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Sterile Filter Validation

Should a pre-filtration bioburden be determined prior to sterile filtering a solution?

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In the United States, the FDA's Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice (cGMP) [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 guidelines to cGMP state specifically that pre-sterilizing filtration bioburden must be < 10 CFU/100 mL, 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 [2].

Although the FDA guidance doesn't implicitly state that bioburden must be known, there has been increased scrutiny by the regulatory authorities on the impact of environmental monitoring on sterile processes. Understanding your pre-filtration bioburden can also be helpful in justifying the use of *Brevundimonas diminuta* ATCC 19146 as the challenge organism for filter validation studies (this was probably used when filter validation studies were performed). Specifically, as stated in PDA Technical Report 26, "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."[3] Without performing bioburden analysis on every raw material and contact surface for any given product, it becomes difficult to see how you can accomplish this without monitoring pre-filtration bioburden levels (qualitative and quantitative assessment).

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

References:

1. FDA Guidance for Industry (2004), Sterile Drug Products Produced by Aseptic Processing.
2. EC, Eudralex Volume 4: EU Guidelines to Good Manufacturing Practice, Annex 1, Manufacture of Sterile Medicinal Products (Brussels, 2008).
3. PDA Technical Report No. 26 (2008), Sterilizing Filtration of Liquids, *PDA J. Pharmaceutical Science and Technology*, 62, No. S-5, 1-60.

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