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Bioprocess, Biologicals, & Pharmaceutical

CUNO Application Brief
LifeASSURE® Prefilters Used Upstream of SterASSURE™ Final Filters

Prefilter - Final Filter Optimization: Consideration of Maximizing Flow Capacities and Minimizing Extractables

Introduction

Nylon membrane sterilizing grade filters have been used for many years by the pharmaceutical industry with excellent results. These filtration systems often use prefilters constructed from a different material, typically cellulose ester or polypropylene, than the final nylon membrane filter. This has been due primarily to the fact that prefilter and final filters were generally developed independently of one another. Recently, concern with extractables in filter systems has become a significant issue. One way to minimize concerns about extractables is to use as few materials of construction as possible in filter systems. An additional concern that is often expressed regarding minimization of filter assemblies is that it is generally preferable to use fewer filters in an operation to minimize cost as well as exposure to filter materials.

This Application Brief presents the advantages, listed below, of using CUNO LifeASSURE multi-zone nylon prefilters upstream of CUNO SterASSURE multi-zone nylon sterilizing grade final filters.

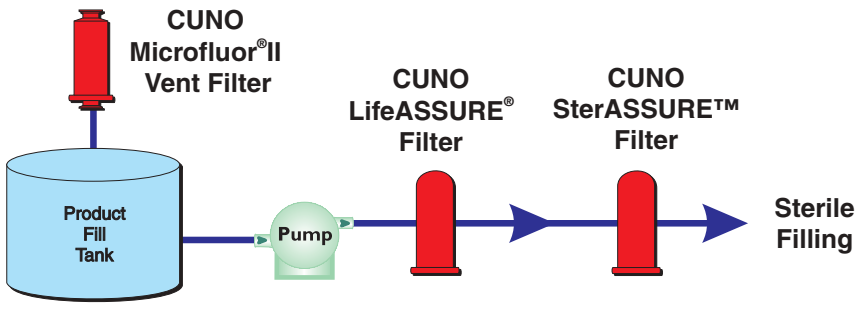
- Use of LifeASSURE prefilters ensures compliance with Parenteral Drug Association (PDA) Technical Report 26, “Sterilizing Filtration of Liquids”, which states that “bioburden should be kept as low as possible at each stage of the process”.
- Use of LifeASSURE nylon prefilters upstream of SterASSURE nylon final filters consolidates materials of filter membrane construction to a single type.
- Validation is simplified as LifeASSURE nylon prefilters and SterASSURE nylon final filters contain the same membrane material and hardware components.
- LifeASSURE prefilters and SterASSURE final filters offer superior flow, contaminant capacity and bioburden reduction capacity when compared to conventional prefilters.

In addition to allowing consolidation of materials of construction, LifeASSURE filters offer superior performance to most commonly used prefilters. LifeASSURE filters provide longer service life, higher flow rates and higher bacterial retention than alternative prefilters. LifeASSURE prefilters can also be tested to ensure they are integral and will provide consistent performance and protection of the downstream SterASSURE final filter.

The Process

Figure 1 represents a typical sterile filling process. Featured are the prefilter and final sterilizing filters used prior to final product filling or packaging. Depending on the complexity of the product formulation and filling process, many additional filters may be required.

Figure 1. Sterile Filling Process



The Problem

Extractables are associated with all types of prefilters and final sterilizing filters and can be soluble materials or they can be particulate matter. Typically extractables are measured by soaking filters in water followed by boiling down the water and weighing the solid residue remaining. The solid residue is referred to as "non volatile gravimetric extractables". Although there are no published limits for allowable levels of extractables in parenteral solutions, particulate levels are limited by USP standards. The need to minimize extractables and particulates is a goal of all aseptic filling filtration systems.

In addition to minimizing the type and level of extractables and particulates, prefilters must also be efficient in reducing bioburden, provide high flow rates and extend the life of the final sterilizing filter. Final filters must be validated for complete retention following American Society of Testing and Materials (ASTM) methodology at a minimum challenge level of 10^7 CFU/cm^2 of filter area.

