Evaluating SIP and Sterilization Methods

Investigating Microbial Contaminations

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CRB

Agenda

• Overview
• “Bioburden” – what is it? Regulatory References
• Investigation Details
• Prevention of microbial ingress
• Sterilization Review
• Case Studies
“Bioburden” – what is it?

PIC/S Glossary:

Bioburden

The level and type (e.g. objectionable or not) of micro-organisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Bioburden happens......

Contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

SOURCES OF POTENTIAL PRODUCT ADULTERATION
Contamination – Let the “fun” begin

• Root Cause Analysis
  • Which tool to use?
• Define the Road Map
• Structure the Process
• Define the Team / RACI
• Communication Plan

Investigation – Team Structure

Operations
- Chronological order
- MBR / Logbook Review
- Interviews

Automation
- Alarm History
- Valve Sequencing
- CIP / SIP report

MSAT / Val
- Batch data review
- Hold time Review
- Testing Protocol Dev.

QC
- Sampling Plan
- Organism ID
- IPT results

Maintenance
- Work order history
- Process maintenance interviews

QA
- Compliance review
- Change Controls
Investigation – Let the “fun” begin

We have a contamination…….relax?

• Isolate the situation, As Found State Review
• Prevent the easy / common RCA. Trust the Process

• Re-Asses Problem Solving tools; 5 Whys, Fault Tree Analysis, PEMME, Ishikawa (Fishbone), etc etc

Investigation Data

Raw Material review – Everything PASSES
Alarm History – Nothing of interest
Review of CIP and SIP cycles
• Vessel – PASS
• Media sterilization filter(s) – PASS
• Inoculation Line – PASS
• Nutrient Vessel – PASS
• Filter Integrity Tests - PASS

• But…….. Lets take a closer look
### Investigation Data – SIP Review

**Vessel SIP PASS?**

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**Transfer Line SIP**

**PASS**
- F₀ – the more the better?
- Look deeper
  - Temp variation between TC's
  - Excessive temperature
Design Standards

ASME BPE-2016

Equipment Longevity – Soft Parts

• \( \leq 130^\circ C \)

**SD-2.3.1.1 Steam-in-Place.** Equipment parts and components subjected to SIP should be designed and constructed to withstand continuous exposure to saturated steam at a minimum temperature of 266°F \((130^\circ C)\) representing 24 psig/1.65 bar under saturated steam conditions) for a duration of at least 100 hr under continuous steady-state conditions. All process contact surfaces subjected to SIP shall reach the required temperatures, under the required saturated steam pressure conditions, during the SIP cycle. Executing SIP operations at temperatures exceeding 266°F \((130^\circ C)\) may cause degradation of elastomers and/or damage to other components, resulting in reduction of overall equipment life. SIP conditions that are more stringent

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**SIP Details**

**Saturated Steam Table**

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<th>Pressure (PSIG)</th>
<th>Temperature °F</th>
<th>Temperature °C</th>
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<tr>
<td>50</td>
<td>298</td>
<td>148</td>
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</table>

- Monitor temperature and pressure
- Effective draining
- No vacuum
- Maintain integrity/closure
Key Factors

Design

- Process / User Requirements
- Single Use? Stainless?
- Sterile Boundary definition
- Utility requirements / sizing
- HAZOP / Risk Assessments
- Automation vs Manual controls
- ASME / BPE Standards – 2016
Design

16. Equipment used during handling of live organisms should be designed to maintain cultures in a pure state and uncontaminated by external sources during processing.

17. Pipework systems, valves and vent filters should be properly designed to facilitate cleaning and sterilisation. The use of "clean in place" and "sterilise in place" systems should be encouraged. Valves on fermentation vessels should be completely steam sterilisable. Air vent filters should be hydrophobic and validated for their scheduled life span.

ANNEX II: PREMISES AND EQUIPMENT

Key Factors

Installation

- Dead legs
- Properly sloped piping
- Weld inspection
- Piping runs / Flexible hose
- Connection alignment
- Walk Downs
5. PROCESS EQUIPMENT

5.1 Design and Construction

5.10 Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.

5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

5.12 Production equipment should only be used within its qualified operating range.

5.13 Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

Key Factors

Qualification

SIP Recipe Development
Temperature Mapping
Biologic Reduction Challenge
Post Validation Monitoring
Qualification

**Process Contact:** a surface under design operating conditions that is in contact with, or has the potential to be in contact with, raw materials, in-process materials, APIs, clean utilities (e.g., WFI, CIP, pure steam, process gases), or components and where there is a potential for the surface to affect product safety, quality, identity, strength, or purity.

**Product Contact:** a process contact surface that is in contact with, or has the potential to be in contact with, a product where product is defined by the owner.

18.34 Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, and sanitized or sterilized.

