Data Strategies and Environmental Monitoring

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Agenda

- How to collect data, including electronic systems
- How to evaluate data
- Trend analysis tools and tips
- Setting alert and action levels
- Data integrity issues
Data Strategies
Focus on data in the Industry
Why do we trend data?

- **Trend Analysis**—Data from a routine microbial environmental monitoring program that can be related to time, shift, facility, etc. This information is periodically evaluated to establish the status or pattern of that program to ascertain whether it is under adequate control. A trend analysis is used to facilitate decision-making for requalification of a controlled environment or for maintenance and sanitization schedules. USP <1116>

- Avoid inaccurate Interpretation of data

- Trending methods
  - Variety of methods to trend EM data
    - Frequency of detection or cumulative count
  - Depends on classification – C&D cfu based levels
  - No universally accepted method
    - Historical
    - CAPA’s
    - Meet the needs of your facility/company

- Ultimately the data trending program must achieve the established and described goals of the EM program and provide detail on the control of your facility
What do we trend?

- CFU – Colony forming unit not a single bacterial cell
  - CFU is informational
  - Technical limitations of detection of traditional plate count methods
  - Zeros are not a guarantee of control
  - Excursions are not always an indication as being out of control

- Typically in sterile manufacturing looking at low numbers.
  - Most critical areas <1%
  - Consider the frequency with which contamination is detected
  - Look at non zero events – Contamination rates

- Need to supplement this with trends of Microbial species
  - Track identities of Microorganisms

- Site, date, test method, classification, organism, personnel

- Trend by room

- Track bacteria & mould and total results

- Basic statistics, average, cumulative frequency,

- Data overlaid in graphical format
What do the regulatory documents say?

Draft Annex 1
- Trends can include but are not limited to
  - Increasing numbers of action or alert limit breaches
  - Consecutive breaches or alert limits
  - Regular but isolated breaches of limits that may have a common cause, for example single excursions that always follow planned preventative maintenance

USP (1116) Microbiological Control and Monitoring of Aseptic Processing Environments
- Significant Excursions - Microbiologists should review recovery rates for at least two weeks before the incident of abnormally high recovery so that they can be aware of other recoveries that might indicate an unusual pattern.

PDA Technical report 13 Fundamentals of an Environmental Monitoring Program
- Trend Analysis – A review performed in response to an alert or action condition. This review provides and analysis of specific environmental monitoring data to identify adverse trends
- .... All data should be documented and trended
- Management must be kept abreast of trends and the subsequent state of operations within facilities with review of quarterly and yearly monitoring reports
Data Collection

Where do you generate data in the process?
Capturing the data

How much of it do you record?

- Date and time of test
- Product identification and Lot
- Individual performing the test
- Test method or reference procedure
- Activity level – dynamic or static
- Equipment & Calibration details
- Sample site
- Area classification
- Diagram showing sample locations
- Test results with units
- Analyst recording the result
- Date results read
- Alert/Action Level
- Incubation details
- Control test results
- Media – lot numbers, expiration, growth promotion
- Identifications – what, who, how
- Reviewer, Approver
- Site trends, Historical data
- How many people in the room
- Person Sampled

*PDA Technical report 13 Fundamentals of an Environmental Monitoring Program lists the types of records that should be maintained..."
What happens when you need to use the data?

- Media-expiration and growth promotion
- Training – gowning qualification
- Product testing results
- Org id
- Other samples in the room – Personnel monitoring, Non Viable
- Building management system
- Room trends – site, hit rates, adverse trends, recent id’s
- CAPA
- Sample Audit trail
- Production review Cleaning records
- OOS – Settle plate during filling exceeds Action level
Evaluating the Data

- Trending is expected by Regulatory agencies
- Paper based vs Electronic systems
- Different room classifications will produce different histograms – ISO 5 vs 8
- Data should be summarized
- Determine if EM programme is in a state of control
- If a trend is exceeded – investigation and any necessary corrective action implemented
**Alert Levels, Action Levels & Adverse Trends**

*Value is knowing what is going on*

- **Action Levels**—Microbiological levels in the controlled environment, specified in the standard operating procedures, which when exceeded should trigger an investigation and a corrective action based on the investigation.

- **Alert Levels**—Microbial levels, specified in the standard operating procedures, which when exceeded should result in an investigation to ensure that the process is still within control. Alert levels are specific for a given facility and are established on the basis of a baseline developed under an environmental monitoring program. These Alert levels can be modified depending on the trend analysis done in the monitoring program. Alert levels are always lower than Action levels.

