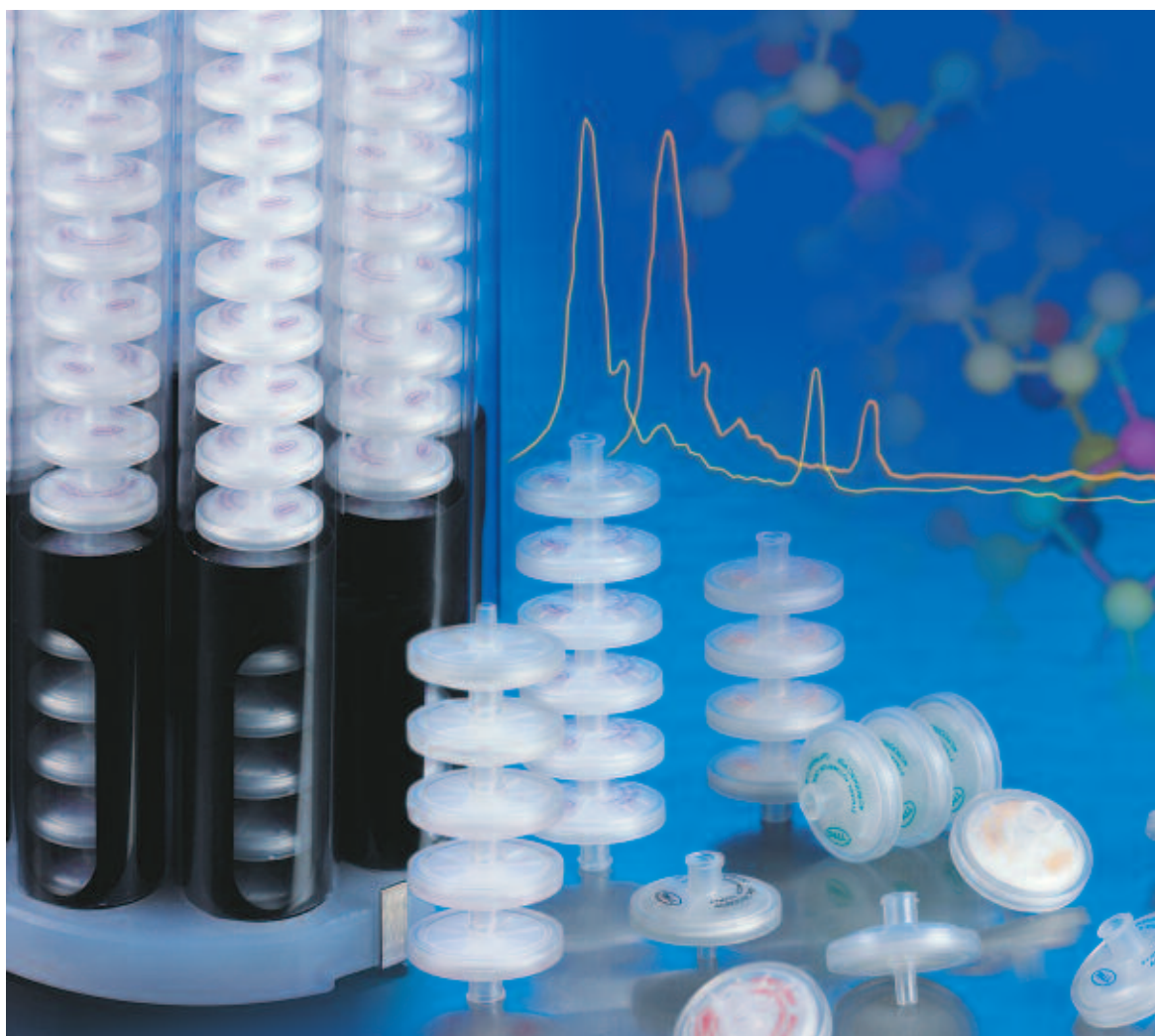




## Use of Acrodisc® Syringe Filters for Analytical Sample Preparation; Including HPLC and Dissolution Testing



### *Analytical Technical Guide For:*

- *Drug Binding*
- *Extractables*
- *Filter Retention Efficiency*

# Introduction

Pall Life Sciences offers a broad range of analytical sample preparation products to protect your analytical instruments and ensure the integrity of your analytical results.

Within this Technical Guide, you'll find Pall quality certifications, performance studies, and useful selection criteria to help you choose the right product for your situation and provide documentation for its use in your lab. This technical guide is also ideal for reviewing filtration requirements and performance criteria with new lab personnel.

This extensive information is designed to move your research forward and help you run a more efficient lab.

We hope you find this tool useful in your lab. For further assistance, contact your local Pall Life Sciences Technical Service department or visit our Web site at [www.pall.com/lab](http://www.pall.com/lab).

The technical guide is divided into several useful sections.

- Pall's product quality assurance and certifications reassure you of our commitment to detail, *pages 1-3*.
- Why filtration is necessary, *pages 4-7*.
- Main considerations for choosing the best filter for your application, *pages 8-10*.
- Improving HPLC column life by as much as 46 times through accurate pore size ratings, *pages 11-13*.
- Minimizing the occurrence of extractables for less chromatographic interference, *pages 16-20*.
- Reducing API (active pharmaceutical ingredients) adsorption, *pages 21-27*.



# Table of Contents

<b>QUALITY ASSURANCE AND CERTIFICATIONS</b>	<b>1</b>	<b>EXTRACTABLES AND MAINTAINING ANALYTICAL INTEGRITY DURING SAMPLE PREPARATION</b>	<b>14</b>
ISO Certification	1	What Are Extractables and Where Do They Come From?	14
HPLC Certification	2	Why Are There so Many Different Acrodisc® Syringe Filter Types?	14
IC Certification	2	When Are Extractables a Concern?	15
Automation Certification	2	How to Avoid Extractables' Detritus Effects?	15
Quality Assurance	3	What Contributes to an Acrodisc Syringe Filter's Quality?	15
<b>NEED FOR FILTRATION</b>	<b>4</b>	What Confidence Can You Have in our HPLC Certification?	15
Solvent Reservoir / Solvent Degassing	4	Experimental and Instrument Conditions	16
Pump	5	PVDF Syringe Tip Filters	16
Injector	5	GHP Hydrophilic Polypropylene and Other Syringe Tip Filters	17
In-line Filters and Guard Columns	6	PTFE Syringe Tip Filters	18
Columns	7	Nylon Syringe Tip Filters	19
Detector	7	Flush Volume Determination	20
Tubing	7	<b>DRUG BINDING STUDY</b>	<b>21</b>
<b>HOW TO CHOOSE A FILTER</b>	<b>8</b>	Drug Binding Study - Suitability of Various Filters for Sample Preparation in Dissolution Testing	21
Automation Certified Filters	8	Experimental	21
Filter Chemical Compatibility	8	General Methodology	22
Most Appropriate EFA (Effective Filtration Area)	9	Filter Evaluation is Conducted Using the Following Methodology	23
Optimal Pore Size Rating	10	Results	24
<b>EXTENDING HPLC COLUMN LIFE</b>	<b>11</b>	Filter Study	26
Background on Column Failure	11	Discussion	27
Methods	11	Conclusion	27
Test Results and Discussion	12	<b>PRODUCT FEATURES</b>	<b>28</b>
Function of Filtration to Extend HPLC Column Life	13	Features and Benefits for Pall Life Sciences' Products	28
Conclusion	13	Materials of Construction	28
		<b>PRODUCT SPECIFICATIONS</b>	<b>29</b>
		<b>CHEMICAL COMPATIBILITY GUIDE</b>	<b>30</b>
		<b>REFERENCES</b>	<b>31</b>

## QUALITY ASSURANCE AND CERTIFICATIONS

Over thirty years ago, Pall Life Sciences revolutionized sample preparation for analytical chemists with the development of the Acrodisc® syringe filter. Today we produce high-quality filters for sample preparation and dissolution testing that meet the unique requirements of every lab we serve. Pall's microporous materials and filtration devices are manufactured under precise, highly controlled conditions. Our global manufacturing operations employ Lean Manufacturing and Six-Sigma

principles, and internationally recognized Quality Management Systems to produce products of exceptional quality and value. Pall's device manufacturing facilities utilize the most advanced sealing technologies, vision systems and robotics platforms to ensure optimum lot-to-lot consistency. Read on to learn more about our quality assurance and certifications.

### ISO Certification - Speaks to The Quality of Pall

All Pall manufacturing facilities adhere to uniform manufacturing procedures and have been granted International Standards Organization (ISO) certification to ISO 9001. This ensures that Pall filtration products and systems will perform exactly as specified, no matter where in the world they are purchased.

Pall's Quality Management Systems are ISO 9001 registered. This represents the most comprehensive and rigorous standard in the ISO series of standards for quality management and quality assurance.

Pall Life Sciences manufactures a wide range of filtration and separation products at its Ann Arbor site, including medical filters, sterilizing grade filters for aseptic processing, and laboratory filters.



## HPLC Certified for Low Extractables

A filter for HPLC applications is designed to increase accuracy by removing unwanted particles. However, the wrong filter can be a source of contaminants in the form of extractables that elute into the sample from the filter device. These undesired artifacts can jeopardize analytical results. Some extractable concerns include coelution, false quantitation, and extraneous peaks.

Pall Life Sciences specifically selects the highest grade of materials and performs rigorous extraction methods on our membrane products to eliminate the occurrence of undesired artifacts.

Pall Life Sciences HPLC certification ensures that analytical results will not be compromised by extractable filter materials. Our membranes have been tested for compatibility with common HPLC solvents (water, acetonitrile and methanol) using established HPLC procedures. In addition, to verify low levels of UV-detectable extractables, samples of the entire HPLC Acrodisc® syringe filter line are evaluated prior to release.

