Preparation of Redundant, Disposable Filtration Systems

Wetting, Integrity Testing, and Drying

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Disposable filtration systems eliminate the need for end users to conduct (and validate) clean-in-place or sterilization steps. Such systems are increasing in use and in design complexity for pharmaceutical processes. Redundant disposable filtration systems are of interest because end users are including two sterilizing-grade filter housings or capsules in series to meet regulatory expectations or process objectives. Disposable systems are prepared similarly to cartridges-in-steel systems and must be able to handle the same pressures and operating steps that will be used before product filtration.

Redundant sterilizing-grade filters can provide an extra margin of safety for final filtration. They are often considered for high-value products and those that cannot be reprocessed. Such filters are useful when filtration takes longer than eight hours and when the first filter in series functions as a prefiltration step to reduce the particulate load and increase efficiency of the final filter.

Redundant filtration also can be implemented as part of an integrity testing strategy, validating each filter individually as the sterilizing step. Postprocessing, if one filter fails the integrity test, the backup is tested. If the backup filter passes the same integrity test, that filtration step can be considered successful.

An increase in use of redundant filtration to address bioburden issues is related to a statement in EMEA

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European Directive 81-852-EEC, *Manufacture of the Finished Dosage Form*, which indicates that not more than 10 colony-forming units (cfu)/100 mL will be acceptable for a bioburden load on a final filter (**1**). However, redundant filtration should not be considered the solution for a high bioburden load. That should be addressed by eliminating the root cause rather than simply filtering it out. This philosophy is supported in the FDA's 2004 guidance for sterile drug products produced by aseptic processing (**2**). It states that the use of redundant filters should be considered and process controls designed to minimize a product's bioburden before filtration.

Using disposable systems for pharmaceutical production eliminates conducting and validating clean-in-place or sterilization steps because systems arrive presterilized and are disposed of postproduction. Nevertheless, such filters must be prepared similarly to those in cartridge-in-steel systems and handle the same pressures used for integrity testing.

Here we describe a method for preparing redundant disposable filters and demonstrate application of filter preparation steps normally executed with cartridges-in-steel. Disposable filters can withstand the prolonged high operating pressures required for compressed air drying (filter blow-down) and integrity testing. They can also remove integrity test gas and flush/wetting liquid when used with a combination hydrophilic/hydrophobic barrier filter to prevent contamination downstream.

Preparation

To describe the steps for preparing a disposable redundant filtration system, we discuss the functionality of a hydrophilic/hydrophobic Millipak barrier filter used with an Opticap XLT redundant disposable filtration system (both from Millipore, www.millipore.com).

The preparatory steps are similar to those for a cartridge-in-steel system. However, unlike a cartridge-in-steel system with valves, disposable system components are isolated by clamping tubing segments using high-pressure tubing clamps.

Preparation for a Preuse Integrity Test: To eliminate false integrity failures, cartridge filters must be wetted thoroughly. In a redundant system, wetting is most efficient when performed sequentially. In this

operation, the first filter housing in a series is isolated from the second housing by placing a high-pressure tubing clamp on the tubing between them. The first housing is slowly filled with the integrity test wetting agent (water or other validated liquid) while entrapped air is vented at the high-point housing bleed. Air is purged from the high-point bleed until a steady flow of liquid with no gas bubbles is observed (Figure 1).

Next, the high-point bleed on the first housing is closed, the hydrophobic–hydrophilic barrier filter is isolated downstream of the second housing, and the line between the filter housings is opened. The second filter is then filled with the wetting agent. Entrapped air is vented through the hydrophobic vent filter on top of the second housing. That vent filter prevents ingress of contaminated room air into the area between the first and second filters (Figure 2). Once liquid is observed in the tubing below the hydrophobic vent filter, the line is isolated using a high-pressure tubing clamp.

Once both filter housings are purged of entrapped air, the line between the second filter and the barrier filter is opened. At this point, the line to the receiving vessel is still closed. The flow is adjusted to deliver approximately 1 Lpm/ft^2 (liter-per-minute per square foot) of membrane surface area for five minutes. Because the barrier filter contains both 0.22-µm sterilizing-grade hydrophobic and hydrophilic membrane areas, the wetting agent and entrapped air can exit the system aseptically without using a flush collection bag or vessel. The line between the first filter and the second filter housing is clamped and held for a minimum of one minute to dissipate residual gas in the system. The line is then unclamped, and the wetting agent is allowed to flow through the system for approximately five minutes (Figure 3).

Preuse Integrity Test

The strategy for preuse integrity testing depends on how a system was validated for use. If a single filter housing was validated as the sterilizing step, then only one of the two housings in a redundant system needs to be tested. If both filters were validated together as the sterilizing step, the procedure is likely to require testing both filters. This section describes testing both filters using an automatic integrity tester. Such testers are preferred because they use upstream measurements, eliminating the risk of downstream contamination inherent with manual integrity-test methods.

Figure 1: Air is purged from the high-point bleed until a steady flow of liquid with no gas bubbles is observed.

Figure 2: Hydrophobic vent filter prevents ingress of contaminated room air into the area between the first and second filter.

Figure 3: The wetting agent flows through the system for about five minutes .

