Environmental Monitoring from the Non-Sterile Perspective

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IVT MICROBIOLOGY WEEK
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OPEN QUESTION

- Why are you here and what are you interested in learning?
What it is

- Document a state of control for your facility
- Includes
  - Water
  - Facility
  - RMs
  - Personnel
I. Regulatory Guidance for Environmental Monitoring of Non-Sterile Operations
   - Evaluate current guidance related to environmental monitoring in GMP environments
   - Appropriate application of sterile guidelines for non-sterile facilities

II. Strategies for Establishing a Meaningful and Compliant Risk-Based Monitoring Program
   - Understanding Your Business
   - Use risk assessment tools (materials, processes, equipment, and facility)
   - Statistical evaluation
   - Establishing appropriate test methods & specifications
   - Combine site-wide monitoring activities into holistic program (raw material screening, EM, water testing, release testing) for better control of your environment

III. Responding to the Data
   - What does trending really entail?
   - What your data means and how you should respond
   - Case studies – Review of typical and OOS data

IV. Interactive Exercise
   Participants will review a number of manufacturing scenarios to determine the frequency and types of testing that may appropriate using a risk-based approach.
I. Regulatory Guidance for Environmental Monitoring of Non-Sterile Operations

- Evaluate current guidance related to environmental monitoring in GMP environments
- Appropriate application of sterile guidelines for non-sterile facilities
(a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

(b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51932, Sept. 8, 2008]
RESOURCES RELATED TO EM IN NON-STERILE FACILITIES

- USP Chapter <1116> Microbiological Evaluation of Clean Rooms and Other Controlled Environments
- IVT Environmental Monitoring Handbook. 2006
Non-sterile facility is not expected to be free of microbes
  - In control and free of objectionables

Intent is that you understand the normal flora of your environment and can respond when Out of Trend results appear.

Why not adhere to sterile requirements
  - Application of sterile requirements add cost and time
  - Certain failure

Challenge is to create a dynamic and appropriate program for your situation
II. Strategies for Establishing a Meaningful and Compliant Risk-Based Monitoring Program

- Understanding Your Business
- Use risk assessment tools (materials, processes, equipment, and facility)
- Statistical evaluation of historical data
- Establishing appropriate test methods & specifications
- Combine site-wide monitoring activities into holistic program (raw material screening, EM, water testing, release testing) for better control of your environment
What do you make and how do you make it?

- Dosage Form
- Route of Administration
- Regulatory Category
- Target Microbiological Attributes
- Type, source, and processing of Raw Materials
- Process & Equipment used to make product
- Overall Quality Program
DOSAGE FORM

- [Link](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071666.htm)

- USP Chapter <1151> Pharmaceutical Dosage Forms
# ROUTE OF ADMINISTRATION

<table>
<thead>
<tr>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonaqueous preparations for oral use</td>
</tr>
<tr>
<td>Aqueous preparations for oral use</td>
</tr>
<tr>
<td>Rectal use</td>
</tr>
<tr>
<td>Oromucosal use</td>
</tr>
<tr>
<td>Gingival use</td>
</tr>
<tr>
<td>Cutaneous use</td>
</tr>
<tr>
<td>Nasal use</td>
</tr>
<tr>
<td>Auricular use</td>
</tr>
<tr>
<td>Vaginal use</td>
</tr>
<tr>
<td>Transdermal patches (limits for one patch including adhesive layer and backing)</td>
</tr>
<tr>
<td>Inhalation use (special requirements apply to liquid preparations for nebulization)</td>
</tr>
</tbody>
</table>
REGULATORY CATEGORY/MARKET

Regulatory Category

- Cosmetic
- Food
- Drug
- OTC Drug
- Medical Device
- Medicinal Food

Market

- North America
- EMEA
- LATAM
- APAC
Table 2. Acceptance Criteria for Microbiological Quality of Nonsterile Dosage Forms

http://www.drugfuture.com/Pharmacopoeia/USP32/pub/data/v32270/usp32nf27s0_c1111h.html
### Table 3. Acceptance Criteria for Microbiological Quality of Nonsterile Substances for Pharmaceutical Use

