Millipore®
Preparation, Separation,
Filtration & Monitoring Products

Tech Note

Millipak® Final Fill Filters Reduce Contamination Risks and Simplify Filtration System Design and Operation

Introduction

Final sterile filtration of parenteral drugs is a key step in assuring microbial integrity of the drug product and is often performed in single-use assemblies. Both final filtration operations, and single-use assemblies in general, are the focus of extensive regulatory guidance and industry interest around practices that assure sterility of the flow path and compatibility of the assembly components with the process fluid.

It is a regulatory expectation that all sterilizing-grade filters are integrity tested after use to confirm the filter has the expected microbial retention performance [1]. In addition to post-use testing, some guidance documents state that *'the integrity of sterilized filter should be verified before use'* [2, 3]. In assemblies containing redundant filters, performing pre-use, post-sterilization integrity testing (PUPSIT) without compromising the aseptic flow path, can be challenging. Reducing the risk of flow path contamination was a driver for the redesigned port on Millipak® Final Fill filters. The port replaces the traditional filter vent and provides an aseptic barrier between the environment and process fluid.

This tech note summarizes the results of microbial challenge studies that confirm the aseptic multi-purpose port (AMPP) prevents microbial contamination entering the flow path. We also show how these results can be leveraged to simplify integrity testing and product recovery following sterile filtration operations.

Confirming the Aseptic Flow Path

The AMPP contains three O-rings designed to form a barrier between the outside air and the aseptic liquid flow path, Figure 1. If air can move from the outside to the liquid flow path, there is a potential risk of flow path contamination. Conversely, if materials can move from the flow path to the outside air, there is a risk of exposing operators and environment to the drug product.

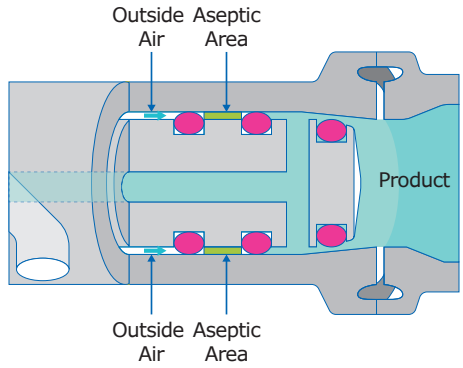

Figure 1. Schematic of AMPP on Millipak® Final Fill Filter showing different zones and key elements for maintaining an aseptic flow path.

Figure 2 illustrates the microbial challenge testing strategy to confirm AMPP performance. No microbial growth was detected in samples collected from any of the treated capsules, confirming the AMPP provides a barrier preventing bacteria from entering the flow path. Importantly, as testing included gamma irradiation, autoclaving under high stress temperature conditions, and multiple actuations of the port, the results show that rigorous filter set-up and use operations do not compromise this barrier. These results confirm the redesigned port can reduce contamination risk in filtration operations, while protecting operators and the filling environment from potential exposure to the drug product.

Microbial Challenge Test Methods

To assess the capability of the AMPP for preventing microbial contamination, challenge testing was performed with *Brevundimonas diminuta* (ATCC® 19146), the standard test organism used for sterilizing-grade filter retention testing[1], Figure 2.

Preliminary tests confirmed low levels of microorganisms (≤ 10 colony forming units (cfu)) could be recovered in 15 mL of Tryptic Soy Broth (TSB), and that low levels of inoculum (≤ 10 cfu) could be recovered after at least 2 hours exposure to filters. Microorganism recovery was confirmed by turbidity and microbial identification within 7 days.

All challenge tests included positive and negative controls.

- Positive controls comprised an AMPP without O-rings from which ≤ 10 cfu *B. diminuta* was recovered.
- Negative controls confirmed testing could be performed aseptically: no microbial challenge in the cam slot, the AMPP was actuated 18 times and no turbidity was observed in the TSB flush.

For each challenge test, at least 10^7 cfu of *B. diminuta*[1] was inoculated into the AMPP cam slot. Following exposure, 15 mL of TSB was flushed through the capsule inlet and out through the AMPP, then incubated at 30 ºC for 7 days before assessing turbidity. All tests and controls were run in triplicate. Two types of test articles were assessed:

- Gamma treatment: devices were subjected to gamma irradiation at 25-40 kGy then challenged with ≥10^7 cfu of *B. diminuta*.
- Gamma-autoclave treatment: devices were subjected to gamma irradiation at 25-40 kGy, at least three autoclave cycles at 126 °C for 90 minutes, then challenged with ≥10^7 cfu of *B. diminuta* before actuation of the AMPP at least 18 times.

