Part 1. General overview on qualification and validation

Part 2. Qualification of HVAC and water systems

Part 3. Cleaning validation

Part 4. Analytical method validation

Part 5. Computerized system validation

Part 6. Qualification of systems and equipment

Part 7. Non sterile product process validation
Qualification of HVAC and water systems

Part 2

HVAC

Objectives

- To understand key issues in
  - commissioning,
  - qualification and
  - maintenance of

HVAC and Water systems
HVAC

Documentation requirements to assist in commissioning, qualification and maintenance

- Description of design, installation and functions
- Specifications, requirements
- Manuals
- Operating procedures
- Instructions for performance control, monitoring and records
- Maintenance instructions and records
- Training of personnel
  - programme and records
HVAC

Commissioning

- Precursor to qualification
- Includes setting up, balancing, adjustment and testing of entire HVAC system to ensure it meets requirements in URS and capacity
- Acceptable tolerances for parameters
- Training of personnel

8.1.1, 8.1.4, 8.1.5
HVAC

Commissioning (2)

Records and data maintained include:

- Installation records – documented evidence of measure capacities of the system

- Data: design and measurement for, e.g. air flow, system pressures

- O&M manuals, schematic drawings, protocols, reports

8.1.2, 8.1.3, 8.1.6
Validation is an extensive exercise

Qualification of the HVAC system is one component in the overall approach that covers premises, systems/utilities, equipment, processes, etc.

See also full guidelines on "Validation" in WHO TRS, No. 937, 2005, Annex 4

Risk based approach for HVAC qualification
HVAC

Qualification (2)

- Described in a Validation Master Plan (VMP)
- VMP to include the nature and extent of tests, and protocols
- DQ, IQ, OQ, and PQ
- Risk analysis to determine critical and non-critical parameters, components, subsystems and controls
HVAC

Qualification (3)

- Direct impact components and critical parameters should be included
- Non-critical systems and components are subjected to Good Engineering Practices (GEP)
- Acceptance criteria and limits defined in design stage
- Design conditions, normal operating ranges, operating ranges, alert and action limits
• **Design conditions and normal operating ranges set to achievable limits**

• **OOS results recorded**

8.2.12 – 8.2.15
HVAC

Qualification – examples of aspects to consider

- **DQ** – Design of the system, URS
  - (e.g. components, type of air treatment needed, materials of construction)

- **IQ** – Verify installation
  - E.g. relevant components, ducting, filters, controls, monitors, sensors, etc.
  - Includes calibration where relevant
Typical parameters to be included in qualification (based on risk assessment):

- Temperature
- Relative humidity
- Supply, return and exhaust air quantities
- Room air change rates
- Room pressures (pressure differentials)
HVAC

Qualification (5)

Typical parameters to be included in qualification (based on risk assessment) (2):

- Room clean-up rate
- Particulate matter, microbial matter (viable and non-viable)
- HEPA filter penetration tests
- Containment system velocity
- Warning/alarm systems
HVAC Qualification (6)

Conduct of the tests:

- Time intervals and procedure to be defined by the manufacturer
- Influenced by the type of facility and level of protection
- See also ISO 14644 for methods of testing
- Requalification, and change control

8.2.18 – 8.2.20, 8.2.9
HVAC

Qualification (7)

- Tests performed according to protocols and procedures for the tests
- Results recorded and presented in report (source data kept)
- Traceability, e.g. devices and standards used, calibration records; and conditions specified
## HVAC

### Schedule of tests to demonstrate continuing compliance

<table>
<thead>
<tr>
<th>Test Parameter</th>
<th>Objective</th>
<th>Maximum time interval</th>
<th>Test procedure* and key aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle count test</td>
<td>Verifies cleanliness</td>
<td>6 months or 12 months depending on Class</td>
<td>Particle counter. Readings and positions</td>
</tr>
<tr>
<td>Air pressure difference</td>
<td>Absence of cross-contamination</td>
<td>12 months</td>
<td>Measure pressure difference</td>
</tr>
<tr>
<td>Airflow volume</td>
<td>Verify air change rates</td>
<td>12 months</td>
<td>Measure supply and return air, calculate air change rate</td>
</tr>
<tr>
<td>Airflow velocity</td>
<td>Verify unidirectional airflow and or containment condition</td>
<td>12 months</td>
<td>Velocity measurement</td>
</tr>
</tbody>
</table>