<table>
<thead>
<tr>
<th></th>
<th>Total Aerobic Microbial Count (cfu/g or cfu/mL)</th>
<th>Total Combined Yeasts/Molds Count (cfu/g or cfu/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substances for pharmaceutical use</td>
<td>1000</td>
<td>100</td>
</tr>
</tbody>
</table>
MICROBIOLOGICAL ATTRIBUTES

- <2023> Microbiological Attributes of NonSterile Nutritional and Dietary Supplements
Hong Kong RTE foods

Table 4: Guidance on the interpretation of results for Specified foodborne pathogens in ready to eat food in general

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Satisfactory</th>
<th>Borderline</th>
<th>Unsatisfactory: potentially injurious to health and/or unfit for human consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Campylobacter</em> spp. (thermotolerant)</td>
<td>n.d. in 25g</td>
<td>N/A</td>
<td>Detected in 25g</td>
</tr>
<tr>
<td><em>Escherichia coli</em> O157 (and other Shiga toxin-producing E. coli (STEC))</td>
<td>n.d. in 25g</td>
<td>N/A</td>
<td>Detected in 25g</td>
</tr>
<tr>
<td><em>Salmonella</em> spp.</td>
<td>n.d. in 25g</td>
<td>N/A</td>
<td>Detected in 25g</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em> (O1 and O139)</td>
<td>n.d. in 25g</td>
<td>N/A</td>
<td>Detected in 25g</td>
</tr>
<tr>
<td><em>Shigella</em> spp.</td>
<td>n.d. in 25g</td>
<td>N/A</td>
<td>Detected in 25g</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● For refrigerated food ° (excluding frozen food) or food intended for infants</td>
<td>n.d. in 25g</td>
<td>N/A</td>
<td>Detected in 25g</td>
</tr>
<tr>
<td>● For other ready-to-eat food</td>
<td>&lt; 10 °</td>
<td>10 - &lt; 100 °</td>
<td>&gt; 100 °</td>
</tr>
<tr>
<td><em>Vibrio parahaemolyticus</em></td>
<td>&lt; 10</td>
<td>20 - ≤ 104</td>
<td>&gt; 104</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> and other coagulase-positive staphylococci*</td>
<td>&lt; 20</td>
<td>20 - ≤ 104</td>
<td>&gt; 104</td>
</tr>
<tr>
<td><em>Clostridium perfringens</em></td>
<td>&lt; 10</td>
<td>10 - ≤ 10³</td>
<td>&gt; 10³</td>
</tr>
<tr>
<td><em>Bacillus cereus</em></td>
<td>&lt; 10³</td>
<td>10³ - ≤ 10⁵</td>
<td>&gt; 10⁵</td>
</tr>
</tbody>
</table>

n.d. = not detected; N/A = not applicable

° To be implemented when the testing capacity for this criterion is ready.
UNDERSTANDING YOUR BUSINESS: MICROBIOLOGICAL ATTRIBUTES

- Cosmetic
- CTFA Microbiology Guidelines, 2013
UNDERSTANDING YOUR BUSINESS: RAW MATERIALS

- Highly refined/food grade
- Natural source/Botanical
- Process required to produce
- Source/company
UNDERSTANDING YOUR BUSINESS: PROCESS & EQUIPMENT

- Coating
- Spraying
- Mixing
- Holding

- Easy to Clean
- Difficult
- High humidity/Low Humidity
**Overall Quality Programs**

- Materials controlled
- Personnel well trained and retained (vs high turn over)
- Cleaning procedures
- Maintenance activities
- **Purpose of Risk Assessment:**
  - Evaluation of risk from potential sources of microbial contamination.
  - Resulting EM method should be appropriate according to the defined risk.

