Understanding Sterile Filtration and Importance of Prefiltration

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Introduction

Sterile filtration may be a common laboratory activity, but it is a critical part of many workflows. If done improperly it may not prevent, and may even introduce contamination downstream. Today's research requires the sterile filtration of a wide range of fluids across many applications. These fluids typically contain a variety of large solids and particles that should be removed first to improve performance of the final sterile membrane.

Sterile filter manufacturers provide an array of membrane medias in a wide range of pore sizes, dimensions, surface areas, and material of construction to meet researcher's needs, such as chemical compatibility, productivity, throughput and quality. In addition, pre-filtration has become an important step to improve sterile filtration performance. Different sterile filters often have different claims and all claims need to be validated. With so many options and claims to choose from, It can be difficult for a user to select the best sterile and prefiltration solution.

This brief provides explanation of the importance of sterile filtration and how sterile filters are validated by the manufacturer. In addition it outlines the process and value of selecting the best prefilter to improve final sterile filtration performance.

Sterile Filtration Testing: The Performance Promise

When laboratory filter manufacturers produce membranes for sterile filtration they must conduct bacterial challenge tests to meet the FDA definition of sterility. Manufacturers conduct validation testing to the U.S. Food and Drug Administration (FDA) standards per modified ASTM F838, (Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration). FDA Guidelines on Sterile Products Produced by Aseptic Processing (1987) defines a liquid sterilizing grade filter as follows:

"A sterilizing filter is one which, when challenged with the microorganism *Pseudomonas diminuta** at a minimum concentration of 10^7 organisms per cm^2 of filter surface will produce a sterile effluent."

"The microorganism *Brevundimonas diminuta* (ATCC 19146) when properly grown, harvested and used, is a common challenge microorganism for 0.2 µm rated filters because of its small size (0.3 µm mean diameter)."

**Today reclassified as Brevundimonas diminuta (ATCC 19146)*

***FDA Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing Current Good Manufacturing Practice (Section IX. Validation of Aseptic Processing and Sterilization), 2004*

**** Liquid challenge is performed to ASTM F838-83 standards or comparable methodology*

A typical filter sterility test workflow will consist of a known concentration of solution containing a minimum concentration of 10^7 organisms per cm^2 of effective filter surface of *B. diminuta* upstream, the 0.2 µm pore size sterile filter membrane to test, and a recovery membrane downstream. The recovery membrane should be equal to the size of the tested filter membrane to capture anything that potentially passes through the membrane test filter. A sterile effluent claim can be made only when zero *B. diminuta* colonies are recovered on the recovery membrane.

Prefiltration: Removing the Rocks and Pebbles Before Filtering the Sand

Final membrane filtration, such as sterile filtration, should not be used to remove solids as its capacities are limited. Instead, final sterile filters should be used to provide a sterile effluent. In most cases, a 1% solid load is too much for efficient final membrane filtration. The question becomes how can we improve throughput through a sterilizing-grade membrane if our solution has a high solid load or various particle size?

One very effective method is to prefilter the solution. Prefiltration creates a multistage filtration train. Consider a river that has big rocks, pebbles, and sand. If we want to filter the river water, we would take the rocks out in our first filtration stage. The pebbles would be removed in the second stage, and the sand would be filtered in the third stage. Only then our river water would be solid-free.

The final sterilizing-grade filter is not designed to filter the rocks or pebbles out of a laboratory solution. Its purpose is to remove the sand (microorganisms). Putting a fluid with large particles or cell debris through a sterile filter will quickly clog it and produce little throughput. By employing different prefiltration stages, the particulate load can be distributed across the prefiltration media, allowing the final membrane filter to efficiently produce a sterile effluent.

In the laboratory, the user doesn't always understand the nature of the fluid being filtered. For example, a lab technician might filter a clear solution through an unprotected sterile filter, yet only recover a few drops of fluid or quickly clog the device. The human eye can only see particles greater than 40 microns, anything smaller is invisible. What appeared to be a clear fluid to the lab technician may actually contain a high concentration of suspended solids that restrict throughput and clog the final membrane.

Testing and Selecting the Best Prefiltration

The first step in prefiltration is to identify the particle size distribution and the total suspended solids in the solution. Then the throughput (volume) of fluid needed to pass through the membrane filter must be determined. Once the two factors are established, one can determine specific prefiltration media to achieve optimal throughput. A properly selected and sized prefilter can increase throughput volume by 2-6X.

There are ways to measure particulate volume in a fluid. A particle-size distribution analysis is a popular method, another method is a spin test where a certain volume of fluid is placed in a centrifuge tube and the solid is spun out and measured. Finally, a total suspended solid test can be performed using drawdown volume of fluid through a membrane.

Prefilters come in a variety of media types, propylene and cellulose-based prefilters are the most popular. Selection of the optimal media is related to the solid load and particle size distribution in the fluid to be filtered. For example, let's consider a fluid that contains a large amount of cell debris. Typically, we would choose a cellulose-based depth prefilter because its media thickness will create a tortuous path that entraps many particles. Alternatively polypropylene prefilters are available with graded pore-sizes which means the pore size on the outer filter layer is larger than the inner layer. This construction design traps the larger particles on the outer layer and the smaller particles within the inner layer.

Our experience has shown that if the fluid has a high concentration of particulates, cellulose-based prefilters tend to outperform polypropylene products. But when the particulate count and total suspended solids are low, polypropylene media is a generally the best prefilter choice.

Both polypropylene and cellulose media come in a variety of pore sizes, retention ratings, and surface areas. It is recommended that a filterability study is conducted with prefilter selection. In a filterability study, a performance baseline is established by using an unprotected final membrane filter first. Followed by the testing of one, two or more prefilters to determine which configuration achieves the desired throughput. When running prefilter trials, it's important to keep constant control of the flow rate and monitor the pressure upstream and downstream of the filters.

If requested, the filter manufacturer can perform filterability studies and particulate size and load studies on behalf of the end-user. Additionally, the manufacturer can provide guidance to the end-user on how to best choose, run, and handle prefilters. Many times, by analyzing the fluid, manufacturers have a good idea which prefiltration products should be applied. A collaboration can help optimize and improve the efficiency of a workflow and offer time savings in the filtration process. The manufacturer's goal is to ensure that users have the proper procedures and guidelines to create a complete filter train that optimizes their research.

Filtration from the Lab to Manufacturing

When selecting optimal sterile and prefiltration membranes it is wise to keep the end goal in mind. If the workflow will eventually scale up to manufacturing or a tech transfer, considerable time and work can be saved by planning ahead. In this scenario the desired filter products should be researched to ensure they are available in the sizes to fit future needs and the support resources are available to aid in this selection.

Conclusion

Selecting the appropriate prefilter and final filter can be a complicated process. Prefiltration is required to optimize throughput through a final membrane filter and provide a sterile effluent. The user should test the solid load and particulate size in the solution. Fluids processed in many biopharmaceutical research labs contain large particles and suspended solid loads that quickly clog a final membrane filter. Appropriate prefilter and final filter leads to throughput, efficiency and performance.

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