



Establishing Bioburden Alert and Action Levels

Why establish bioburden alert and action levels?

Establishing product bioburden alert and action levels is a regulatory expectation in ensuring consistent microbiological quality prior to a sterilization process. Control of the amount and types of microorganisms in a product's bioburden is a critical component of ensuring the proper sterility assurance level is maintained. Results are evaluated as trends, and single data points do not necessarily indicate an issue regarding the terminal sterilization process or the determined sterility assurance level of the product. Understanding the types of microorganisms can also be valuable in assessing the impact of an elevated bioburden trend to the sterility assurance of the product.

What if historical product bioburden data is not available?

Typically, alert and action levels for a product will be set using historical bioburden data. In the absence of such data it is recommended to create temporary alert and action levels, often utilizing data from the first few production batches. Historical bioburden data from similar products could also be used to set temporary levels, provided there are comparable manufacturing materials, design, processes, and environment.

What considerations are important when determining bioburden alert and action levels?

When determining long-term alert and action levels, it may be important to account for seasonal variations in bioburden from conditions such as humidity or temperature changes that might impact the number, types, and associated resistance to sterilization of microorganisms present on a product.

When determining action and alert levels, consideration for the use of the bioburden data and an assessment of risk should be included. For example, bioburden alert and action levels can be used to evaluate various raw material suppliers or qualify or demonstrate control of selected suppliers and are important for bioburden control of some of the inputs into the final product bioburden. The final product bioburden is more representative of the challenge to the sterilization process, and the alert and action levels for this bioburden measurement might be considered more critical to control of sterility assurance.

Another instance might be for VDmax25 where the upper action level could be capped at less than 1000 CFU, as this is the maximum allowed bioburden average per ISO 11137-2 table 9 for VDmax25.

Bioburden alert and action levels are not stand-alone acceptance criteria but rather should be used as a means for monitoring the manufacturing process. The method used for sterilization and the amount of overkill in the process should also be considered when setting these levels.

How do process changes impact bioburden trends and level setting?

Quality systems should include a process and actions for addressing an alert or action level excursions. Changes implemented to the manufacturing process in response to an exceeded level may have an impact on ongoing trends. New bioburden data should be obtained, and an evaluation of whether new levels are established for the new/revised process should be completed. Even in the absence of significant changes to the manufacturing process, suppliers, and other factors, the long-term bioburden levels set should be reviewed at a defined period to ensure their appropriateness and, where necessary, the levels should be revised.

What role does trend analysis play in managing product bioburden?

Quality system processes or actions should reflect that bioburden consists of living microorganisms. As a result, the number and types of microorganisms will fluctuate, and bioburden tests are an estimate. It is not uncommon to have variance in bioburden data, and data trending may not follow conventional statistical distributions. It is common industry practice to determine an average bioburden and to determine variance based on standard deviations for establishing alert and action levels. For instance, utilizing one or two standard deviations from the average for alert level and two or three standard deviations for the action level. The goal of setting limits is to trigger alerts and alarms to the loss of microbiological quality control. The purpose is not to be in a constant state of alarm or action. The purpose of setting levels is to identify and facilitate investigation of results for significantly higher or lower bioburden that could be the outcome of an unknown change, or data that is abnormal of the trend. It is also important to incorporate actions or responses

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to results such as “no growth” or “too numerous to count” (TNTC) results. A trend would usually be considered three or more data points and bioburden data should be treated in this manner, but investigation into individual excursions can also be significant in mitigating patient and product risk.

References:

AAMI TIR106:2024 Microbiological methods- Understanding and use of product bioburden data

ISO 11737-1:2018 Sterilization of health care products – Microbiological methods – Part 1: Determination of a population of microorganisms on products

ISO 11137-2:2013 Sterilization of health care products – Radiation - Part 2: Establishing the sterilization dose

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