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

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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 guidance documents that specifically state this as a requirement. However, there is an expectation that end-users control their pre-filtration bioburden levels, with the maximum acceptable level of pre-filtration bioburden dependent on whether the final product is sterilized by terminal sterilization or sterilizing grade filters.

In the United States, the U.S. Food and Drug Administration's (FDA) "Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice" document [1] states that for products sterilized using sterilizing grade filters "The manufacturing process controls should be designed to minimize the bioburden of the unfiltered product. Bioburden of unsterilized bulk solutions should be determined to trend the characteristics of potentially contaminating organisms." No specific bioburden limits or sampling frequencies are defined, though it is stated that pre-filtration bioburden limits should be established by the end-user.

In contrast, for products that are sterilized by sterile filtration, the European Medicines Agency (EMA) document "Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container" [2] states "For routine commercial manufacturing, bioburden testing should be performed on the bulk solution immediately before sterile filtration. In most situations, a limit of Not More Than (NMT) 10 Colony Forming Units (CFU)/100 mL (Total Aerobic Microbial Count [TAMC]) would be acceptable for bioburden testing." For fluids with negligible bioburden (where the pre-filter is added only as a precaution), this bioburden limit is also recommended pre filtration. However, there is recognition that some fluids may have a pre-filtration bioburden level that exceeds 10 CFU/100 mL. For situations such as this, the guidance states "In such cases, it should be demonstrated that the first filter is capable of achieving a bioburden of NMT 10 CFU/100 mL prior to the last filtration". Therefore, end-users may elect to have process-specific bacterial challenge studies performed as proof that the prefilter can achieve this level of removal.

The same document states that for most terminally sterilzed products, a maximum bioburden level of 100 CFU/100 mL is expected.

Eudralex recently revised the document "Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use", Annex 1 "Manufacture of Sterile Medicinal Products" [3]. For products that are sterilized using sterile filtration, Annex 1 states "Suitable bioburden reduction prefilters and/or sterilising grade filters may be used at multiple points during the manufacturing process to ensure a low and controlled bioburden of the liquid prior to the final sterilising filter." The document goes on to state "Bioburden samples should be taken from the bulk product and immediately prior to the final sterile filtration. In cases where a redundant filtration set-up is used, it should be taken prior to the first filter."

For terminally sterilized products, Annex 1 provides the following guidance "Processing of the bulk solution should include a filtration step with a microorganism retaining filter, where possible, to reduce bioburden levels and particles prior to filling into the final product containers…."

Importantly, Annex 1 clearly states that there is an expectation that any bioburden recovered from sampling is identified. The results of this should be incorporated into a risk assessment to determine any impact on the final sterilizing process used.

To summarize, end-users are expected to control bioburden before final sterilization, and maximum acceptable levels are dependent on whether the process is sterilized by terminal sterilization or filtration using sterilizing grade filters. While there is no specific requirement that mandates that process-specific bacterial retention studies are performed on a pre-filter, the decision should be based on risk assessment, and the end-user should assess this step as part of their overall contamination control strategy.

References

[1] U.S Food and Drug Administration, "Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice," October 2004. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sterile-drug-products-produced-aseptic-processing-current-good-manufacturing-practice.

[2] European Medicines Agency (EMA), "Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container - Scientific Guideline," 06 March 2019. [Online]. Available: https://www.ema.europa.eu/en/sterilisation-medicinal-product-active-substance-excipient-primary-container-scientific-guideline.

[3] Eudralex, European Commission, "EudraLex - Volume 4 EU Guidelines for Good Manufacturing Practice (GMP) for Medicinal Products for Human and Veterinary Use- Annex 1 Manufacture of Sterile Medicinal Products," 22 August 2022. [Online]. Available: https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf.

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