Supplementary Training Modules on Good Manufacturing Practice

Water for Pharmaceutical Use

Part 3: Operational considerations

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World Health Organization

Water for Pharmaceutical Use

Objective of this part is to discuss the operational considerations of water systems including:

- Start up and commissioning
- Qualification and validation
- Continuous system monitoring
- Maintenance
- Water system review

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Commissioning

- Planned, well defined, well documented commissioning can help to ensure appropriate qualification and validation
- Includes
  - setting to work and system set-up
  - controls and loop tuning
  - System performance parameters
- If commissioning is part of qualification – then appropriate level of documentation and compliance with VMP

7.1

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Qualification

- WPU, BPW, BHPW, BWFI are "direct impact, quality critical“ systems
- Should be qualified and be subjected to DQ, IQ, OQ, PQ
- DQ: Design review influenced by source water and required water quality
- IQ: Installation verification of the system
- OQ: operational qualification

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Qualification (2)

- This presentation will focus on PQ
  - PQ demonstrates consistent and reliable performance of the system
- Three phase approach - over extended period
- Proves reliability and robustness
- Include tests on source water (drinking water quality)

7.2

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Phase 1.

- Daily sampling (or continuously monitor) of incoming feed-water
- Cover two weeks of intensive monitoring
- System should operate continuously without failure or performance deviation
- Water is not used for finished pharmaceutical product (FPP) manufacturing during this period

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The testing approach in Phase I:

- Chemical and microbiological testing – follow a defined plan
- Include incoming feed-water daily to verify its quality
- After each step in the purification process
- Each point of use and at other defined sample points
- Develop appropriate operating ranges
- Develop and finalize operating, cleaning, sanitizing and maintenance procedures

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The testing approach in Phase I:

- Demonstrate product water of the required quality and quantity
- Use and refine SOPs (operation, maintenance, sanitization and troubleshooting)
- Verify provisional alert levels
- Develop and refine test-failure procedure

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Phase 2.

- *Follows Phase 1– further t*wo week test period with intensive monitoring using refined SOPs
- Sampling scheme generally the same as in phase 1
- May use water if commissioning and Phase 1 data “okay”
- Phase 2 to show:
  - 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

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***Phase 3*.**

- Normally over one year after the satisfactory completion of phase 2
- Water can be used for FFP manufacturing
- Objectives of phase 3 include
  - to demonstrate reliable performance over an extended period
  - to ensure that seasonal variations are evaluated
- The sample locations, sampling frequencies and tests should be reduced to the normal routine pattern based on established procedures proven during phases 1 and 2

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Continuous system monitoring

- After completion of phase 3 – do a system review
- Then implement a routine monitoring plan (based on results from phase 3)
- A combination of on-line monitoring and off-line sample testing with qualified alarm systems
- Verify that the water met the pharmacopoeia and in house specification

7.3.1. – 7.3.2.

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Continuous system monitoring (2)

- Parameters to be monitored include:
  - flow, pressure, temperature, conductivity and total organic carbon, physical, chemical and microbiological attributes
- Offline samples taken from points of use or dedicated sample points (where points of use cannot be sampled)
- Water samples to be taken in the same way as when water is taken for use in production. (A suitable flushing and drainage procedure followed)
- Data analysed for trends – RCA and CAPA

7.3.1. – 7.3.3.

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Maintenance

A controlled, documented maintenance programme covering:

- Defined frequency for system elements; a calibration programme
- SOPs for tasks; control of approved spares
- Maintenance plan and instructions
- Review and approval of systems for use upon completion of work
- Record and review of problems and faults during maintenance

7.4

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System reviews

- Regular intervals by a team (from engineering, QA, microbiology, operations and maintenance) and cover:
  - 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 status of the current SOP list

7.5.1.

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System reviews (2)

For new / instable / unreliable systems, also review:

- The need for investigation
- Corrective actions and preventative actions (CAPA)
- Qualification (DQ, factory acceptance test (FAT), IQ, site acceptance test (SAT), OQ, PQ) or equivalent verification documents
- The monitoring phases of the system

7.5.2.

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Summary

In Parts 1, 2 and 3 – we looked at:

- Water requirements and uses
  - general principles for pharmaceutical water systems
  - water quality specifications
  - application of specific types of water to processes and dosage forms
- Water purification systems
- Water storage and distribution systems
  - Operational considerations
- In Part 4 discuss approaches to inspection of water systems