ESTABLISHING BIOBURDEN ALERT & ACTION LEVELS

Authors:
Harry Bushar
Ashley Ferry
Esther Patch
Wendy Wangsgard
Martell Winters
Establishing Bioburden Alert and Action Levels – Part 1

Introduction

Most national and international standards regarding bioburden, sterilization, or environmental testing refer to establishing alert and action levels to assist in demonstrating continued control over a process or product. The standards sometime include guidance on evaluating the data but seldom go any further. Oftentimes, what information is provided in a standard is more descriptive rather than prescriptive, which is necessary in a national or international standard.

One common practice in the medical device industry involves using standard deviations to set the alert and action levels. Other practices refer to bioburden values which are provided as a limit in a table, for example, a radiation sterilization dose substantiation table. Even though these practices can work well, it is important to understand the different concepts being employed in taking different approaches. Some approaches are more appropriate for overkill sterilization methods (e.g. ethylene oxide or steam) where others are more appropriate for bioburden-based sterilization methods (e.g. radiation).

It is the intent of this article to provide insights to the many facets involved in establishing bioburden alert and action levels in a variety of situations. These practices are not intended to be rigidly applied, as different situations might necessitate a different approach than those provided. Comments or suggestions are welcomed and can be sent to any of the authors.

Background

ANSI/AAMI/ISO 11737-1:2006 on bioburden testing provides guidance on establishing bioburden alert and action levels. (1) Clauses A.8.5 through A.8.7 give general guidelines for setting environmental or bioburden levels. This guideline is intentionally vague so that it can be applied to many situations. Following is a summary of the guidance provided:

- Base levels on historical data.
- Use means and/or standard deviations.
- Perform continued trend analysis and data evaluation to determine if the established levels remain appropriate.
- Watch for periodic spikes, even if averages stay within levels.

Note that the AAMI guideline does not dictate or provide guidance on how to use the data to establish action and alert levels. Nor does it provide guidance regarding how to interpret the data depending on the sterilization modality in use.

The ISO standard for radiation sterilization, ANSI/AAMI/ISO 11137-2:2006, assumes that dose audits are being performed quarterly. (2) This document, in Clause 10.1 states:

"A review of environmental and manufacturing controls, together with determinations of bioburden should be conducted in conjunction with sterilization dose audits. If the review indicates lack of control, appropriate action should be taken.”
Background (continued)

Note, however, that no definition is provided for the phrase "indicates lack of control". This does make it clear, however, that some criteria should be established. Most companies comply with this requirement by establishing alert and action levels for bioburden and environmental counts.

There is information from the FDA regarding bioburden levels mostly in the form of audit findings or guidance for aseptic processing. (5) This information mentions alert and action levels but does not provide guidance on how to establish them. The information does explain the importance of performing thorough investigations of excursions above the levels, trending the data, and periodically reviewing the appropriateness of the established levels.

The Normal Distribution

The 11737-1 document discusses the fact that bioburden data seldom fit into a Normal distribution (i.e. a standard bell-shaped curve). (1) In evaluating bioburden data it is appropriate to consider whether it is important or not that the data fit a standard statistical model (e.g. Normal distribution).

Whether the data fit a standard statistical model or not is less critical than whether the established levels are based on empirical data and whether they provide safety from a sterilization perspective.

One primary reason that bioburden data does not fit a Normal distribution is due to bioburden spikes. It is common to obtain most bioburden values near the mean, but to occasionally have a value which is well above the mean (i.e. a bioburden spike). Bioburden spikes are common in the medical device industry, especially when manual assembly is used in manufacturing. Additional information is provided on bioburden spikes in the article.

The other primary reason for not fitting a Normal distribution is because of the frequent occurrence of zero colony forming units (CFUs) results (e.g. < 1 CFU/sample). Determination of a standard distribution in this case may be zero. This makes use of standard distributions impossible and a different approach will need to be used. See (9).
Alert & Action Level Definitions

Often the term alert/action “limits” is used rather than “levels”. The term “limit” implies that product has been impacted by an excursion above that value. Use of “levels” does not imply that the product has automatically been impacted and is the generally accepted term.

A search into the established documents and standards provided the following definitions regarding alert and action levels or limits.

