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Technical Regulatory Topic

How are the Principles of Sterility Assurance Levels (SAL) Applied to the Sterilization of Liquids by Filtration?

Approach to Sterility

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Answer

Sterilization techniques based on bioburden destruction by heat or irradiation require a statistical validation of the sterilization process, as the efficiency is based on a combination of various factors, including:

- The intensity of exposure (temperature or irradiation level)
- Time of exposure
- Bioburden reduction factor to be attained

For example, at a given steam temperature, doubling the exposure time will double the bioburden reduction factor logarithmic value. To ensure a reasonable safety level to the sterilization process, a safety margin is required. Users are asked by most international pharmacopeias to ensure sterilization conditions that would be able to destroy a bioburden level 10^6 higher than the maximum bioburden level expected on the product to be sterilized.

Sterility achieved by filtration is not based on the same principles. A sterilizing membrane is composed of a multitude of pores that retain contaminants present in the filtered fluid, typically by size-exclusion retention mechanisms, as a screen would do. A microorganism larger than the largest pores of the membrane will not pass through the membrane whatever the upstream microorganism concentration as long as the membrane is integral. The security of the sterilization by filtration is therefore not based on the membrane surface area or the bioburden level, but on the pore size distribution of the membrane and on its integrity when in use on the process line. The concept of a 10^6 safety factor is therefore not applicable to sterilizing filters. The core validation of a sterilizing grade filter, performed by the filter manufacturer, and the process-specific filter validation studies conducted by the end user but generally with the filter supplier's assistance, provide the necessary sterility assurance.

These validation studies include bacterial challenge studies on typical membrane discs or filters aimed at proving the total retention of test organisms loaded on the filter, in the tested conditions. It is generally well accepted that the challenge level in these studies should be equal to or greater than 10^7 colony forming units per cm^2 of effective filtration area (CFU/cm^2), as per the FDA's guidelines for aseptic processing of liquids. Integrity test parameters correlated to bacterial retention allow the user to verify that the filter in the process is not damaged and is in conformance to its claimed specifications.

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