The CUNO Solution

In many filtration systems, the prefilter and final filter contain different membrane materials which results in multiple sources of extractables. One way to reduce sources of extractables is to utilize prefilters and final filters constructed with like materials. Nylon 6,6 is a commonly used membrane material in final sterilizing filters. CUNO LifeASSURE prefilters and SterASSURE final filters are both constructed with nylon membrane and thus, offer a solution allowing use of prefilters and final filters constructed with like materials.

In addition to reducing extractables, CUNO LifeASSURE prefilters and SterASSURE final filters offer distinct performance advantages. The unique multi-zone structure resulting from CUNO's proprietary membrane forming process called Flex-N, provides LifeASSURE prefilters and SterASSURE final filters with superior flow rates, contaminant capacity and bacteria retention efficiency compared to competitive prefilters used in pharmaceutical filtration systems.

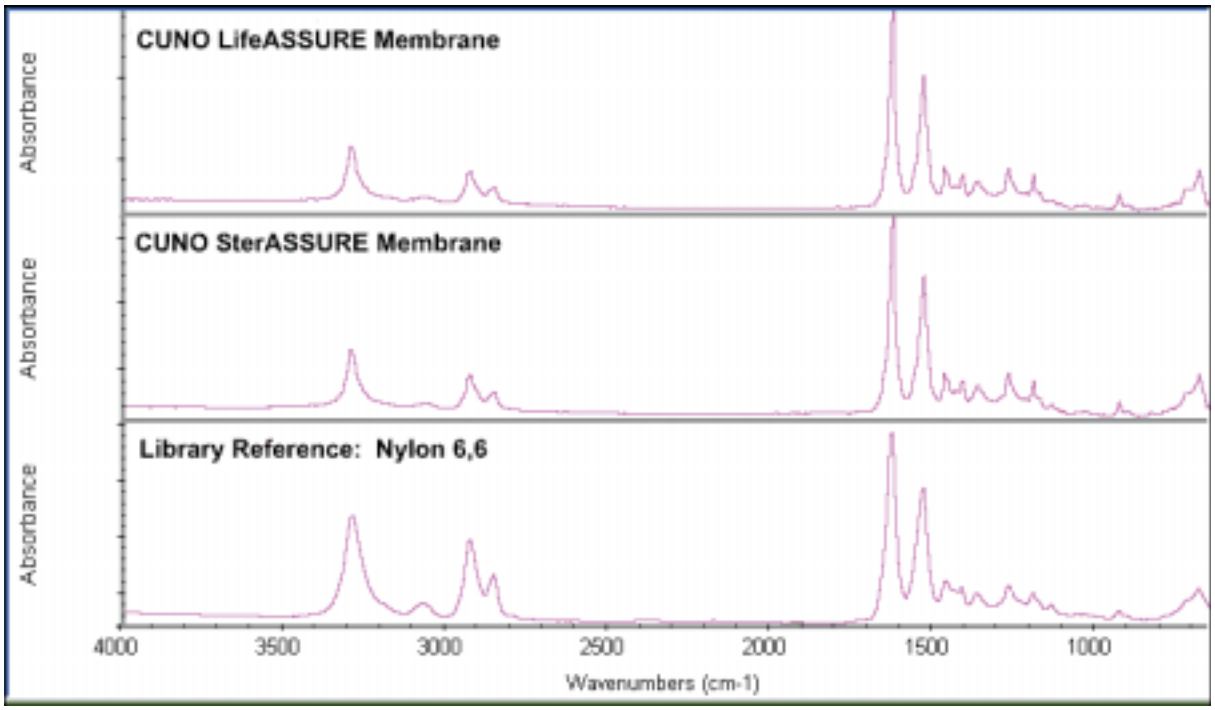
EXTRACTABLES - Comparison of Nylon Membrane From LifeASSURE and SterASSURE Filters

The data presented here demonstrate that the nylon used in CUNO LifeASSURE filters is indistinguishable from the nylon membrane used in CUNO SterASSURE sterilizing filters as determined by Fourier Transform Infrared Spectroscopy (FTIR) analysis. Additionally, where alternative nylon final sterilizing filters are used, this eases validation needs and simplifies changing to CUNO LifeASSURE prefilters.

