

Bacterial Penetration of 0.2 μm Sterilizing-Grade Filters with a Cholesterol Liposome Carrier: A Comparison of Data

Michael Moussourakis, Marketing Manager

The occurrence of bacterial penetration of integral 0.2 (or 0.22) μm sterilizing-grade filters, although rare, is not a new phenomenon.¹ As noted in a review of bacterial retention studies, adjuvanted vaccines, liposome drug delivery, and similar surfactant or emulsion-based product fluids can increase the potential for sterilizing-grade filter penetration events.¹

While 0.2 μm rated filters are the accepted biopharmaceutical industry standard for sterilization in aseptic processes, the rare penetration occurrence creates an opportunity to investigate retention mechanisms and to identify robust solutions with increased retention assurance. Due to the high microbial load and worst-case process parameters applied in bacterial challenges conducted during validation of sterilizing filtration, risk of microbial penetration can be determined and avoided well before patient safety or commercial risk is possible. However, retesting to confirm penetration and evaluate alternate filters during process validation is costly for both the filtration validation service provider and the drug manufacturer. When not considered until final process validation conducted late in clinical development, these costs can extend to delays to market as well as financial impact of materials required for what can be multiple tests and retests of filter choices.

Scientists at Pall have been studying the mechanisms of bacterial filter penetration and developing strategies and tactics to avoid costly rework. Figure 1 summarizes results of bacteria challenges of several integral Pall and competitor filters, where penetration of *Brevundimonas diminuta* bacteria was observed with a cholesterol liposome carrier. This liposome carrier was previously determined through

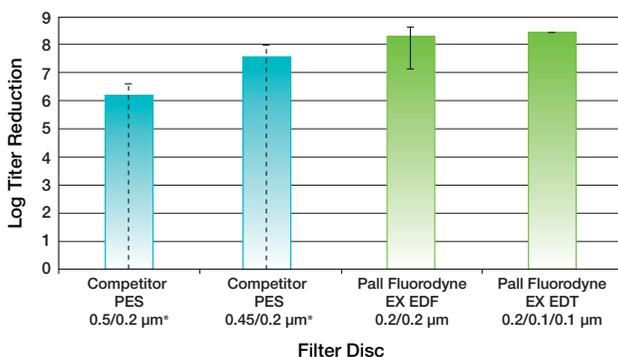
repeated trials at Pall to have a high probability of bacterial penetration associated with it. Penetration was through a variety of filters with bacterial challenges conducted under worst-case bacteria loading conditions.

Based on the data presented here, only the Pall Fluorodyne® EX EDT sterilizing-grade filter (0.2 μm nominal PES membrane over two layers of 0.1 μm PVDF membrane) consistently provided complete retention. The Pall Fluorodyne EX EDT filters have high permeability 0.1 μm membranes in a patented high area laid-over pleat and narrow core 10-inch module cartridge construction for high filtration area (0.95 m² EFA per 10-inch module). The filter thus provides enhanced capacity for biological fluids such as culture media, even though the filter is 0.1 μm rated. This makes it a viable sterilizing alternative for complex fluid streams like cholesterol liposomes normally filtered with 0.2 μm membranes.

Despite this development, there are some conditions that may still require filtration with a 0.2 μm filter instead of 0.1 μm due to filterability requirements. When 0.2 μm filtration is deemed necessary, the filter showing highest probability of sterilization in known penetrative fluids and conditions is the Fluorodyne EX EDF filter. This filter incorporates a nominal 0.2 μm asymmetric PES prefilter membrane layer over a symmetric 0.2 μm PVDF sterilizing membrane. The 0.2 μm rated Fluorodyne EX EDF filter provided enhanced retention and reduction of the risk of bacterial penetration even in the highly penetrative liposome carrier fluid used for this study. The results demonstrated complete retention in 3 of 6 trials and the highest titer reductions when penetration did occur.

All other 0.2 μm rated filters tested showed penetration in all cases with lower average titer reductions. This indicates that the Fluorodyne EX EDF filter provides the highest probability for a successful sterilizing filtration validation effort, even in fluids known to have a greater risk for bacterial penetration. After the Fluorodyne EX EDT 0.1 μm rated sterilizing-grade filter, the Pall Fluorodyne EX EDF filter should be considered a lead candidate for 0.2 μm sterilizing filtration of liposomal or other emulsion products in vaccine and drug manufacturing industries. See Folmsbee and Moussourakis for further details of this study.² Pall is pleased to work with you to qualify the most appropriate filter to ensure sterilization of your drug or vaccine product. Please contact Michael Moussourakis at mmoussourakis@pall.com for further information.

Figure 1



* TNTC recovery made LRV incalculable.

A comparison of the average *B. diminuta* titer reductions on bench-scale filter discs. Only the Pall Fluorodyne EX EDT 0.1 μm rated filter (on right) consistently provided sterile effluents. Three additional sterilizing-grade filters (not shown) had average titer reductions below the measurable limit in all cases (recovery TNTC, TR <10⁵).

References

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2. Folmsbee, M.; Moussourakis, M., Sterilizing filtration of liposome and related lipid containing solutions: Enhancing successful filter qualification. Accepted for review, *PDA Journal of Pharmaceutical Science and Technology*.

w: www.pall.com/biopharm
e: biopharm@pall.com



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