## IC Certified for Low Levels of Inorganic Extractables

Pall Life Sciences certifies that Ion Chromatography (IC) Acrodisc syringe filters have been tested using a highly sensitive IC protocol to monitor inorganic extractables. For Ion Chromatography applications, our IC Acrodisc polyether-sulfone (PES) syringe filters are certified for low levels of inorganic extractables. Actual background levels of filter extractables are typically less than 20 ppb for chloride, 6 ppb for nitrate, 1 ppb for phosphate, and 10 ppb for sulfate.



## Automation Certification



Pall Life Sciences has specifically designed and certified our Acrodisc PSF syringe filters to be fully compatible and reliable for use with automated equipment. The following special features make our syringe filters reliable for worry-free performance 24 hours a day:

- Smooth filter-to-filter release
- Consistent turret advancement
- Exceptional housing strength
- Strict “outside filter geometry”

Acrodisc PSF syringe filters from Pall Life Sciences are the only syringe filters to receive Caliper Life Sciences’ Automation Certified guarantee. This certification is granted to syringe

filters that meet the stringent requirements for automated dispensing and robotic handling. Pall is manufacturing these products working in close partnership with Caliper Life Sciences Manufacturing and Engineering teams to ensure proper fit, function, and compatibility with Caliper workstations.

Caliper Life Sciences is the manufacturer of the Caliper® TPW™ Workstation, the APW® Workstation, the MultiDose® Workstation, and the Prelude® Workstation. These robotic workstations are uniquely designed to work best with Caliper “Automation Certified” filters for proper operation.

## Manufacturing Quality Assurance

### Manufacturing Environment

Pall Life Sciences strictly adheres to cGMPs and cleanroom practices. In addition, we are registered to the ISO 9001 Quality Systems Standards.

### Quality Control

In addition to the HPLC Certification performed to evaluate UV extractables, Acrodisc® syringe filters undergo several other detailed quality control tests. These tests ensure compliance with the product's specifications. The quality control tests include:

- visual quality tests
- liquid flow rates
- bubble point
- burst test
- liquid UV/IC extractables for certification

### UV Absorbing Extractables

UV absorbing extractable testing is performed to verify that a product intended for use in HPLC sample preparation will not contribute a significant amount of UV extractable materials to the sample fluid. This test is intended for all filters that are HPLC Certified.

For more information on extractables see page 14.

### Bubble Point

Statistically representative samples from each lot of Acrodisc syringe filters are selected and tested by the bubble point test to confirm pore size and integrity of the membrane seal. A bubble point is the measure of the amount of air pressure required to force an air bubble through a wetted pore and is in inverse proportion to the size of the hole. The bubble point rating is determined when the largest pore yields a bubble; the larger the pore, the less pressure required to form the bubble. Bubble point is expressed in units of pounds/square inch (psi), bar or mbar, or kPa for membranes. (ASTM: F216-80)

### Burst/Pressure Test

Acrodisc syringe filters are tested for resistance to pressure. This test is a quality and safety test to ensure the Acrodisc syringe filter housings will not rupture at their rated operating pressures. The maximum operating pressure listed in the product literature is well below the actual burst pressure. This pressure rating is tested on every lot of filters.

### Visual Examination

A machine vision system inspects Acrodisc PSF syringe filters throughout the production process for cosmetic defects. Operators and technicians verify the pad printing on the Acrodisc syringe filters. Lettering quality, accuracy, and proper color-coding stamped on each device are inspected. Package labeling is examined for accuracy of label information.

### Ion Chromatography Extractables

The IC Acrodisc filter is eluted with 18-MO $\Omega$ m water to determine that the quantity of ionic extractable materials are sufficiently low and that the product will yield accurate analytical results when used in Ion Chromatography experiments. This test is applicable to all filters certified for use in IC Chromatography.

### Liquid Flow Rate Test

Liquid flow-rate tests are performed to ensure that the Acrodisc product meets flow-rate specifications. To perform this procedure the syringe filter is attached to a regulated, pressurized source of test fluid and the flow rate is determined from the volume of fluid processed in a specific time interval.

### HPLC Certified Membranes from Pall Life Sciences

Membrane	Recommended Uses			
	Strong Bases	Acids	Aqueous Solutions	Keytones
GHP (hydrophilic polypropylene)	X	X	X	X
Fluorodyne® II (hydrophilic PVDF)		X	X	
Nylaflo® (Nylon)	X		X	X
TF (PTFE)	X	X		X
IC Supor® (PES)	X	X	X	
Glass (borosilicate glass fiber)	X	X	X	X

Note: Be sure to review the Chemical Compatibility Guide on page 30 before choosing a filter.

## NEED FOR FILTRATION

Sample and mobile phase filtration are simple, economical practices that serve to extend the life of consumable HPLC parts, decrease system wear and tear, and preserve the integrity of the HPLC system. The adverse effects of improper filtration practices that occur to each component of the HPLC system are systematically and thoroughly explored in this section. By reviewing these consequences, the analyst can become familiar with the early warning signs of filtration-related problems and avoid the expense and downtime related to lengthy maintenance repairs and replacement costs.

*Sample and mobile phase filtration are simple, economical practices that serve to extend the life of consumable HPLC parts*

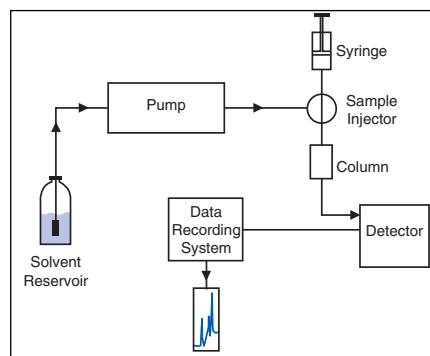
Serious problems in HPLC can be avoided by being alert to preliminary warning signs and performing routine maintenance. Most HPLC part replacement tasks, such as changing pump seals, are readily recognized as necessary maintenance; however, mobile phase and sample filtration are also maintenance practices. Routine sample and mobile phase filtration are simple, inexpensive and convenient ways to decrease HPLC problems. Regardless of the technical intricacies and cost of the system chosen, all HPLC systems have the same basic components, indicated in Figure 1.

A basic HPLC system consists of a solvent reservoir, pump, injector, column, detector, and data recording system. Particles and microbial growth not removed by filtration interfere with nearly every system component.

This paper serves as a troubleshooting guide to problems associated with inefficient filtration. It is ordered in sections corresponding to the specific HPLC component affected.

**Figure 1**

A Basic HPLC System Configuration



## Solvent Reservoir / Solvent Degassing

The solvent reservoir traditionally includes an inert container, vented cap, PTFE solvent inlet line, and a 10  $\mu\text{m}$  gross inlet sinker frit. The solvent reservoir is generally equipped to degas solvents by removing dissolved air. Frequent mobile phase degassing reduces erratic pump delivery of the solvent due to pressure fluctuations, and hence reduces detector noise. Degassing also removes dissolved oxygen that can result in oxidative degradation of the sample and mobile phases, and reduces the sensitivity and operating stability of ultra-violet, refractive index, electrochemical and fluorescence detectors. By filtering mobile phase, analysts can reduce debris capable of plugging the sinker and column frits, causing contamination, damaging pump valves, blocking capillaries, causing poor peak performance, and contributing extra peaks and excessive chromatographic noise.

Mobile phase filtration is performed prior to placing the solvent into the solvent reservoir. Buffered mobile phase solvents require daily filtration with a 0.2  $\mu\text{m}$  filter to eliminate microbial growth that could increase the baseline. A typical solvent filtration apparatus is depicted in Figure 2. Contamination concerns from the filtration apparatus deter many analysts from filtering solvents. By dedicating a reservoir to each solvent, and frequently changing and cleaning the reservoir bottle and sinker frit, contamination problems are reduced.

The primary concern when choosing a solvent filter is solvent compatibility with the filter material. Pall offers several filters to accommodate the various types of HPLC solvents. Pall's GHP (hydrophilic polypropylene) membrane is a universal solvent membrane to reduce confusion with filter selection. Typical solvent filters range in size from 25 to 90 mm in diameter and are available in a 0.2 or 0.45  $\mu\text{m}$  membrane pore size.

**Figure 2**

Mobile Phase Filtration Apparatus



## Pump

The pump is the single most important component in the HPLC system. Reliable pump operation requires attention to system cleanliness, solvent and reagent quality, mobile phase filtration, and mobile phase degassing. The four most common pump problems involve 1) check valves, 2) pump seals, 3) blockage, and 4) air bubbles. Incorrect pump functioning results in increased baseline noise, irreproducible retention times and increased operating pressures.

A pump delivers flow rates between 10  $\mu\text{L}/\text{min}$  and 10  $\text{mL}/\text{min}$ . Pumping fluid at 10  $\text{mL}/\text{min}$  against a small particle column generates considerable pressure. When a pump will not deliver degassed solvent, particulate build-up is possible. Monitoring pressure changes allows quick assessment of blocked frits, or columns, through exaggerated pressures. Retention times also may be affected. Bubbles form in the pump when mobile phase mixtures become air saturated. Bubbles interfere with piston and check valve operations, causing erratic flow and pressure fluctuations. To resolve blockage or bubbles, contact your system manufacturer for the best preventive maintenance procedures.

Check valves control the solvent flow direction through the pump head and ensure steady pressures when sealed properly. Particulate in check valves can leak or stick causing flow and/or pressure problems. Check valve leakage is prevented by filtering HPLC-grade solvents, using a solvent line sinker frit, flushing the system daily with non-buffered mobile phase,

and regularly replacing pump seals to remove particles and entrapped air causing leakage and pump pulsation noise. Pump pulsation noise is the flow change sensed by the detector from piston movement and check valve operation. Filtering the mobile phase solvent aids in decreasing this contribution to noise. A series of increasing polarity solvent flushes should be sufficient to remove problems due to sticking and particulates.