- **Risk Assessment Process**
  - Identify the potential risk factors
  - Perform risk assessments for identified risk factors
  - Develop a Mitigation Plan
  - Develop and implement appropriate monitoring method
Risk Factor Categories
- Raw Materials
- Personnel Controls
- Utilities
- Room/Area/Equipment Cleaning, Sanitizing and Storage
- Sanitary Design of Processing Equipment
- Manufacturing Process
- Packaging Components
- Bioburden Control and Reduction Steps
IDENTIFY POTENTIAL RISK FACTORS

- Combine Risk Factor Categories with what you know about these areas:
  - Dosage Form
  - Route of Administration
  - Regulatory Category
  - Target Microbiological Attributes
  - Material Quality
  - Process & Equipment
  - Overall Quality Program
RISK ASSESSMENT TOOLS

- Simple Tabular Approach
- HACCP
- FMEA
Tabular Approach to Risk Assessment

Area or Equipment: Sterility Testing Isolator

Risk: Contamination due to build-up of microbial counts in the isolator environment

Failure or Situation: Failure to adequately clean after use

<table>
<thead>
<tr>
<th>Effect</th>
<th>Minimising the Risk (Mitigations to Reduce Risk)</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>• When isolators are not cleaned regularly, there is a possibility of micro-organisms remaining in the environment.</td>
<td>• Cleaning surfaces using water to remove dirt or spillages prior to the application of a suitable disinfectant.</td>
<td>• An environmental monitoring programme (using settle plates, air samples, contact plates, swabs, or finger plates) will show the areas of greatest risk. This data should be examined for trends.</td>
</tr>
<tr>
<td></td>
<td>• The disinfectant used must have a wide spectrum of efficacy, but not be aggressive to the isolator material.</td>
<td>• For out-of-limits environmental monitoring results, appropriate Corrective and Preventive Actions (CAPA) should be put in place.</td>
</tr>
<tr>
<td></td>
<td>• The isolator should be designed so that it is easy to clean.</td>
<td></td>
</tr>
</tbody>
</table>
**Principle 1:** Conduct a hazard analysis.
- Determine the food safety hazards; identify the preventive measures the plant can apply to control these hazards.

**Principle 2:** Identify critical control points.
- A critical control point (CCP) is a point, step, or procedure in a food process at which control can be applied and, as a result, a food safety hazard can be prevented, eliminated, or reduced to an acceptable level. A food safety hazard is any biological, chemical, or physical property that may cause a food to be unsafe for human consumption.

**Principle 3:** Establish critical limits for each critical control point.
- A critical limit is the maximum or minimum value to which a physical, biological, or chemical hazard must be controlled at a critical control point to prevent, eliminate, or reduce to an acceptable level.

**Principle 4:** Establish critical control point monitoring requirements.
- Monitoring activities are necessary to ensure that the process is under control at each critical control point. FSIS is requiring that each monitoring procedure and its frequency be listed in the HACCP plan.

**Principle 5:** Establish corrective actions.
- These are actions to be taken when monitoring indicates a deviation from an established critical limit. The final rule requires a plant's HACCP plan to identify the corrective actions to be taken if a critical limit is not met. Corrective actions are intended to ensure that no product injurious to health or otherwise adulterated as a result of the deviation enters commerce.
**Principle 6: Establish record keeping procedures.**
- The HACCP regulation requires that all plants maintain certain documents, including its hazard analysis and written HACCP plan, and records documenting the monitoring of critical control points, critical limits, verification activities, and the handling of processing deviations.

**Principle 7: Establish procedures for verifying the HACCP system is working as intended.**
- **Validation** ensures that the plans do what they were designed to do; that is, they are successful in ensuring the production of safe product. Plants will be required to validate their own HACCP plans. FSIS will not approve HACCP plans in advance, but will review them for conformance with the final rule.
- Verification ensures the HACCP plan is adequate, that is, working as intended. Verification procedures may include such activities as review of HACCP plans, CCP records, critical limits and microbial sampling and analysis. FSIS is requiring that the HACCP plan include verification tasks to be performed by plant personnel. Verification tasks would also be performed by FSIS inspectors. Both FSIS and industry will undertake microbial testing as one of several verification activities. the occurrence of the identified food safety hazard.

http://www.fao.org/docrep/005/y1390e/y1390e0a.htm
EXAMPLE

- Making a Ham and Cheese Sandwich
RISK ASSESSMENT: HACCP

HACCP FLOW DIAGRAM

Process
- purchase and storage of ingredients
- preparation of environment, personal hygiene
- making the sandwich
- serving and eating