A CUNO LifeASSURE filter (P/N PLA020) and a CUNO SterASSURE filter (P/N PSA020) were dissected. A portion of the outer cage from each cartridge was cut and carefully removed. A section of the pleat pack was cut and removed from each cartridge. The upstream and downstream support layers were carefully removed from the section of the pleat pack and the membrane was prepared for FTIR analysis to identify the material of construction of the membrane.

The spectra resulting from the FTIR analysis of both cartridges are shown in Figure 2. The results of the FTIR analyses performed on the membranes removed from the CUNO LifeASSURE cartridge and

Figure 2. Comparison of nylon membrane from CUNO LifeASSURE and SterASSURE filter cartridges.



the CUNO SterASSURE cartridge yielded indistinguishable FTIR spectra that are consistent with the FTIR spectrum of Nylon 6,6 from a reference library.

Comparison of Gravimetric Extractables from CUNO LifeASSURE and Millipore Milligard® Filter Cartridges.

The level of extractables is kept to a minimum by using CUNO LifeASSURE prefilters. A comparison between extractables levels of LifeASSURE filters and Millipore Milligard CWSS filters, a commonly used prefilter, is presented in Table 1, which demonstrates that there were substantially lower levels of extractables measured with CUNO LifeASSURE prefilters.

Gravimetric extractables are a measure of non-volatile residues following aqueous extraction of whole filter cartridges. A goal of any filtration system is to contribute as few extractable materials as possible. Autoclaved CUNO LifeASSURE PLA020 0.2 micron rated filter cartridges were extracted in deionized water over a four hour period. At completion of the extraction, the filter was removed and the aqueous extraction fluid was evaporated to dryness. The remaining non-volatile water extractables were weighed. The results are shown in Table 1. Results of gravimetric extractables for the Millipore Milligard CWSS filter were obtained from Millipore literature*. Extractables were determined after 24 hours in ASTM Type 1 reagent-grade water at controlled room temperature. The data show that CUNO LifeASSURE filters have < 12 mg extractables compared to < 50 mg extractables for the Millipore filter.

* Milipore literature CA1000EN00

Table 1. CUNO LifeASSURE and Millipore Milligard Filter Cartridge Gravimetric Extractables Comparison	
Filter	**Gravimetric Extractables**
CUNO LifeASSURE PLA020	< 12 mg
Millipore Milligard CWSS	< 50 mg

CUNO LifeASSURE-SterASSURE PERFORMANCE

Comparison of LifeASSURE-SterASSURE Water Flow Capacity with Selected Prefilter-Final Filter Combinations

The relative water flow rate performance of LifeASSURE prefilter and SterASSURE final filter cartridges was compared to conventional prefilter final filter combinations commonly used by pharmaceutical manufacturers. Water flow rate is measured by comparing clean water flow as a function of differential pressure across the filter device. A system exhibiting a lower initial "clean" pressure drop at a fixed flow rate is desirable since this results in greater system throughput (service life) or the ability to use smaller system assemblies (fewer filter cartridges to provide a given flow rate). The combined pressure drop of 10-inch LifeASSURE/SterASSURE filter systems for a 3 gallon per minute (11.4 lpm) water flow rate is compared to competitive 10-inch filter systems in Table 2.

Sizing in this manner allows for an increase in differential pressure as contaminant is removed from feed streams.

