Industry Trends and Best Practices for Aseptic Process Simulations

Anne Connors
Field Marketing Manager
EMD Millipore
Environmental Monitoring, Media Fill & Services
(781) 533-5438
anne.connors@emdmillipore.com
Overview

- Design criteria for a successful aseptic process simulation
- Guidance and trends
- Best practices in aseptic process simulations
- Interactive exercise
Overview

What is an aseptic process simulation?

- Incorporation of all validated components of the normal production process (Equipment, Materials, Personnel, Environmental Monitoring)
- A media fill has all the components of a typical production run, except the product is replaced by a nutrient media.
- The media fill test is one component of the overall validation of an aseptic manufacturing process.
Purpose of a Media Fill Campaign

- **When do you perform a process simulation run?**
  - During validation of a new aseptic manufacturing process
    - three consecutive, successful runs
  - Routine, semi-annual qualification “Continuous Verification”
  - When any changes to the product or process have been modified and could have an impact on the aseptic process
    - Facility or equipment modifications
    - Upward trends in Bioburden or EM testing
    - Significant changes in personnel
    - Container closure changes
    - Prolonged shutdown periods (any planned or unplanned event that would extend beyond normal at-rest periods)
    - Sterility test failure
Design Criteria

- Regulatory Drivers for Aseptic Process Simulation
- Demonstration of Continuous Sterility Assurance
  - Supports selection of design CQA’s (Critical Quality Attributes)
  - Supports operator training program
  - Demonstrates production environment is in a state of control

- Support of Environmental Monitoring Program
  - Confirmation that the environment and process is in control, even during “worst case” runs
  - Confirms that the EM program is appropriate
Design Criteria

- Selection of critical attributes
  - All critical attributes should be selected based on determination of risk to product sterility and patient safety

  - Established procedures/SOP's
  - Master Batch Record
  - Operator Training and Qualification Program
  - Validated Cleaning & Disinfection Procedure
  - Established Environmental Monitoring program
  - Selection of appropriate container
Design Criteria

- Selection of critical attributes
  - Incorporate a “risk-based” approach to simulate “worst case” production conditions. These conditions include:
    - Planned operator interventions (e.g. filter changes, filling needle changes)
    - Performance of runs covering all operating shifts
    - Container sizes
      - Established matrix or “bracket” approach
    - Determination of line speed
    - Duration of run
      - Long enough to challenge process and environmental conditions
      - Operator fatigue > contribution to potential contamination
    - Size of run (5-10K units, or equal to batch size if less than 5,000)
Design Criteria

- Additional key elements
  - Fill volume
    - Enough to contact container, support growth, yet keep oxygenated head-space
  - Media selection and preparation
  - Incubation requirements
  - Acceptance Criteria
    - Target is ZERO positives!
  - Investigation plan
    - Correct/Preventative actions established
Design Criteria

- Sequence of simulation events
  - Validation of operational, processing and sterilization systems in place
    - Aseptic Qualifications performed
    - Disinfectant qualification and disinfection validation
    - Equipment, container closure and component sterilization validation
    - Environmental controls and qualifications (ISO classification, temp/RH controls, air flow)
    - Materials and Personnel flow patterns
Design Criteria

- **Sequence of simulation events**
  - Define “routine” process simulation based on actual process
    - Formulation, required equipment and operations
    - Filling process
    - Operation Conditions (# of operators, operator shifts)
    - Set-up process and interventions
    - Length or size of run
    - Appropriate EM of validated conditions
Design Criteria

- **Sequence of simulation events**
  - Define execution conditions based on appropriate
    - Formulation, required equipment and operations
    - Filling process
    - Operation Conditions (# of operators, operator shifts)
    - Set-up process and interventions
    - Length or size of run
    - Appropriate EM of validated conditions
Design Criteria

- Planned vs. unplanned interventions
  - Simulation of typical production run interventions
    - Aseptic set-up
    - Weight adjustments
    - Stopper bowl/container filling
    - Fallen/broken containers
    - Environmental Monitoring
What are typical planned interventions during an aseptic process simulation?