Hazard
- pathogenic bacteria multiplying in ham (high risk food) and cheese (medium risk food)
- cross-contamination from equipment, hair hands and clothes
- bacteria entering food during preparation through cross-contamination from equipment, hair hands and clothes
- bacteria entering food before consumption

Control
- purchase as close to preparation as possible, refrigerate ham and cheese, store bread in cool, dry conditions
- clean surfaces using anti-bacterial cleaner, use PVC tablecloths, set up washing-up facilities, tie back hair, remove jewellery, wear apron, wash hands
- ongoing cleaning of food surfaces and utensils, good personal hygienic practices (including hand washing), return of unused ingredients to fridge
- wash hands, use clean serving plates, eat immediately or cover sandwiches and place in fridge

Monitor
- check use by date, check fridge temperature is 5 degrees centigrade or below
- responsible teacher/TA/adult to ensure that personal and kitchen hygiene is being undertaken
- responsible teacher/TA/adult to monitor that the activity is being carried out hygienically
- responsible teacher/TA/adult to monitor time between making the sandwich and safe storage/eating and check children wash hands immediately before eating
FMEA schemes vary in their approach, scoring, and categorisation. All methods share a numerical approach. The example presented here, based on a sterility testing isolator, assigns a score (from 1 to 5) to each of the following categories:

- Severity
- Occurrence
- Detection

Where:
- Severity is the consequence of a failure
- Occurrence is the likelihood of the failure happening based on past experience
- Detection is based on the monitoring systems in place and on how likely a failure can be detected
By asking a series of questions, each main part of the cleanroom or isolator system can be grouped or classified into key parts.

Such questions include:
- What is the function of the equipment? What are its performance requirements?
- How can it fail to fulfil these functions?
- What can cause each failure?
- What happens when each failure occurs?
- How much does each failure matter? What are its consequences?
- What can be done to predict or prevent each failure?
- What should be done if a suitable proactive task cannot be found?

The scoring is 1 (very good) to 5 (very bad). Therefore, a likelihood of high severity would be rated 5; high occurrence rated 5; but a good detection system would be rated 1.

*Using these criteria, a final FMEA score is produced from:

- Severity score
- Occurrence score
- Detection score*

Decisions on further action will depend upon the score produced. There is no published guidance on what the score that dictates some form of action should be. However, 27 is the suggested score for the cut-off value at which action is required. This is based on 27 being the score derived when the mid-score is applied to all three categories (i.e., the numerical value '3' for severity 3 x occurrence 3 x detection 3) and the supposition that if the mid-rating (or a higher number) is scored for all three categories, then at a minimum, the system should be examined in greater detail.
Example

- Change
  - Ham Source
  - Add a spicy sauce
  - Heat it
<table>
<thead>
<tr>
<th>ID</th>
<th>Description</th>
<th>Potential failure modes</th>
<th>Effects of failure</th>
<th>SEVERITY</th>
<th>Likely causes that lead to occurrence</th>
<th>OCCURRENCE</th>
<th>Current Methodologies to Detect</th>
<th>DETECTION</th>
<th>Recommended Actions to Reduce EPA</th>
<th>SEVERITY</th>
<th>DETECTION</th>
<th>EPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No Preventive maintenance</td>
<td>contamination in products being made in room</td>
<td>7</td>
<td>contamination in area of room not sampled</td>
<td>2</td>
<td>Finished Product MIL Testing</td>
<td>1</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Processes failed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Compressed Air Supply leak</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>New analysis for EM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Change to personal cleaning devices in the wetting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Change to procedures for the wetting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Change to cleaning material</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Modification to the facility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Modification to the facility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Adding or removing equipment in the wetting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Trying to mitigate contamination of product or proliferation of microbes

- You thoroughly understand your business/product/manufacturing and have assessed and mitigated potential risks

- Mitigation Plan
  - How you plan to reduce the risk
    - Environmental Monitoring Program
    - Bioburden Testing
What are you going to monitor?
- Raw materials
- Facility
  - Equipment
  - Air
  - Compressed gas
- Cleaning procedures
- Personnel
- Product & Components