### *Pump seal life can be extended by filtering the mobile phase solvents*

A pump seal facilitates piston movement in the pump head. Pump seals wear more quickly than other pump parts, and therefore require changing every three to six months. A failing pump seal is evident from an inability to pump at high pressures, leakage behind the pump head, and change in sample retention. Pump seal wear can result in sloughing seals and contamination from this material. Buffer crystals built up from evaporated mobile phase also will accelerate wear. Pump seal life can be extended by filtering the mobile phase solvents to remove the particles responsible for accelerated seal wear.

## Injector

Injecting clean samples prolongs injector and column life. Samples are cleared of particulate and bacteria with disposable syringe tip filters. Disposable filters range in size (3-25 mm) and pore size (0.2 to 1.0  $\mu\text{m}$ ). Syringe tip filters are membranes configured in plastic housings that attach to a syringe with a luer fitting. Samples are filtered by drawing fluid into the syringe, attaching the filter, and dispensing the sample through the filter into a vial. Table 1 lists various types of membrane filters incorporated in syringe tip housings, housing material, and prefilter materials. To reduce physical and chemical variability among manufacturers, sample and mobile phase filtration products should be purchased from the same manufacturer.

*Filtering your sample prior to injection can prolong your injector and column life*

**Table 1**

Standard Materials Incorporated in Syringe Tip Filters

<b>Membrane Material</b> Nylon, PTFE, Polyvinylidene fluoride (PVDF), Cellulose (mixed esters, acetate), Nitrocellulose, Polysulfone, Polyethersulfone, Acrylic Copolymer, Polypropylene
<b>Housing Material</b> Polypropylene (PP), Polyethylene (PE), Polyvinylchloride (PVC), Modified Acrylic, Nylon
<b>Prefilter Material</b> Glass, Polypropylene, Cellulose Nitrate, Polyethersulfone

## Injector *(continued)*

Choosing the proper filter requires a knowledge of filter/solvent compatibility and the chemical/physical characteristics of the filter. These characteristics include pore size, pore distribution, filter thickness, extractables, hydrophobic/hydrophilic character, binding properties, pyrogenicity, gas and liquid flow rate, burst strength, autoclavability, absolute pore size, and nominal particulate retention. Typically for HPLC applications, the 0.45 µm pore size filter is selected, or the 0.2 µm filter for bacterial removal from buffers. For particulate-laden samples, Pall incorporates large pore size prefilters in one device with smaller pore size membranes. Low protein binding and sterile filters also are available. For detailed information on how to select the best filter for your application, see page 8.

### *Sample and solvent filtration deters low-volume injector fittings from blockage, scratching and leakage*

HPLC injectors are available in several styles including a septum, septumless stop-flow device, and a valve system, either manual or automated. A valve injector is most typical. An injector should ensure reproducible sample introduction. Sample and solvent filtration deters low-volume injector fittings from blockage, scratching and leakage. Loop or

waste line blockage results in high back pressure and loop filling difficulty. Low dead volume fittings, located between the valve injector and column to decrease band broadening, are also subject to blockage. Other contributors to HPLC problems include mismatched or damaged injector components, variable sample volumes, leaks, and increased system pressure. Backflushing is recommended prior to disassembly. With filtration, properly adjusted and clean injectors should last 5,000 injections.

Autosamplers run unattended, so clean filtered samples will decrease malfunction. Clean sample vials, free of dust and other particulates, also contribute to clean samples. Particulate-free samples are essential to decrease blocked sample needles, connection tubing and injectors. Connection tube blockage results from sample particulate, septum fragments or small internal diameter tubing. Sample, mobile phase and in-line filtration products deter these situations. For blockage at the injector's low pressure side, the needle and needle valve tubing should be checked. Symptoms include smaller than expected peak heights and peak absence. On the high pressure side, find the location by loosening the connection fitting, starting at the column head, and working upstream. Once the blockage is located, backflush with a clean filtered solvent.

## In-line Filters and Guard Columns

In-line filters and guard columns can remove particulate before the main column. These two filters are configured into the HPLC system as follows: sample injector—in-line filter—guard column—main column. They are not intended to replace sample pretreatment, or sample and solvent filtration. Particulate-laden samples will quickly overload the in-line filter and guard column allowing particles to enter the main column.

In-line filters are ideal because it is impossible to avoid particulate from system wear, such as polymeric seal wear from the pump and sample injector, except with an in-line filter. In-line filters function to reduce blockage of the column frit and the back pressure restrictor. The in-line filters should have removable frits of 0.45 to 2.0 µm for frequent replacement, and low dead volume housings.

Guard columns can collect chemical and physical waste that block the main column inlet, cause column voids and degrade performance. The guard column retains irreversible and strongly retained components that degrade the column and decrease its lifetime, providing an inexpensive alternative to frequent column replacement. The frits of a guard column are typically 2.0 µm, which is not sufficient for particulate removal. Sample and mobile phase filtration will preserve the capacity of the guard column for its intended use: chemical contamination removal.

### *Sample and mobile phase filtration will preserve the capacity of the guard column for its intended use*

## Column

Proper HPLC column selection is crucial for efficient compound separation and identification. High performance columns are composed of small particles of narrow size distribution. Optimal peak profiles depend on column operating characteristics and should be instrument independent. Columns, depending on sample type, sample preparation, and operator filtration practices, can handle a few to several thousand injections.

Two significant problems with HPLC columns are chemical and physical changes. Chemical changes are prevented with guard columns. Physical changes involve blocked frits and channel voids. Voids are created by particulate matter and pressure shock. If poor peak shapes become evident by badly tailing, splitting, and non-gaussian bands, without a change in retention time, blocked frits or a column void has occurred.

Tips from instrument manufacturers to prevent physical changes include:

- filtering solvents through a 0.2 or 0.45  $\mu\text{m}$  filter, such as Pall Acrodisc® syringe filter
- prefiltering mobile phase buffers daily with a 0.2  $\mu\text{m}$  filter to remove bacterial growth,
- filtering samples through a 0.2 or 0.45  $\mu\text{m}$  filter,
- utilizing a 0.5  $\mu\text{m}$  in-line filter to trap injector and pump particulates.

Prior to any action, ensure that the problem is from blockage or a void volume and not from a change in solvent strength, pH, temperature, or mobile phase additives, such as an ion-pairing reagent, which show the same effects.

For more information on extending column life, see page 11.

## Detector

Detectors for HPLC are classified as bulk property or solute property detectors. A bulk property detector measures the physical property difference of the solute in the mobile phase compared to the mobile phase alone. The solute property detector responds to physical or chemical properties of the solute and is independent of the mobile phase. Examples include spectrophotometry, fluorescence and electron capture detectors.

### *Solutions for removing the negative effects of oxygen in detectors include filtering buffers through a Pall 0.2 or 0.45 $\mu\text{m}$ membrane filter*

Insufficient mobile phase degassing causes pressure fluctuations and/or sharp noise spikes due to bubbles. Bubbles form when the mobile phase mixture becomes

saturated with air. This interferes with detector operation. Degassing methods include mobile phase filtration followed by a continuous degassing through helium sparging, ultrasonic treatment, vacuum application, or heating with vigorous stirring.

Air bubbles cause problems with detector response due to excessive oxygen interference. Solvent degassing removes dissolved oxygen from the mobile phase which may result in oxidative degradation of the sample, a reduction in sensitivity, and decreased operating stability of UV/VIS, fluorescence, refractive index, and electrochemical detectors.

Solutions for removing the negative effects of oxygen in detectors include continuous sparging, filtering buffers through a Pall 0.2 or 0.45  $\mu\text{m}$  membrane filter, and using HPLC-grade solvents.

## Tubing

Tubing length and internal diameter require careful selection to prevent system degradation. The internal diameter is dictated by pressure requirements and can vary from 0.18 to 1.0 mm depending on flow requirements. Injector-to-column and column-to-detector tubing, typically stainless steel or Teflon, is generally 0.25 mm. Applications where small peak volumes are required use microbore tubing. Small i.d. tubing blocks faster, but tube blockage is rare. More commonly, blockage occurs at in-line filters or frits. Effects of blockage include significant pressure rises, and fitting and seal leakage. Blockage, partial or complete, can be due to poorly filtered mobile phases, articles in the injected sample, pump/injector seal wear, leakage of silica particles from guard or analytical columns, precipitation of mobile phase salts, and any particulate matter in the HPLC system.



## HOW TO CHOOSE A FILTER

There are four main considerations in choosing the best filter for your application. They are:

1. Is your filter application automated or manual?
2. What is the filter's chemical compatibility?
  - a. Resistance of membrane to fluid contact
  - b. Extractables
  - c. Adsorption
3. What Effective Filtration Area (EFA) is needed for your filtration?
4. What pore size rating is optimal for sample clean-up?



### 1. Automation Certified Filters



If you are using a filter in automated workstations it is important to choose filters that are reliable and will move consistently and smoothly within the automated sample handling apparatus.

- Acrodisc® PSF syringe filters from Pall Life Sciences are the only syringe filters to receive Caliper Life Sciences Automation Certified guarantee. This certification is granted to syringe filters that meet the stringent requirements for automated dispensing, robotic handling, and fit.

- Acrodisc PSF syringe filters are designed specifically to meet the exacting requirements of automation systems. They demonstrate smooth filter-to-filter release, consistent turret advancement, exceptional housing strength, and a strict outside filter geometry to ensure proper alignment and consistent operation.

### 2. Filter Chemical Compatibility

Does the filter need to be resistant to bases, acids, or organic solvents? Chemical compatibility is a critical consideration when selecting the sample prep syringe filter or mobile phase disc filter for your application. The broad guidelines below can be used for basic information. Please refer to the chemical compatibility chart on page 30 to determine which filter is best for your application.

