
• Temperature and humidity should meet the user requirements.
• If sterile space, room classification is 100 (M3.5; ISO 5 – Less than 100 particles of <0.5 micron/ft³)
• If critical space, the air should flow from it to less critical space.
• If user requirements are not clear, use engineering specifications, regulatory guidance, standards, or compendial values.
# Particulate Count

USP 23 and FDA Guidance on Sterile Drug Products, 2004

<table>
<thead>
<tr>
<th>Room Classification</th>
<th>Particles/ft³*</th>
<th>cfu/ft³</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 (M3.5; ISO 5)</td>
<td>100</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>10,000 (M5.5; ISO 7)</td>
<td>10,000</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>100,000 (M6.5; ISO 8)</td>
<td>100,000</td>
<td>&lt;2.5</td>
</tr>
</tbody>
</table>

* Less than the indicated number of particles of diameter <0.5 micron/ft³
Microbial Count

USP <1116>

• New perspective on environmental control relying on incident rates rather than action / alert levels.

• Best clean room environment design and operating practices cannot prevent the shedding of microorganisms into the environment by human operators.

• Therefore expectation of zero contamination at all locations during every aseptic processing operation is technically wrong and unrealistic.

• Criteria should be based on risk and experience.
Air Changes

Based on: ISO Standard 14644 and IEST-RP-CC012.1

• Room Classification
  – 100 (M3.5)
  – 10,000 (M5.5)
  – 100,000 (M6.5)

• Air Changes per hour
  – 500-700
  – 60-90
  – 12-40

* Relative pressurization standard is 0.05” of water relative to adjacent less clean areas.
# Temperature

Based on USP; 8th supplement, dated May 15, 1998

<table>
<thead>
<tr>
<th>Room (Condition) Description</th>
<th>Temperature Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freezer</td>
<td>-25°C to -10°C</td>
</tr>
<tr>
<td>Cold</td>
<td>2°C to 8°C</td>
</tr>
<tr>
<td>Cool</td>
<td>8°C to 15°C</td>
</tr>
<tr>
<td>Controlled Room Temperature</td>
<td>20°C to 25°C (68-77 F)</td>
</tr>
<tr>
<td>Warm</td>
<td>30°C to 40°C</td>
</tr>
<tr>
<td>Excessive Heat</td>
<td>over 40°C</td>
</tr>
</tbody>
</table>

Always insure that material is not in cold or hot spots.

* Relative Humidity 50% +/- 10% unless product requires differently.
Example

PQ Acceptance Criteria for HVAC

• Maintain temperature at 72°F ± 5° (design).
• Maintain Relative Humidity at 50% ± 15% (design).
• Provide 12 (or 20) air changes per hour (design standard).
• Maintain a positive air pressure in the room with respect to the hallway (GMP-prevent cross contamination).
• Maintain class 100,000 (GMP requirement, Compendial requirement).
Instruments to Use

• Data Loggers for temperature and humidity monitoring (e.g. Hobo).
• Particle counters for particulate monitoring (e.g. Met One).
• Smoke sticks or magnahelic gauges for airflow/relative pressurization.
• Active microbial sampling techniques
• Possibly use data from BAS and its instruments if calibrated and verified a-priori.
Example Procedure

• Verify the direction of airflow between the production rooms and adjacent areas by performing a smoke profile around each door between the spaces. When performing the smoke test, ensure all other doors within the area are closed.
Example Data Sheet Attachment

<table>
<thead>
<tr>
<th>Expected Airflow Direction</th>
<th>Actual Airflow Direction</th>
<th>Pass (P) / Fail (F)</th>
<th>Verified By / Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room 101 Air-Lock ⇒ Corridor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Room 102 Air-Lock ⇒ Corridor</td>
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<tr>
<td>Room 101 Air-Lock ⇒ Room 101</td>
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</tr>
<tr>
<td>Room 102 Air-Lock ⇒ Room 102</td>
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</tr>
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</table>
Continued Verification; Stage-3
Continued Process Verification

• Establish an environmental monitoring program:
• Collect data and ensure that no negative trends are observed
• Define alert and action levels (limits) a-priori
Where to Monitor?

- All Production Areas (including corridors and airlocks)
- Storage areas for product, intermediates, and raw materials (especially if affected by environmental conditions, especially in critical areas near doors, ceilings, etc.)
- Clean Rooms and Laminar Flow Hoods
- Critical Surfaces
- Environmentally Controlled Rooms/Chambers
- Freezers, Refrigerators, Incubators
What You Should Monitor?

- Temperature
- Humidity
- Pressure
- Particulate
- Microbial / Biological Load
How to Establish Criteria & Frequency?

• Product requirements (temp sensitivity)
• Regulatory requirements (Microbial content for sterile areas)
• Based on experience and history
• Compendial, engineering, and federal standard
• Literature and industry experience
How to Monitor?

- Temperature probes, thermocouples, chart recorders
- Humidity probes, chart recorders
- Temperature and humidity mapping devices and data loggers
- Magnahelic gauges
- Building Automation Systems (BAS) when several HVAC systems are used (T, RH, Pressure deferential)
- Particle counters
- Active microbial air sampling
- Settling plates*
  - *Use appropriate media for organisms to be detected, e.g. TSA for bacteria, SDA for mold and yeast
Data from routine monitoring should conform to a random pattern, and should be within the action limits to indicate that the environment is under control.
Defining Alert & Action Limits

- Use historical data for variable to calculate Standard Deviation
- One way is to use 3 Standard Deviations around the mean as Action Level and 2 Standard Deviations as Alert Level
- Usually Alert level is based on where you expect to operate and action levels are based on design/process capability values.
- Make certain the limits you chose do not adversely affect the product when reached
- Be mindful of any pattern or trends in your historical data
Example Monitoring data
Trends and Not Single Event
What to Look for?

• Data trends towards deviations; Do not overreact to individual events - FDA Guidance on Process Validation January 2011

• Repeat occurrences, which may indicate a certain problematic event

• Patterns in the data

• Any changes/differences from what you have been observing in the past
Summary

- HVAC is one of, if not, the most important utility in health product manufacturing operations.
- HVAC systems are critical and represents increased risk as the complexity and cleanliness of the operation increases.
- Validation of HVAC systems is necessary.
- HVAC systems must be properly designed for the intended application, qualified, and their operation monitored continuously to complete the validation.