How often will you monitor it?
- Depends on what you monitor

What methods will you use?
- Depends on what you monitor
- What will be your acceptance/failure?
**Vary according to:**
- Type of manufacturing process
- Facility Design/process design
- Amount of human intervention
- Use of terminal sterilization
- Historical data

**Key is to select monitoring frequency that can identify potential system deficiencies**

**Changes in frequency may need to be made based on:**
- Changes in practice
- New equipment/process/product
- Compendia change
- Construction (new room, significant changes to facility)
- Microbiological trends
Established based on:
- Regulatory requirements
  - Very difficult for non-sterile product
- Historical data

Require
- Periodic review

Statically meaningful
- 99th based on Percentile (more to come)
ADDITIONAL MONITORING OPPORTUNITIES
SYSTEM SURVEILLANCE

- Raw Materials
- Facility
  - Equipment
  - Air
  - Compressed Gas
- Water
- Personnel
- Product or Component Monitoring
- Cleaning Procedures
Current literature indicates that surface sampling does not provide useful information.

Routine monitoring may be eliminated through an effective Cleaning Validation Program:

- Program validation and routine checks
- Validation based on equipment, ingredient, and product classes
  - Ease of cleaning
  - Solubility of ingredients and product
**Guidance:**
- Use what you know about the business
- Intended to provide meaningful data that can help prevent or identify potential contamination problems
- Sample sites that are more likely to lead to product contamination

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**Table 5: Examples of Environmental Sampling Sites**

<table>
<thead>
<tr>
<th>System</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental Air</td>
<td>Near Open containers</td>
</tr>
<tr>
<td>Room air</td>
<td>Around work area</td>
</tr>
<tr>
<td>Surface (facility)</td>
<td>Floor, handles, walls, curtains</td>
</tr>
<tr>
<td>Surface (equipment)</td>
<td>Control panels, filling line</td>
</tr>
<tr>
<td>Laminar air flow</td>
<td>Near high activity areas</td>
</tr>
</tbody>
</table>
Compressed gas is commonly used during processing and cleaning

Should be monitored on a frequency that aligns with the type of use
- Raw Materials can be the cause of product contamination but may also be a cause of environmental contamination.
Water is a widely used raw material, during processing and formulation, and cleaning.

Incoming water in the US should meet the requirements of drinking water established by the National Primary Drinking Water Regulations (40 CFR 141) issued by the EPA.

“Water for Pharmaceutical Purposes” USP <1231> outlines quality and testing methodologies for processed water.

Monitoring program ensures validated system remains in a state of control.
PERSONNEL

- Personnel are the primary source of contamination
- Lab surveillance is suggested to assist with trending the environmental flora and input from lab personnel

Everyone Emits Unique Cloud of Microbes
Appropriate training:
- personal hygiene: cleanliness of fingernails, clothing, hair, skin, no-make-up, eating drinking, etc.
- Illness: report colds, flu, infections, wounds
- gowning techniques: Certification of ability to properly gown
- introduction to Microbiology: common sources and consequences of contamination

Re-training: appropriate schedule based on risk
Product is not expected to be sterile
- USP 61, 62, 1111; 2021, 2022, 2023
- FDA BAM
- Specific country regulations and guidance
- CFTA

Bioburden testing: performed to determine its microbial load

Factors that may impact product or component bioburden
- Raw material source & variations in grades
- Water
- Components: grade or quality variations
- Manufacturing environment
- Processing of formulation
- Equipment
- Antimicrobial activity
- Water activity
• Significance of microorganisms recovered should be evaluated in terms of the following:
  • The use of the product: hazard varies according to the route of administration (eye, nose, respiratory tract).
  • The nature of the product: does the product support growth? does it have adequate antimicrobial preservation?
  • The intended recipient: risk may differ for neonates, infants, the debilitated.
  • Use of immunosuppressive agents, corticosteroids.
  • The presence of disease, wounds, organ damage.
Routine review and analysis of environmental data is essential to aid in the interpretation of process stability and assess overall control performance

