Millipore®
Preparation, Separation,
Filtration & Monitoring Products

Technical Brief

How Millipak® Barrier and Millidisk® Barrier Filters Streamline Final Sterile Filtration

Introduction

In pharma and biopharma manufacturing, final sterile filtration is the focus of extensive regulatory interest. Regulatory guidelines recommend that critical filters used for the sterilization of liquids in aseptic processing should be flushed, pre-conditioned, integrity tested, and dried before product filtration.

Executing these operations in either single use or stainless-steel systems involves wetting and drying multiple filters and must be performed without compromising system sterility. As Millipak® Barrier and Millidisk® Barrier filters contain both hydrophilic and hydrophobic sterilizing-grade 0.22 µm Durapore® membranes, they allow passage of both liquid and air, and simplify wetting and drying in steam-sterilized, autoclaved or gamma-irradiated systems.

The purpose of this Tech Note is to highlight the benefits of Millipak® Barrier and Millidisk® Barrier filters in final filtration operations and provide practical guidance for implementation.

Streamlined Operations

Final filtration can be performed in either stainless steel or single use systems, with system designs tailored to the needs of individual manufacturers, **Figure 1**. Irrespective of the design, before processing, manufacturers of medicinal products need to sterilize the system, confirm filter integrity and dry the system before processing product. These steps need to be performed without compromising sterility. Millipak® Barrier and Millidisk® Barrier filters provide a simple solution.

Millipak® Barrier and Millidisk® Barrier filters contain both hydrophilic and hydrophobic sterilizing-grade Durapore 0.22 µm membranes and enable passage of both liquid and air in a single filter. These filters can simplify final filtration operations and streamline system design, **Table 1**.

Table 1. Summary of Benefits of Millipak® Barrier and Millidisk® Barrier filters for Streamlined Filtration Operations

System flushing and filter wetting

Before processing, extractables from the system components need to be flushed from the system. Millipak® Barrier and Millidisk® Barrier filters maintain sterility as flushed liquids flow directly to the drain.

Filters sometimes fail pre-use integrity tests, prompting retesting. Millipak® Barrier and Millidisk® Barrier filters simplify repeat integrity retests without increasing the assembly footprint.

Filter integrity testing

For integrity testing, the system needs to be wet with water then dried with air. By allowing passage of both air and water, these filters effectively vent the system, thus simplifying system design and reducing the number of filters.

System drying and maintaining sterility

As Millipak® Barrier and Millidisk® Barrier filters contain sterilizing-grade Durapore® 0.22 µm membrane, they can be used downstream of the product filter to maintain a sterile boundary around critical sterilizing filters following pre-use integrity testing, system drying and during product processing.

Figure 1. Single-Use Redundant Filtration (SURF) Assembly

System Design Considerations

System Flushing and Filter Wetting

System flushing and filter wetting with water for injection (WFI) are part of preparing the filtration line for processing. Extractables from system components and filter element are flushed, minimizing the risk to the product.

Insufficient filter wetting is a frequent root cause of integrity test failures and, as filter wetting requires large volumes of WFI, the system should be designed with sufficient capacity to collect wetting fluid from both the initial test and potential retests. If the re-wetting volume is limited, an end-user may discard an integral filter that has marginally failed due to improper wetting.

Implementation of Millipak® Barrier and Millidisk® Barrier filters into the assembly design simplifies flushing and filter wetting while avoiding the volume constraints and increased footprint of oversized flush bags and cans. Flushed liquid can pass through these filters and flow directly to the drain.

Using wetting medium other than WFI

Compatibility and intrusion pressure/wettability for the hydrophobic filter within the Millipak® Barrier and Millidisk® Barrier filters should be verified before use. If the hydrophobic membrane in the filters is wet, it may reduce the filter's breathability, leading to increased pressure drop across the filter assembly during integrity testing or product filter blow down. Chemical compatibility information is summarized in the filter's supporting documentation.

