Preparing Your Aseptic Processing Facility for an FDA Inspection

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Bayer HealthCare
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Agenda

• Regulatory Requirements
  – Aseptic Controls Master Plan
  – Media Fill Protocol
  – Executive Summary Reports

• Establishing your Approach
  – Aseptic Controls Master Plan
  – Media Fill Protocol
  – Executive Summary Reports

• Preparing Your Facility
  – 1st Impressions
  – Process, Material, Personnel
  – Tour Routes
  – Planned Operations

• Preparing Your Employees
  – Competencies
  – Subject Matter Experts
  – The Art of Audit Facilitation

• Interactive Exercise; Learn from the Mistakes of Others
Expectations are Just That….Expected
Regulatory Requirements & Expectations

- **GMP’s**: 21 CFR Part 210/211
  - 211.113 (b) validation of aseptic processing – prevention of microbial contamination
  - 211.110 (a) inclusion of Bioburden testing as an in-process test
- **FDA’s Aseptic Processing Guideline**: Sterile Drugs & Biologics
- **FDA Compliance Manual, Chapter 56 – Drug Quality Assurance 7356.002A**
- **ISO**: ISO 14644-1:1999 Clean rooms and associated controlled environments: Part 1: Classification of air cleanliness
- **ORA**: ORA-Lab.5.3; Facilities and Environmental Conditions: Defines requirements for FDA/ORAlaboratories
- **CDRH/QSR**: 21 CFR Part 820- Production & Process Controls: Adequate control of environmental and personnel to assure no adverse effect on product quality
- **USP**: Monographs specific to execution of Microbiological Testing; General chapters are strongly encouraged to be adopted.
- **Many More…..**
Key to Success: State of Control

• ICH Q-10 *Pharmaceutical Quality System*
  – *Achieve Product Realization*
  – *Establish and Maintain a State of Control*
  – *Facilitate Continual Improvement*

• FDA-Compliance Program
  Guidance Manual; Chapter 56
  Drug Quality Assurance Program 7356.002A: *Sterile Drug Process Inspections*
The Design of your Controlled Environments will dictate the Elements of your Control Strategy
Aseptic Controls Master Plan

The purpose of the Prevention of Microbial Contamination and Aseptic Processing Controls Master Plan is to direct and document the general principles, responsibilities, and procedures to ensure that the appropriate microbial contamination prevention and aseptic processing control measures are in place to mitigate risk of contamination.

This Master Plan details the approach to ensure that sterile drug products manufactured using aseptic processing meet the requirements of the current good manufacturing (cGMP) regulations (21 CFR parts 210 and 211)
Roadmap to Compliance

• Purpose
• Scope
• References
• Definitions
• Responsibilities
• General Principles supporting your Sites “State of Control”
  – Facilities and Equipment
  – Personnel & Training
  – Starting Materials
  – Aseptic Processing
  – Environmental, Personnel, Utility Monitoring
Key Partnerships

• Supply Chain
• Engineering
• Manufacturing
• Quality Unit
• Validation
• Technical Services
• Facility Cleaning and Sanitization Group
Responsibilities

Supply Chain

• Source and purchase materials of appropriate microbial and handling quality
• Ensure proper storage and handling of all raw materials, components and finished products

Engineering

• Assure facilities are designed, controlled and monitored to provide the appropriate level of contamination control
Responsibilities

- Ensure personnel are appropriately trained and qualified and report any adverse medical conditions to mgt.
- Execute manufacturing instructions per approved quality records
- Assure environmental and procedural controls are enforced
- Execute Aseptic Processing Simulations
Responsibilities

- Ensure personnel are appropriately trained and qualified and report any adverse medical conditions to mgt.
- SME’s for: Cleaning/Sanitization of Facility, Environmental Controls Plan, Aseptic Gowning Certification, Aseptic Processing Simulations,
- Provide Quality Oversight to the Aseptic Process
Responsibilities

Validation / Technical Services
- Facility Qualification
- Equipment Qualification
- Aseptic Processing Simulations
- Container Closure Validation
- Cleaning Validation

Facility Sanitization Personnel
- Do not underestimate the criticality of this group
- Must be trained in contamination risk mitigation
Responsibilities

- Ensure appropriate Microbial Controls are in place
- Ensure a diverse array of control measures are implemented in order to mitigate risk
- Ensure that adequate resources are available and that personnel are adequately trained to perform their assigned function
General Principles

Define everything and anything that you consider relevant to the State of Aseptic Control of your facility…Bullets only...see Bonus Material

• Facilities and Equipment
• Personnel & Training
• Starting Materials
• Aseptic Processing
• Environmental, Personnel, Utility Monitoring
The Media Fill Protocol