- **Significant excursions** - A key consideration for an abnormally high number of recovered colonies is whether this incident is isolated or can be correlated with other recoveries
  - Look at site & room trends
  - Ability to view viable and particulate data together

- **Adverse trends**
  - What are your rules?
  - How easily can you track these

*USP <1116>
Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. Alert levels should be established based on results of Performance Qualification (PQ) tests or trend data and should be subject to periodic review. – Annex 1

Alert and Action decisions are made by designated authorized personnel qualified to make such decisions. PDA TR13

Typically Action levels are driven by regulatory guidelines (e.g. Annex 1, USP <1116>, ISO 14464-1, and the Parenteral Drug Association Technical Report 13)

Alert levels are driven by historical analysis of EM data

Once in place there should then be a process to track and trend them as necessary

What is the frequency to review them?
Methods for setting Alert and Action Levels

- **Cutoff Value Approach**
  - Take test data for site or group in a histogram. The Alert and Action Levels are set at values @ 1% & 5% higher than the level selected.
  - 95th and 99th percentile is a variation of this.

- **Normal Distribution approach**
  - Mean and standard deviation are calculated.
  - Alert and Action levels are set at mean plus 2 and 3 times the standard deviation.
  - Used for high counts and when data is normally distributed.

- **Nonparametric Tolerance Limit Approach**
  - Recommended as data is not normally distributed.
  - 95th and 99th percent confidence intervals are commonly used – where 95 percent of the samples will pass the established alert limit.

- Whichever method is used to determine the alert and action levels, it should be based on historical data, or for the initial levels a deliverable from the EM qualification programme.
Focus of USP 1116 on incident rate

Incident rate is the rate at which environmental samples are found to have microbial contamination. An incident rate of 1% would mean the 1% of the samples taken had contamination regardless of the colony numbers.

The objective of each user should be to use contamination recovery rates to track ongoing performance and to refine the microbiological control program to foster improvements.

A Critical Recovery Rate report calculates the average recovery rate for a duration of time and compares a month's recovery to establish if there is an excursion or trend, based upon USP 1116 Requirements.
### Table 3. Suggested Initial Contamination Recovery Rates in Aseptic Environments

<table>
<thead>
<tr>
<th>Room Classification</th>
<th>Active Air Sample (%)</th>
<th>Settle Plate (9 cm) 4 h Exposure (%)</th>
<th>Contact Plate or Swab (%)</th>
<th>Glove or Garment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolator/Closed RABS (ISO 5 or better)</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>ISO 5</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>ISO 6</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>&lt;3</td>
</tr>
<tr>
<td>ISO 7</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>ISO 8</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

*a All operators are aseptically gowned in these environments (with the exception of background environments for isolators). These recommendations do not apply to production areas for nonsterile products or other classified environments in which fully aseptic gowns are not donned.*
CUSUM Graphs for EM Data

- **Cumulative SUM** graph
- A technique used to spot changes trend(s)
- Good for large quantities of data with low counts
- Helps visualize shifts in the process
- Can be run in excel or statistical software
- Takes into consideration the normal performance of the data set and cumulatively sums the deviations from it.
- If the deviations are equally positive and negative the graph will behave neutral
- If there is a shift from the norm, this will be visualized in the graph.
- How steep the slope is, is important
The cusum is calculated as follows:

- Calculate the Target value. The target value is the mean of the found counts per zone and aspect (air or surface) over a set period of time.
- Subtract from the observed result a (previous selected) “target” value.
- The result is added to the cumulative sum result of the previous results.
- This sum is plotted on a graph (cusum on Y-axis, sample date on the X-axis).
Room 12345 is sampled once a week, every week 1 location is sampled and the results are reported in CFU (=Colony Forming Units).

For this example the target is set on "15"

1. Result week 1 = 16
   Result – target = 16 – 15 = +1; no previous result, so plot in graph +1
2. Result week 2 = 13
   Result – target = 13 – 15 = -2; add result to previous sum = -2 + +1 = -1
   plot cumulative sum of -1 in graph
3. Result week 3 = 13
   result – target = 13 – 15 = -2; add result to previous sum = -1 + -2 = -3 observation = 13
4. etc

