

# Microbiological Considerations for Non- Sterile Pharmaceutical Products

Dr. Leonard W. Mestrandrea  
Principal Consultant  
MESTRANDREA CONSULTING LLC



## Microbial Control Considerations

- Product Development
- Routine Monitoring
- Water systems and Usage
- Active Ingredients
- Equipment Design and Use Conditions
- Personnel
- Manufacturing Environment



## Overview

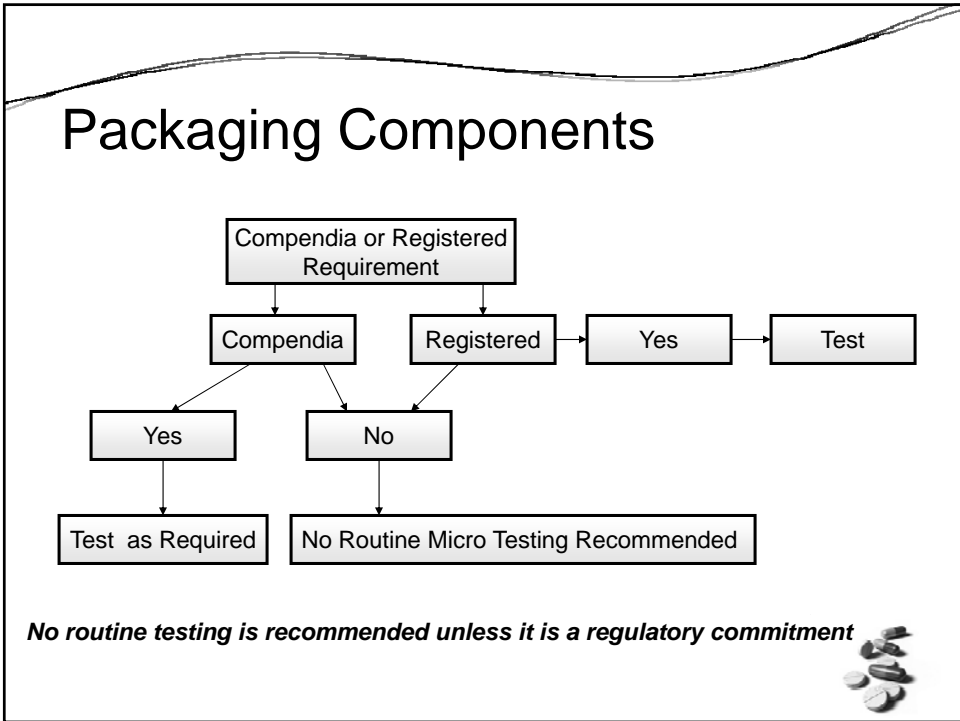
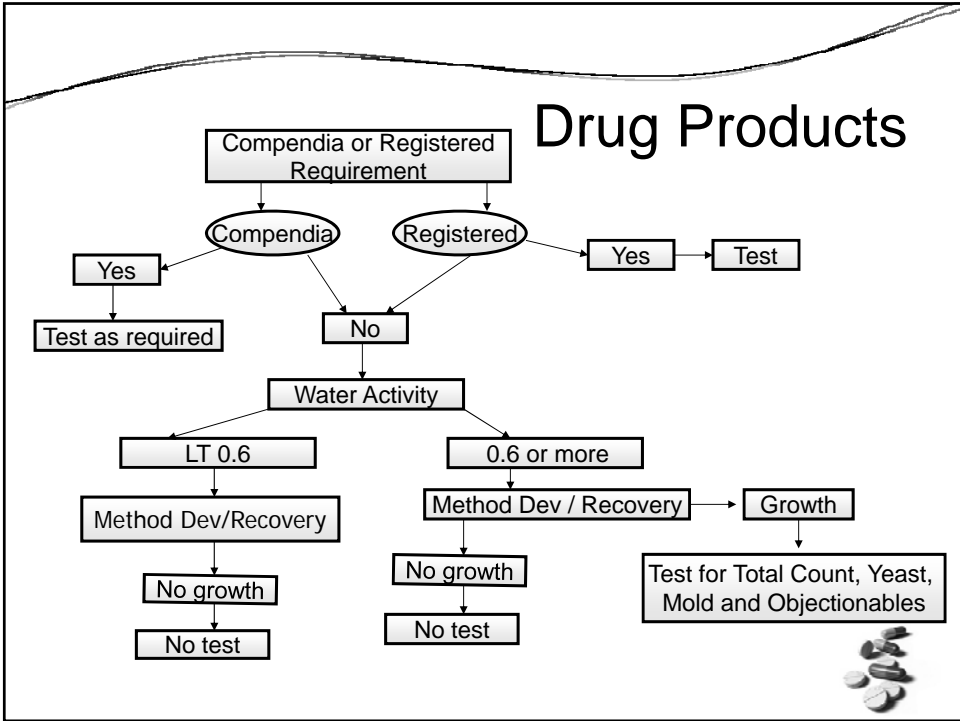
- Significance of microorganisms in non-sterile pharmaceutical products
- It is recognized that there is no current regulatory requirement for microbial control in the manufacture of non-sterile pharmaceutical products