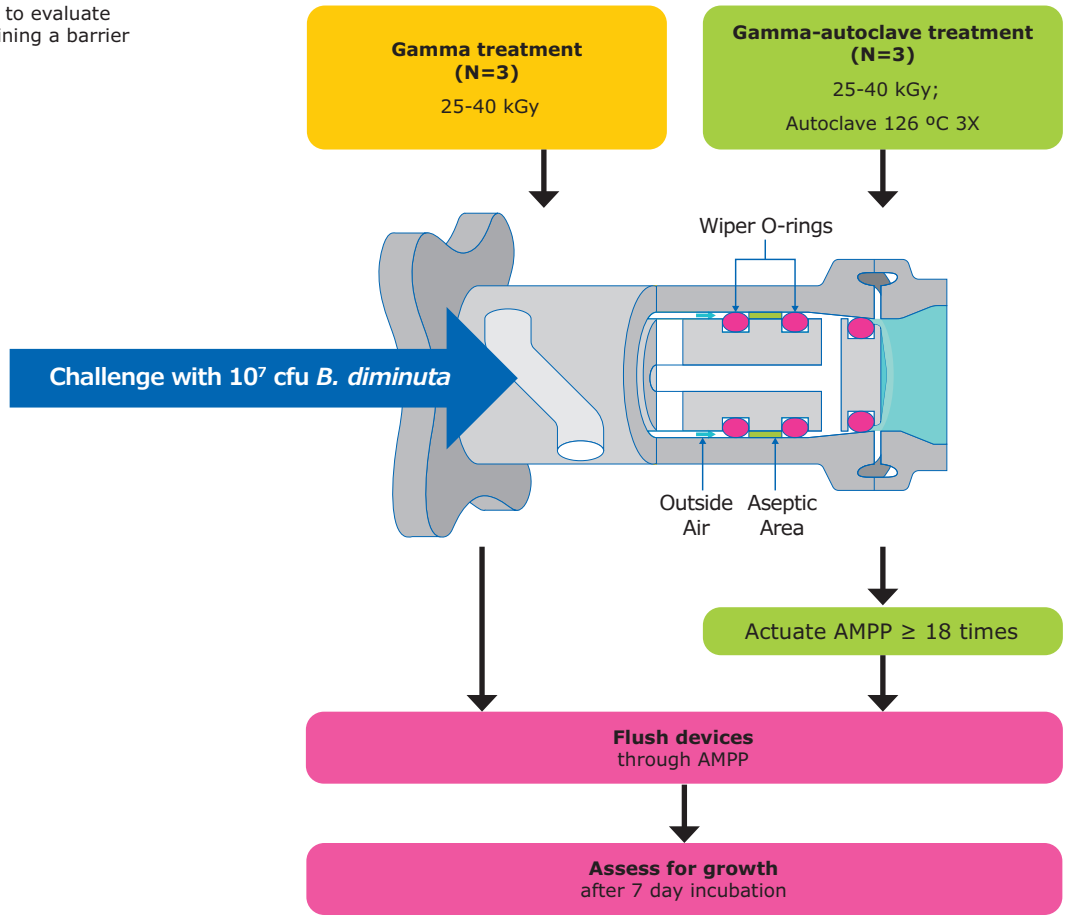

Figure 2. Summary of tests to evaluate integrity of AMPP for maintaining a barrier between air and flow path.

Simplified Integrity Testing and Filtration System Operation

The AMPP's assured aseptic barrier allows operations such as air flow into the filter capsule through an open vent port without increasing risk of contamination. This provides the opportunity for simpler and shorter assembly designs.

For typical filter integrity tests through the filter inlet, a tee with a vent filter and clamp are positioned upstream of the sterilizing filter, isolating the filter from wetting fluid. A second tube clamp isolates the filter from the air-line connection, Figure 3A. Figure 3B highlights the simplified filtration system design for filter integrity testing through the AMPP. A single line connects the wetting fluid to the filter, and the air-line connection is through the AMPP. This configuration eliminates both the second tube clamp and 3-point connection tee, simplifying the filtration system.

Filter integrity can also be confirmed by air diffusion testing, however this should always be performed with a direct air connection to the filter inlet, unless additional process and test qualification is performed.