1. No definitions are provided in the AAMI/ISO 11737 document. (1) Levels are discussed but no actual guidelines are given.

2. PDA (2001) (3)
   "Alert Level: A level that, when exceeded, indicates a process may have drifted from its normal operating condition. Alert levels constitute a warning, but do not necessarily warrant corrective action."
   "Action Level: A level that, when exceeded, indicates a process has drifted from its normal operating range. A response to such an excursion should involve a documented investigation and corrective action."

3. USP (1116) (4)
   "Alert Level: 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."
   "Action Level: 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"
   "An Action level in microbiological environmental monitoring is that level of microorganisms that when exceeded requires immediate follow-up and, if necessary, corrective action."

4. USP (1231) (7)
   "Alert levels are events or levels that, when they drift or are exceeded, indicate that a process may have drifted from its normal operating condition."
   "...constitute a warning and do not necessarily require a corrective action."
   "...usually leads to alerting the personnel involved...as well as QA."
   "...may lead to additional monitoring with more intense scrutiny of resulting and neighboring data as well as other process indicators."
   "Action levels are events or higher levels that, when they occur or are exceeded, indicate that a process is probably drifting from its normal operating range."
   "Examples...include exceeding alert levels repeatedly, or in multiple simultaneous locations, a single occurrence of exceeding a higher microbial level, or the individual repeated recovery of specific objectionable microorganisms."
Alert & Action Level Definitions (continued)

5. **FDA** (5)
"Alert Level: An established microbial or airborne particle level giving early warning of potential drift from normal operating conditions and triggers appropriate scrutiny and follow-up to address the potential problem. Alert levels are always lower than action levels."

"Action Level: An established microbial or airborne particle level that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation."

A review of the above definitions provides the following similarities:

**ALERT LEVEL**
Indicates when a process **might** have drifted from normal operating conditions. An investigation may be performed and corrective action may be implemented but no action is required. It can be assumed that repetitive excursions above the alert level may be addressed as if it were an action level.

**ACTION LEVEL**
An action level indicates that a process **has** drifted from normal operating conditions. An investigation must be performed and corrective action must be implemented.

**Bioburden Based Versus Overkill Based Sterilization Methods**

A different approach should be taken when establishing alert and action levels for a bioburden-based (usually radiation) versus an overkill based (usually all other types) sterilization method.

**Radiation:**

In radiation sterilization the sterilizing dose is closely tied to the product bioburden. Both the bioburden number and the resistance are taken into account during the dose establishment exercises. In Method 1 and VDmax the bioburden number is taken to a table to determine the verification dose. An acceptable test of sterility at that verification dose verifies that the sterilization dose in question is appropriate for the product's bioburden count and resistance.

When establishing a sterilization dose using Method 2 the bioburden count is not used per se but together the bioburden count and resistance of the microorganisms drive the resulting verification and sterilization dose.

Because of the close connection that radiation sterilization doses have with the bioburden count, it is important that bioburden alert and action levels be established accordingly. This will result in the established levels being closer to the bioburden average than is typical for an overkill sterilization method (e.g. Ethylene Oxide (EO) or steam). Because of the way the sterilization doses are determined within the different radiation methods, some should be allowed more flexibility in bioburden than others. A review of the primary dose establishment
Bioburden Based Versus Overkill Based Sterilization Methods (continued)

methods and their connection to bioburden counts/resistance results in the following order:

\[ VD_{max} > Method 1 > Method 2 \]

(Most to Least flexibility in counts)

Overkill methods (primarily Ethylene Oxide, steam and dry heat):

Sterilization cycles for overkill methods are based on inoculation of the most difficult to sterilize locations using at least one million CFU of the most resistant organism (MR0). Then, the cycle which can kill all of those microorganisms is typically doubled in length for a full sterilization cycle.

This type of sterilization method accounts not only for high bioburden on the product, but also for a large degree of bioburden fluctuation. This means that the overkill method is almost completely removed from the product’s naturally occurring bioburden count or resistance. In this case the alert and action levels might be established at a higher level to take advantage of the large degree of overkill in these methods. As a result, overkill methods should normally be permitted more flexibility than bioburden-based methods.

\[ Overkill \text{ methods} > Bioburden \text{ based methods} \]

(Most to Least flexibility in counts and types)

Establishing Bioburden Alert and Action Levels – Part 2

General

Medical device or pharmaceutical manufacturers are responsible for setting their own internal specifications for bioburden and environmental alert and action levels. Alert and action levels should be used as a means to monitor manufacturing processes and not as stand-alone product acceptance criteria.