*Test procedure as per ISO 14644
## Recommended optional strategic tests

<table>
<thead>
<tr>
<th>Test Parameter</th>
<th>Objective</th>
<th>Maximum time interval</th>
<th>Test procedure* and key aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filter leakage</td>
<td>Verify filter integrity</td>
<td>12 months</td>
<td>Filter media and filter seal integrity</td>
</tr>
<tr>
<td>Containment leakage</td>
<td>Verify absence of cross-contamination</td>
<td>12 months</td>
<td>Airflow direction and pressure differential</td>
</tr>
<tr>
<td>Recovery (time)</td>
<td>Verify clean-up time</td>
<td>12 months</td>
<td>Time taken maximum 15 minutes</td>
</tr>
<tr>
<td>Airflow visualization</td>
<td>Verify required airflow patterns</td>
<td>12 months</td>
<td>Airflow direction, documented evidence</td>
</tr>
</tbody>
</table>

*Test procedure as per ISO 14644

8. Table 3
Cleanroom monitoring programme (1)

- Routine monitoring programme as part of quality assurance
- Additional monitoring and triggers, e.g.
  1. Shutdown
  2. Replacement of filter elements
  3. Maintenance of air-handling systems
  4. Exceeding of established limits
Cleanroom monitoring programme (2)

Particles and Microbiological contaminants

- Number of points/locations for monitoring determined, specified, documented in procedure and or protocol
- Sufficient time for exposure, and suitable sample size
- Identification and marking of sampling points
- Definition of transport, storage, and incubation conditions
- Results to reflect the procedure/protocol followed
- Define alert and action limits as a function of cleanliness zone/class

See also ISO 14644
Cleanroom monitoring programme (3)

Cleanrooms should be monitored for microorganisms and particles.

Example of a sampling point
HVAC

Definition of Conditions

as built

at rest

in operation
HVAC

Qualification – examples of aspects to consider in qualification (OQ, PQ)

<table>
<thead>
<tr>
<th>Test</th>
<th>Uni-directional airflow / LAF</th>
<th>Turbulent / mixed airflow</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differential pressure on filters</td>
<td>2</td>
<td>2</td>
<td>1 := As built (ideally used to perform IQ)</td>
</tr>
<tr>
<td>Room differential pressure</td>
<td>N/A</td>
<td>2, 3</td>
<td>2 = At rest (ideally used to perform OQ)</td>
</tr>
<tr>
<td>Airflow velocity / uniformity</td>
<td>2, 3</td>
<td>Optional</td>
<td>3 = Operational (ideally used to perform PQ)</td>
</tr>
<tr>
<td>Airflow volume / rate</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Parallelism</td>
<td>2</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Airflow pattern</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
## HVAC

### Qualification – examples of aspects to consider in qualification (OQ, PQ)

<table>
<thead>
<tr>
<th>Test</th>
<th>Uni-directional airflow / LAF</th>
<th>Turbulent / mixed airflow</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery time</td>
<td>N/A</td>
<td>2</td>
<td>1 := As built (ideally used to perform IQ)</td>
</tr>
<tr>
<td>Room classification (airborne particle)</td>
<td>2</td>
<td>2,3</td>
<td>2 = At rest (ideally used to perform OQ)</td>
</tr>
<tr>
<td>Temperature, humidity</td>
<td>N/A</td>
<td>2,3</td>
<td>3 = Operational (ideally used to perform PQ)</td>
</tr>
</tbody>
</table>
Maintenance

- Procedure, programme and records for planned, preventative maintenance
  - *e.g. Cleaning of filters, calibration of devices*
- Appropriate training for personnel
- Change of HEPA filters by suitably trained persons
- Impact of maintenance on:
  - *Product quality*
  - *Qualification*
Inspector the air-handling system

- Verification of design documentation, including
  - description of installation and functions
  - specification of the requirements
- Operating procedures
- Maintenance instructions
- Maintenance records
- Training logs
- Environmental records
- Discussion on actions if OOS values
- On site verification (walking around the site)
Air-handling systems:

- Play a major role in the quality of pharmaceuticals
- Should be designed properly, by professionals
- Should be treated as a critical system
Further proceedings

This series of explanations will now be followed by:

