:Session 3:
Aseptic Practices of Microbiology Laboratory versus Manufacturing

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Aseptic Processing Workshop:
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Aseptic Techniques – Basic Requirements

- Design of aseptic zone and process flow
- Operational challenges
- Regulatory expectations
- Assessment of the techniques employed

Aseptic Techniques – Basic Requirements

➢ Sterility Testing : Regulatory Expectations

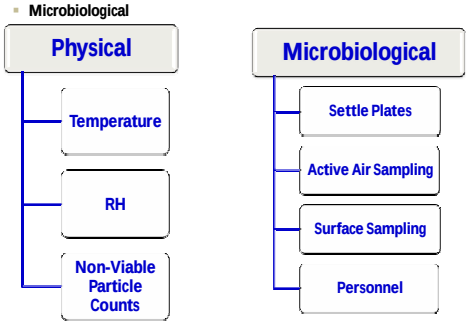
- USP: The facilities used to conduct sterility tests should be similar to those used for manufacturing product
- The facility for sterility testing should be such as to offer no greater a microbial challenge to the articles being tested than that of an aseptic processing production facility
- Proper design would, therefore, include a gowning area and pass-through airlock.
- Environmental monitoring and gowning should be equivalent to that used for manufacturing product.

Design: Common Requirements for Manufacturing and Laboratory

- Grade “A” zone with Grade “B” background
- Supporting adjacent clean rooms including well designed change rooms for personnel movements
- Aseptic gowning procedures
- Appropriate differential pressures across the rooms (very critical)
- Control and monitoring of differential pressure with alarms

Common Requirements for Manufacturing and Laboratory

- *Environmental Monitoring:*
  - Physical
  - Microbiological



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➢ Environmental Separation for Grade "A" Zone

Manufacturing

- Flexible Curtains
- Rigid barriers with glove ports
- C-RABs
- Isolators

Laboratory

- Horizontal LAF
- C- RABs
- Isolators

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Process Flow

- **Manufacturing**
- **Integrated Line operations for :**
  - **Depack**
  - **Washing of Containers / Closures**
  - **Sterilization / Depyrogenation**
  - **Filtration**
  - **Filling and Stoppering**
- **Lyophilization**
  - **Manual Loading / Unloading or**
  - **Fully Automated Loading / Unloading**
  - **Advanced aseptic processing through automation or environmental separation**

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Process Outlines – Laboratory

- Horizontal LAF
- Double Door Autoclave
- Dynamic Pass Box
- Physical Shifting into LAF through sanitization methods
- Manifold method
- Direct Inoculation
- Closed Systems (Highly secured)
- C-RABs or Isolators with VHP cycle

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Operational Challenges-MFG

- Improvements:
  - ❑ Transfer / Transport of Sterilized components
  - ❑ Set-Up (Assembling)
    - ❑Filling / Stoppering / Sealing
  - ❑Interventions
    - ❑Inherent
    - ❑Corrective
  - ❑Blocking the first-air
  - ❑Transfer through interface between Grade "A" and Grade "B" Zone

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Operational Challenges-MFG /LAB

- **Improvements**:

Manufacturing:

- Pre-assembled/ connected tubings etc before sterilization and reduce the number of aseptic connections
- Risk minimized with CRAB or Isolators

Laboratory:

- Transfer of samples, media containers canister packs into the Grade "B" Zone and then through the interface between Grade "A" Zone and Grade "B" Zone
- CRAB and Isolators with VHP are the solutions for eliminating adventitious contamination

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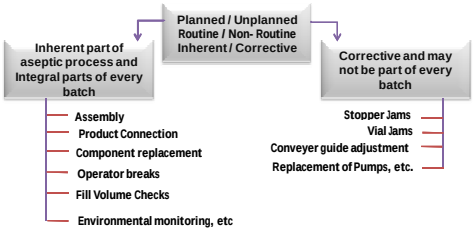
Operational Challenges- Manufacturing

- ***Human interventions-Potential for Contamination:***



Caution : Be cautious not to interpret frequent occurrence of particular corrective interventions as routine as it had to be performed during the execution of the batch – This interpretation violates the principle that no intervention is safe
- They should be resolved under continuous process improvement

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Operational Challenges-Manufacturing

- **The Perfect intervention is the one that is not required**
- **The fewer the interventions, the lower the potential for contamination**

Elimination:

- ***Process and procedural design***
- ***Improving component quality***
- ***Process automation***
- ***Resolve the interventions under continuous process improvement***
- ***Excessive tolerance of interventions amounts to settling for an inferior design***

"Ref: Interventions in Aseptic Processing –James P Agalloco,Akers Pharmaceutical technology Vol 35,Issue-4,PP 69-72"

- ***Sterility – Accomplish through design more than any other means***

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Operational Challenges-Sterility Testing

- **Wipe all exposed surfaces** of sample containers, tubes of culture media and other containers with surface disinfectant before placing in LAF workbench
- Outer wrapping of sterilized items be removed at the **edge of the LAF** workbench and the sterile inner items be introduced into LAF bench
- **Change into a new pair of gloves** after transferring supply items into the LAF workbench. Preferably, partner will then perform critical steps using uncontaminated gloves
- Remove over seals of the necks of the samples, **wipe** rubber diaphragm of the vials & necks of the ampoules with 70% of alcohol

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Assessment of Aseptic Techniques

	Manufacturing	Microbiology Lab
Personnel:	•Trained into microbiological aspects , Aseptic gowning ,Aseptic techniques/On the Job and aseptic media fill participation	Trained into microbiological aspects , Aseptic gowning, Aseptic techniques/On the Job and manipulative controls
Simulations :	•Sterilization of components & other items •Hold times •Filling ,Stoppering & Sealing •Interventions •Inspection	•Sterilization •Hold times •Testing manipulative controls •Incubation •Inspection •Positive & Negative controls

Aseptic Processing - Overview

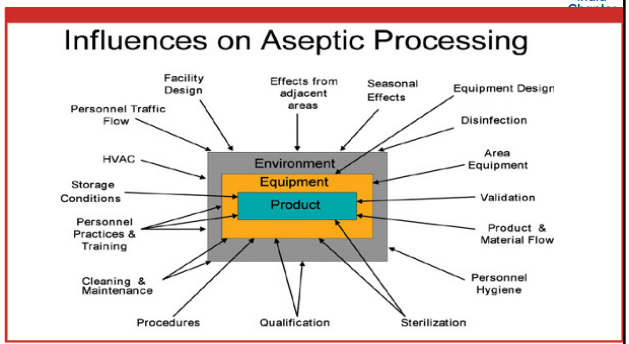

Figure 1: Influences on aseptic processing (Adapted from Leonard Mastrandrea).

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Aseptic Processing-Overview

D= Design
M = Maintenance

- *Richard L. Friedman, M.S.*
- *FDA/CDER*

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PDA
Parenteral Drug Association
India Chapter

Thank You

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