#### Aqueous Samples

Hydrophilic membranes, which have an affinity for water, are preferable when filtering aqueous samples. Use Pall Life Sciences filters with GHP, PES, Nylon, or PVDF membranes.

#### Gases and Aggressive Organic Solvents

Hydrophobic membranes repel water and are inert to aggressive organic solvents, making them ideal for gases and organic solvents. Choose Pall Life Sciences filters with PTFE membrane.

#### Aqueous and Organic-Solvent Solutions

Different polymeric membranes have different chemical compatibilities. Based on the application and chemical compatibility, there may be one or several membrane and Acrodisc syringe filter possibilities. Generally, one filter type will not function for all applications due to limitations in hydrophobicity/hydrophilicity and chemical compatibility. However, Pall Life Sciences' patented hydrophilic polypropylene (GHP) membrane is a universal membrane for both aqueous and organic applications.

#### Exceptionally Low Extractable Levels

A filter is designed to increase accuracy by removing unwanted particles. However, the wrong filter can be a source of contaminants in the form of extractables that elute into the sample from the filter device. These undesired artifacts can jeopardize analytical results. Some extractable concerns include coelution, false quantitation, and extraneous peaks.

*A filter is designed to increase accuracy by removing unwanted particles*

Pall Life Sciences specifically selects the highest grade of materials and performs rigorous extraction methods on our membrane products to remove the occurrence of undesired artifacts.

For more information on extractables see pages 14-20.

#### HPLC Certified for Low Extractables

Pall Life Sciences HPLC certification ensures that analytical results will not be compromised by extractable filter materials. Our membranes have been tested for compatibility with common HPLC solvents (water, acetonitrile and methanol) using established HPLC procedures. In addition, to verify low levels of UV-detectable extractables, samples of the entire HPLC Acrodisc syringe filter line are evaluated prior to release.

## 2. Filter Chemical Compatibility *(continued)*

### IC Certified for Low Levels of Inorganic Extractables

Pall Life Sciences certifies Ion Chromatography (IC) Acrodisc® syringe filters have been tested using a highly sensitive IC protocol to monitor inorganic extractables. For ion chromatography applications, only the IC Acrodisc (PES) syringe filter is certified for low levels of inorganic extractables. Actual background levels of filter extractables are typically less than 20 ppb for chloride, 6 ppb for nitrate, 1 ppb for phosphate, and 10 ppb for sulfate.

## 3. Most Appropriate EFA

The particulate contained within a fluid affects the life of a filter. As particles are removed from the fluid, they block pores and reduce the useable portion of the filter. Particulate-laden fluids generally plug a filter more quickly than "clean" fluids. Increasing the Effective Filtration Area (EFA) can lengthen the life of a filter.

Filters come in a variety of sizes ranging from the area within a single well of a 96-well plate, to spin filters and syringe tip filters.

25 mm Acrodisc PSF syringe filters, as well as 13 and 4 mm diameters for smaller sample volumes, are available in a variety of membrane and pore size choices.

Another aspect of choosing the right filter size is the hold-up volume. This is the volume of liquid remaining in the filter after use. A filter with a low hold-up volume is recommended for use with expensive fluids or those with limited availability. What device size will assure complete sample filtration with minimal hold-up volumes? Pall Life Sciences offers a broad range of device sizes. The minispikes outlet, available on the 13 mm device, allows for minimal sample hold up and easy dispensing into autosampler vials. Additional options include the 4 mm Acrodisc syringe filter, the Nanosep® MF centrifugal device, or AcroPrep™ filter plates.

### Syringe Filter and Spin Device Selection

The table below outlines general guidelines to the appropriate filter size for different volumes of fluid.

**Table 2**

Volume to be Filtered	Filter Type	Typical Hold-up Volume
< 500 µL	Nanosep MF Device	< 2 µL
< 2 mL	4 mm Acrodisc Syringe Filter	< 10 µL
< 10 mL	13 mm Acrodisc Syringe Filter (Minispikes Outlet)	< 14 µL
< 10 mL	13 mm Acrodisc Syringe Filter	< 30 µL
< 125 mL	25 mm Acrodisc PSF Syringe Filter	< 200 µL

### Sample Adsorption

Unwanted drug binding as well as the presence of possible extractables eluted from the filter during routine pharmaceutical sample analysis can be a serious problem and cause out-of-specification results. No single analytical method can provide reliable information on comparative filter properties and the full range of extractables for all filters. Therefore, choose a low adsorption filter such as the Acrodisc syringe filter with GHP membrane. GHP membrane is extremely low in biomolecule binding. Typical binding levels are far below 1%.

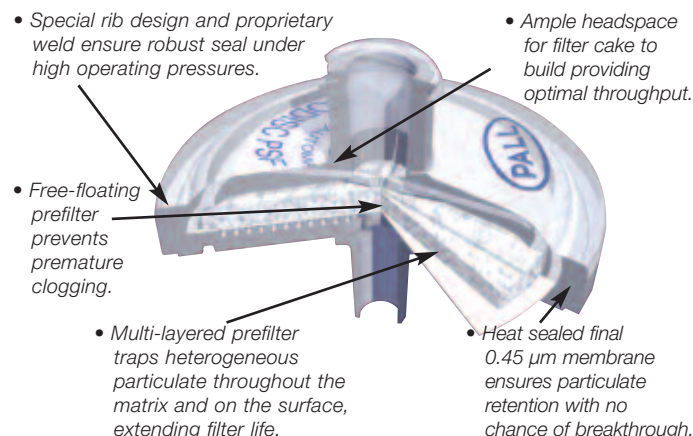
See Drug Binding section pages 21-27.

*For difficult-to-filter samples, the Acrodisc PSF syringe filter with GxF multi-layered glass fiber prefilter is the best option*

### Consider Prefiltration

For difficult-to-filter samples, it is best to use a syringe filter with a glass fiber prefilter over the membrane. The Acrodisc PSF syringe filter with GxF multi-layered glass fiber prefilter is the best option for extremely particulate-laden samples. Our traditional Acrodisc syringe filters with GHP and Nylon membranes are also available with a single-layer glass fiber prefilter.

**Figure 3**



The Acrodisc PSF syringe filter has a serial glass fiber (GxF) prefilter to allow for maximum throughput and faster flow rates than standard glass fiber prefilter devices. The multi-layered prefilter, rated from > 40 to 1 µm, traps particulate, thereby extending filter life.

### Easy Identification

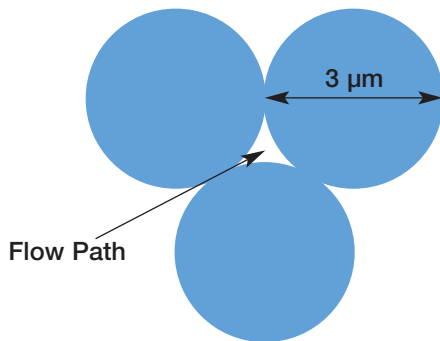
13 and 25 mm Acrodisc syringe filters and their packaging have color-coded printing with membrane type and pore size on each filter:

- GHP
- Nylon
- PTFE
- Glass Fiber
- PVDF
- Polyethersulfone (PES)

## 4. Optimal Pore Size Rating

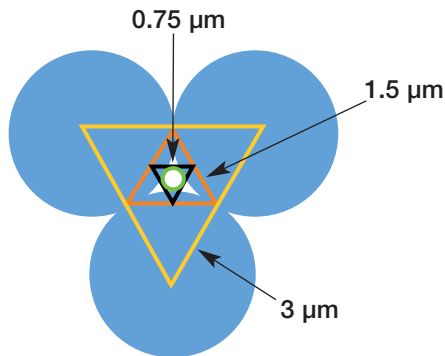
To extend the life of your column and reduce maintenance due to particulate in the pumping system, thereby giving more analyses per dollar spent, a filter's pore size should be determined based on the column packing size. As you can see in Figure 4, the column packing particles touch each other. Ideally, you would not want contamination to fit into the space between the particles of packing. This space (labeled Flow Path) is identified in Figure 4 below. The idea is to find out how large that space is and remove particles that size.

**Figure 4**

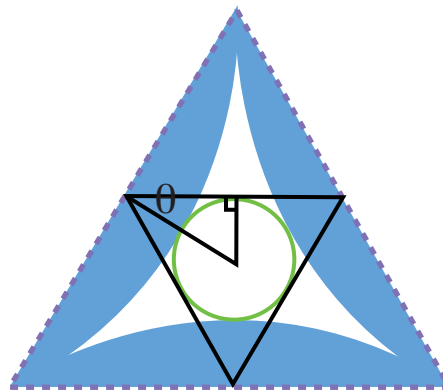


For example: start with a 3 μm packing size and draw a few well-placed equilateral triangles as suggested in Figure 5. Determine the largest particle capable of fitting through the column by circumscribing an equilateral triangle with a side length of 0.75 μm.

**Figure 5**



**Figure 6**



Now enlarge the diagram and look further. Visualize a series of equilateral triangles whose side length gets down to 0.75 μm. Figure 6 illustrates a right triangle whose short side describes the radius of the sphere. The angle  $\theta$  is one half of 60°, or 30°. The horizontal side of this new right triangle has a length of 0.375 μm (half of 0.75 μm). Calculating the tangent of 30° gives the ratio of the length of the opposite side over the adjacent side, in this case 0.58. This means that the short side of the triangle is equal to 0.58 x 0.375 or 0.217 μm. Coincidentally, this is also the radius of the particle. So, if the column packing is 3 μm in diameter, the flow path is 0.43 μm.

When an HPLC column has a packing size of 3 μm or smaller, you should use a 0.2 μm filter because a 0.45 μm filter may let particles through that will plug the column.

