Development of a Prefiltration Membrane Technology: Integral Multiple-Zone LifeASSURE™ PLA Series Filter Cartridges

3M

Abstract

This paper describes the development of a microporous membrane structure optimized to extend the service life of sterilizing grade final membrane filters. A unique membrane casting technique has been developed resulting in a membrane structure with multiple, contiguous zones of varying pore size. The porosity of each zone can be independently controlled to produce a membrane structure optimized for a given feed contaminant profile. The unique membrane structure results in a filter which provides high flow rates, high bioburden retention and exceptional contaminant capacity.

The multi-zone membrane can be pleated into an exceptionally high area to volume configuration while maintaining ability to be integrity tested by users. The performance of this membrane is compared to existing conventional isotropic and asymmetric membranes with respect to water flow rate, contaminant capacity and bioburden reduction capability with *Brevundimonas diminuta.*

Introduction

Sterile filtration is ubiquitous and many of the products of the food, beverage, pharmaceutical and biopharmaceutical industries depend upon the total reduction of pathogenic and spoilage organisms by such filtration. Typically, sterile filtration is provided by pleated microporous phase inversion polymer membrane filter cartridges. A number of manufacturers produce such "final" filter cartridges and the sterilizing performance, quality and reliability of these filter cartridges are excellent. Typically such cartridges are subjected to 100 percent "integrity" testing, by both the manufacturer and user, to verify that each individual cartridge meets the criteria established by the qualification or validation process to verify that the cartridge is capable of providing a sterile filtrate (absolute filtration) under the operating conditions.

Unfortunately, this very necessary but narrow focus on "absolute filtration" leaves the filter manufacturer little room in the way of options to improve the cost effectiveness of such sterilizing final filters in these applications. The need to improve user economics has driven the development of a whole class of filter cartridges called "prefilters". In difficult applications these prefilters may, themselves, require prefilters. It is not uncommon to see applications where whole trains of very expensive filter assemblies are lined up in series in an attempt to improve the process throughput and economics.

3M Purification Inc. developed a microporous membrane process that allows us to produce integral, multiple-zone membranes with each zone having its own precisely and independently controlled pore size. We have determined that such membrane, in developed high area pleated cartridge construction, can provide the users of final sterilizing membrane cartridges with a level of prefiltration performance and cost effectiveness that obsoletes currently available prefilters. The ability to independently control zone pore size further offers us the opportunity to provide integral multiple-zone membranes optimized for specific applications and contaminant size distribution.

In applying the multi-zone membrane process, development was driven by the following prefilter requirements:

- It must have particle reduction efficiency (beta ratio or LRV) that is sufficient to significantly reduce the contaminant loading to which the final filter is exposed. This will help maximize service life of the final filter.
- It must have sufficient contaminant capacity to handle the imposed contaminant loading while maintaining a throughput between replacements adequate to reduce the overall filtration cost to the user.
- It should be capable of undergoing and passing a non-destructive test to verify functional integrity sufficient to provide that it will provide the prefiltration efficiency required to help protect the final cartridge.
- It should be capable of withstanding repeated thermal processing intended to sanitize (hot water) or sterilize (steam).
- It should be constructed of materials fully compliant with pharmaceutical and food and beverage service applications.

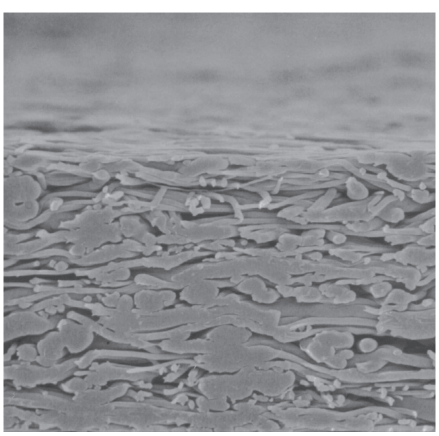

Figure 1. Scanning Electron Micrograph (SEM) of a typical polypropylene depth filter.