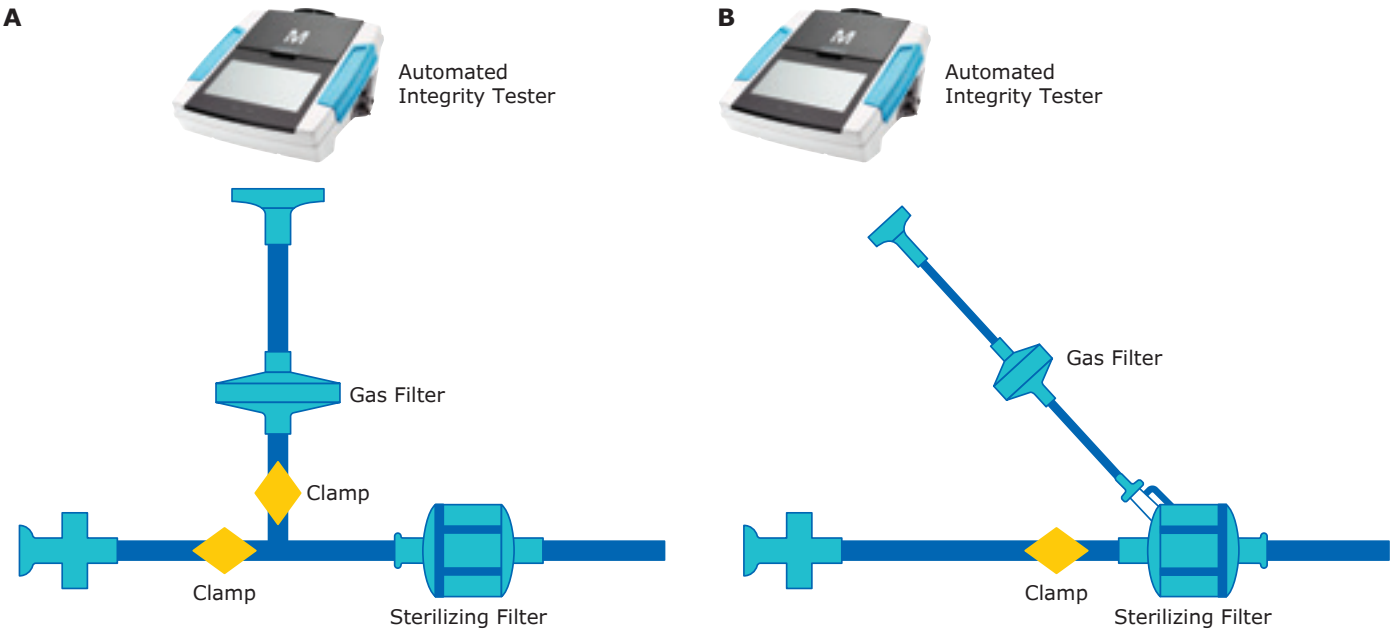

Figure 3: Configuration for connecting automated integrity testing instruments to sterilizing filters - A: connection through the filter inlet, B: connection through the AMPP on Millipak® Final Fill filters.

Figure 4 shows the results of integrity tests through the AMPP and the filter inlet using an automated Integritest® instrument. The bubble point (BP) specification for Durapore® 0.22 µm sterilizing-grade membrane at 23 ºC is ≥ 50 psi. Bubble point measurements through both the filter inlet and AMPP met this specification, confirming the AMPP can be used to assess filter integrity.

Together with the results of microbial challenge testing, these results provide manufacturers with a secure option for reducing contamination risk during integrity testing, particularly during PUPSIT. In addition to reduced contamination risks, the AMPP offers opportunities for a simpler and shorter filtration system design.

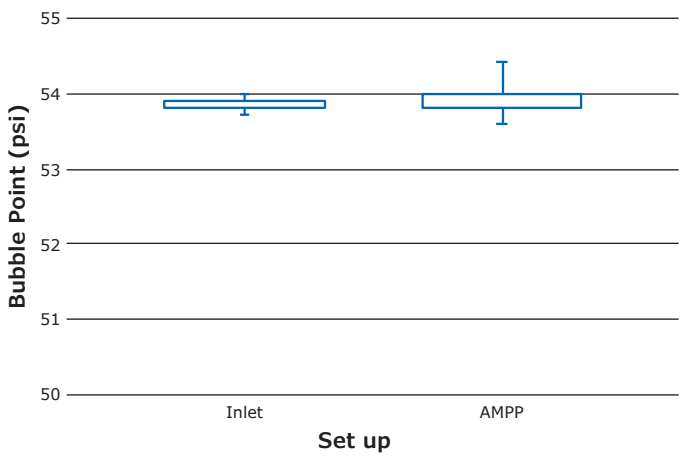

Figure 4: Bubble point results of Durapore® 0.22 µm sterilizing-grade membrane following integrity testing through the Millipak® Final Fill filter inlet and AMPP using an automated Integritest® instrument.

Increase Product Recovery with Filter Blow-down

After processing fluid through sterilizing-grade filters, some manufacturers may perform additional steps to improve product recovery. These might include draining by gravity, using a pump to recover hold-up on the upstream side of the filter, or blowing-down the filter with air.

Blowing-down a filter with air maximizes product recovery as compared to other draining methods, which can translate to substantial economic benefits, particularly for high-value parenteral products. Millipak® Final Fill filters can be blown-down through the filter inlet [4], similar to traditional sterilizing filters, or through the AMPP, which maintains an aseptic barrier. Figure 5 shows the hold-up volumes of Millipak® Final Fill 200 filters following different draining and blow-down procedures.