### Are You Concerned About Accurate Retention of Particulate?

For liquid chromatography systems using columns with larger than 3 μm packings, the filtration industry standard is 0.45 μm for syringe filters and mobile phase membranes. For columns with 3 μm or smaller packings, microbore columns, or when concerned about microbial growth, a 0.2 μm filter is recommended.

Once the best pore size rating is chosen for the application, you must rely on the filter manufacturer to provide an accurate pore size rating. As shown in the article "Column Protection", see pages 11-13, accurate pore size rating is important to the economics of the appropriate filter choice.

## EXTENDING HPLC COLUMN LIFE

Injection of particulate-laden samples will plug High Performance Liquid Chromatography (HPLC) columns, shorten injector life, and result in extensive maintenance on pumps. Particulate finding its way into a column results in increased column backpressure, disrupted nominal band shape, and reduced plate number, consequently shortening column life and making analytical results difficult to interpret. Using Pall Acrodisc® PSF syringe filters with GHP (hydrophilic polypropylene) membrane is the most efficient way to remove particulate and prolong the life of HPLC system components. Pall Acrodisc PSF syringe filters with GHP membrane are widely used for this purpose. The average retention efficiency

of 0.45 µm rated Acrodisc PSF syringe filters with GHP membrane at removing 0.45 µm average diameter latex spheres is 94.9%. Compared to filters from two other manufacturers, Pall Acrodisc PSF syringe filters significantly prolonged HPLC column life with virtually no backpressure increase after 972 injections.

*Compared to other manufacturers, Pall Acrodisc PSF syringe filters significantly prolonged HPLC column life*

### Background on Column Failure

Of the four common causes for HPLC column failure (plugging, voids, adsorbed sample, and chemical attack), plugging is the most frequently encountered by analytical chemists or analysts. Injection of samples containing particulate will eventually block the column inlet, cause high column backpressure, and shorten the normal lifetime of the column. Operations of pump components, injectors, and detectors can be expected to be less troublesome when fluids are filtered. For HPLC applications, the 0.45 µm pore size filter is typically selected for removal of particulates. Although there are several seemingly equivalent such products on the market, lack of knowledge about the differences between filters leads to frequent column replacement and extensive operation downtime.

Filtration as a preventative maintenance tool for HPLC analyses is well documented. It is commonly taken for granted that column life will be extended if samples are filtered prior to injection, but the extension of the column life has not been

well quantified. It is the intent of this work to demonstrate that filter efficiency must be considered when choosing an HPLC sample-prep filter and that filtration will lengthen the life of a column.

In this paper, retention efficiency of three effectively equivalent 0.45 µm rated syringe filters was examined using 0.45 µm average diameter latex spheres. This work was conducted with latex spheres to offer the best possible reproducibility in both sample preparation and filter efficiency measurements.

In order to correlate the retention of spheres to the actual application, the quantitative effect of filtration on HPLC column life was investigated. This involved examining column life without filtration compared to column life when samples were filtered. It should be recognized that extending the column life is dependent on the particulate within the sample and actual column life extension may vary.

### Test Methods

#### Materials

- Latex spheres and surfactant were purchased from Sigma. 0.45 µm average diameter latex spheres: L/N 31K1123, Cat #: LB-5 Triton X-100 L/N: 121K0090, Cat #: X-100
- 25 mm syringe filters with 0.45 µm pore size ratings were obtained from Pall, Company A, and Company B
  - Pall Acrodisc PSF Syringe Filters with GHP membrane: P/N AP-4557, L/N: A224102521, A224227411, and A22422044
  - Company A syringe filters with PVDF membrane: L/N F2EN42569, F0BN28908, and F2NN83751
  - Company B syringe filters with PVDF membrane: L/N: 11067, 11146, and 99297

#### Instrumentation

- High Performance Liquid Chromatography (HPLC)
- Waters (Milford, MA, USA) 616 Pump
- Waters 600s Controller
- Waters 717plus Autosampler
- Ultraviolet/Visible Spectrophotometer (UV/VIS), HP 8452A Diode Array

#### Columns

- Luna® 5 µm C18(2), columns were purchased from Phenomenex (Torrance, CA, USA): Size: 30 x 3.0 mm, P/N: 00A-4252-Y0, S/N: 160111-3, 159485-4, 159742-3, and 159485-3

## Test Methods *(continued)*

### Testing

The UV/VIS Spectrophotometer was used for measuring absorbance of latex-sphere solutions. The maximum absorbance of the latex-sphere solution was observed at 272 nm, which was used to correlate latex sphere concentrations with absorbance. The surfactant solution, 0.1% Triton X-100 that is free of latex spheres, was measured as the blank at 272 nm. A series of standard solutions of 0.0025%, 0.0050%, 0.0075%, and 0.01% 0.45 µm latex sphere concentrations were made and used for creating the calibration curve. The linear relationship between latex sphere concentrations and absorbance was established, which is in accordance with Beer's law. A correlation coefficient of 0.9999 was obtained. The 0.01% 0.45 µm average diameter latex spheres solution was used for the retention efficiency study. The challenge solution was passed through each individual syringe filter and a 3 mL eluted aliquot was collected and analyzed at 272 nm. Three different filters from each of the three lots were tested (i.e., nine filters from each manufacturer were individually analyzed).

The HPLC was utilized for the column-plugging study. Column life was evaluated by comparing initial backpressure to backpressure after injections. A new LUNA® C18(2) 00A-4252-Y0 column (S/N: 160111-3) was installed. The outlet of the

column was disconnected from the detector and allowed to run to drain. This modification allowed quicker injections for a more efficient determination of column backpressure. Acetonitrile:Water (35:65, percentage by volume) was used as mobile phase, with a flow rate of 1 mL/min. Column temperature was controlled at 25 °C. The system was set to automatically inject 50 µL each time. The column-plugging solution consisted of 0.05% (by weight) 0.45 µm average diameter latex spheres in 0.002% Triton X-100 solution. The first step was to inject this solution without any filtration to see how long the column would last without filtration. After the column was plugged (i.e., column backpressure reached 3500 psig, 241.3 bar, 507.6 kPa), a new LUNA C18(2) 00A-4252-Y0 column (S/N: 159485-4) was installed. This time the same latex-sphere solution was subjected to filtration using Company A filters. Thirty samples were generated with 30 Company A filters (ten from each of the three lots). The injections were carried out from sample vial one through vial 30 and then repeated in this sequence. The column backpressure was recorded with the number of injections. This procedure was repeated with new columns, S/N 159742-3 and 159485-3, for studies with Company B and Pall filters, respectively.

## Test Results and Discussion

### Latex Sphere Retention for Filters from Three Manufacturers

Tables 3 to 5 list latex sphere retention capabilities of Pall, Company A, and Company B syringe filters. Pall Acrodisc syringe filters with GHP membrane are able to retain an average of 94.9% of the 0.45 µm average diameter latex spheres. By comparison, other syringe filters can only remove averages of 90.5% and 33.0% of the 0.45 µm average diameter latex spheres. Pall syringe filters show greater lot-to-lot consistency with a relative standard deviation (RSD) of 3.5%.

**Table 3**

0.45 µm Latex Sphere Retention Efficiency (in Percentage) with 0.45 µm Pall GHP Filters

Filters	L/N: A224102521	L/N: A224227411	L/N: A22422044
Filter 1	98.2	95.8	92.5
Filter 2	97.8	97.1	90.5
Filter 3	97.0	93.8	91.0
Average from each lot	97.7	95.6	91.3
Average from three lots/RSD	94.9/3.5		

**Table 4**

0.45 µm Latex Sphere Retention Efficiency (in Percentage) with 0.45 µm Company A Filters

Filters	L/N: F2EN42569	L/N: F0BN28908	L/N: F2NN83751
Filter 1	30.1	39.5	33.3
Filter 2	28.2	38.6	29.0
Filter 3	28.4	33.6	36.2
Average from each lot	28.9	37.2	32.8
Average from three lots/RSD	33.0/12.7		

*These syringe filters from different manufacturers may appear similar and are all assigned a pore size rating of 0.45 µm from the manufacturer, but the test results show that they perform quite differently.*

## Test Results and Discussion *(continued)*

**Table 5**

0.45  $\mu\text{m}$  Latex Sphere Retention Efficiency (in Percentage) with 0.45  $\mu\text{m}$  Company B Filters

Filters	L/N: 11067	L/N: 11146	L/N: 99297
Filter 1	91.7	86.7	96.6
Filter 2	88.6	86.9	95.0
Filter 3	87.0	85.5	96.1
Average from each lot	89.1	86.4	95.9
Average from three lots/RSD	90.5/5.4		

*These syringe filters from different manufacturers may appear similar and are all assigned a pore size rating of 0.45  $\mu\text{m}$  from the manufacturer, but the test results show that they perform differently.*

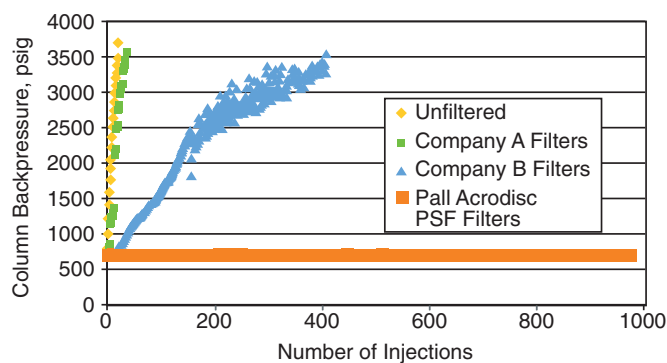
## Function of Filtration to Extend HPLC Column Life

Figure 7 depicts the relationship between column backpressure and number of injections. Without filtration, the column failure due to plugging occurred after only 21 injections. After the 0.05% latex-sphere solution was filtered with competitive filters, the columns were plugged after 37 and 487 injections, respectively. In addition, the effluents from both competitive filters were hazy, indicating the presence of a significant number of latex spheres.