## Overview *(continuation)*

- Guidance and Recommendations for performing a microbiological assessment considering a total program of facility, material and personnel management
- Recommend a program of control for the manufacturing environment rather than control by direct environmental monitoring of the manufacturing area.





## Water

- Requirements stated in FDA Guide to Inspections of High Purity Water Systems, July, 1993
- USP34/NF 29 – Water for Pharmaceutical Purposes
- APHA Methods for the Examination of Water & Waste Water



## Purpose

To describe Microbial Monitoring and Control in Non-sterile Manufacturing Areas that emphasizes a Risk Based Approach



## CFR Citation

### **211.110 Sampling and testing of in-process materials and drug products**

- To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.



## CFR Citation (*continuation*)

Such control procedures shall include, but are not limited to, the following, where appropriate:

- Tablet or capsule weight variation
- Disintegration time
- Adequacy of mixing to assure uniformity and homogeneity
- Dissolution time and rate
- Clarity, completeness, or pH of solutions
- Bioburden Testing



## Approach

How do we effectively apply microbial control in the manufacture of non-sterile products?

- Use HACCP to understand the process
- Define where microbial contamination could occur
- Effectively determine the best control and monitoring methods



## ***Development of an Environmental Monitoring Program Through the Use of HACCP Risk Management Process***



## Presentation Overview

- Why Risk Based control
- Industry survey results
- Risk Assessment
- Aspects of Unclassified Manufacturing Areas
- Monitoring and Control
- Sampling Methods and Frequency
- Setting Alert and Action Guidelines
- Environmental Monitoring Program and Response to Excursions



## Why Risk Based Control?

- No well defined regulatory standards or guidance exists for the microbiological control of non-sterile pharmaceutical manufacturing environments
- Environmental control and monitoring of non-sterile processes either range from non-existent to parallel programs to aseptic processing
- Data generated from some programs may be of little value for the control of the microbiological quality of non-sterile environments in which the product is manufactured



## Why Risk Based Control?

- Surveys of environmental practices for non-sterile sites showed a wide range of monitoring practices:
  - 1994 PhRMA Survey
  - 1998 AAI Micro Seminar Survey
  - 2002 Pharmaceutical Systems Inc. Survey
  - 2006 PDA Survey



## Survey Results

- Misapplication of EM monitoring as a means of microbial and process control;
- Questions on how the data would be used;
- Questions on the interpretation of the data and its significance to product quality and safety to the consumer;
- Widespread variability in programs resulting in confusion.





## Approach

So, how do we effectively apply microbial control in the manufacture of non-sterile products?

One approach is to use a risk based approach to understand the process, define where microbial contamination could occur and effectively determine the best control and monitoring methods.