Review of Currently Existing Membrane Structures

Currently available prefilters to final sterilizing filters fall into three broad classes: depth or fibrous filters, asymmetric membrane filters and isotropic membrane filters.

Figure 1 shows the membrane structure formed by melt extruded polypropylene fibers. The ability of the filter to reduce contaminants is a function of the fiber diameter, packing density and thickness. In order to reduce submicron contaminants, it is not possible to produce fibers fine enough to create a sufficient number of submicron pores. In an attempt to reduce the effective pore size of such filters, the fibrous structure is tightly interwoven and calendered. Calendering is a process by which the fibrous structure is compressed to reduce the amount of open area to in turn reduce effective membrane pore size. This process, while effective in reducing pore size, also results in reducing contaminant holding capacity and hence results in shortened filter life. In addition, the flow characteristics of such filters are significantly lower than more open structures.

The development of phase inversion cast polymeric membranes allowed production of filters with pore sizes capable of removing submicron particles. These filters have pore structures with significant open area (voids) to hold contaminants, yet are fine enough to reduce the submicron particles that block downstream sterilizing membrane filters. Figure 2 shows a typical single zone isotropic membrane prefilter. Isotopic refers to the uniform pore size distribution throughout the thickness of the membrane. Because this type of filter has a uniform pore structure, particles are often trapped near the upper membrane surface and the rest of the membrane remains relatively open. The layer of trapped contaminant is unable to fully penetrate the membrane and becomes compacted, impeding further flow requiring the membrane to be replaced. Because the full open membrane area is not utilized, these membranes are not efficient in contaminant capacity. In addition, the uniform membrane structure does not allow particles of varying size to be trapped within the structure, hence these membranes cannot be optimized to accommodate the wide size distribution of particles typically encountered in biological fluids.

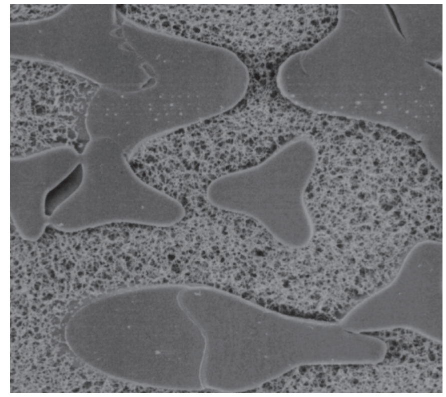

Figure 2. SEM of single zone isotropic membrane.

In an attempt to address the inefficient contaminant capacity and uniform pore size of isotropic membranes, a class of filters with asymmetric membrane structures were developed.

Asymmetric membranes have a relatively open structure and a thin, smaller pore size “skinned” surface structure. The open structure is typically oriented upstream, while the skinned surface is oriented downstream. The purpose of the open structure is to allow contaminants to become trapped, while the skinned structure controls particle size retention. Controlling pore size distribution of asymmetric membranes is inherently difficult due to the pore forming process. There is often a relatively wide pore size difference between the open and “rated pore size controlling” regions. This disparity can result in a mismatch of particle size retention zones such that small particles easily penetrate through to the tighter zone, resulting in membrane blocking. Further, because the pore size-controlling zone is very thin, imperfections in the membrane forming process can compromise membrane integrity. While imperfections or “open pore micro-environments” exist in isotropic membranes, particle retention efficiency is often not compromised due to the tortuous pore pathway of these membranes.

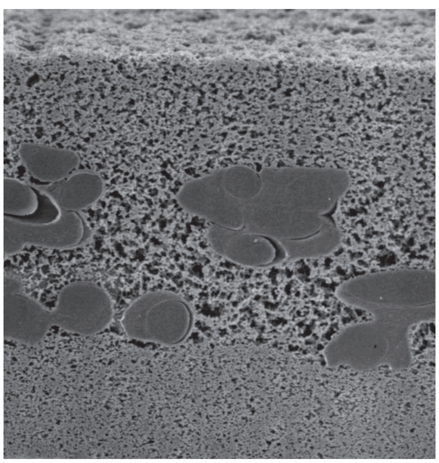

Figure 3. LifeASSURE™ PLA series integral multi-zone microporous membrane.