- Management should be kept abreast of trends
- Used to make risk-based decision
Data Approach

a. Determine objective of analysis (site location; alert/action limit, action level review, management update)
b. Specify data set to be analyzed
c. Apply data plots such as histograms or pictorial plots to evaluate distribution
d. Observe distribution to determine appropriate mathematical model
e. Typically, an action level in the 99\textsuperscript{th} percentile is used
<table>
<thead>
<tr>
<th>Analysis Objective</th>
<th>Report Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using alert/action results to determine “corrective action”</td>
<td>Plot data over time to observe trends and process variation; Use to Modify cleaning, process, or equipment</td>
</tr>
<tr>
<td>Determine appropriateness of current action/alert levels</td>
<td>Calculate action level using historic data and compare to current</td>
</tr>
<tr>
<td>Management/periodic reporting</td>
<td>Trending; adjustments to action/alert, identifications, investigations, etc.</td>
</tr>
<tr>
<td>Determine process capability</td>
<td>Determine quality study to determine specs; calculate action limit based on historical data</td>
</tr>
</tbody>
</table>
- **Quantitative**
  - Counts
- **Qualitative**
  - Presence/absence
- **Characterization of Isolates**
Using historical data, appropriate alert and action limits can be set

- Typically data that falls within the 99th percentile is used to set limit
- How much historical data?
- How often should you review/revise?
HOLISTIC MONITORING PROGRAM

- Combine site-wide monitoring activities into holistic review/trending
  - Raw material screening
  - Water testing
  - Product & Component release testing
  - Personnel
  - Surface & Air Sampling
III. Responding to the Data

- What does trending really entail?
- What your data means and how you should respond
- Case studies – Review of typical and OOS data
Collecting information and attempting to spot a pattern, or trend, in the information.

For extracting an underlying pattern of behavior in a time series which would otherwise be partly or nearly completely hidden by noise.
What your data means and how you should respond

- Responding to a single OOS?
- What do you do if you identify a pathogen?
- Is it a problem that you consistently well below you action/alert levels?
What type of data and results are you reviewing?

Type of OOS/OOT or interesting results that you would like to share or discuss?
Case studies – Review of typical and OOS

Personnel Monitoring
- Garden activity

USP Water
- OOS lead to discovery of undocumented changes and municipal water

Review of 3rd party data
EXAMPLE #1

- Food
- Distributed globally
- Company makes a selection of sweet sauces and syrups
  - Natural/organic ingredients
  - Would like to move to “preservative free”
  - New process and equipment
MANUFACTURE OF SAUCES
RAW MATERIALS

INGREDIENTS: VEGETABLE OIL (SOYBEAN AND/OR CONOLA), WATER, EGG YOLK, SUGAR, SALT, CULTURED NONFAT BUTTERMILK, NATURAL FLAVORS (MILK, SOY), LESS THAN 1% OF: SPICES, DRIED GARLIC, DRIED ONION, VINEGAR, PHOSPHORIC ACID, XANTHAN GUM, MODIFIED FOOD STARCH, MONOSODIUM GLUTAMATE, ARTIFICIAL FLAVORS, DISODIUM PHOSPHATE, SORBIC ACID AND CALCIUM DISODIUM EDTA AS PRESERVATIVES, DISODIUM INOSINATE, DISODIUM GUANYLATE, CONTAINS: EGG, MILK, SOY. GLUTEN FREE
Several mixers and holding tanks that are open to the air
## POTENTIAL RISK FACTORS: EXAMPLE #1

<table>
<thead>
<tr>
<th>Type</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage Form</strong></td>
<td>Liquid</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Regulatory Category</strong></td>
<td>Dietary Supplement/Medicinal Food</td>
</tr>
<tr>
<td><strong>Microbial Attributes</strong></td>
<td>TAMC Less than 1000 CFU/ml</td>
</tr>
<tr>
<td></td>
<td>TYMC Less than 100 CFU/ml</td>
</tr>
<tr>
<td></td>
<td>Absence of E.coli</td>
</tr>
<tr>
<td><strong>Material Quality</strong></td>
<td>Food Grade</td>
</tr>
<tr>
<td><strong>Process &amp; Equipment</strong></td>
<td>See slides</td>
</tr>
</tbody>
</table>
## POTENTIAL RISK FACTORS: EXAMPLE