PDA TR13, page 8 states: "These levels are conservative measures designed to signal potential or actual drift from historical or design performance characteristics." (3) Additionally PDA TR13 states that alert and action levels are "intended to flag changes so that corrective action may be taken before product quality is adversely affected." Alert levels are always established at lower values than action levels. Neither alert nor action levels should be based solely on environmental or bioburden counts without considering, for example, the method of sterilization, the amount of overkill in the sterilization cycle, and the presence of resistant microorganisms.

In setting the levels there should be a balance between demonstrating adequate control over bioburden without frequently triggering the alert and action levels. It is best to be conservative when setting alert and action levels to avoid binding yourself to unnecessary specifications.
General (continued)

that cannot routinely be achieved.

Often times setting levels is not purely a mathematical exercise, but also involves looking at the proposed levels from a common sense point-of-view. This perspective might result in taking a different approach for a particular data set.

Data Analysis of TNTCs/ spreaders/ spikes

A bioburden or environmental agar plate may have growth covering the entire surface where distinct colonies cannot be enumerated. These are usually called too numerous to count (TNTC) or spreaders (also called lawns). TNTC describes individual colonies that are indistinguishable because of high numbers of colonies on the filter or plate. Spreaders describe one or more colonies that have covered a portion of or the entire filter or plate. Spreading can be caused by particulates, the nature of the microorganisms, or by fluid on the filter or plate.

TNTC results should not be assigned a CFU value because there are too many CFUs to yield any count. Using an assigned value beyond the countable range, such as 300, would likely result in an underestimation of the bioburden. In review of any bioburden data, a TNTC result likely indicates a bioburden problem and an investigation should be initiated. The investigation may result in the need to perform additional testing.

Spreaders do not allow for an accurate count. The count should be discarded when gathering historical data for the establishment of bioburden levels. Spreaders are generally an indication of a problem with the testing method. If spreaders are observed, different test methods should be explored to diminish the potential for spreading.

Occasionally, spikes are observed in bioburden testing. Currently there is no harmonized definition for a bioburden spike. One common definition is an individual value which is greater than or equal to twice the mean. A statistical approach will be described for determining spikes in part 3.

Values which are considered spikes or outliers should be investigated. New samples from the same lot or family can be tested to determine if the spike is an actual representation of that lot or family or if it is a one-time or infrequent event. If it is determined that they are not true values, then either that value or the entire data set should be discarded. If the investigation determines that they are true values, it indicates that there may be a bioburden problem in the manufacturing or testing process. It is unwise to set alert and action levels while such a problem is present. If at all possible, the cause of the spike should be identified and corrected. If this is not done, what infrequently shows up as a spike may eventually become more frequent.

As part of the investigation, it should be determined if the spike value raises a potential concern regarding the ability of the current sterilization cycle to provide product which is sterile to the desired sterility assurance level (SAL). This evaluation will vary depending on the sterilization modality being used and on the bioburden counts at the time of the validation.
Table 1—Example of bioburden data with and without a spike

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Bioburden estimate: 174.6 Bioburden estimate: 114.7
Standard deviation: 209.8 Standard deviation: 40.9
Recovery efficiency: 0.587 Recovery efficiency: 0.587

(Sample data with spike) (Sample data without spike)

The two most common instances of establishing alert and action levels are temporary, when little or no data are available or long-term when sufficient data are available. Depending on the sterilization method used, the approach to establishing temporary or long-term levels may differ. Each product or product family should be evaluated and established independently. Some approaches are discussed as well as guidance for investigation when levels are exceeded. The key to establishing bioburden and environmental alert and action levels is that they are based on historical trends.

Initial/Temporary Levels

Each company has an individual responsibility to assess all variables in setting alert and action levels. When establishing alert and action levels for a new product, initial or temporary levels can be used until enough data are gathered to establish long-term levels. There is no industry requirement that temporary levels be established, but depending on circumstances, they may be beneficial.