Confirming breathability of Millipak® Barrier and Millidisk® Barrier filters during flushing/wetting

The dryness of the hydrophobic layers in the Millipak® Barrier and Millidisk® Barrier filters following flushing/wetting can be verified with low pressure bubble stream test. This requires disconnecting the filter from the assembly and determining the gas flow rate level at 100 mbar (1.5 psi) pressure and comparing it to the nominal flow rate level of a new unit wetted optimally at low pressure for 5 min. Flow rates in the 30%-100% range are characteristic.

Filter Integrity Testing

Integrity testing of critical sterilizing filters reduces processing risk and provides assurance that the filter has the expected microbial retention properties. Integrity tests should be performed before and after processing, **Figure 2**.

To mitigate the risk of a critical sterilizing filter failing an integrity test, FDA guidance recommends redundant filtration[1]. Redundant filtration systems contain a secondary sterilizing filter connected in series to the primary sterilizing filter. Each filter must be capable of being integrity tested independently in compliance with relevant guidance expectations, and filtration systems should be designed to accommodate this [1,2,3].

Interference in product filter integrity test

As Millipak® Barrier or Millidisk® Barrier filters are downstream of the product filter(s) they should not interfere with integrity testing. For confirmation, the product filter(s) can be integrity tested with and without the Millipak® Barrier or Millidisk® Barrier filters in place. The integrity test results should fall within 70 mbar for a bubble point test and 5% for diffusion flow test, the recommended test for large systems.

To simulate 'worst case' scenario Millipak® Barrier or Millidisk® Barrier filter can be fully wet (WFI at 3 bar) to compromise the filter's breathability before performing the filter integrity test.

Integrity testing the Millipak® Barrier and Millidisk® Barrier filters

For critical product applications Millipak® Barrier and Millidisk® Barrier filters should be integrity tested offline with IPA 70/30% in water before product filtration. They can be wet with dynamic flushing or static soak of 15 minutes. The bubble point specification at 23 ºC is ≥ 1280 mbar (18.5 psi).

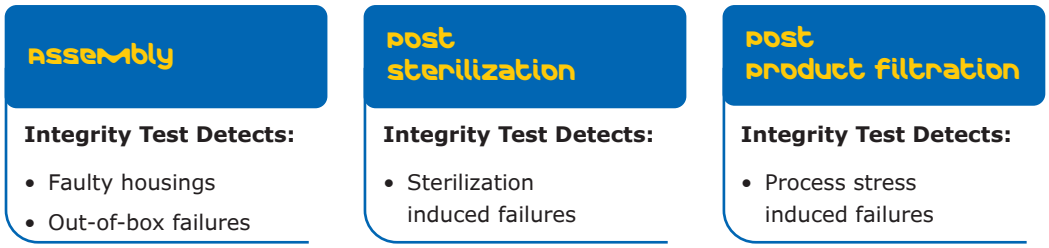


Figure 2. Product filter integrity tests

System Drying and Maintaining Sterility

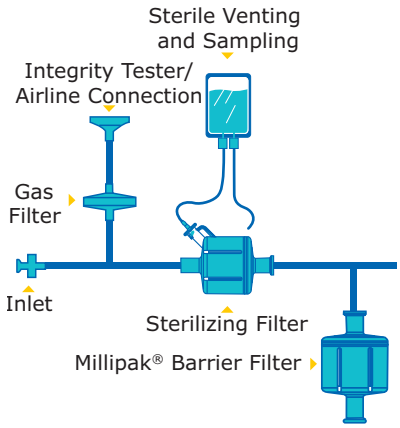
After Pre-Use Post Sterilization Integrity Testing (PUPSIT), the system should be dried to minimize product dilution or contact with wetting liquid before product filtration. Current industry practice involves blowing down the filtration system with air.

Exact drying times for each system should be verified by weight and visual checks. Applied pressure should not exceed the maximum allowable pressure of the 'weakest link' in the system. In addition, the system should be designed to minimize air flow restrictions through fittings, connectors, tubing or piping.

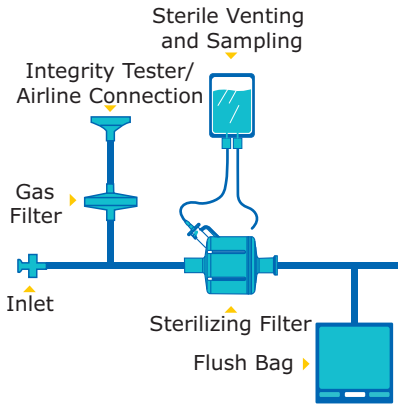
There are different approaches to maintaining sterility downstream the product filter during and after PUPSIT. **Table 2** summarizes these options.