• Follow your standard Process Validation Protocol Format
  – Purpose
  – Scope
  – References
  – Responsibilities
  – Procedures and Acceptance Criteria
    • Steal Shamelessly from Aseptic Processing Guidance
• Batch Record must represent Routine Process
The Media Fill Protocol

- Attachment 1 Protocol Discrepancy Log
- Attachment 2 Protocol Discrepancy Form
- Attachment 3 Signature Log
- Attachment 4 Training Checklist
- Attachment 5 Interim Read
- Attachment 6 Final Read
- Attachment 7 Growth Promotion/Fill Volume
- Attachment 8 Contamination Rate and Pass/Fail Results
- Attachment 9 Accountability
- Attachment 10 Growth Promotion Results
- Attachment 11 QC Microbiology Test Forms
- Attachment 12 Batch Records
- Attachment 13 Routine/Non Routine Interventions and Aseptic Technique Log
Protocol Test Plan

Pulling the dynamic components out of the Protocol

– No. of Runs
– Components
– Line Speed
– # of Units
– Over Gassing

Variable information outside of Static Protocol
# Test Plan Summary:

<table>
<thead>
<tr>
<th># of separate successful simulations:</th>
<th>1 simulation</th>
<th>3 simulations</th>
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<table>
<thead>
<tr>
<th>Vial size:</th>
<th>10 mL</th>
<th>100 mL</th>
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<tbody>
<tr>
<td>BTL 10mL T1 Flint tubing 20mm</td>
<td>Flint Type 1 2222</td>
<td></td>
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<tr>
<td>250 mL</td>
<td>500 mL</td>
<td></td>
</tr>
<tr>
<td>BTL 250mL T1 Flint Serum 30mm</td>
<td>BTL 500mL T1 Flint Serum 30mm</td>
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</table>

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<thead>
<tr>
<th>Line Speed:</th>
<th>Minimum</th>
<th>Maximum</th>
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<tbody>
<tr>
<td>Minimum cpm</td>
<td>Maximum cpm</td>
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</table>

<table>
<thead>
<tr>
<th>Justification:</th>
<th>6 month routine simulation</th>
<th>Requalification following shutdown</th>
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<tr>
<th>Sterile Oil Free Compressed Air:</th>
<th>Yes</th>
<th>No</th>
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<tr>
<th>Duration:</th>
<th>Not less than (NLT) hours: (encompassing set up, 2 intervals of active filling of media and 1 interval of dynamic operation of the filling line without the addition of media into the vials)</th>
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<tbody>
<tr>
<td>Not less than 10,000 units</td>
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| # of Units incubated per simulation run: | |
|-----------------------------------------| |

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<tr>
<th>Downtime:</th>
<th>Not less than 1 hour (continuous) during one of the active filling runs (to simulate a shift change or lunch break downtime).</th>
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<table>
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<th>Incubation Time/Temperature:</th>
<th>Not less than 14 days at 30-35 °C</th>
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<tr>
<th>Stopper:</th>
<th>20mm RFS double wrapped Bags: checked component codes may be used:</th>
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<tbody>
<tr>
<td>xxx</td>
<td>FM-140 Grey Chlorobutyl, 4405/50 Grey Bromobutyl, 4405/50 Grey Chlorobutyl</td>
</tr>
<tr>
<td>yyy</td>
<td>zzzz</td>
</tr>
<tr>
<td>aaaaa</td>
<td>bbbbb</td>
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</table>

<table>
<thead>
<tr>
<th>Seal:</th>
<th>20mm Center Tear Silver: ccc 30mm Center Tear Silver: ddd</th>
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## Test Plan Approval

<table>
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<tr>
<th>DEPARTMENT</th>
<th>NAME (PRINT)</th>
<th>SIGNATURE</th>
<th>DATE</th>
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<tr>
<td>Tech Services</td>
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<td>Operations</td>
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<tr>
<td>Quality Control</td>
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<td></td>
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<tr>
<td>Quality Management</td>
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</table>
The Executive Summary Report

• All data compiled on attachments from the validation batch protocol run, will be included in a Final Summary Report. The final report will present an analysis of the results and be reviewed for compliance and adherence to protocol acceptance criteria and batch record requirements. Each discrepancy shall be discussed in detail in the Discrepancy section of the Final Report and must include a statement of impact, if any, on the aseptic process and/or sterile filling suite.