<table>
<thead>
<tr>
<th>Define</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw Materials</td>
<td></td>
</tr>
<tr>
<td>Personnel</td>
<td></td>
</tr>
<tr>
<td>Utilities</td>
<td></td>
</tr>
<tr>
<td>Room/Area/Equipment Cleaning, Sanitizing and Storage</td>
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<tr>
<td>Manufacturing Process</td>
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<tr>
<td>Packaging Components</td>
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<tr>
<td>Bioburden Control and Reduction Steps</td>
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</tbody>
</table>
What type of monitoring would be appropriate?
EXAMPLE #2: EM PROGRAM UPDATE

- **GMP Pilot Plant**
  - Liquids, tablets, topical
  - Confectionary, Drugs, DS, cosmetics

- **Manufacture and release of**
  - Consumer Supplies
  - Salesmen Samples
  - Clinical Supplies
  - Stability Batches

- **15 years of EM data**
  - Contact
  - Air
  - Compressed Air
  - 1/3 of isolates identified

- **Quarterly trending and annual management update**
  - **Air**
    - Bacterial Action/Alert 500/250
    - Yeast/Mold Action/Alert 500/250
  - **Contact**
    - Bacterial Action/Alert
    - Yeast/Mold Action/Alert
EXAMPLE #2: EM PROGRAM UPDATE

- **Data Trending**
  - Raw Material
  - Product but not component testing
  - Compressed air
  - Air
    - Bacterial
    - Yeast/Mold
  - Contact
    - Bacterial
    - Yeast/Mold
  - Occasional investigations; consistent with cleaning and activity

- Would like to adjust action/alert limits, reduce sample quantity, and limit compressed air to once/year
Is the program running smoothly?
Does it indicate a state of control?
What improvements could be made?
<table>
<thead>
<tr>
<th>Function or Description</th>
<th>Potential failure modes</th>
<th>Effects of failure</th>
<th>SEVERITY</th>
<th>Likely causes that lead to occurrence</th>
<th>DETECTION</th>
<th>Current Methodologies to Detect</th>
<th>DETECTION</th>
<th>Recommended Actions to Reduce RPN</th>
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### FMEA

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<tbody>
<tr>
<td>ww material pre-screening</td>
<td>contamination in product being made in room</td>
<td>contamination in area of room not sampled</td>
<td>7</td>
<td>2</td>
<td>Finished Product MLT Testing</td>
<td>1</td>
<td>14</td>
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<tr>
<td>untrained</td>
<td>contamination in product being made in room</td>
<td>contamination in area of room not sampled</td>
<td>7</td>
<td>2</td>
<td>Finished Product MLT Testing</td>
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<td>ressed Air Sampling once a year</td>
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<td>contamination not detected for a year</td>
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<td>1</td>
<td>Finished Product MLT Testing</td>
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<td>7</td>
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<td>analyst for EM sampling</td>
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<td>contamination not detected for a year</td>
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<td>ge in personal cleaning the rooms in the wing</td>
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<td>contamination not detected for a year</td>
<td>1</td>
<td>2</td>
<td>Finished Product MLT Testing</td>
<td>1</td>
<td>10</td>
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<tr>
<td>es in the procedures for the west</td>
<td>contamination in product being made in room</td>
<td>contamination not detected for a year</td>
<td>1</td>
<td>2</td>
<td>Evaluation via Risk Assessment</td>
<td>1</td>
<td>5</td>
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<td>ps in the cleaning material</td>
<td>contamination in product being made in room</td>
<td>contamination not detected for a year</td>
<td>1</td>
<td>2</td>
<td>Finished Product MLT Testing</td>
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<tr>
<td>ications to the facility</td>
<td>contamination in product being made in room</td>
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<td>7</td>
<td>1</td>
<td>Increased sampling</td>
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**Notes:**

- RPN: Risk Priority Number
- SEVERITY: Severity of the failure
- OCCURRENCE: Frequency of the occurrence
- DETECTION: Likelihood of detection
- RPN: Risk Priority Number calculated as SEVERITY x OCCURRENCE x DETECTION
THANK YOU! QUESTIONS?