## HACCP Risk Management Process

- Describe each manufacturing process/control area
- Develop process flow diagram
- Determine Critical Control
- Establish Environmental Monitoring Procedures



## Microbiological Assessment Areas for Review

- Engineering control of the air system to those areas, e.g. relative humidity, temperature, air changes, filter integrity inspections, pressure differentials, etc.
- Product and material flow
- Personnel traffic flow
- Personnel practices and training
- Cleaning and maintenance measures
- Collection, transportation and storage of wastes



## Points to Consider when Performing a Risk Assessment

- Synthesis, isolation and final purification of the drug substance
- Microbiological attributes of active pharmaceutical ingredients
- Microbiological attributes of the pharmaceutical excipients and inactive ingredients
- Inherent antimicrobial properties of the drug product
- The formulation of the drug product and hold point storage conditions
- Water activity of the drug product



## Points to Consider when Performing a Risk Assessment (*continuation*)

- Processing conditions for the drug product facility
- Equipment design
- Cleaning and sanitization
- Process water production, storage, distribution and use
- Housekeeping and disinfection procedures
- Packaging of the drug product, with particular attention to integrity and vapor barriers



## Points to consider when Performing a Risk assessment (*continuation*)

- Storage conditions and packing of intermediates and finished dosage forms
- Route of administration of the drug product
- Is the product to be used chronically or acutely
- Age and general health of the patient population expected to use the drug product



## Risk Assessment

- The order of risk of pharmaceutical products based on the invasiveness of the route of administration:
  - Injectable products (sterile)
  - Ophthalmic products (sterile)
  - Inhalation solutions (sterile)
  - Metered-dose and dry powder inhalants
  - Nasal sprays
  - Otics
  - Vaginal suppositories

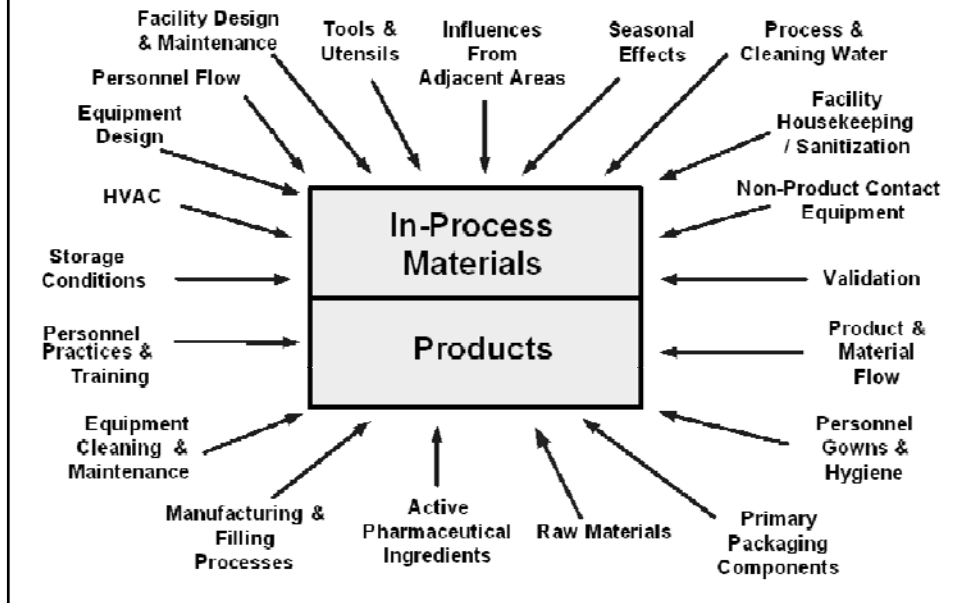


## Risk Assessment *(continuation)*

- Topicals
- Oral liquids (aqueous)
- Oral liquids (non-aqueous)
- Rectal suppositories
- Liquid-filled capsules
- Oral tablets and powder-filled capsules



## Non-Sterile Product Microbial



## Important Aspects of Unclassified Manufacturing Areas

- All walls, ceilings and floors should be constructed with non-porous, cleanable materials;
- All processing, sampling and packaging areas should be temperature and humidity controlled;
- All rooms used for manufacturing should be positive to surrounding areas;
- Air handling systems should contain centralized HEPA or ASHRAE filters at the supply.