Development of Integral Multi-Zone Microporous Membrane Structure

Development of an optimized prefilter membrane required attributes of both isotropic and asymmetric membranes. The result was a multi-zone integral membrane structure. This unique structure is shown in Figure 3.

The scanning electron micrograph shows a structure with distinct, yet integral pore size zones. Using this membrane casting process, up to three distinct pore size zones can be configured in a single integral membrane layer. Further, the pore size distribution of any and all zones can be essentially infinitely varied to match a given contaminant size distribution range. In this way, each zone can provide effective prefiltration to the successive integral “downstream” zones. Particle size retention efficiency is maintained, because each zone is relatively thick compared to the thin “pore size controlling” zone of asymmetric membranes. Because multi-zone membrane structure can be formed integrally, a single membrane layer can be used to provide both effective submicron particle reduction and efficient contaminant holding capacity. The use of a single membrane layer allows further optimization in fabricating cartridges, as Advanced Pleat Technology can be used to provide high effective prefiltration area.

Multi-zone Microporous Membrane Characterization

Well accepted methods of characterizing membrane pore structure are the “bubble point” and “diffusive flow” techniques. The bubble point method involves filling the pores of a microporous membrane with a fluid, typically water or alcohol, followed by pressurizing the wetted membrane with compressed air in the upstream to downstream direction. When the pressure is gradually increased, a critical pressure will be reached where the fluid is forced out of the largest filter pores and free air flow results. The critical pressure at which the fluid is expelled and free air flow is initiated is called the bubble point. The bubble point is a measure of the largest pores within the membrane structure. For a perfectly wetted membrane, the bubble point pressure follows the relationship:

$$BP = \frac{k \gamma \cos \theta}{D}$$

Equation 1.

Where:

- BP = critical bubble point
- k = constant
- γ = wetting fluid surface tension
- $\cos \theta$ = contact angle of wetting
- D = pore diameter

According to this relationship the bubble point is inversely proportional to membrane pore diameter.

A second membrane characterization technique is the diffusive flow test. As with the bubble point test, the diffusive flow test involves pressurizing a wetted membrane. At the applied pressure, air flow is continuously measured on the downstream membrane side or filter outlet. At pressures below the bubble point, air on the upstream membrane surface will diffuse across the membrane and this diffusive air flow can be quantitatively measured. For most microporous membrane structures, the diffusive air flow slightly and gradually increases as the upstream pressure is increased. The measured diffusive air flow is a function of several factors including membrane pore size, thickness and contact angle of the wetting fluid with the membrane. The amount of diffusive air flow is directly proportional to membrane pore diameter and inversely proportional to membrane thickness.

The principles of the bubble point and forward-flow tests were used to characterize multi-zone microporous membranes. Figure 4 shows the forward flow profile and bubble point for a 0.2 micron rated multi-zone microporous membrane cartridge wetted with 60/40 v/v isopropyl alcohol. With the more "open" zone structure in the upstream orientation, a distinct increase in forward flow can be noted at approximately 8 psig, followed by a relatively flat flow profile until bulk air flow is obtained at approximately 13 psig. The increase in forward flow at 8 psig is a result of pores dispelling fluid from the more open upstream membrane region. A continuation into bulk flow or bubble point, however, is not immediately observed as fluid within the "tighter" downstream membrane zone remains within the filter pores. Above 13 psig, the wetting fluid is completely expelled and bulk air flow results.