Initially the samples should be tested more frequently (e.g. weekly or monthly) to establish a baseline. With these baseline data, temporary alert and action levels can be established.
Initial/Temporary levels (continued)

Testing on a typical basis (e.g. quarterly) for the remainder of the year will result in sufficient data for determining long-term alert and action levels.

Three initial sets of data representing three batches can provide a good statistical basis for temporary levels. The options outlined below in the approaches to overkill and radiation discuss appropriate sample sizes. Use of the same mathematical approaches for establishing temporary versus long-term levels is appropriate with the understanding that the temporary levels may be triggered more frequently.

A plan of action for setting long-term alert and action levels should be documented. It should cover the transition of temporary to long-term levels and the frequency of re-evaluation.

Long-term levels

Once sufficient bioburden data have been gathered, long-term alert and action levels should be established. When gathering data, consider the points listed below to ensure that sufficient data representative of the product have been gathered.

1) Samples should represent the entire lot.
   PDA TR21 states: “Samples should be pulled from various locations within the lot so as to represent the entire lot. (6) Typically, the samples are randomly selected, usually including beginning, middle and end of batch locations in the sampling plan.”

   If a manufacturing batch is made specific for testing, extra care must be taken to ensure that the testing batch is representative of routine manufacturing.

2) Bioburden data should be gathered over an extended period of time.
   PDA TR21 1990, V44 page 52 states: “Data should be trended to determine if seasonal variation in raw material or process bioburden is occurring.” (6)

   It is typical to gather data over one year.

3) At least four sets of data should be used.
   Naturally, the more data collected to establish the alert and action levels, the more representative the data will be. Moreover, with a small data set, the margin of error can be quite large. As more data are gathered, the margin of error will decrease. For example, one set of ten samples per quarter of the year (forty data points) generally provides sufficient trending to establish levels.

4) Employ a validated recovery efficiency for product bioburden levels.
   A recovery efficiency validation should be performed for each sample product type (e.g. minimum of three samples) and applied to all data points before data evaluation begins. If multiple recovery efficiencies are determined over time, take the mean of all recovery efficiencies and apply the mean recovery efficiency to each set of data. Applying the same recovery efficiency to all data provides for less variation when comparing bioburden estimates. This concept is applicable as long as the same extraction method is used for each set of data. In the bioburden standard the correction factor can be derived from the recovery efficiency (1).
Establishing Bioburden Alert and Action Levels – Part 3

There is no required or established method in the standards or in the industry for setting bioburden or environmental levels. Use of standard deviations to set levels is a common approach due to the simplicity and ease of use. A misleading argument against using standard deviations is that microbiological data may not fit a Normal distribution. However, the standard deviation is a useful measure of the dispersion of the data, whether or not the data are Normally distributed. Therefore, use of standard deviations is appropriate for this type of evaluation.

As a larger sample size of bioburden data becomes available, a move towards a Normal distribution may not always be seen, if not observed initially. Although a larger sample size could result in a Normal distribution of microbiological data, the presence of a just a single very high value could result in the data not being Normally distributed.

Additionally, a larger sample size of bioburden may not necessarily move towards a Normal distribution, if there is no growth observed (e.g. 0 CFU observed). In this situation, the sterilization method may be used to establish the alert and action levels. Another option is to use other distributions and their corresponding statistics to establish levels. Although low bioburden data are said to follow a Poisson distribution, in our evaluation of 47 data sets of product with high bioburden, the Poisson distribution was generally not found.

It is not desirable that the alert level be triggered often, as that would be an indication that there is either too much variability in the bioburden results or that the alert level is too low. It is best to use the bioburden estimate to establish values rather than bioburden averages or maximum values. This would require that a recovery efficiency be validated for each product type to calculate the bioburden estimate, as stated earlier. However, for environmental monitoring, the bioburden average would be used since a recovery efficiency is generally not performed.

Initial evaluation of the data
In this example, tests were performed monthly for the first quarter and then quarterly for the rest of the year. Using the bioburden data for the product in question, the mean, standard deviation, and bioburden estimate for each set was calculated as well as the overall mean, average standard deviation, and average bioburden estimate. The sum of aerobic bacterial and fungal data for each sample was used in all calculations.

Additional calculations were performed to determine the bioburden estimate plus two and three standard deviations as well as the bioburden estimate times ten.
### Table 2.