## Gowning in Manufacturing Areas

<b>Protective Clothing</b>	<b>Operators in formulation and packaging areas</b>
Plant uniform or plant uniform with overall for higher risk product and environment	Yes
Hair/beard covering	Yes
Safety glasses	Yes
Dedicated shoes or shoe coverings	Yes
Gloves	Yes (if in direct product contact)
Face Masks	Yes (if in direct product contact)



## ***Environmental Monitoring Decision Tree***



# Monitoring

*Monitoring is the act of conducting a planned sequence of observations or measurements of control parameters.*



## Monitoring (continued)

- Steps to establish monitoring procedures:
  - Identify best monitoring procedure for each Critical Control Point
  - On-line Systems
  - Off-line System
  - Observational Procedures
  - Sampling location
  - Determine frequency of monitoring
  - Determine procedures
  - Identify responsibilities



## Microbiological Samplings Methods

- Air Sampling:
  - Active
  - Passive
- Surface Sampling:
  - Contact Plates
  - Swabs
  - Rinse Sampling



## Setting Alert/Action Guidelines

- Develop Data Base
  - Review on a monthly basis
  - Analyze on a yearly basis
- Follow ISO Class 8 Clean Room criteria as a bench mark for preliminary action levels





## Overall Management of an Environmental Monitoring Program

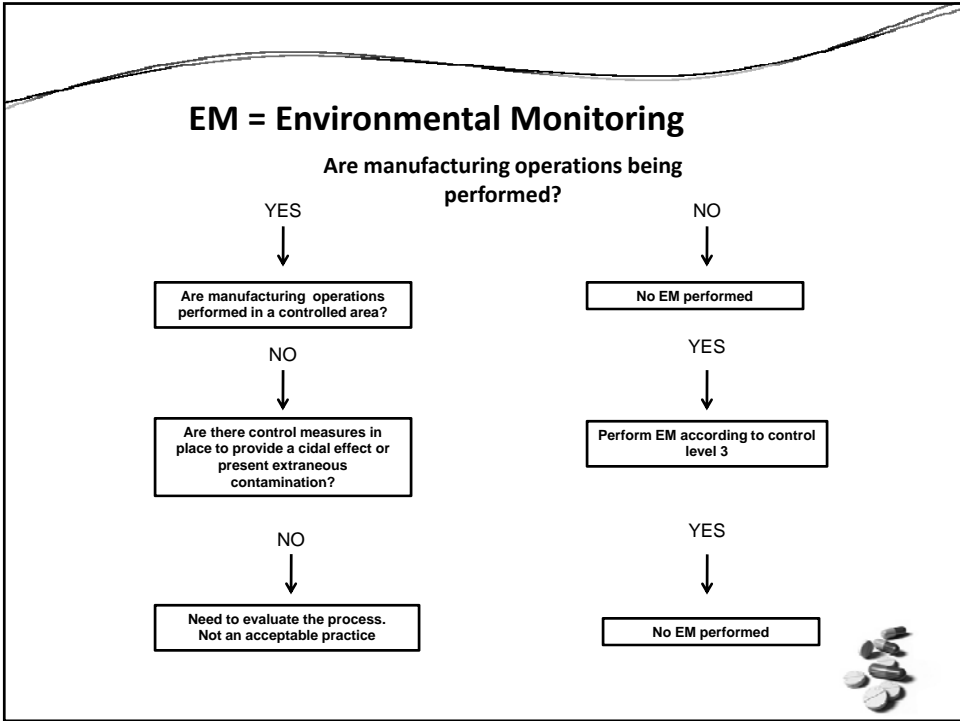
- All equipment should be qualified
- Suitability of monitoring methods demonstrated
- Standard Operating Procedures written
- Pharmaceutical Operators trained
- Data Management Systems established.



## Response to Environmental Monitoring Excursions

- Review microbial quality attributes of pharmaceutical ingredients and process equipment used to manufacture product.
- Review cleaning validation process.
- Review data to include isolate identification.
- Review products manufactured with implicated equipment to determine its capacity to support microbial growth.
- Review intended patient population





### Environmental Monitoring Frequency Example

Type of Sample	Frequency	Alert & Action Levels
Airborne	All Sites – 1X Week	<b>Levels to be established</b>
Surface	1X after sanitization program	
Personal Monitoring	Not Applicable	
Non-Viable Particulates	1X per year	

*Questions ?*



*Thank You!*