When the 0.05% latex-sphere solution was filtered through Pall Acrodisc<sup>®</sup> PSF syringe filters with GHP membrane and injected to the HPLC system, the column backpressure did not increase after even 972 injections. The clear effluents from the filters suggested a more successful retention of latex spheres.

**Figure 7**

Effects of Filters on HPLC Column Life



## Conclusion

Among 0.45  $\mu\text{m}$  rated filters from three manufacturers, the Pall Acrodisc PSF syringe filters with GHP membrane have the highest average retention efficiency (94.9%) of latex spheres, as well as greater lot-to-lot consistency.

We have shown that it is imperative that samples be filtered prior to their introduction into an HPLC system. Apparently, equivalent filters from various manufacturers with the same removal rating differ in capabilities. Using Pall Acrodisc PSF syringe filters with GHP membrane prolonged the column life 46 times with no increase in column backpressure.

*Using Pall Acrodisc PSF syringe filters with GHP membrane prolonged the column life 46 times with no increase in column backpressure*

## EXTRACTABLES AND MAINTAINING ANALYTICAL INTEGRITY DURING SAMPLE PREPARATION

Pall Life Sciences manufactures a complete line of Acrodisc® and Acrodisc PSF syringe filters for analytical sample preparation. Because High Performance Liquid Chromatography (HPLC) and other analytical methods are very sensitive and serve as qualitative and quantitative

techniques, it is important to preserve the integrity of the sample. To demonstrate Pall Life Sciences quality product offering, an investigation to evaluate the amount of extractable materials added from analytical syringe filters follows.

### What are Extractables and Where Do They Come From?

A syringe tip filter extractable is an undesired artifact contributed to the sample fluid from the filter device. This material may be a membrane or housing formulation component, or a component introduced during the manufacturing or packaging process. There are several mechanisms (solubility, particle displacement, chemical interaction, and diffusion) whereby extractable materials may leach into the sample during sample preparation. Of these mechanisms, solubility and particle displacement are more prevalent.

The appearance of extractable materials from a syringe tip device depends on the solubility of device components in the sample fluid. The polymeric resins, solvents, pore formers and other chemical components such as housing materials utilized during device manufacturing may potentially extract. Solubility relates to chemical compatibility. As membrane and/or housing components become more soluble with sample fluid

components, extractable materials will increase. To determine whether a syringe filter is compatible with the sample fluid, all sample constituents (both major and minor components) require consideration. Because solubility is dependent on temperature, concentration, and exposure time, all of these parameters are significant in determining chemical compatibility.

Displacement can occur when residual manufacturing materials, once caught in the pore structure of the membrane, are dislodged. Pall Life Sciences performs rigorous extraction methods on their membrane products to hinder this occurrence.

### Why are There So Many Different Acrodisc® Syringe Filter Types?

Different polymeric membranes have different chemical compatibilities. Based on the application and chemical compatibility, there may be one or more Acrodisc or Acrodisc PSF syringe filter possibilities. For example, PVDF, GHP or PTFE membranes are recommended for sample fluids possessing strong acidic character. Nylon membrane is not recommended for such samples. Conversely, Nylon, GHP, or PTFE would make a better choice for fluids characterized as strong bases, and PVDF membrane is not suggested for these fluids. If the fluid contains aggressive organics, GHP or PTFE membranes are recommended. Reviewing and understanding the Pall Life Sciences chemical compatibility guide will assist in making the best choice. (Refer to the Chemical Compatibility Guide on page 30.)

Generally, one filter type will not function for all applications due to limitations in hydrophobicity/hydrophilicity and chemical compatibility. However, Pall Life Sciences Hydrophilic Polypropylene (GHP) membrane comes very close to being a universal membrane for all applications. It has excellent chemical compatibility for aqueous and aggressive organic solvents. GHP membrane is hydrophilic and ideal when selection is difficult for complex sample matrices. The option of a built-in glass prefilter (GHP GF or GxF/GHP) is also available for heavily particulate-laden samples.

There are two lines of Acrodisc syringe filters. From the perspective of extractables, the standard Acrodisc and the Acrodisc PSF syringe filters are identical, with the exception that the effective filtration area of the PSF product line is larger. It is 31% greater based on the 3.9 square centimeter EFA compared to the 2.8 square centimeters of the standard Acrodisc. This study will show that the extractable levels found in both filter versions are negligible and both product lines are appropriate for use in HPLC sample preparation.

*Pall Life Sciences GHP membrane can be considered a universal membrane for all applications*

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## When are Extractables a Concern?

Extractable materials can jeopardize analytical results. For chromatographic analysis, scenarios resulting from extractable materials include sample absorption, coelution, and extraneous peaks. Anomalous results are an analyst's nightmare as procedures typically require action to remedy or identify miscellaneous and unexpected peaks. If unknown peaks in a pharmaceutical chromatogram (extractables) equal 0.1% of the total area then they must be investigated.

Extractable materials become even more of a concern as the amount of analyte diminishes. With recent HPLC column trends utilizing smaller inner-diameter columns (<1 mm for micro LC) and smaller packing sizes, the ability to separate and detect trace quantities of material is increasing. With these improvements comes increasing concern for the effects of extractable materials.

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## How to Avoid Extractables' Detritus Effects?

There are three primary methods to avoid the detritus effects of extractable materials. Application testing preserves analysis validity. To application test, analyze the sample fluid before it is filtered. Compare these results to the results obtained after the sample is filtered. If any quantitative or qualitative differences occur, select another filter type. Another method of application testing involves evaluating the results obtained from passing the matrix solvent through the syringe tip filter

and evaluating the results. This will demonstrate if material will extract with the neat solvent. Flushing is a third method (see page 20). When excess sample fluid is available, discard the first few milliliters of fluid eluting from the syringe tip device. Generally, the amount of extractable materials eluted from the filter diminishes with the volume passed through the filter. As will be shown in this study, a 3 mL flush is usually adequate to reduce extractables to an acceptable level.

---

## What Contributes to an Acrodisc® Syringe Filter's Quality?

Membrane manufacturers use proprietary formulations and different manufacturing techniques. For this reason, Pall Life Sciences' membranes, Acrodisc and Acrodisc PSF syringe filters are not the same as other look-a-like products. The specific quality of raw materials, amount of quality control, membrane extraction procedures and post treatments all affect the resultant membrane properties and amount of extractable materials. Pall Life Sciences specifically selects

the highest grade of materials and performs several extractions to ensure that the product is free from extractable materials for sample preparation. Additionally, our polypropylene housing material, also used in Pall Life Sciences medical devices, is the highest grade of plastic with minimal additives, and passes United States Pharmacopeia (USP) Biological Reactivity Test, *In Vivo* <88> plastics testing.

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## What Confidence Can You Have in Our HPLC Certification?

The following extractable experiments are provided to demonstrate the quality of the Acrodisc and Acrodisc PSF syringe filter product lines, which include PVDF, GHP, Nylon, and PTFE. To suit a broad audience, extractable experiments were performed under typical HPLC conditions with common

mobile phases and extraction solvents. This information extends to the corresponding membrane disc for mobile phase filtration and other sizes of Acrodisc syringe filters, as the filter materials are the same.

## Experimental and Instrument Conditions

The first set of extractions represented by the enclosed chromatograms resulted from volumetrically collecting the first milliliter of solvent through the Acrodisc® syringe filter. This step was repeated with two additional filters. All three extracts were combined in an autosampler vial and analyzed, so that three filters contributed to one sample. Three filters were selected to remove potential variability among the filters. By collecting only one milliliter of eluent per filter, the ability to detect extractable materials was enhanced.

HPLC analysis was performed on all fluid extracts with a Waters System (Milford, MA, USA) consisting of a 616 Fluid Pump, 717 Plus Autoinjector, 600S Controller, 996 Photodiode Array (PDA) Detector and Millennium 2010 Software. The column, also supplied by Waters, was a NovaPak 4 µm C18, 4.6 mm x 150.0 mm. All extraction and mobile phase fluids, acetonitrile, water, and methanol were HPLC Grade Solvents supplied by EM Science (Gibbstown, NJ, USA).

The extracted fluid and neat solvent blanks, 100 µL, were analyzed under gradient mobile phase conditions. Initial conditions were held for three minutes, 95% water: 5% acetonitrile, and altered in a linear gradient over 40 minutes to the final conditions, 100% acetonitrile: 0% water, which were retained for five minutes. The system was equilibrated for 10 minutes before reinjecting. The wavelengths of interest, 214, 254, 280 nm, were acquired simultaneously with the PDA Detector.

Six manufacturers of 25 mm syringe tip filters were included in this analysis. Only the Pall Life Sciences products will be identified. For anonymity, the other manufacturers will be identified as Manufacturers A, B, C, M, and S. All filters were extracted according to the outlined procedure with three extraction solvents (methanol, acetonitrile, and water), and analyzed at three wavelengths (214, 254, and 280 nm). From this data set, the chromatograms that present the most useful information will be presented. In all studies the neat solvent was simultaneously analyzed. The solvent analysis, when compared to the other chromatograms, helps to determine if the peaks are from the solvent or the syringe tip device. In each category of membrane type (PVDF, hydrophilic polypropylene [GHP], Nylon, and PTFE) the intensity scales were uniformly adjusted to facilitate visual analysis of the amount of extractable material.