- Fallen vial/container: 0%
- Filling needle change: 10%
- Manual Stoppering: 20%
- Manual Capping: 30%
- Filling pump change: 40%
- Broken vial/container: 50%
- All of the above: 50%
Planned Interventions

Are corrective interventions during routine processing added to the next simulation?

- Yes: 59.3%
- Not sure: 37.0%
- No: 3.7%
Design Criteria

- **Common problems**
  - Concern of manufacturer that the media itself is a source of contamination
  - Production of media is not a sterile process
  - BSE/TSE concerns
  - MYCOPLASMA
  - Dust generation
  - Preparation of media
  - Production “down-time”
Is your facility concerned about the risk of BSE/TSE?

- **Manufacturing & Validation**
  - Not Concerned: 13.3%
  - Somewhat Concerned: 16.7%
  - Very Concerned: 36.7%
  - Not sure: 33.3%

- **Quality Control**
  - Not Concerned: 0.0%
  - Somewhat Concerned: 22.2%
  - Very Concerned: 38.9%
  - Not sure: 38.9%
Design Criteria

- **Solutions**
  - Heat sterilized or Irradiated media
    - Elimination of contamination & mycoplasma
    - Time and risk reduction of media preparation
  - Media peptone sourced from low risk countries (for BSE/TSE) or use of alternative peptone source
Design Criteria

- Acceptance criteria and interpretation of results
  - The target is ALWAYS zero!
  - Inspection should be performed by QC operators qualified to identify contamination
  - For any run, microbial contamination at low levels should be investigated.
  - Gross contamination throughout the run can be indicative of failed sterility assurance, and the investigation should include all batches manufactured since the last passing media fill run.
  - Documentation of deviations and interventions is particularly important during an investigation where release product is at risk and can lead to the root-cause.
## Interpretation of Results

<table>
<thead>
<tr>
<th>FDA, EU, PIC/s</th>
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<tbody>
<tr>
<td><strong>When filling fewer than 5000 units, no contaminated units should be detected.</strong></td>
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<tr>
<td>-- One (1) contaminated unit is considered cause for revalidation, following an investigation.</td>
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<tr>
<td><strong>When filling from 5,000 to 10,000 units:</strong></td>
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<tr>
<td>-- One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill.</td>
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<tr>
<td>-- Two (2) contaminated units are considered cause for revalidation, following investigation.</td>
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<tr>
<td><strong>When filling more than 10,000 units:</strong></td>
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<tr>
<td>-- One (1) contaminated unit should result in an investigation.</td>
</tr>
<tr>
<td>-- Two (2) contaminated units are considered cause for revalidation, following investigation.</td>
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</table>
Design Criteria

Impact of a Positive Media Fill

- Risk to sterility assurance of all product lots manufactured since last media fill campaign.
- Costly investigation of manufacturing process
- Time and cost of repeated media fill run
- Time and cost of re-validation of process possible
- Cost of down-time during investigation or re-validation
- Potential recall of product on market
- Associated cost of microbial identification
Design Criteria

Investigation Plan

- Detailed specifics of contamination event
- List of systems involved in process
- Review of batch records, previous history and validation
- Supporting documentation (sterilization, EM and Bioburden data)
- Risk assessment of potential effects on previous batches since last process simulation
- Corrective/preventative actions with provided justification
- Conclusion of root cause (if identified)
Guidance and Trends


- EU Annex 1 - Manufacture of Sterile Medicinal Products

- USP Chapter <1116> - Microbiological Control and Monitoring of Aseptic Processing Environments
Guidance and trends

- PIC/S – Validation of Aseptic Processes PI007-6
- ISO 13408 – Aseptic Processing of Healthcare Products
- PDA Technical Report 44 – Quality Risk Management for Aseptic Processes
What guidance(s) is most closely followed at your facility for media fill testing?