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<td>Bioburden Estimate x 10</td>
<td>$3.48 \times 10^3$</td>
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The following is a summary of the data:

1. Initial three sets of data from the first three months:
   Overall Average Bioburden Estimate: 89.4 CFU
   Average Std. dev: 123.3 CFU
   Bioburden Estimate + 2 Standard Deviations: 336.0 CFU
   Bioburden Estimate + 3 Standard Deviations: 459.3 CFU
   Bioburden Estimate x 10: 894 CFU

2. Data from the first year:
   Overall Average Bioburden Estimate: 81.4 CFU
   Average Std. dev: 89.5 CFU
   Bioburden Estimate + 2 Standard Deviations: 260.4 CFU
   Bioburden Estimate + 3 Standard Deviations: 349.9 CFU
   Bioburden Estimate x 10: 814 CFU

Note that the established recovery efficiency of 58.7% was applied to all data for consistency. This is appropriate, because all testing was performed using the same extraction method.

From a bioburden perspective a comparison of the first three months versus the entire year shows the bioburden estimate and bioburden estimate plus standard deviations are similar. This demonstrates that, as the manufacturing process was refined over time, there was not a significant change and the bioburden is similar.

In this example, standard deviations were used to establish the bioburden levels, which is similar to the “Normal distribution approach” in PDA TR13 2001 V55. As part of analyzing the bioburden data, the mean and standard deviation are calculated for each set of data. The alert level was set at two standard deviations above the historical bioburden estimate, and the action level was set at three standard deviations above the historical bioburden estimate. This approach results in tight alert and actions levels, which would be appropriate for bioburden based methods such as radiation.

For radiation sterilization using VDmax there is an established bioburden count that should not be exceeded, which is the maximum bioburden count permitted in the sterilization table being used in AAMI/ISO 11137-2 and ISO 13004 (2 and 10). For example, for 25 kGy, the maximum allowable bioburden count is 1000 CFUs. This would be an example of when the term “limit” might be appropriate.

When establishing levels for overkill based methods (e.g. EO), alert and action levels could be based using the Bioburden Estimate + 3 Standard Deviations and the Bioburden Estimate x 10 respectively.
Establishing Bioburden Alert and Action Levels – Part 3

A good limit for such products using overkill methods could be when the bioburden approaches or exceeds the titer of the biological indicator. The amount of safety provided in overkill cycles should allow for greater flexibility in the alert and action levels.

Evaluation of Data Normality

The SAS program PROC UNIVARIATE was used to evaluate the normality of 47 different data sets (10 samples per data set). The following four different statistical tests were used in these evaluations: Shapiro-Wilk, Kolmogorov-Smirnov, Cramer-von Mises, and Anderson-Darling. Each of these tests did agree reasonably well on the determination of the Normality of each of these data sets. Many data sets were found to be not Normal due to a single outlier, which was over twice the standard deviation beyond the mean (33 out of 47 or 70%).

During the evaluation of these data sets, it was determined whether or not each data set had a single outlier, which was defined as a single data point over twice the standard deviation beyond the mean (i.e. Mean + 2 Standard Deviations). Most data sets were found to be either not Normal due to an outlier or Normal due to no outlier (39 out of 47 not Normal or 83%). This result demonstrates that using this as a rule-of-thumb may be a simple and reasonably accurate way to determine whether or not a given data set has an influential outlier.

When the initial sets of ten were grouped into sample sizes of twenty or thirty data points based on product type and evaluated as described above, it was found that the data did not become Normal solely based on a larger sample size. In fact the rule of thumb described worked with each of the data sets in determining Normality (10 out of 10 or 100%).

Alternative statistical approaches

If the data do not conform to a Normal distribution, and if a Normal distribution is desired, other statistical models may be utilized to transform your data to fit a Normal distribution, for example using a log transformation. Also, PDA TR 13 discusses using a “cut-off value approach” and a “non-parametric tolerance limits approach”. (3) Although the log transformation could be used to make microbiological data appear to be Normally distributed, if there are a few very large values, this transformation may result in these, possibly important, outliers being missed.

Investigation of exceeding the alert and action level

It is important to understand what would be included in an investigation, as a way to help establish proper levels. Levels should not be established that are too restrictive.