- Group discussion, with a simple exercise
- Short test
HVAC

Group Session

- Air Shower
- Sampling Room
- Warehouse
- Air Lock 2
- Weighing
- Tablet 1
- Tablet 2
- Liquids Mix
- Softgel Capsule Packing
- Service Corridor (contains Vacuum & RO water supply)
- Clean Corridor
- Sterile eyedrops dispensing & aseptic filling
- 2 Stage personnel entry for eyedrops
- Male Change 2
- Female Change 2
- Male Change 1
- Female Change 1
- Packed Goods Quarantine
- Primary & Secondary Packing
- Air Lock 4
- Equipment Wash
- Air Lock 3

Emergency Exit
Supplementary Training Modules on Good Manufacturing Practice

Commissioning, Qualification and validation of Water systems

HVAC

Objectives

- To understand key issues in
  - commissioning,
  - qualification and
  - maintenance of

HVAC and Water systems
Objectives

To discuss the operational considerations of water systems including:

- Start up, commissioning and qualification
- Monitoring
- Maintenance
- System reviews
Water for Pharmaceutical Use

Start up and commissioning

- Precursor to qualification and validation
- Should be planned, well defined, well documented
- Includes setting to work
- Includes system set-up
- Includes recording of system performance parameters
- Controls loop tuning
Qualification

- WPU systems are "direct impact systems"
- Therefore stages to be considered in qualification should include DQ, IQ, OQ, PQ
- DQ: Design review influenced by source water and required water quality
- IQ: Installation verification of the system
Qualification

- OQ: operational qualification
- Presentation focusing on PQ
- PQ demonstrates consistent and reliable performance of the system
- Three phase approach recommended over extended period – proves reliability and robustness
Phase 1 (1)

- A test period of 2–4 weeks - monitoring the system intensively
- System to operate continuously without failure or performance deviation

The following should be included in the testing approach:

- Undertake chemical and microbiological testing in accordance with a defined plan
Water for Pharmaceutical Use

**Phase 1 (2)**

- Sample daily:
  - incoming feed-water
  - after each step in the purification process
  - each point of use and at other defined sample points

- Develop:
  - appropriate operating ranges
  - and finalize operating, cleaning, sanitizing and maintenance procedures
**Water for Pharmaceutical Use**

**Phase 1 (3)**

- Demonstrate production and delivery of product water of the required quality and quantity
- Use and refine the standard operating procedures (SOPs) for operation, maintenance, sanitization and troubleshooting
- Verify provisional alert and action levels
- Develop and refine test-failure procedure
Phase 2 (1)

- A further test period of 2–4 weeks – further intensive monitoring the system
- Deploying all the refined SOPs after the satisfactory completion of phase 1
- Sampling scheme generally the same as in phase 1
- Water can be used for manufacturing purposes during this phase
Phase 2 (2)

Demonstrate:

- Consistent operation within established ranges
- Consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOPs.
Phase 3

- Over one year after the satisfactory completion of phase 2
- Water can be used for manufacturing purposes during this phase

Demonstrate:
  - *extended reliable performance*
  - *that seasonal variations are evaluated*

- Sample locations, sampling frequencies and tests should be reduced to the normal routine pattern based on established procedures proven during phases 1 and 2
Ongoing system monitoring

- After Phase 3 – system review needed

- Based on review including results, establish a routine monitoring plan

- Monitoring to include a combination of on-line monitoring and off-line sample testing

- Data analysed for trends
Ongoing system monitoring (2)

- Monitoring parameters to include:
  - flow, pressure, temperature, conductivity, TOC

- Samples taken:
  - From points of use, and specific sample points
  - In a similar way how water is used in service

- Tests to include physical, chemical and microbial attributes
Water for Pharmaceutical Use

Maintenance

A controlled, documented maintenance programme covering:

- Defined frequency with plan and instructions
- Calibration programme
- SOPs for tasks
- Control of approved spares
- Record and review of problems and faults during maintenance
System review

- WPU (PW, HPW and WFI) systems to be reviewed at appropriate regular intervals
- Review team includes engineering, QA, operations and maintenance
System review (2)

- The review to cover, e.g.
  - changes made since the last review;
  - system performance;
  - reliability;
  - quality trends;
  - failure events;
  - investigations;
  - out-of-specifications results from monitoring;
  - changes to the installation;
  - updated installation documentation;
  - log books; and
  - the status of the current SOP lists
Group session