- PDA Technical Report No. 22 (Process Simulation for Aseptically Filled Products)
- FDA Guidance (Sterile Drug Products Produced by Aseptic Processing)
- ISO 13408 (Aseptic Processing of Health Care Products)
- EU GMP Part I annex 1
- PIC/S PI 007-2 (Recommendations on the Validation of Aseptic Process)
- Other (please specify)
Guidance and trends

Top of mind industry concerns and problems

- Personnel Contamination
- Aseptic Connection failure
- Inadequate environmental monitoring, or failure to investigate upward trending
- Undocumented change in process or environment (HVAC installation, mechanical failures)
- Inadequate or non-validated sanitization procedures
1. “Your firm has not established appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, including procedures for validation of all aseptic and sterilization processes” (21 C.F.R. § 211.113(b)). For example:

a. Your firm has failed to conduct a media fill representative of the different packaging configurations of your drug products for the past two years. Your firm has been using a volume of (b)(4) for media fills; however, commercial products are available in (b)(4) and (b)(4). In addition, you have not established maximum aseptic fill duration.

In your response, your firm states that you have amended your Standard Operating Procedure (SOP) (b)(4) to “bracket” the container sizes by utilizing both the (b)(4) and (b)(4) volumes. Your response, however, is inadequate because you have not provided a risk assessment that examines the effects of differences between product fill sizes (i.e., fill speed, operating methods, container opening size, mass) to determine if bracketing is appropriate.
Best practices in aseptic process simulations - Selecting the right media (or placebo)

- **Growth Media Selection**
  - Broad range growth medium preferred (TSB)
  - When should FTM be used?
    - Manufacture in strictly anaerobic conditions (less than 0.1% oxygen)
    - When anaerobes have been recovered in environmental testing, or sterility test failures (i.e. *P. acnes*)
  - Selected media should be demonstrated to grow aerobic bacteria, yeast and molds.
  - Choose formulation that best suits your most strict requirements for quality standards.

- **Placebo Selection**
  - (Bulk production, powders, ointments)
  - Sterile placebo or powder
    - Generally, lactose, mannitol, TSB

- **Considerations**
  - Ensure sterility
  - Process compatibility
  - Growth promotion capabilities
  - Solubility
Best practices in aseptic process simulations

- What is critical? What can be modified?
  - Selection of product container
  - Media fill volume
  - Selection of medium or placebo for (Bulk, Ointments, Powders)
  - Lyophilization process
  - Validated Sterilization filter
    - The sterilization filter is validated independently of the aseptic process simulation, and may not be identical to the one used for simulation.
    - Pre-filtration may be necessary, with the goal to simulate operations.
Best practices in aseptic process simulations

- Media preparation and filtration practices
  - Minimize hold time of media
    - Preparation at >60°C reduces risk of vegetative growth
  - Use of a pre-filter to remove insoluble components will reduce clogging of sterilizing grade filter.
  - Optimal temperature for media should be <35°C before use
Best practices in aseptic process simulations

- Pre and Post incubation reconciliation
  - Perform unit reconciliation and accountability
  - Reconciliation of units
    - # of units inspected = # units filled - # units rejected
  - Accountability
    - Account for all rejected units
    - Detail reasons for removal of units (container closure defects, manual interventions)
- Inspection should be performed by QC operators qualified to identify contamination
Incubation and Examination of Units

- Most Guidances state minimum of 14 days @ 20-35C
- 7 days each at 20-25C then 30-35C acceptable also
  - This dual temperature incubation must be included in the validation
  - Pre-incubation
    - Inspect all containers
    - Remove only those that would be typically discarded
    - Incubate all filled containers
  - Post-incubation
    - Inspect ALL containers regardless of conditions.
    - If they passed the pre-incubation inspection, they are still counted
    - Compare test containers to a known sterile container
Best practices in aseptic process simulation

- Personnel Qualification
  - Training should include:
    - general instruction on aseptic technique
    - materials handling
    - potential sources of contamination
    - clean room air dynamics

- Viewing of your facility smoke studies may be helpful in training the operators to visualize how manipulations in critical areas can affect air flow.
Best practices in aseptic process simulations

*MFG - What are your primary concerns when VALIDATING a process simulation?

- Operator Training
- Aseptic Technique
- Production delay
- Environmental Controls
- Introduction of growth...
- Production Downtime
- Disinfection program
- Cost

*Data presented represents top two ranking selections out of eight
Interactive Session

- Form groups and develop critical quality attributes for assigned “product”
- Consider manufacturing process, dosage form, personnel, and product flow.
- Each group presents study design and master plan