• The Final Report will include a conclusion documenting that the sterile filling operation is capable of producing sterile filled vials and that the Aseptic Processing Area meets cGMP expectations, 21 CFR parts 210 and 211 regulations, and all internal requirements.
Comprehensive and Holistic

Aseptic Controls Master Plan, Aseptic Processing Protocol and Executive Summary Report….the Goal Is:

• **Comprehensive**
  – Defined / Documented Program
    • Policies
    • Procedures
  – Start Global / End Local
  – Support with Regulatory References

• **Holistic**
  – Build on Data – Systems Approach
  – Roll Information Up
  – Take Credit for Everything…Sell your story
  – Provide Immediate Picture of Compliance
  – Don’t Forget Training
Preparing your Facility

• Facility Design & First Impressions
• Understand your Process, Material, & Personnel Flows
• Practice your Tour Routes
  – Pictures & Maps in Opening Presentation
• Plan to be in Operation
Facility Impressions

• One opportunity to make that impression
• Must Have Robust procedures and visible practices for facility maintenance
  – Employee Driven Site Pride
  – Management: Positive reinforcement

• Visible Messaging
  – Mirrors
  – Instructional and Reminder Placards
Facility Design...Understanding what You Are Up Against
Facility Design

You get 1 opportunity to set the stage for your audit…

– Facility must show well
– Process, Material, Personnel, and Waste flows must be documented through controlled drawings, approved SOP’s, and documented practice.
– Surfaces must be visually cleanable and visually clean
– Assume all doors, drawers, cabinets will be opened
What’s in?

• Facility
  – Design
    • Commissioning and Qualification of Facility
    • Design and Qualification of Environmental Monitoring Strategy
  – HVAC
    • Smoke Profiles
  – Cleaning & Disinfection Programs
    • Qualification of Cleaning Agents on your surfaces using USP panel and your organisms
    • Looks Clean is Clean?

• Utilities
  – Design
  – WFI / Purified Water ….Back to Generation
  – Compressed Gases
HVAC

- Building Monitoring System
  - Operations monitored & alarmed 24/7
  - Visual Indicators–light bar
  - All rooms are monitored and alarmed independently.
  - Minimum allowable room pressure 0.01 inches W.C.
- Terminal HEPA’s-99.97% ASHRAE rating
  - Certified every 6 months-
    - Integrity and Velocity (Unidirectional)
      - Velocity at work surface
  - Certified every 12 months-
    - Filter Loading (Volume- Flow, used for room pressurization)
      - Smoke Profiles; Static, Dynamic, w Change Control
- Minimum 20 air changes
  - Total air changes is excess of 100 (make up and recirc. Included)
Process Utilities

• Water
  – Criticality of Use- monitor / control back to Generation
  – Monitor as-is Conditions (Tubing)
  – Applicable Compendia
  – Thermophiles
  – Annual Summary

• Compressed Gases
  – Point of Use Filtration
  – Rationale for selected Sites
    • Criticality of Use point
    • Physical Logistics
  – Time Driven Summary
Manufacturing Space

- Legacy
- State of the Art
- Products
- Conditions
- History
Process Filters: Regulatory Expectations

FDA Expectations

– Validation Encompassing
  • Chemical Compatibility
  • Extractable / Leachable Determination
    – Firm must conclude that levels are acceptable
  • Microbial Retention
    – Viability Determination

Suggested Facilitation Tools

– Executive Summary Report
– Include all Process Filters
Support Area Space

Cascade of Control

Traffic Flow

Automation vs. Manual
Impact to Controlled Environments

- Surfaces
- Personnel
- Incoming Materials
- Air
- Water
- Facilities & Equipment

Manufacturing Environment
“Microbial monitoring programs for controlled environments should assess the effectiveness of cleaning and sanitization practices by and of personnel that could have an impact on the bioburden of the controlled environment. Microbial monitoring, regardless of how sophisticated the system may be, will not and need not identify and quantitate all microbial contaminants present in these controlled environments. However, routine microbial monitoring should provide sufficient information to ascertain that the controlled environment is operating within an adequate state of control.”

United States Pharmacopeia General Chapter <1116>
Routine Monitoring: A Holistic Approach

- Environmental Monitoring
  - HVAC
  - Process Utilities
  - Dynamic Manufacturing Process
- Disinfectant Program
- Personnel Monitoring
  - Qualification
  - Routine
- Bioburden / Endotoxin Monitoring
  - Components
  - Product
  - Vendor Certification
Your Environmental Program

Must Demonstrate a Holistic Program of Control
• Understand the Regulation (s)
  – Requirements
  – Applicability to your operation
  – No more 209E-replaced with ISO standard in 1999
• Understand your Process Requirements
  – Weaknesses
  – Strengths
  – Emotional vs Technical concerns
• Understand the “c” in CGMP for your District and your Customers
• Stay Current, and be part of the review process!

Your Environmental Monitoring Program must be designed as applicable to your unique needs
Risk Assessment

- Product Process
- Commodity Preparation
- Staging
  - Holding Time
- Controlled Environment Cascade
  - Air Flow
  - Personnel Flow
  - Product Flow
Bioburden and Endotoxin

• Document Formal Position
• Components-API and Excipients
• Commodities
• Formulated Solutions
  – Pre filtration (Bulk solution)
  – Post filling (pre- sterilization) sampled from end of fill
• Any recovered organisms are identified
  – Heat Shock all Gram + Spore formers
  – Defined Response to Gram -
  – Objectionable Organisms
Approach and Control
It’s all about Negating the Risk

Continuous Monitoring
Isolation Technologies
Certified Vendors
Comprehensive Training
Extra Sampling when Warranted
Robust Trending
CAPA
So What’s a Legacy Facility to do?