PDA TR3 V55, p 8 states: “An occasional excursion from these levels is expected at frequencies characteristic for the specific mathematical model utilized in their derivation.” (3) For example, an alert level established at 2 standard deviations beyond the mean is expected to be exceeded with probability = 0.02275 for a Normally distributed bioburden.
Investigation of exceeding the alert and action level (continued)

It should be noted that even when a process is in control, occasionally there will be a single value outside of the alert or action level. When a single value exceeds an action level, it is not expected that a long list of corrective actions be triggered, but it could be investigated. Generally, the main focus should be on trends, not individual values.

Product bioburden may come from the environment, personnel, raw materials, equipment, manufacturing process, etc. Each of these sources could be used in the investigation of a bioburden excursion to determine the root cause and what should be done to prevent a recurrence.

At the alert level the following items could be considered, although generally no action or investigation is required:
- numbers and types of routine bioburden trends (product and environment)
- identification of recovered microorganisms
- evaluation of microorganism for resistance to the sterilization process
- production personnel impact (e.g. proper training or new personnel)
- manufacturing process changes
- sampling and testing procedures changes
- evaluation of laboratory controls and monitors
- additional testing
- thorough cleaning of production area
- modification of sampling plan
- raw materials and supplier changes
- water-source contamination

At the action level, the above-mentioned items are usually required in addition to the following:
- root cause analysis/investigation
- determination of potential impact on sterilization specifications

When establishing alert and action levels, corresponding investigative plans should be identified. These plans should not be too specific to allow for flexibility depending on the situation. Documentation of the investigation and any actions taken is expected.
(PDA TR13 2001 V55, p 8, 11, 13) (3)

Bioburden alert and action levels should not be the only criteria for release of product. Certainly values above the alert levels should not dictate discard of the product and even values above the action levels, by themselves, do not indicate that the product is non-conforming. It is only, when the bioburden counts may call into question the appropriateness of the sterilization cycle, that the counts really become an issue.

As part of the investigation of repeated excursions above alert or action levels, consider the potential impact on the sterilization process (e.g. the SAL). If there is no potential impact on the sterilization process and if the high bioburden cannot be corrected, then re-establishing the alert and action levels should be considered.
Investigation of exceeding the alert and action level (continued)

If it is determined that there could be an impact on the sterilization process, then re-establishing the sterilization cycle either for short- or long-term should be considered. This situation is more likely to occur with a bioburden-based process than an overkill-based process.

As part of the investigation additional testing of current batches may be helpful in understanding whether the excursions have a consistent trend. However, due to the timing (i.e. the time which has passed during testing and incubation) the additional test results may not provide details of the source of contamination.

The AAMI/ISO standards and USP <1116> recommend identifying the bioburden recovered under initial or typical conditions to assist in understanding if excursions are due to new microorganism types or the same ones which are usually present. (1, 2, and 4) If identification has not been done previously, identification of possible excursions should still be done, but will not be as helpful to identify the source of contamination. Therefore, it is highly recommended to obtain a good baseline of microorganisms typically recovered.

When changing manufacturing location or process

Establishing bioburden levels when changing a manufacturing location and/or process should be similar to establishing bioburden levels for a new product. However, the process might not be as rigorous. Evaluation should be performed on a batch-to-batch or more frequent basis for a period of time to assess if the previously determined levels are still appropriate. If not, the levels should be re-established according to the new location or process.

Conclusion

This article provides insights to many facets involved in establishing alert and action levels for product and environmental bioburden. The authors recognize that there are many options to evaluating data and establishing these levels. A thorough review of bioburden data can assist in selecting the best approach for the situation. The approaches discussed here have functioned well for a variety of product and sterilization types.

There is often discussion in the industry regarding the appropriateness of standard distributions for evaluating bioburden data. It is the opinion of the authors that fitting the bioburden data into a specific statistical distribution is less critical than understanding the ranges of bioburden over time.

An important part of this process is a good definition for alert and action levels and understanding what should occur when each is triggered. It's important to find a balance for the specified actions when exceeding alert or action levels. Specified actions that are either too rigid or provide no structure can both be problematic. Different sterilization types should require different numerical levels as well as specified follow up actions.

Comments or suggestions are welcomed and can be sent to any of the authors.
References


Further Reading

