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Validation and Control of SIP

IMB GMP Information Seminar

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Introduction

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Introduction

SIP

Steam In Place

Sanitisation In Place

Sterilisation In Place

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Introduction

- Do you use SIP for:

1. Sanitisation?
2. Sterilisation?
3. Both?

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Introduction

- SIP is a widely adopted method for the in-line sterilisation of processing equipment.
- The main advantage of SIP is reduction of aseptic connections and manipulations that might compromise the integrity of the downstream equipment.
- Likely to be applied more and more with isolator and RABS technology.

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Scope

- Expectations
- Guidance
- Key Points for:
  - Validation
  - Control
- Expectations

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Expectations

- Good Science:
  - Does the company understand the mapping profiles? Are they reproducible?
  - Is there a steam/temperature correlation applied?
  - Independent and continuous control and monitoring?

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Guidance

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Guidance

- "Lack of guidance!"
- High level GMP requirements
- Autoclave standards?

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Guidance

- **Available**

  ISO 13408-5:2006

  Aseptic processing of health care products —

  Part 5: Sterilization in place

- **Pending**

  Upcoming PDA technical report on Steam in Place

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Guidance

- **ISO 13408-5:2006**

  Specifies the general requirements for sterilisation in place (SIP) applied to product contact surfaces of the equipment used in the manufacture of sterile health care products by aseptic processing and offers guidance on qualification, validation, operation and control.

  It acknowledges that SIP can be achieved by using steam or other gaseous or liquid sterilising agents.

  Specific guidance on steam sterilisation in place, which is the most common method used, is given in Annex A.

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Key Points

- The most important issue to consider in establishing sterilisation-in-place technology is the design of the system(s) to ensure that they be able to successfully sterilise manufacturing equipment to the desired level of sterility assurance.

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Key Points

The critical requirements associated with SIP include:

- Proper steam distribution,
- Noncondensable gases removal, and
- Continuous condensate elimination.

Facilitated by:

- Good engineering practices,
- Adequate piping design,
- Steam traps, Valves, and
- Monitoring instrumentation.

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Key Points

Process and equipment characterisation

- A process flow diagram that outlines the processing equipment layout to be sterilised, including valve sequencing.

- Drainability of the system (e.g. slope of piping to ensure the complete removal of remaining liquid in the system).

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Key Points

- Compatibility of materials of construction (e.g. pipes, tanks, valves, nozzles, filters, gaskets, sensors) with the sterilising agent, over the anticipated number of sterilisation cycles.

- Provisions for maintenance of sterility during and after completion of SIP (e.g. by elevated pressure).

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Key Points

Filter Sterilisation

- Condensate drainage should be equipped at the lowest part of both the sterile side and the non-sterile side of each filter housing.

- Steam bleed(s) should be positioned, where necessary, in the part of housing that might cause air retention.

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Key Points

Filter Sterilisation

- The pressure differential across the filter element at the operating temperature should not exceed the manufacturer's recommendations.
- Steam pressure and differential pressure should be monitored.
- Temperature should be measured downstream of the filter.

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Key Points - Validation

Process parameters shall be adequate to ensure sterilisation of the equipment being subjected to SIP.

- Critical process parameters for steam SIP are time, temperature and steam pressure.

- Minimum and maximum limits should be specified and controlled throughout the sterilisation cycle.

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Key Points - Validation

Qualification shall include but not be limited to:

- Distribution of the sterilising agent within the equipment to be sterilised.
- Maintenance of effective sterilisation conditions throughout the equipment to be sterilised.

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Key Points - Validation

- Controlling and monitoring of the sterilisation conditions in the defined locations.

- The most-difficult-to-sterilise locations within the equipment to be sterilised shall be determined and it shall be demonstrated that, at these locations, sterilisation is effective to the pre-determined acceptable level.

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Key Points - Validation

- **Biological Indicators**

- Do you use BI's for validation of SIP?

  1. Initial validation only
  2. Routinely
  3. Do not use BI's

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Key Points - Validation

- Biological indicators or inoculated carriers shall be used during the performance qualification. The number and locations of biological indicators shall be specified.

- Documented evidence shall be provided to show that the number and locations of biological indicators are sufficient to demonstrate that the requirements for SIP of the equipment have been met at locations presenting the greatest sterilisation challenge.

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Key Points - Validation

- Performance qualification shall include a series of at least three consecutive and successful runs of the SIP process to demonstrate the reproducibility and effectiveness of the process.

- The successful SIP runs shall be determined by measurement of physical parameters and inactivation of biological indicators or inoculated carriers which shall demonstrate the required microbicidal effectiveness.

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Key Points - Validation

Loss of Biological Indicators

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Key Points - Validation

Aspects not discussed

- Validation at suboptimal conditions.
- Thermometric acceptance criteria.

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Key Points - Validation

Other guidance available in relation to validation and control considerations

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Key Points - Validation

Filter manufacturer recommendations

- Maximum differential pressure.
- Maximum exposure temperatures.
- Filter Manufacturer X indicates the pipework downstream of the filter housing should be as short as possible and recommends a maximum of 100cm.

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Key Points - Routine Control

Effects of SIP on system components

- Valve diaphragms
- Gaskets
- Flexible tubing

Link to Preventative Maintenance

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Key Points - Routine Control

- Routine monitoring and control shall be performed on each SIP process. Data shall be recorded to demonstrate that the validated and specified SIP process parameters have been delivered to the system.
- Temperature / Pressure correlation.
- Steam quality.

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Key Points - Routine Control

- Integrity testing against established limits.
- "Complex sequences of opening and closing of valves in the pipes of a system is generally required."
  - Where this is controlled manually, detailed documentation of individual steps is required.
  - Where automation is used, electronic automation validated.

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Expectations

- System thoroughly assessed and understood with respect to design suitability for SIP.
- Justified process parameters.
  - Validation
  - Routine control
- Personnel training
- Review

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Questions

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