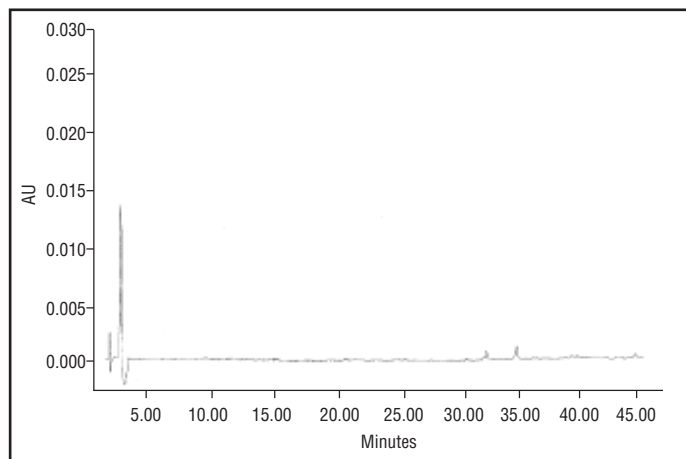
## PVDF Syringe Tip Filters

Figures 8-12 are HPLC chromatograms of acetonitrile extractions by the method described with PVDF syringe tip filters. To eliminate redundancy and maximize useful information, only the acetonitrile extractions at 280 nm are presented. Figure 8 is the chromatogram of the acetonitrile solvent. Any peaks that appear in Figures 9-12, which are not in Figure 8, are

extractable materials from the syringe tip filter. Figure 9 is Pall Life Sciences LC PVDF Acrodisc syringe filter. Figures 10-12 are from Manufacturers A, B, and M respectively. The differences in the amount of extractables from the various manufacturers demonstrate differences in formulation, housing materials and washing procedures.

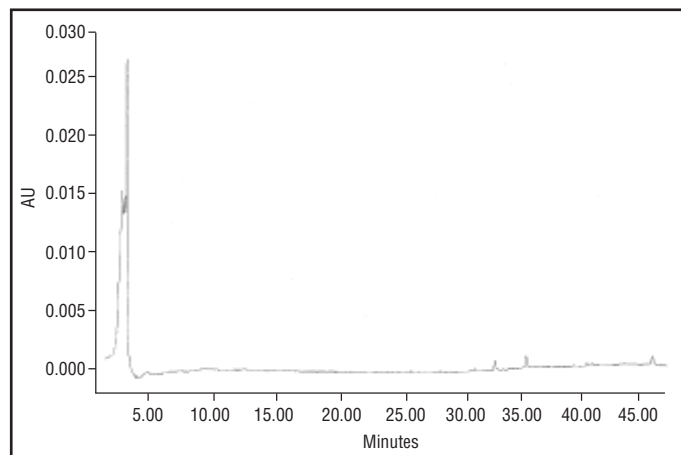
**Figure 8**

Acetonitrile Extraction: Blank



**Figure 9**

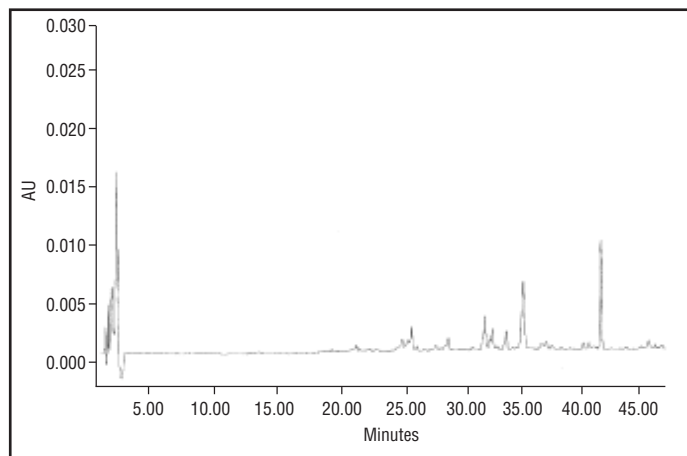
Acetonitrile Extraction: Pall Life Sciences PVDF Acrodisc Syringe Filter



## PVDF Syringe Tip Filters (continued)

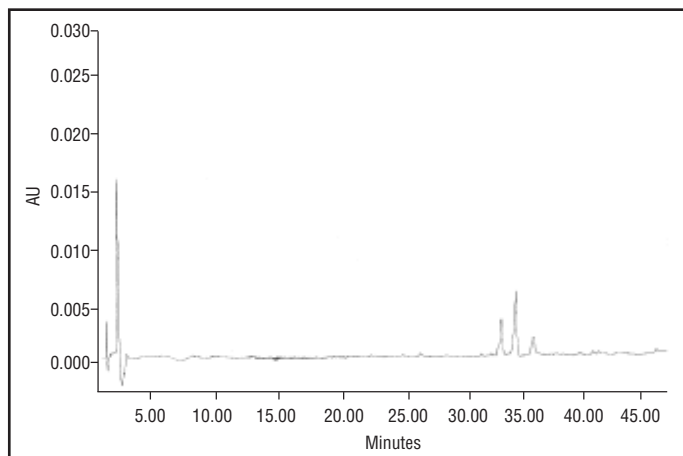
**Figure 10**

Acetonitrile Extraction: Manufacturer A Syringe Filter



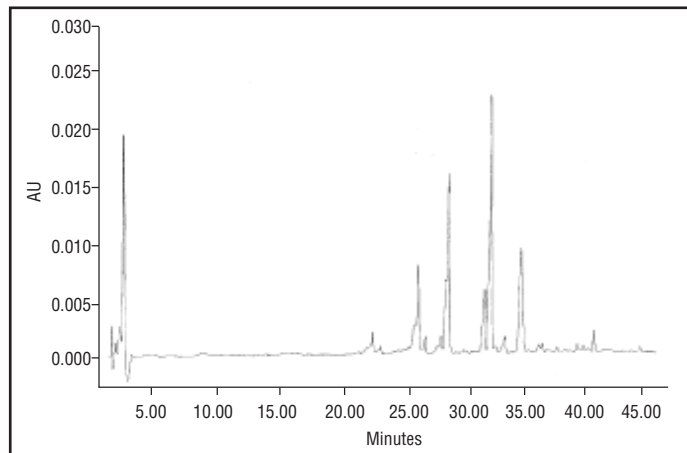
**Figure 12**

Acetonitrile Extraction: Manufacturer M Syringe Filter



**Figure 11**

Acetonitrile Extraction: Manufacturer B Syringe Filter

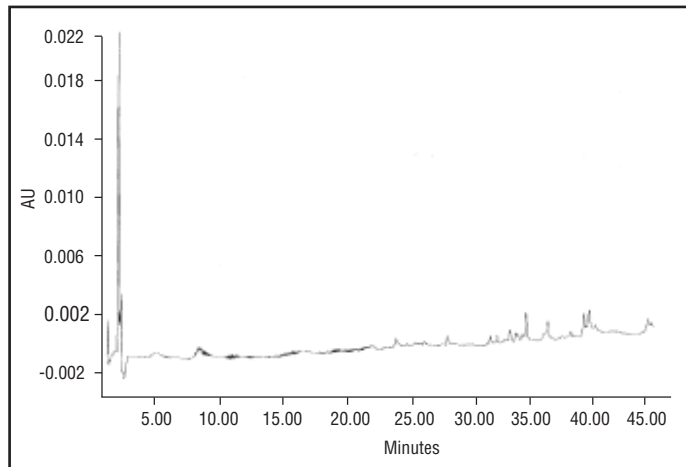


## GHP Hydrophilic Polypropylene and Other Syringe Tip Filters

Pall Life Sciences offers a GHP hydrophilic polypropylene membrane. A similar product, hydrophilic PTFE from Manufacturer M, was selected. Figure 13 represents the extraction solvent, Figure 14 the GHP Acrodisc syringe filter, Manufacturer M is displayed in Figure 15. Typically PTFE is a relatively clean material, based on the manufacturing process; therefore, the extractable materials in Figure 15 are potentially from the hydrophilic treatment or from the housing material.

