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Should a Pre-Filtration Bioburden be Determined Prior to Sterile Filtering a Solution?

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In the United States, the Food and Drug Administration's (FDA) Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice (cGMP) [1] 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 guidelines to cGMP state specifically that pre-sterilizing filtration bioburden must be < 10 Colony Forming Units (CFU)/100 mL [2]. Further, the recently revised "Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use". Annex 1 "Manufacture of Sterile Medicinal Products" [3] states "bioburden samples should be taken from the bulk product and immediately prior to the final sterile filtration" and "There should be defined limits for bioburden immediately before the final sterilising grade filter or the terminal sterilisation process, which are related to the efficiency of the method to be used". Finally, International Organization for Standardization (ISO) 13408-2 [4] *Aseptic Processing of Health Care Products — Part 2: Sterilizing Filtration* says "The intention is that the pre-sterilizing filtration bioburden is controlled and maintained at a level substantially below the validated retention performance of the filtration system".

A qualitative assessment of pre-filtration bioburden is also expected by global regulatory agencies. Performing a qualitative analysis on pre-filtration bioburden is required to justify the use of *Brevundimonas diminuta* American Type Culture Collection (ATCC♦) 19146 as the challenge organism for process-specific filter validation studies. The following statements reflect current regulatory and industry thinking:

- "Product bioburden should be evaluated when selecting a suitable challenge microorganism to assess which microorganism represents the worst-case challenge to the filter" [1]
- "Minimum 10^7 CFU/cm^2 using a justified indicator organism and the actual solution" [2]
- "The challenge organism used in the bacterial retention test should be justified" [3]
- "Process bioburden should be evaluated in order to establish *B. diminuta* as a relevant organism. Evaluation should be based on bioburden identification and risk assessment" [5]
- "If there is concern that the indigenous bioburden might include microorganisms that are smaller than *Brevundimonas diminuta*, or small enough to challenge the retention capability of the sterilizing grade filter, then a suitable challenge microorganism (other than *B. diminuta*) shall be selected for use" [4]

Consequently, it is Pall's recommendation that qualitative and quantitative bioburden analysis be performed pre sterile filtration.

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.

[4] International Organization for Standardization (ISO), *“ISO 13408-2:2018 Aseptic Processing of Health Care Products- Part 2: Sterilizing Filtration,”* 2018.

[5] Parenteral Drug Association (PDA), “PDA Technical Report No. 26, (TR 26), Sterilizing Filtration of Liquids,” Parenteral Drug Association (PDA) Journal of Pharmaceutical Science and Technology , vol. 62, no. S-5, pp. 1-60, 2008.

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