Table 2. Combined Pre-filter/Final Filter Pressure Drop Comparison		
Prefilter	**Final Filter**	**Pressure Drop (psid/mbar)**
CUNO LifeASSURE PLA045	CUNO SterASSURE PSA020	3.5/241
CUNO LifeASSURE PLA020	CUNO SterASSURE PSA020	4.2/290
Millipore Milligard CWSS	Millipore Durapore CVGL	7.25/500
Pall HDC J006	Pall Ultipor NF	7.4/510

The results of water flow versus differential pressure testing show the highest flow at a given pressure drop coming from the CUNO LifeASSURE prefilter, followed by Millipore Milligard CWSS and Pall HDC II J006 filters. The relatively low pressure differential to flow ratio for LifeASSURE prefilters translates to high liquid flow capacity. Maximum flow capacity of the LifeASSURE prefilter is accomplished by combining the Flex-N membrane structure with a unique membrane pleating technique, termed MaxMedia™. MaxMedia pleating technology allows the effective membrane surface area per cartridge to be increased by up to 50% above conventional filter cartridge pleating technologies.

Comparison of LifeASSURE and SterASSURE Contaminant Capacity with Selected Prefilters and Final Filters

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 differential pressure 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 prefilters maximize contaminant holding capacity. In order to evaluate the relative contaminant holding capacity of LifeASSURE prefilters and SterASSURE final filters, along with commonly used competitive prefilter and final filter membranes, further studies with a carbohydrate model solution were conducted in CUNO laboratories. The results are shown in Figures 3 and 4.

The results in Figure 3 show that LifeASSURE 0.45 and 0.2 micron rated prefilters have the highest contaminant capacity followed by Millipore CWSS and Pall HDC II J006. These results follow the water flow capacity previously shown in Table 2 and demonstrate the performance advantage achieved with LifeASSURE filters combining Flex-N membrane and MaxMedia pleating technology. The results in Figure 4 show that SterASSURE final filters have the highest contaminant capacity among final filters tested, including Pall Ultipor NF and Millipore Durapore CVGL. Figure 5 shows the combined effect on contaminant capacity in a prefilter-final filter train. The LifeASSURE 0.8 micron-SterASSURE 0.2 micron filter combination provided a significant contaminant holding capacity advantage (up to 5 time greater) when compared to other filter combinations tested.

Figure 3. Comparison of LifeASSURE Contaminant Capacity with Selected Prefilters

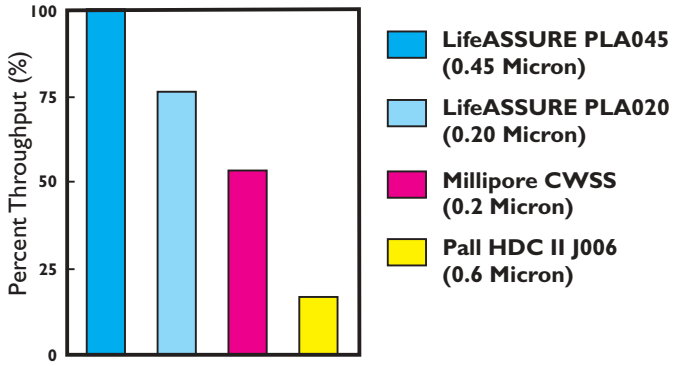


Figure 4. Comparison of SterASSURE Contaminant Capacity with Selected Final filters

