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Technical Regulatory Topic

Is there a Regulatory Requirement to Perform Process-Specific Bacterial Retention Studies on Pre-Filters?

Approach to Sterility

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Answer

There is no regulatory requirement to perform process-specific bacterial retention studies on pre-filters or bioburden reduction filters. Although this is somewhat up to the interpretation of individual regulators, there are no published regulations or guidances that specifically state this as a requirement.

In the United States, the FDA's "Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice"[1] document states:

> *"The manufacturing process controls should be designed to minimize the bioburden of the unfiltered product".*

No specific bioburden limits or sampling frequencies are stated.

In contrast, the EU current Good Manufacturing Practice Guidelines(GMP) state specifically that pre-sterilizing filtration bioburden must be < 10 CFU/100 mL[2], and as per Annex 1, aseptic processed drugs subjected to sterilizing filtration and terminally sterilized drugs under parametric release must have pre-sterilization bioburden determined for every batch[3].

Non-parametric released terminally sterilized drugs are subjected to a less stringent sampling schedule. As per EU Guidelines to GMP Annex 1:

"The bioburden should be monitored before sterilization. There should be working limits on contamination immediately before sterilization, which are related to the efficiency of the method to be used. Bioburden assays should be performed on each batch for both aseptically filled product and terminally sterilized products. Where overkill sterilization parameters are set for terminally sterilized products, bioburden might be monitored only at suitable scheduled intervals. For parametric release systems, bioburden assays should be performed on each batch and considered as an in-process test".

Integrity testing of a bioburden reduction filter (with manufacturing claims to support bioburden reduction by the filter), and demonstration of a pre-sterilizing filtration bioburden load of <10 CFU/100 mL should typically be sufficient to demonstrate the bioburden reduction filter is performing satisfactorily. Some customers will also analyze bioburden levels pre- and post-filtration to provide further evidence of microbial control.

Ultimately, the decision to implement a bioburden reduction filter or a sterilizing grade filter to maintain a low bioburden prior to final filtration comes down to risk. With increasing efforts to implement Quality by Design (QbD) into manufacturing processes, there is less emphasis placed on the results of a single sample, and more emphasis on trending of bioburden data.

References:

[1] FDA Guidance for Industry (2004), Sterile Drug Products Produced by Aseptic Processing.

[2] European Medicines Agency (EMA), "Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container," *Guidelines* 31, no. March (2019): 1–25, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-sterilisation-medicinal-product-active-substance-excipient-primary-container_en.pdf.

[3] EC, Eudralex Volume 4: EU Guidelines to Good Manufacturing Practice, Annex 1, Manufacture of Sterile Medicinal Products (Brussels, 2008).

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