Both user safety and accuracy of test results rely on assuring that filter housings, tubing, connectors, and clamps will withstand required pressures. Integrity tests can subject a system to pressures upward of 90 psig. Tubing rupture could injure users. Flexible tubing on the upstream side could expand during the test, resulting in a false integrity-test failure. If that occurs, the automatic tester would detect a change in upstream volume from the tubing expansion and produce a failing result.

After filter wetting, the T-line inlet to the first filter is isolated by a high-pressure tubing clamp. The line between the first and the second filter housing is opened. The vent filter upstream of the second filter housing and the line to the barrier filter downstream of the second filter housing are opened (Figure 4). When the first filter is integrity tested, residual wetting agent will flow through the second filter and exit through the barrier filter. Because the second filter is fully wetted, bulk gas flow from the first filter integrity test exits through the vent filter on the second filter housing. That bulk gas will not discharge the wetting agent from the pores of the second filter unless pressure exceeds the minimum bubble point of the second filter.

After the first filter is integrity tested, the line between the first and second filter housings is isolated with a high-pressure tubing clamp. The automatic integrity tester line is attached to the vent filter outlet on the second filter housing (Figure 5). Because the vent filter is hydrophobic, its pores will be devoid of wetting agent (assuming it is an aqueous-based wetting agent) and will offer no resistance to air flow during the automatic test. During the test, residual wetting agent in the system passes through the second filter and exits through the barrier filter. Bulk gas also passes through the second filter (again assuming an aqueous-based high surface tension wetting agent).

Figure 4: The vent filter upstream of the second filter housing and the line to the barrier filter downstream of the second filter housing are opened.

Figure 5: The automatic integrity tester line is attached to the vent filter outlet on the second filter housing.

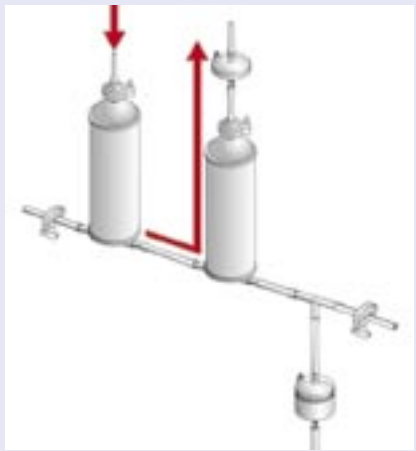

Figure 6: The process continues until differential pressure of the first filter decreases to at least 5 psid; bulk gas flow will be observed through the vent filter upstream of the second filter housing dome.

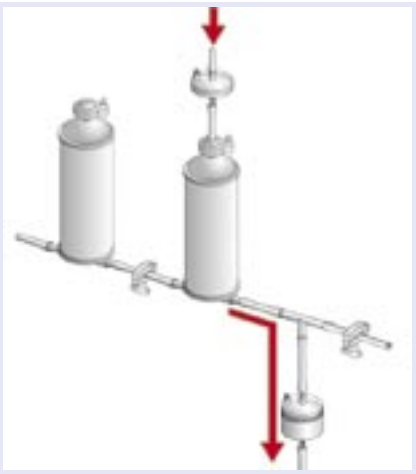

Figure 7: Once the differential pressure on the second filter decreases to at least 5 psid, the system is ready for product filtration.

Once the integrity test is complete, the system is ready for product filtration or for filter drying, if that is required.

Filter Drying

End users sometimes require filter drying. An example is pharmaceutical preparations that are immiscible in water. Another example is when users are concerned about product dilution. A filter-drying step can significantly reduce the amount of residual wetting agent within a filtration system. That drying step, however, can add considerable time to a preparatory process and may be unnecessary.

The line between the first and second filter housings is opened. Then compressed air is introduced to the first filter housing either at its T-line inlet or through the housing dome inlet. The pressure is set at a minimum of 10 psig above the highest bubble point value for the two filters. The process continues until differential pressure of the first filter decreases to at least 5 psid (Figure 6). This step can take from 15 minutes to several hours depending on the pore rating of the membrane filter, the surface area, and the set pressure. Bulk gas flow will be observed through the vent filter upstream of the second filter housing dome.

After the differential pressure on the first filter decreases to at least 5 psid, a system is depressurized. The compressed gas line is transferred to the vent filter on the second filter housing, and the process is repeated. In this case the bulk gas flow is observed from the barrier filter downstream of the second filter housing. Once the differential pressure on the second filter decreases to at least 5 psid, the system is ready for product filtration (Figure 7).

Integrity Testing of the Vent Filter and the Barrier Filter: The hydrophobic vent filter and the hydrophilic/hydrophobic barrier filters can be bubble-point integrity-tested off-line using an isopropanol and water solution with nitrogen as the test gas.

Efficiently Redundant

Filter preparation steps normally executed with cartridges-in-steel can be applied to Opticap XLT redundant disposable filtration systems with Millipak barrier filters. These systems can withstand the prolonged high operating pressures required for filter blow-down and integrity testing. The high-pressure clamps, disposable compression fittings, and braided flexible silicone used in this study withstand pressures in excess of 90 psig without leaking or bursting.

Using a barrier filter allows for exhausting test gas and removing a wetting agent from a system from the production line port. It also eliminates the need for a flush bag or collection vessel.

References

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2 US Food and Drug Administration. *Sterile Drug Products Produced By Aseptic Processing — Current Good Manufacturing Practices* (Guidance for Industry). September 2004; www.fda.gov/cber/gdlns/steraseptic.pdf.

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