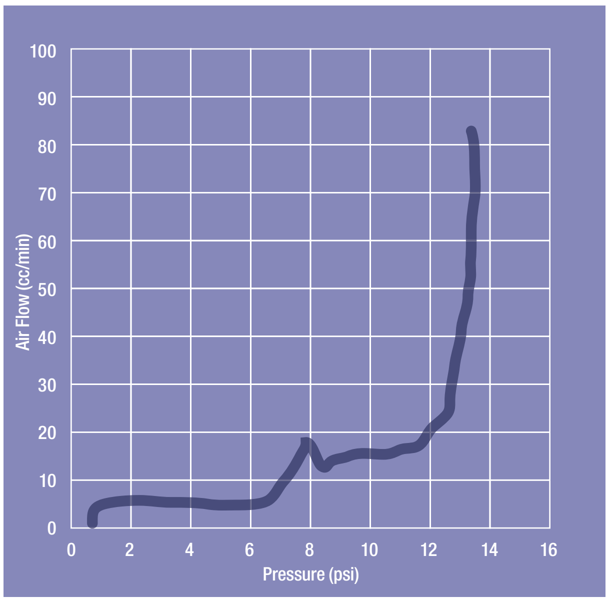

Figure 4. Forward flow bubble point wet in 60/40 IPA/H_2O.

The use of sensitive diffusive flow measurement techniques allow for the independent measurement and control of the different porosity zones within a single membrane structure.

The bubble point and diffusive flow measurements are shown to be effective in characterizing the multi-zone microporous membrane structure. These techniques are useful in development of various membrane structures and in quality control of the manufacturing process. Further, these measurement techniques can be employed by users to verify membrane pore size and integrity during use. The ability to test membranes in a non-destructive manner allows users to verify the assembled filter cartridge remains integral, that the desired pore size membrane is installed and that protection to a downstream sterilizing membrane will be maintained.

Multi-zone Microporous Membrane Optimization

The ability to create and characterize multi-zone membranes has been demonstrated. Using these capabilities membranes with different porosity upstream zones and a defined porosity downstream zone were formulated and evaluated for contaminant capacity. The test contaminant consisted of a mixture of a 1.6% concentration of complex carbohydrate and 0.014% concentration of kaolin clay. The contaminant system was used to challenge test filers at an ingression rate of 300 ml/minute plus filtered water at a total challenge flow rate of 2.5 gallons per minute (gpm) per ten-inch filter element. The throughput of contaminant solution was recorded at differential pressures ranging from 0.5 psid to 25 psid above initial pressure.

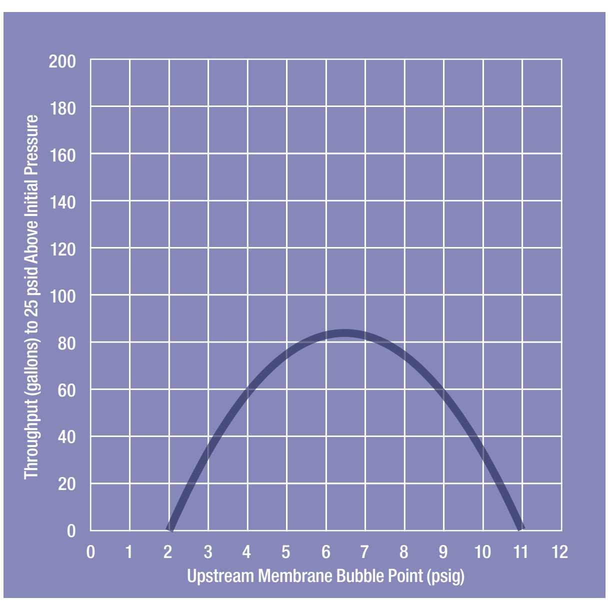

Figure 5. LifeASSURE™ PLA series multi-zone microporous membrane optimization.

Figure 5 shows results of capacity as a function of varying bubble point upstream membrane zones while maintaining a constant 0.2 micron rated downstream zone. The lower bubble point indicates a more open upstream zone and conversely, a higher bubble point indicates a tighter upstream membrane zone. Contaminant capacity is noted to decrease if the upstream zone is either too tight or too coarse as determined by the bubble point value for the upstream membrane zone. Based on the contaminant solution, an optimum capacity membrane system consists of an upstream zone with a bubble point of approximately 6.5 psig, alcohol wet. Inherent in these results is that the multi-zone microporous membrane technology allows for optimization of membrane structure for a given contaminant system.