Table 2. Options for creating sterile boundary downstream of the sterilizing product filter.

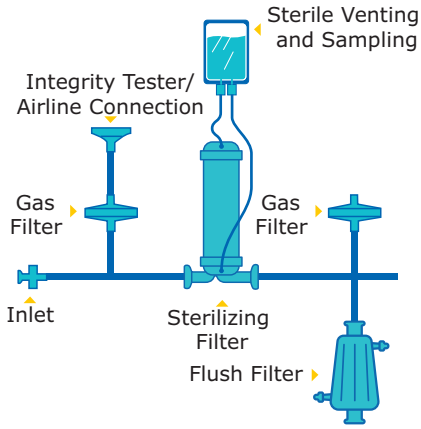
Barrier Filters



Flush Bag

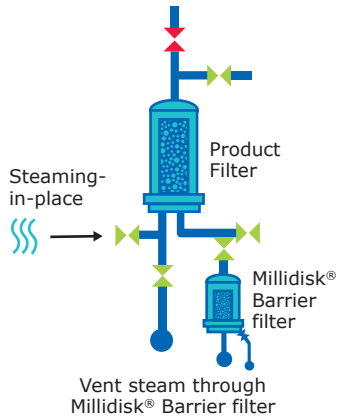
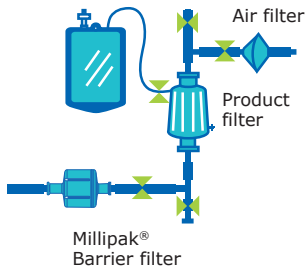
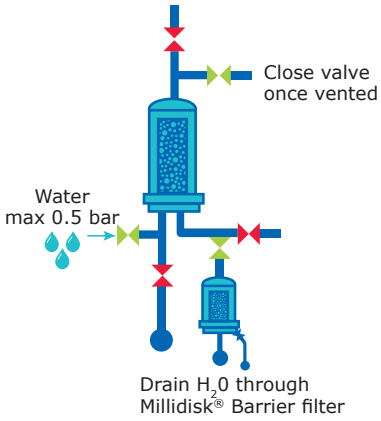
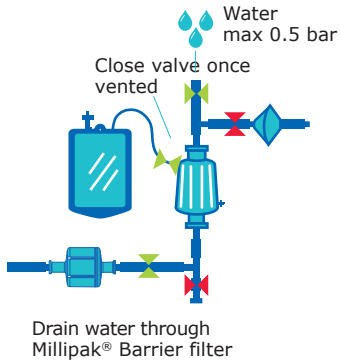
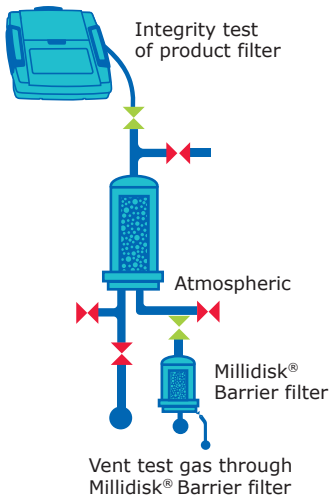
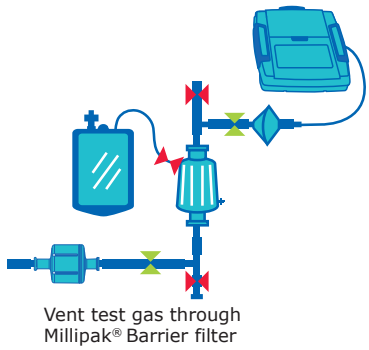