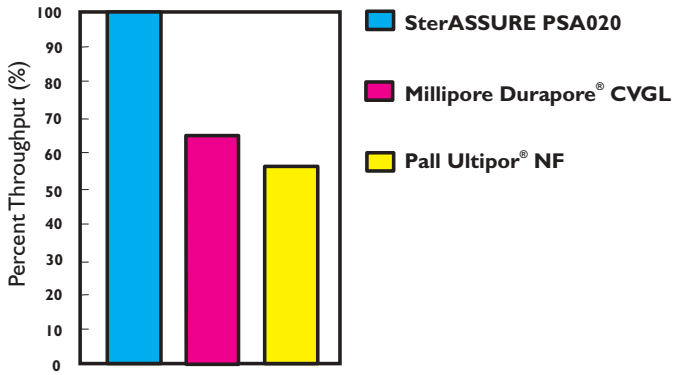
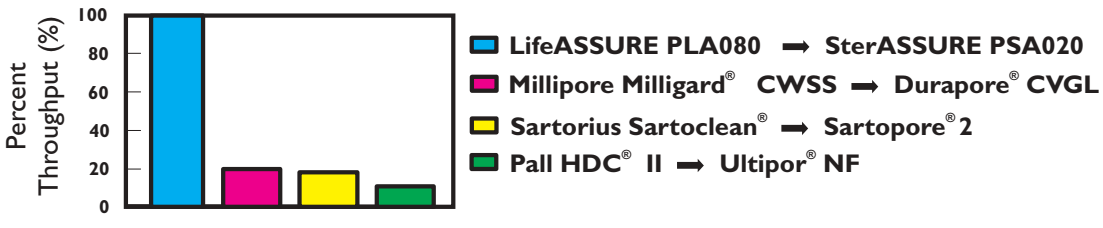


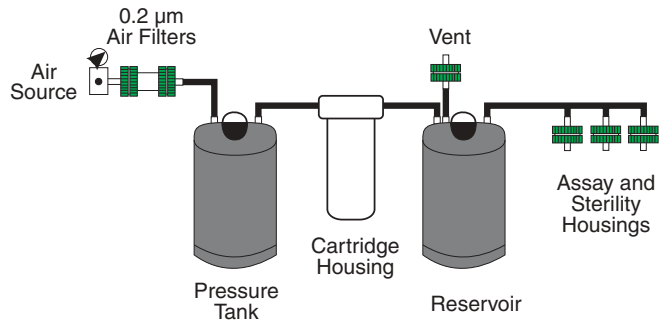
Figure 5. Throughput Comparison of Pre- and Final Filter Combinations



Comparison of LifeASSURE Bacteria Retention with Selected Prefilters

In addition to contaminant capacity, a prefilter must also be efficient in extending the service life of downstream filters by effectively removing small contaminants. To evaluate the efficiency of submicron filters, bacterial retention studies are often performed. Bacterial retention studies are not only extremely sensitive indicators of efficiency, they also address a primary need in pharmaceutical filtration applications, namely, bioburden control. Bacterial retention studies were conducted using the test system shown in Figure 6. Bacterial retention testing of submicron has been well described. Essentially, a monodisperse suspension 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:

Figure 6. Bacteria Retention Test System



The log reduction value of LifeASSURE filter and several competitive prefilters, using *B. diminuta* as the test organism, is shown in Table 3.

$$\text{Log Reduction Value (LRV)} = \text{Log}_{10} \frac{\text{Number of Influent bacteria}}{\text{Number of Effluent bacteria}}$$

Table 3. Comparative Log Reduction Values (LRV) with *B. diminuta*

Filter (retention rating, microns)	Average LRV
CUNO LifeASSURE PLA020 (0.2)	7.3
CUNO LifeASSURE PLA045 (0.45)	3.5
Millipore CWSS (0.2)	4.4
Millipore CWSC (0.45)	2.5
Pall HDC II J006 (0.6)	0.4

The LRV values obtained for LifeASSURE 0.2 micron rated prefilters ranged from 5.9 to 8.0 with *B. diminuta.* For LifeASSURE 0.45 micron rated prefilters the LRV values for *B. diminuta* ranged from 3.2 to 4.6. 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 0.4. 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 removal efficiency. The LifeASSURE 0.2 micron rated prefilter is shown to have the highest efficiency, while the LifeASSURE 0.45 micron rated prefilter and the Millipore CWSS filter had average LRV values of 3.5 and 4.4, respectively. The Pall HDC filter had the lowest LRV or bioburden reduction 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 CUNO Applications Brief describes the benefits of using CUNO LifeASSURE nylon prefilters upstream of CUNO SterASSURE nylon final filters. Due to increasing concerns with filter extractables, a filtration system which uses prefilters and final filters that contain like membrane materials of construction reduces regulatory concerns. In systems which use prefilters that do not contain nylon membrane, validation issues with substituting LifeASSURE prefilters are simplified as the nylon membrane in LifeASSURE is equivalent, based on FTIR analysis, to alternative nylon final filters currently qualified for use.