In addition to contaminant capacity, an effective prefilter must adequately extend the service life of downstream membrane filters. In order to evaluate prefiltration efficiency, the ability of multi-zone microporous membrane to extend the service life of a downstream 0.2 micron rated membrane was determined. The 0.2 micron rated membrane was challenged with the test contaminant system described above, with and without the multi-zone microporous membrane upstream. The results are shown in Figure 6.

The unprotected downstream 0.2 micron membrane is represented by the solid line. Differential pressure across the unprotected membrane is observed to rapidly increase with contaminant added. After approximately 38 grams of added contaminant, the membrane service life is essentially complete.

The dashed line represents the same 0.2 micron rated downstream membrane protected, or with the multi-zone microporous membrane installed upstream. The results show little to no increase in differential pressure across the 0.2 micron rated downstream membrane as contaminant added is increased up to greater than 200 grams, when the test was terminated. During this second test, the pressure differential across the prefilter multi-zone microporous membrane was also measured. The results show effective service life of the prefilter to be approximately 220 grams added contaminant.

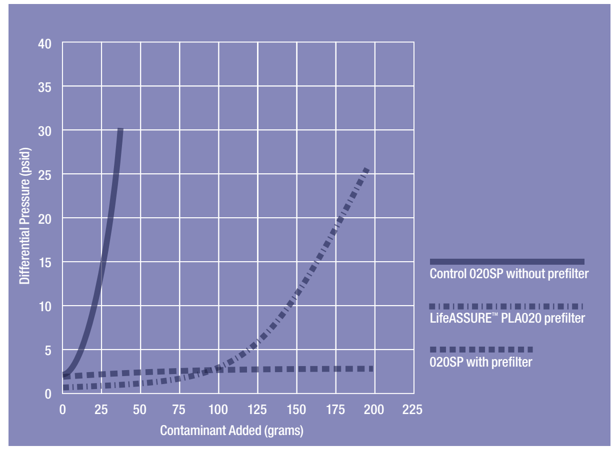

Figure 6. LifeASSURE PLA series multi-zone microporous membrane prefiltration efficiency.

In this example, the prefilter membrane is providing essentially complete protection of the downstream membrane. In this situation, the prefilter can be replaced while allowing the downstream filter to remain in service. In some instances, such as batch filtration where all filters must be replaced after each filtration campaign to avoid batch to batch contamination, it may be desirable for the prefilter and final filter to plug at equal rates. This allows full utilization of all filters and may be the most economical filtration system design. By optimizing the prefilter selection by controlling the integral membrane zones as described above, the desired filtration performance can be obtained and selected for use.

Comparative Performance Characteristics of Multi-zone Microporous Membrane and Conventional Prefilter Membranes

Water Flow Capacity

The relative performance of LifeASSURE™ PLA series multi-zone microporous membrane was compared to conventional prefilters commonly used by pharmaceutical and food and beverage manufacturers. Performance criteria used to compare prefilters were water flow capacity, contaminant holding capacity and bioburden reduction capability.

Water flow capacity is measured by comparing clean water flow as a function of differential pressure across the filter device. This characteristic is important in determining installed filter area required and can also be a predictor of contaminant capacity. In general it is best to design filtration systems with an initial clean differential pressure of less than 2 or 3 psid. Sizing in this manner allows for increase in differential pressure as contaminant is reduced from feed streams and is energy efficient, as most fluid supply systems require positive displacement pumps. The comparative water flow capacities of several LifeASSURE PLA series multi-zone microporous membrane grades and Pall Corporation and Millipore Corporation prefilter cartridges is shown in Figure 7.