Hold-up volume of product in the filter is reduced by implementing a blow-down as compared to gravity draining alone. The minimum hold-up volume was achieved when the filter was subjected to a pressure hold at 70 psig applied through either the filter inlet or the AMPP. Running a bubble point integrity test on the filter through the AMPP reduced hold-up as compared to gravity drain but resulted in more liquid being retained in the filter as compared to the higher pressure conditions of 70 psig.

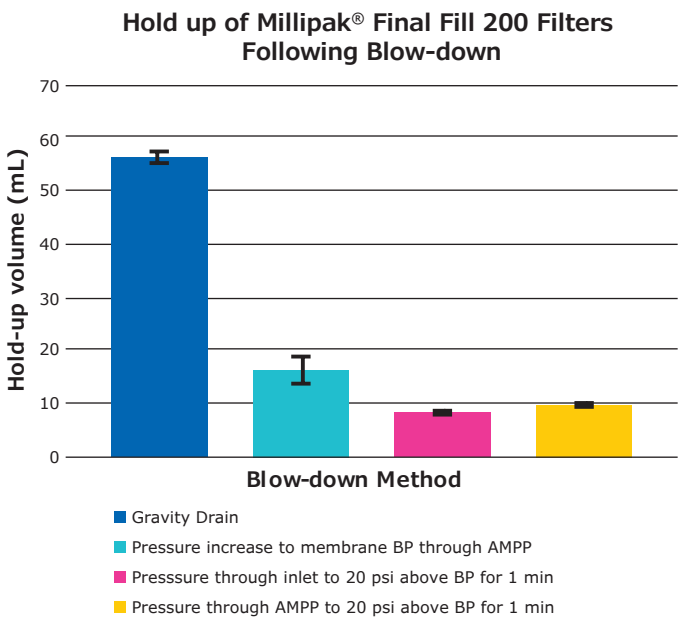

Figure 5. Mean hold-up volume of Millipak® Final Fill 200 filters containing sterilizing grade Durapore® 0.22 µm membrane after different drain or blow-down methods. Each value represents the mean and standard deviation from three replicate filters.

Methods for Determining Filter Hold-up Volume

Hold-up volume of Millipak® Final Fill 200 filters containing Durapore® 0.22 µm membrane was determined after different methods of filter draining or blow-down. Hold-up volume was the difference in filter weight after draining or blow-down and the dry weight of the filters (with no fittings).

Hold-up volume following draining by gravity was determined by filling the upstream and downstream sides of the filter with water, then opening the outlet and allowing liquid upstream and downstream of the filter to drain. The hold-up volume following inlet blow-down was determined by connecting an air source to the inlet of prewetted filters and applying pressure to 70 psig for one minute, 20 psi above the membrane's bubble point specification. Blow-down through the AMPP was performed in two ways: the first involved connecting an automated Integritest® instrument to the AMPP with tubing and running a pressure hold routine (70 psig for 1 minute), similar to the inlet blow-down described above. The second involved using an automated Integritest® instrument to increase pressure to the membrane bubble point of ≥50 psi.

Importantly, using the AMPP, rather than the filter inlet to perform blow-down offers advantages. Firstly, the automated Integritest® instrument can be directly connected to the AMPP, eliminating the need to switch to a controlled pressurized gas source which streamlines integrity testing and product recovery. Secondly, using the AMPP reduces the number of connections and removes the need for a tee connector and clamp, minimizing contamination risks while simplifying operations.

Conclusions

Our results demonstrate that the aseptic multi-purpose port on Millipak® Final Fill capsule filters protects the aseptic flow path and maintains a barrier to the environment, even after multiple actuations. Leveraging this protection, an automated Integritest® instrument tester can be connected to this port to simplify both integrity testing, especially PUPSIT, and product recovery while minimizing the risk of introducing microbial contaminants into the flow path.

References:

1. FDA. Guidance for Industry Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice. 2004; http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070342.pdf.
2. European Commission. EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. 2008; http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm,
3. European Agency for the Evaluation of Medicinal Products. Note for Guidance on Manufacture of the Finished Dosage Form. 1996; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002916.pdf.
4. Improve Product Recovery Using Blow-down and Millipak® Final Fill Filters. Lit No. MS_TB4382EN

MilliporeSigma
400 Summit Drive
Burlington, MA 01803

To Place an Order or Receive Technical Assistance

Please visit **EMDMillipore.com/contactPS**

For additional information, please visit **EMDMillipore.com**

Lit. No. MS_TN4709EN Ver. 1.0
2019-25248
12/2019