18.35 Culture media should be sterilized before use when appropriate to protect the quality of the API.

Qualification- Define Closed

- Select Subject Matter Experts (SMEs): Quality, Manufacturing, R&D
- The Program. Define “Closed”. Set the Risk Assessment Parameters
  - Develop Impact (Severity) & Likelihood Criteria
  - Pre-Establish Risk Matrix
  - Use Tools for systematic evaluations
  - Develop Closure Philosophy and Strategy

- Understand your process & systems, PFDs, Protocols, Batch Records
  - Evaluate and Confirm “Closed”
  - Assess & Develop Sound Risk Mitigation Plan Based on Science & Engineering NOT on Perception of Regulatory Requirements or Legacy
Key Factors

**Operations**

- Procedural Controls (SOPs)
- Process Training – Levels
- Operational Controls
- In Process Testing / Monitoring

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**Operations / Maintenance**

Operations is *not* a 1-Department activity

- Design/ Start-up
- Shut-Down
- Return to Service (RTS) execution
- Data Review via Dashboards, KPI’s

Maintenance Involvement

- Supe / Operator Involvement
- Building collective expertise & competency
- Training: Competency-based / future SME’s
- Co-Ownership / Shared R&R : FE, Metrology, QA, Eng, Ops
- OEM
18.30 Where aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.

18.31 Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.

**Design & Qualification**

- Sterile Boundary & Visibility
- SIP Strategy and Validation
- Bio-Waste Venting
- Sanitary Connections
- Diaphragm Valve Maintenance
- J-Tube (2k) direction into the overlay
- Exhaust Heat Exchanger

**Implementation Fixes**

- Exhaust Filter Condensation Removal
- Standard Torque Valve Installation
- Correct Line Slopes To Remove System Low Points
- Align Pipework & Filter Connections
- Sanitary Connection Evaluation
- Bioreactor design (Complex)
- Gasket Replacement
- Implement SIP/CIP Automation Changes

**Operation & Maintenance**

- Maintenance Program
- General Housekeeping
- Training & Awareness
- Maintenance Program Enhancements
- Return to Service Protocol
- Major Change Management Plan
- Training Enhancements
- Training – Manufacturing
- Training – Facilities
- Equipment Reliability
Key Factors

Maintenance

Preventative vs Predictive

Training

SOP’s / PM / Checklists

“Like for Like” changes

5.2 Equipment Maintenance and Cleaning

5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.

5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs.

5.24 Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.

5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.
Basic Practices
- Minimal Maintenance Program
- Calendar Based PMs
- Some “repair as you go”
- Technical Training

Good Practices
- Maintenance Plan & Program
- CMMS
- Change Management
- Assessment Management Program
- Approved Vendors/Contractors
- Job Descriptions/Development Plans
- Deviation Reporting
- cGMP Training
- Maintenance Controls
- Spare Parts Management

Best Practices
- Trend Analysis
- Metrics
- Audit Program (internal & external)
- Risk Assessments
- Continuous Improvement Program
- Equipment Reliability Program
- Return to Service Program
- Contractor Control/Training
- Predictive Maintenance
- Life Cycle Management
- Master Planning
- FMEA Analysis
- Run Time Maintenance

Low - High: Asset Utilization/Optimization
“Maintenance” – Routine Monitoring

In-Process Testing (Process vs Product)
Alert Level vs Action Level – when to ID?
Develop a library of local flora – know your enemy!!!
• Gram (+), Gram (-), Facultative Anaerobe, Spore forming?

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<th>Downstream</th>
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<td>Scale Up</td>
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<td>2</td>
<td>Harvest</td>
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<td>3</td>
<td>Sterility – Harvest</td>
<td>10 CFU / 1 mL</td>
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Is Maintenance Important?
Is Maintenance Important?

[Images of maintenance-related equipment and parts, showing signs of wear and maintenance needs.]
Summary

- Cannot over come design deficiencies with increased steam pressure
- Air and water hold up are SIP enemies
- Design using ASME BPE – that’s why it’s there
- Utilize Risk Based Maintenance NOT Calendar
- Evaluate process closure / Monitor routinely / Prepare & React accordingly

Questions?
Please use the microphone indicated so our recording includes audio of your question
Valve Handling

**Table: EPDM and PTFE Torque Values**

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<th>Diaphragm size (MG)</th>
<th>Fastening bolts</th>
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<th>PTFE Torque [Nm]</th>
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WHY ARE CLOSED SYSTEMS IMPORTANT?

Process Area
- Raw Materials
- Batch 1
- Batch 2
- Product 1
- Product 2
- Environmental Contamination
- Crossover
- Carryover
- CIP
- Personnel
- Equipment
- Airborne Contaminants
- Packaging

PROCESS AREA

CIP

Carryover
Crossover
Environmental

Batch 1

Batch 2

Product 1

Product 2

Raw Materials

Ever Changing
Impossible to Control
For further information, please contact
<title> <firstname> <lastname>
at <email>

Presenter 1 Name
Presenter 1 Title
Presenter 1 Company
Presenter 1 Company Address
Presenter 1 email

Presenter 2 Name
Presenter 2 Title
Presenter 2 Company
Presenter 2 Company Address
Presenter 2 email