Manufacturer	Grade Designation	Specific Pressure Drop (gpm/psid)	Relative Flow Capacity (Pall HDC=1)
Pall Corporation	HDC® II J006	0.75	1
Millipore Corporation	Milligard® CWSS	1.6	2.1
3M Purification Inc.	LifeASSURE™ PLA series PLA020	2.5	3.3
3M Purification Inc.	LifeASSURE™ PLA series PLA045	4.5	6
3M Purification Inc.	LifeASSURE™ PLA series PLA065	6.0	8
3M Purification Inc.	LifeASSURE™ PLA series PLA080	7.5	10

Figure 7. Comparative water flow capacities of selected prefilter cartridges.

The results of water flow versus pressure differential testing show the highest resistance or specific pressure differential for Pall HDC II AB1J0063H4 filters followed by Millipore Milligard CWSS01S03 followed by 3M Purification LifeASSURE PLA series multi-zone microporous membrane filter cartridges ranging in pore size rating from 0.2 micron to 0.8 micron.

The relatively low pressure differential to flow ratio for LifeASSURE PLA series prefilters translates to high liquid flow capacity. Maximum flow capacity of LifeASSURE PLA series membrane filters is accomplished by combining the multi-zone microporous membrane structure with a unique membrane pleating technique, termed Advanced Pleat Technology. Advanced Pleat Technology allows effective membrane surface area per cartridge to be increased up to 50% over conventional filter cartridge pleating technologies.

Contaminant Holding Capacity

Flow capacity is a significant factor for prefiltration as it can be predictive of contaminant capacity and impacts installation size, or number of prefilters required for a given application. Filters which provide high initial flow rates often have increased contaminant capacity. Factors such as contaminant type and membrane structure also affect contaminant capacity. The relatively low initial differential pressure allows for particulate and colloidal contaminants to be retained while the available margin for increase in pressure differential remains high. In addition, a low pressure differential provides protection against compaction of trapped contaminants on the membrane surface. Contaminant compaction, sometimes referred to as gel layer compaction or membrane polarization, can result in irreversible and premature fouling of membranes. Thus, by providing high flow capacity, LifeASSURE™ PLA series prefilters maximize contaminant holding capacity. The ability of various LifeASSURE PLA series membranes to retain contaminants is shown in Figure 8.

The contaminant used in these studies was the complex carbohydrate used in the previous membrane efficiency studies. The results show that contaminant holding capacity increases as pore size of the various LifeASSURE PLA series membranes increase. This result reflects the increase in open area due to larger pore size for the LifeASSURE PLA series membranes.

In order to evaluate the contaminant holding capacity of LifeASSURE PLA series and commonly used competitive prefilter membranes, the relative contaminant capacity for the complex carbohydrate solution was conducted. The results are shown in Figure 9.

The results show that LifeASSURE PLA series 0.45 and 0.2 micron rated membranes have the highest contaminant capacity followed by Millipore CWSS and Pall HDC II. These results follow the water flow capacity previously shown in Figure 8 and demonstrate the performance advantage achieved with LifeASSURE PLA series filters combining multi-zone microporous membrane and Advanced Pleat Technology.

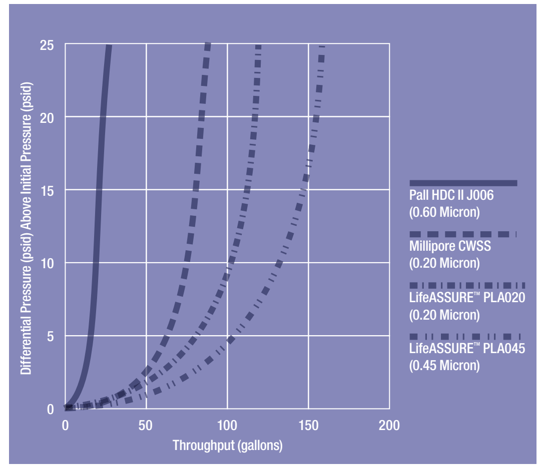

Figure 8. Contaminant capacity of LifeASSURE™ PLA series multi-zone microporous prefilter membranes.