Negate the Risk through the implementation of Robust Monitoring and Data Collection Programs….

- Certified Vendors-Understand potential for introduction of Bioburden and Endotoxin
- Comprehensive Training-Clean room personnel are No. 1 source of contamination
- Extra Sampling when Warranted-Be sure programs contain detailed instructions for additional samples when OOS occurs
- Robust Trending-LIMS is now a must have
- CAPA-Procedurally ensure that all excursions are appropriately investigated. A count of (1) in a sea of zeros will be questioned.
Prepare your Employees

- Need to Document and Understand required Competencies
- Define and Support through Evidence-Contamination Control Subject Matter Experts
- Practice and Prepare for Regulatory Audits
Preparation Considerations

Personnel
  – Job Descriptions and Training Documentation
  – Prepare Subject Matter Experts
    • Microbiologists
    • Controlled Environment Engineers

The Art of the Audit
  • Define and Prepare the Team
  • Document your Opening Presentation
  • Understand what will be Requested and have Immediately Available
Audit Facilitation Tips

Don’t wait until FDA at your Door to prepare Audit Ready…All the Time

• Defined Audit Team and Procedure
• Prepared and printed Opening presentation
  – Facility Overview with Pictures
  – Organizational Charts
  – Approved Drawings: Personnel, Material, Waste Flows and Controlled Environment Classes related to HVAC
  – High Level Process Flows, CAPA Flow,
• Tools for managing Audit
  – SharePoint or equivalent
  – “Prep” Room Ready
Aseptic Personnel

- Gowning
  - Qualification
  - Control
- Routine Monitoring
  - Finger Impressions
  - Garments
- Disqualification
- Training
  - Hygiene
  - Basic Microbiology
  - Simulations

Program inclusive of all entering Controlled Environments
Aseptic Training

• Initial aseptic core certification requires:
  - SOP review and quiz
  - Aseptic Gowning Technique Presentation and quiz
  - Aseptic Manipulation Course and quiz
  - Microbial Orientation class and quiz
  - Aseptic Gowning certification

• Re-certification required for:
  – Annual gown re-certification
  – Re-occurring personnel monitoring OAL’s
  – Leave of absence over 3 months
Inspections

Investigator will request reports associated with environmental trends. Provides -road into:

– Management Controls, MDR
– Design Controls, Change Control
– CAPA
– Production / Process Controls

• Trending: Open / Closed / Aging
• Product specific – Across Process
Risk Assessment

Inspector Will Expect Documented Risk Assessment, with identified Mitigations

Aseptic Manufacturing

– Traditional
– Isolated
– Liquids vs. Powders
– Complexity: Liquid vs. Lyo.
– Multiple Shifts
Requests your Aseptic Audit team Must be able to Provide

• Please Provide a document that defines your facilities Aseptic Risk Assessment and Mitigation Strategy
• Please provide a documented “Facility Design” with considerations and rationale for:
  – Materials, surfaces and finishes
• Please provide an Environmental Program Document with considerations and rationale for:
  – Sample Sites
  – Frequencies
  – Disinfectants
• Please provide evidence that EM trends are reviewed annually and conclusions are documented… don’t forget the CAPA
Requests your Aseptic Audit team Must be able to Provide

• Please provide evidence that your aseptic processing simulation represents actual manufacturing operations
  – Frequency, Duration, Parameters, and Conditions
  – Statistical execution of Interventions
• Please provide a trend of all your controlled utilities for the last 2 years
• Please provide a trend of all bioburden monitoring for the last 2 years
• Please provide the qualifications and evidence of those qualifications for all Aseptic Operators …and their Management
Tying it all Together

• Know the Requirements and Document how your Site Meets them..
  – Aseptic Controls Master Plan
  – Aseptic Processing Protocols & Reports

• Prepare your Facility
  – Understand Weaknesses
  – Instill Site Pride
  – Walk throughs—multiple!

• Prepare your Employees
  – Competencies
  – Predefined Audit Team, Space & Tools
Getting Help: References

- FDA guidance
  - Aseptic Processing Guideline
- EU-Orange Guide
- PDA Technical Report 13
- USP General Chapters
- ISO 14644 series, replaced Fed. Std. 209E
- GMP Trends
- Industry Organizations and Publications
  - IVT
  - PMF
  - PDA
  - AAMI
  - Discussion Groups
Questions?
Thank you!

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