LifeASSURE prefilters offer superior performance and economic advantages. The high flow rate capacity of LifeASSURE filters allows fewer filters to be used resulting in smaller, more economical assemblies and fewer filters required at change out. LifeASSURE prefilters also have demonstrated advantages in service life over competitive prefilters. The bacterial retention data presented shows that LifeASSURE prefilters remove higher levels of bacteria than competitive filters. This assures compliance with PDA Technical Report 26 which states that filters with the highest bioburden capacity should be used. Taken together, LifeASSURE prefilters and SterASSURE final filters offer eased regulatory compliance and proven performance advantages.

Related Reference Literature

Reference Title/Description	**Literature Identification**
LifeASSURE Product Literature	LITCLAPB
LifeASSURE Regulatory Support File	LITTDRSFLA
LifeASSURE Technical Paper	LITTDRC
SterASSURE Product Literature	LITZRSTR1
SterASSURE Integrity Testing	LITTDSTAINT
SterASSURE Validation Guide	LITVGSTA

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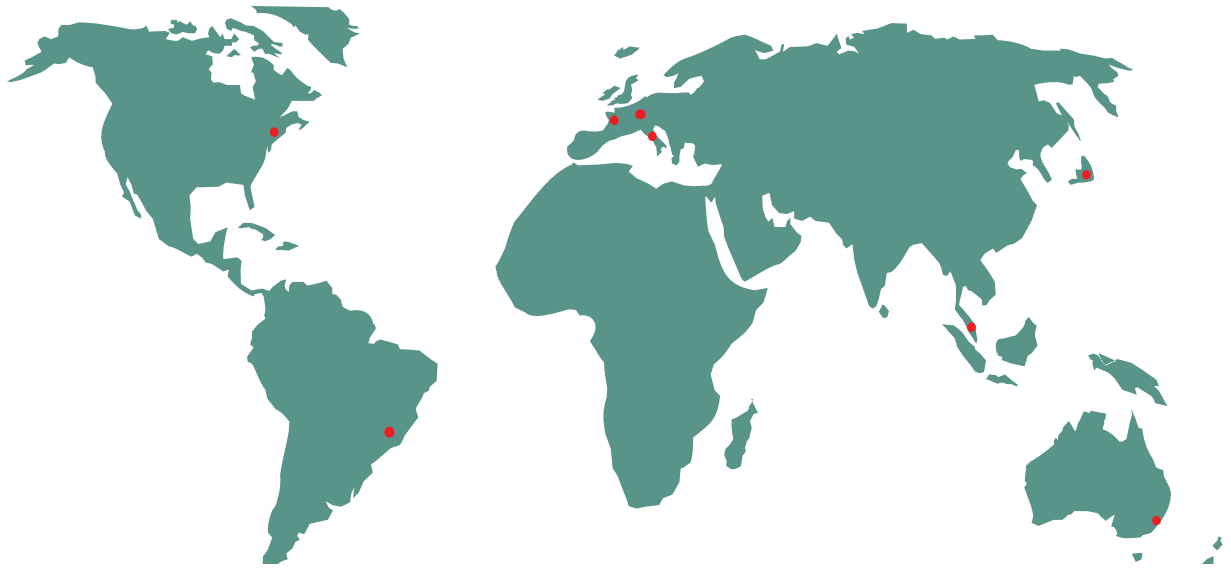

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