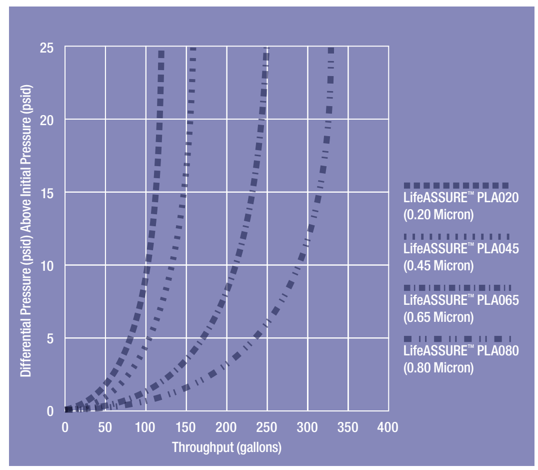

Figure 9. Contaminant capacity of LifeASSURE™ PLA series multi-zone microporous membranes and competitive prefilter membranes.

Bioburden Reduction Capacity

In addition to contaminant capacity a prefilter must also be efficient in extending the service life of downstream filters and effectively reduce small contaminants. To evaluate the efficiency of submicron filters, bacteria retention studies are often performed. Bacteria retention studies are not only extremely sensitive indicators of efficiency, they also address a primary need in pharmaceutical and food and beverage filtration applications namely, bioburden control. Bacteria retention studies were conducted using the test system shown in Figure 10.

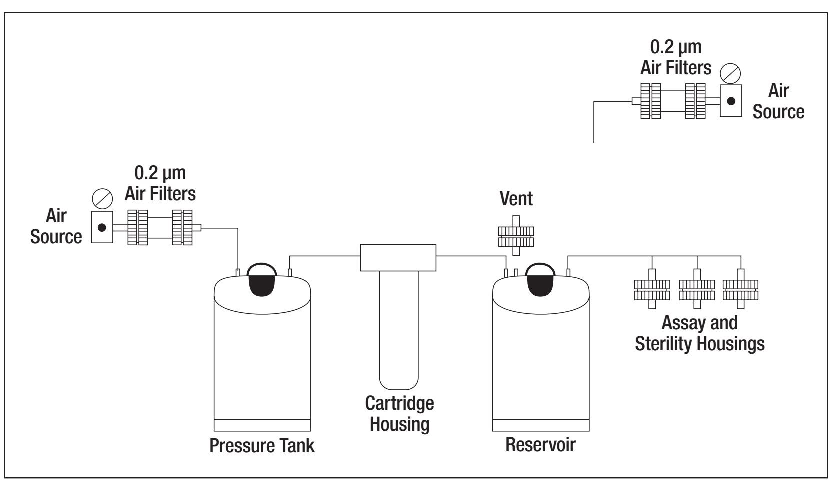

Figure 10. Bacteria retention test system.

Bacteria retention testing of submicron filters has been well described. Essentially, a monodisperse solution of a known bacteria is used to challenge the test filter. The test filter effluent is monitored by passage through an analysis membrane filter disc which is subsequently incubated for enumeration of bacterial colonies. A comparison of the number of influent bacteria to the effluent bacteria is made. The comparison is often expressed logarithmically according to the formula:

Where: LRV = Log Reduction Value

$$LRV = \log_{10}\left[\frac{\text{Number of Influent Bacteria}}{\text{Number of Effluent Bacteria}}\right]$$

Equation 2.

The log reduction value of LifeASSURE™ PLA series and several competitor prefilters, using *B. diminuta* as the test organism, is shown in Figure 11.

Filter Tested (micron)	Average LRV
LifeASSURE™ PLA series 0.2	7.3
LifeASSURE™ PLA series 0.45	3.5
Millipore Milligard® CWSS 0.2	4.45
Millipore Milligard® CWSC 0.45	2.56
Pall HDC II J006 0.6	0.41

Figure 11. Comparative Log Reduction Values (LRV) with *B. diminuta*.