Downstream Filters

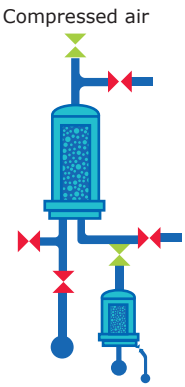
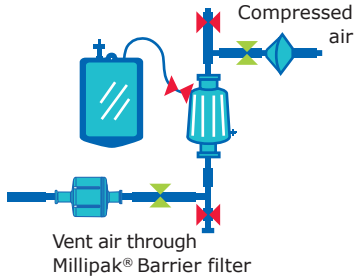
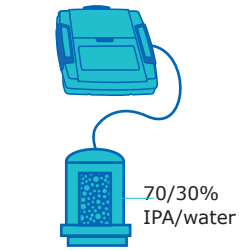
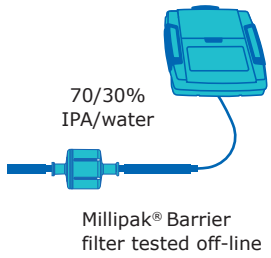
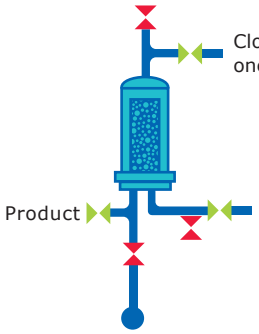
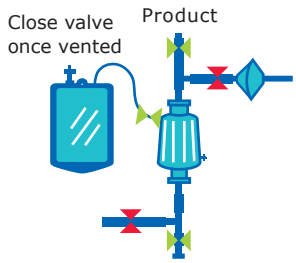


	Millipak® Barrier Filter	Flush Bag	Downstream Filters
Ability to Retest	✓	×	✓
Ability to Dry the Product Filter	✓	×	✓
Simple Design	✓	✓	×

Product Filter Preparation from Sterilization to Product Processing

Product filter preparation steps for steamable line		Product filter preparation steps for single-use assemblies
Sterilized by SIP 	**Sterilizing** Sterilize the filtration system by Steaming-in-place (SIP) (Left), or autoclaving/gamma-irradiation (single–use) (Right). During SIP, the Millidisk® Barrier filter drain valve is open. Condensate, steam and air will go through the filter into the drain. When the cycle ends, the drain valve is closed. The system is cooled down by applying compressed gas to maintain a positive pressure in the filtration system and maintain its sterility.	Sterilized by autoclaving or gamma-irradiated as part of an assembly 
	**Wetting** The product filter needs to be wet with water for the integrity test. This step also flushes away extractables from the sterilized product filter. To prepare the filter train independently, the isolation valve to the downstream equipment is closed. Water is directed to the drains through the Millidisk® Barrier or Millpak® Barrier filter. Enhanced wetting with increased applied pressure drop through the product filter can be implemented by isolating the flow path to the Millidisk® Barrier or Millipak® Barrier filters.	
	**Testing** Perform PUPSIT either by diffusion or bubble point determination (depending on the product filter). In all cases, pressurized gas is applied on the upstream side of the product filter, which is isolated from the upstream or downstream filtration system elements. Only the drain line with the the Millidisk® Barrier or Millipak® Barrier filter is open to allow the free flow of test gas.	

Open Valve Closed Valve

Product filter preparation steps for steamable line		Product filter preparation steps for single-use assemblies
	**Drying** Before introducing product in the line, the product filter is typically blown down/dried to avoid diluting product with WFI. The gas is vented through the Millidisk® Barrier or Millipak® Barrier filter.	
	**Millidisk® Barrier or Millipak® Barrier Filter Testing** The Milllidisk® Barrier or Millipak® Barrier filters are integrity tested offline under 70/30% IPA/water wetted conditions.	
	**Process** Once the integrity of the Millidisk® Barrier or Millipak® Barrier filters is confirmed, the system is ready to filter product.	

Open Valve Closed Valve

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1. Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice. U.S. Department of Health and Human Services Food and Drug Administration. September 2004
2. EudraLex. The Rules Governing Medicinal Products in the European Union. Volume 4. EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. Annex 1. Manufacture of Sterile Medicinal Products. EUROPEAN COMMISSION. Brussels, 25 November 2008
3. https://www.pda.org/pda-letter-portal/home/full-article/the-use-of-scientific-data-to-assess-and-control-risks-associated-with-sterilizing-filtration

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