This gives this result table

<table>
<thead>
<tr>
<th>Week</th>
<th>result (CFU)</th>
<th>target</th>
<th>deviation</th>
<th>cusum</th>
</tr>
</thead>
<tbody>
<tr>
<td>week 1</td>
<td>16</td>
<td>15</td>
<td>+1</td>
<td>1</td>
</tr>
<tr>
<td>week 2</td>
<td>13</td>
<td>15</td>
<td>-2</td>
<td>-1</td>
</tr>
<tr>
<td>week 3</td>
<td>12</td>
<td>15</td>
<td>-3</td>
<td>-4</td>
</tr>
<tr>
<td>week 4</td>
<td>15</td>
<td>15</td>
<td>0</td>
<td>-4</td>
</tr>
<tr>
<td>week 5</td>
<td>15</td>
<td>15</td>
<td>0</td>
<td>-4</td>
</tr>
<tr>
<td>week 6</td>
<td>17</td>
<td>15</td>
<td>+2</td>
<td>-2</td>
</tr>
<tr>
<td>week 7</td>
<td>25</td>
<td>15</td>
<td>+10</td>
<td>8</td>
</tr>
<tr>
<td>week 8</td>
<td>14</td>
<td>15</td>
<td>-1</td>
<td>7</td>
</tr>
<tr>
<td>week 9</td>
<td>13</td>
<td>15</td>
<td>-2</td>
<td>5</td>
</tr>
<tr>
<td>week 10</td>
<td>13</td>
<td>15</td>
<td>-2</td>
<td>3</td>
</tr>
<tr>
<td>week 11</td>
<td>16</td>
<td>15</td>
<td>+1</td>
<td>4</td>
</tr>
<tr>
<td>week 12</td>
<td>14</td>
<td>15</td>
<td>-1</td>
<td>3</td>
</tr>
</tbody>
</table>
Different ways to set Target

- The period of data reviewed can be used (Target is the average of all data for that period)
  - This is a very good tool for detecting changes in trends
  - A powerful tool to assess the effects of a change
  - The graph will always start and end at 0

- A selected historical period can be used (example: mean over the last two years)
  - A descending cusum graph gives an indication of EM results which are better compared to the results of the last 2 years.
  - A neutral cusum graph gives an indication of EM results which are comparable compared to the results of the last 2 years.
  - A rising cusum gives an indication of EM results which are higher compared to the results of the last 2 years.

- The target can be calculated for a complete grade (for example all surface samples for all grade C rooms over a selected period)
  - You can plot the CUSUM of a specific room using the target value of the whole grade to see how an individual room related to the whole grade. This is a good tool to assess localized problems.
Conditional formatting in Excel

- Visual aid in Excel to highlight above alert or action levels
- Using color makes it easier to see trends
- Very basic Action level and above is red, Alert Level up to action is Yellow
- Can set prevalence on the rules to determine which one triggers first
Data Integrity and Data Analytics

Can you trust the data?

- Build Data Integrity into the process how is that maintained when using Excel
  - Secondary verification of the entire process of all data entered into spreadsheets
  - Time-consuming
  - Still errors

- How to protect the data
  - User controls around access
  - Password protected
  - Restricted drive
  - SharePoint – check in and out

- Where is the audit trail in Excel?

- Still no visibility into changes that have been made to the data

- Training in Excel
  - Tribal Knowledge
  - Only know what you have been taught, not industry standard
Considerations for Electronic Systems

Detailed URS – developed by the business

- Follow the data
  - What do you need to capture
  - When in the process it is available
  - **How do you need to use it, trending & investigations**

- Detailed user requirements
  - Must be able to trend date – not specific enough
  - Ability to trend data together

- The system should generate a report that includes a chart of sample results within a room or location for a specified date range and test method.

- The system should generate a report that includes a visual bar chart of the number of organism identifications per organism species, over a period of time for a specified set of Locations, Classifications and Organism Types.

- The system will allow for the generation of reports by utilizing sorting and filtering functions. For example by date range, sample type, sample status, above limit result, room (EM), system (utility) room classification, micro-organism etc.

- The system should have the ability to associate alert and action limits to each unique sample.

- **Should make the workflows more efficient**
What is the value of your EM data?
Or is it just a cost…..

<table>
<thead>
<tr>
<th>Process</th>
<th>Customer Annual Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entering data into Charts Wizards, etc.</td>
<td>260</td>
</tr>
<tr>
<td>Data Gathering</td>
<td>130</td>
</tr>
<tr>
<td>Redundant Data Checking for Integrity</td>
<td>260</td>
</tr>
<tr>
<td>Aggregating Data for OOS Investigation reporting</td>
<td>130</td>
</tr>
<tr>
<td>Trending Efforts (ROE)</td>
<td>87</td>
</tr>
</tbody>
</table>

2,500 samples per month – EM and Utilities
Thank You

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