

as well as over time to assess continued microbiological health of the manufacturing environment.

### **How should the data be organized?**

EM data in isolation provides a snapshot of microbial control at a discrete time point, but does not provide information on adverse trends that may be developing. It is only when it is put in a framework of whom, where, and appropriate timeframe does it become useful for trending purposes. Therefore, it is vitally important to determine the type of trending information needed prior to monitoring. For example, if it is important to summarize the ongoing microbiological status of a Plant's Grade A areas, data segregated solely by time and room number will not be sufficient. The key is to design data classifications prior to needing the trend reports so that the reports can be assembled easily and provide the required information in as short a time as possible.

### **Suggested classifications of EM data include:**

- Location (including air classification)
- Date
- Shift
- Lot
- Room
- Operator
- Process
- Isolate Recovered

### **How often should trend data be reviewed?**

Trend data should be reviewed at sufficiently brief intervals to allow timely response to contamination problems before serious threats are realized. However, trending should also be of sufficient length to analyze seasonal effects. These opposing goals necessitate multiple frequencies of data review and report generation. In addition to the batch release EM results, reports on a monthly or even weekly basis are recommended for rapid response to potential problems.

Quarterly or yearly reports should be sufficient to recognize seasonal variations in microbial control. It is also important to remember that the criticality of the area will have an impact on how frequently trend information is compiled. For example, it may be sensible to examine Grade A and B data for both short and long term trends while analysing Grade C and D data only for long term trends.

### **How should the data be analyzed and what constitutes a trend that requires investigation?**

The goal of trending is to identify gradually deteriorating environmental conditions that may eventually lead to product contamination. A thorough knowledge of the environment and the processes that take place within that environment can accomplish this goal.

When EM data is analyzed with appropriate statistical and qualitative techniques, knowledge of the environment becomes more significant and decisions based on this knowledge easier to defend. The easiest form of trending is to consider a certain

where,

$p$  = proportion nonconforming (from historical data)

$\sigma$  = standard deviation

$n$  = sample size

Since sample sizes are rarely identical from one time period to the next, the upper control level can be established once using an average sample size or with each trend analysis using the sample size for the time period in question. Once the upper control level is established, it can be compared to the percentage of EM data points that do not conform to the chosen attribute.

Further, it is possible to construct a control chart consisting of the predetermined percent non-conforming, upper control levels, and each data point representing the percentage non-conforming from a particular time point. This will provide a visual representation of how each time interval compares with each other in terms of percentage of EM data non-conforming. It will also illustrate how percentage nonconformities perform relative to the established control levels.

***Alert Level Time Interval.***

Another method of long-term EM data trending is to determine the expected time interval between alert level excursions. Time interval distributions are most often positively skewed and for this reason are particularly well suited to the log-normal or Weibull distributions. As above, fitting EM data to these distributions will allow setting of the expected time interval between alert level excursions. Two alert level excursions within this interval would then be an indicator of a potential adverse trend.

While this method can provide valuable insight into EM trends, it may not be as practical as the percentage non-conforming approach described above.

Skewed distributions are relatively complicated and may require dedicated statistical software to analyze. Further, tracking of time intervals between alert level excursions is not usually performed, so reprocessing of the raw data to generate this new parameter will most likely be necessary.

It is recommended that environmental monitoring programs include procedures for trending data in the aseptic manufacturing practice.

It also recommended to

- Trending as tabulation or graphical plot of actual data used to determine ongoing performance.
- Assigning trend review responsibility
- Suggesting tabulation tools
- Defining the purpose for trending
- Delineating responses to adverse trends