The LRV values obtained for LifeASSURE PLA series 0.2 micron rated prefilters ranged from 5.93 to 8.0 with *B. diminuta*. For LifeASSURE PLA series 0.45 micron rated prefilters the LRV values for *B. diminuta* ranged from 3.22 to 4.69. Two Millipore Milligard® CWSS filters were tested and found to have LRV values for *B. diminuta* of 4.0 and 4.9. One Pall HDC® II J006 filter was tested and found to have an LRV for *B. diminuta* of 0.41.

These data indicate the relative efficiencies of the filters tested for their ability to retain *B. diminuta* and thus, their ability to reduce bioburden. The microbial retention efficiency is also an indication of their particulate reduction efficiency. The LifeASSURE PLA series 0.2 micron rated prefilter is shown to have the highest efficiency, while the LifeASSURE PLA series 0.45 micron rated prefilter and the Millipore Milligard CWSS filter had average LRV values of 3.5 and 4.45, respectively. The Pall HDC filter showed the lowest LRV or bioburden capability. The ability to reduce bioburden is an extremely important criteria of filter selection as referenced in the PDA Technical Report 26, “Sterilizing Filtration of Liquids” in that filters with the highest bioburden capacity should be used.

Conclusion and Summary

This paper has presented the development of a class of membrane prefilters. LifeASSURE PLA series filters are the result of combining multi-zone microporous membrane structure with Advanced Pleat Technology.

The most important aspect of this development is the ability to produce membrane filters with high bioburden capacity while retaining high contaminant capacity and flow characteristics. Both Current Good Manufacturing Practice (CGMP) and PDA Technical Report 26, “Sterilizing Filtration of Liquids” state that filters which provide high bioburden reduction capability should be used in pharmaceutical applications such as aseptic processing and other critical applications.

The bioburden reduction capacity of LifeASSURE PLA series prefilters was shown in retention studies using *B. diminuta* as the challenge organism. For 0.2 micron rated LifeASSURE PLA series prefilters, the average log reduction value (LRV) obtained was 7.3 logs. This compared to 4.45 log LRV for Millipore CWSS prefilters and 0.41 log LRV for Pall HDC II prefilters.

While some filters, such as final sterilizing grade filters, will provide high bioburden reduction capacity, these filters often have limited service life due to limited contaminant holding capacity. It is for this reason that prefilters able to extend the service life of final filters are required. As shown in this study, LifeASSURE PLA series prefilters have contaminant capacity higher than competitive prefilters, by a factor of up to 4 times. The high contaminant capacity of LifeASSURE PLA series prefilters is obtained without sacrificing bioburden retention capability.

The water flow characteristics of LifeASSURE PLA series prefilters was also evaluated. An inverse relationship of pore size rating to water flow pressure drop was demonstrated, as expected. LifeASSURE PLA series prefilter flow capacity was compared to competitive prefilters and was found to be higher for similarly rated filters. Water flow rate versus pressure differential is an important criterion for sizing filter assemblies. For most pharmaceutical and food and beverage applications an initial pressure differential of less than 2-3 psid is desirable to allow long on-stream filter life and efficient pump packages. Thus, for a given process flow rate, filters with high flow capacity mean that fewer overall filters may be required and initial filtration capital cost as well as operating costs will be lower.

The ability to produce a prefilter with high bioburden reduction and without sacrificing contaminant and water flow capacities is due to the combined use of multi-zone microporous membrane construction and Advanced Pleat Technology. By producing distinct, contiguous isotropic membrane zones rather than a continuous asymmetric zone or a single pore size isotropic membrane zone, the attributes of LifeASSURE PLA series membranes are obtained.

Inherent in the multi-zone microporous membrane process is the ability to produce a membrane structure optimized for a given contaminant size distribution profile. LifeASSURE PLA series membranes offer users the ability to obtain filter cartridges for their specific process requirements.

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3M Purification Inc.
400 Research Parkway
Meriden, CT 06450, U.S.A.
Tel (800) 243-6894
(203) 237-5541
Fax (203) 630-4530
www.3Mpurification.com

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