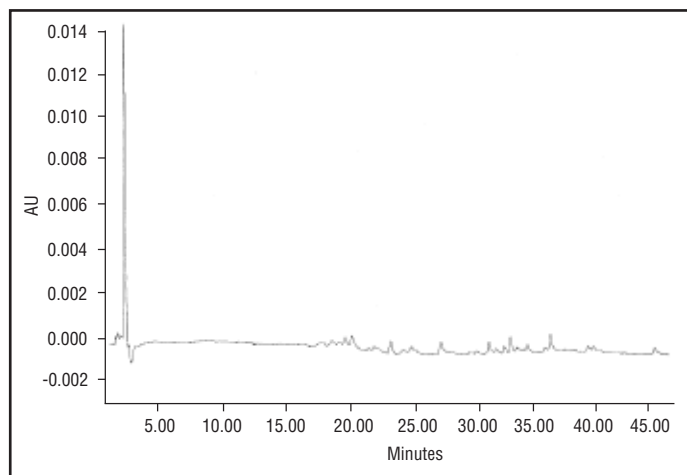
**Figure 13**

Acetonitrile Extraction: Blank



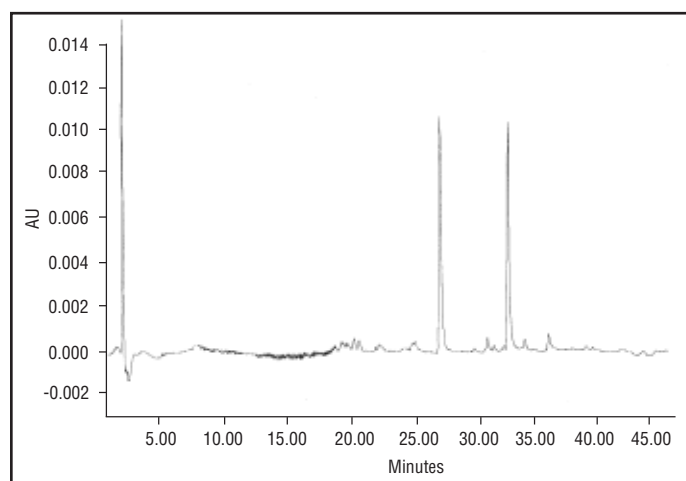
**Figure 14**

Acetonitrile Extraction: Pall Life Sciences  
GHP Acrodisc Syringe Filters



**Figure 15**

Acetonitrile Extraction: Manufacturer M Syringe Filter

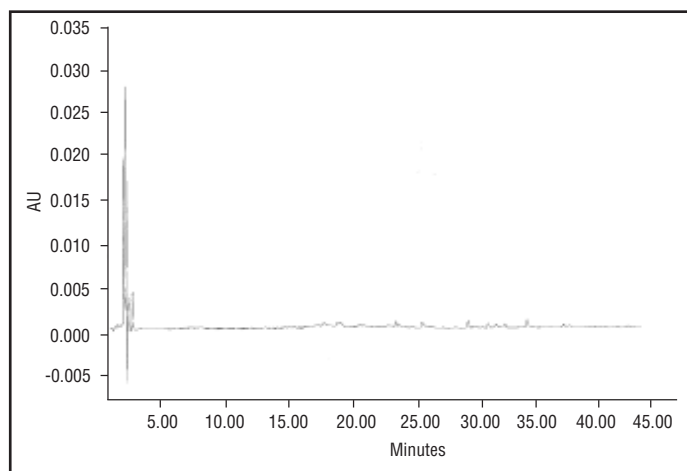


## PTFE Syringe Tip Filters

Figures 16-18 provide examples of the neat methanol, and extractions of the Pall Life Sciences CR PTFE Acrodisc syringe filter and Manufacturer B's syringe tip filter read at 214 nm. Once again, the results are indicative of the differences in membrane and housing materials, and manufacturers' procedures.

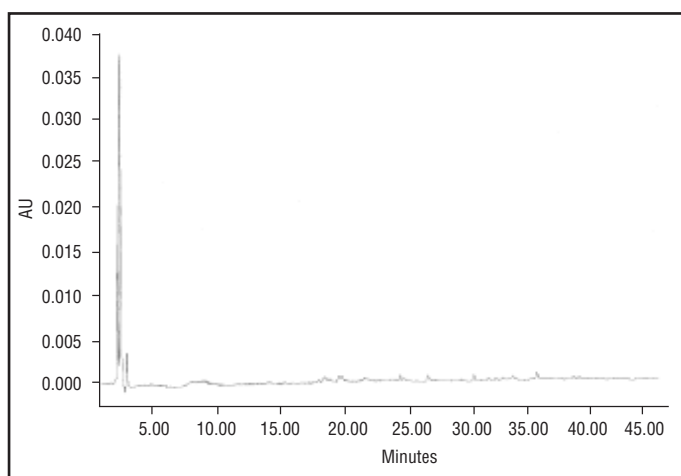
**Figure 16**

Methanol: Blank



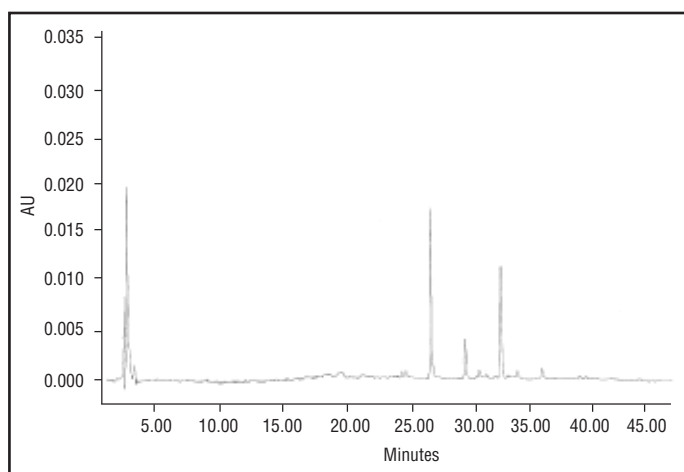
**Figure 17**

Methanol: Pall Life Sciences CR PTFE Acrodisc Syringe Filter



**Figure 18**

Methanol: Manufacturer B Syringe Filter

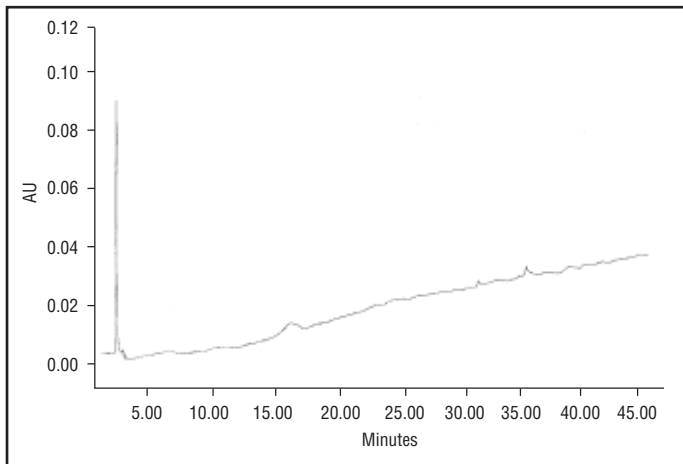


## Nylon Syringe Tip Filters

Figures 19-22 represent methanol extractions for three nylon filter brands read at 214 nm. Figure 19 represents methanol, the reference solvent. Any peaks in Figures 20-22 which are not in Figure 19 are due to the syringe filters. Figure 20 is Pall Life Sciences Nylon Acrodisc® syringe filter. Figures 21-22 represent Manufacturers' C and S products, respectively.

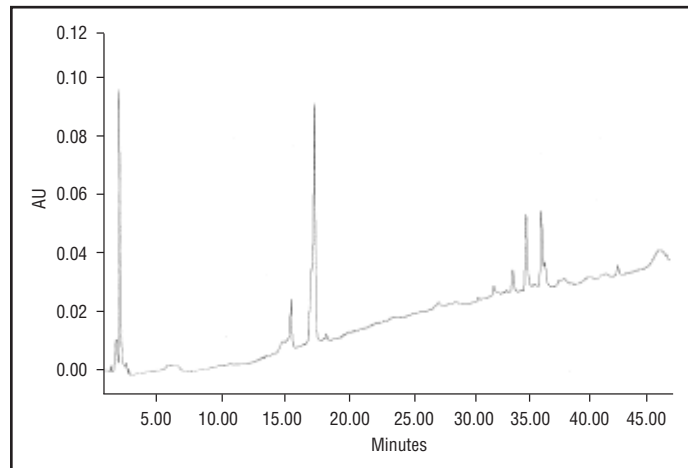
**Figure 19**

Methanol: Blank



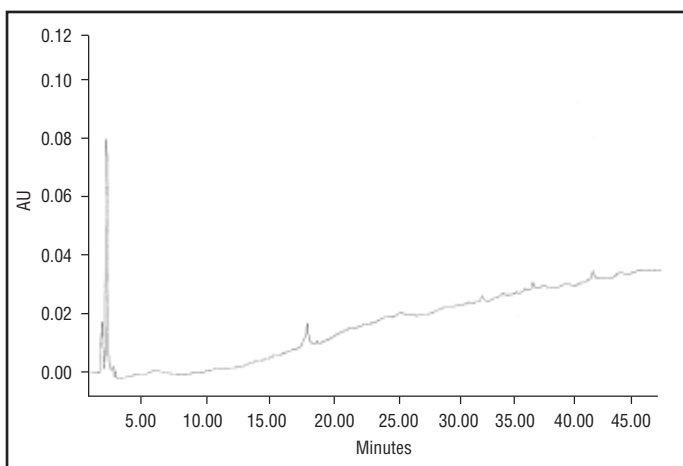
**Figure 21**

Methanol: Manufacturer C Syringe Filter



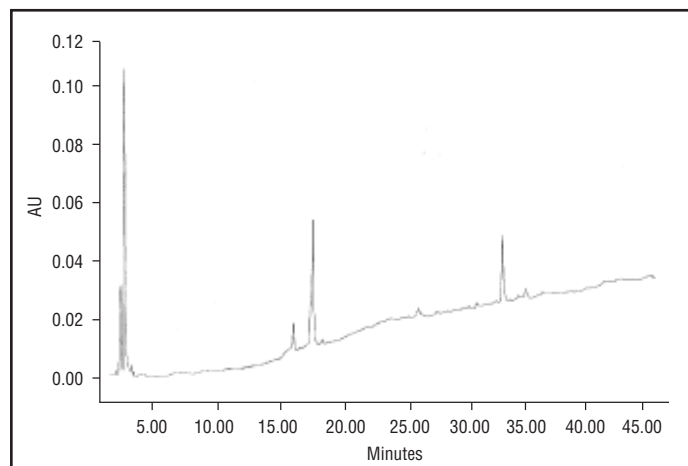
**Figure 20**

Methanol: Pall Life Sciences Nylon Acrodisc



**Figure 22**

Methanol: Manufacturer S Syringe Filter



## Conclusion

From perusal of Figures 8 - 22, it should be quite obvious that all syringe tip filters, although similar in design, are not similar with regard to extractable materials. Pall Life Sciences uses high quality raw materials and performs thorough post treatment processes on membranes that will be used in its HPLC product line to minimize the occurrence of extractables. To verify low levels of UV-detectable extractables, samples of the entire HPLC Acrodisc syringe filter product line are evaluated during the manufacturing process.

The Pall Life Sciences HPLC Certification is additional assurance that Acrodisc and Acrodisc PSF syringe filters

have been optimized to minimize extractable materials. This conveys to our customers that each and every lot meets the high standards demanded by Pall Life Sciences quality assurance department.

It also means our customers can expect reliable, reproducible results without compromising the integrity of the sample being filtered. With little or no extractables from the filter, extraneous peak identification due to filtration can be eliminated.

Application testing is recommended to determine the best membrane filter selection for specific applications.

## Flush Volume Determination

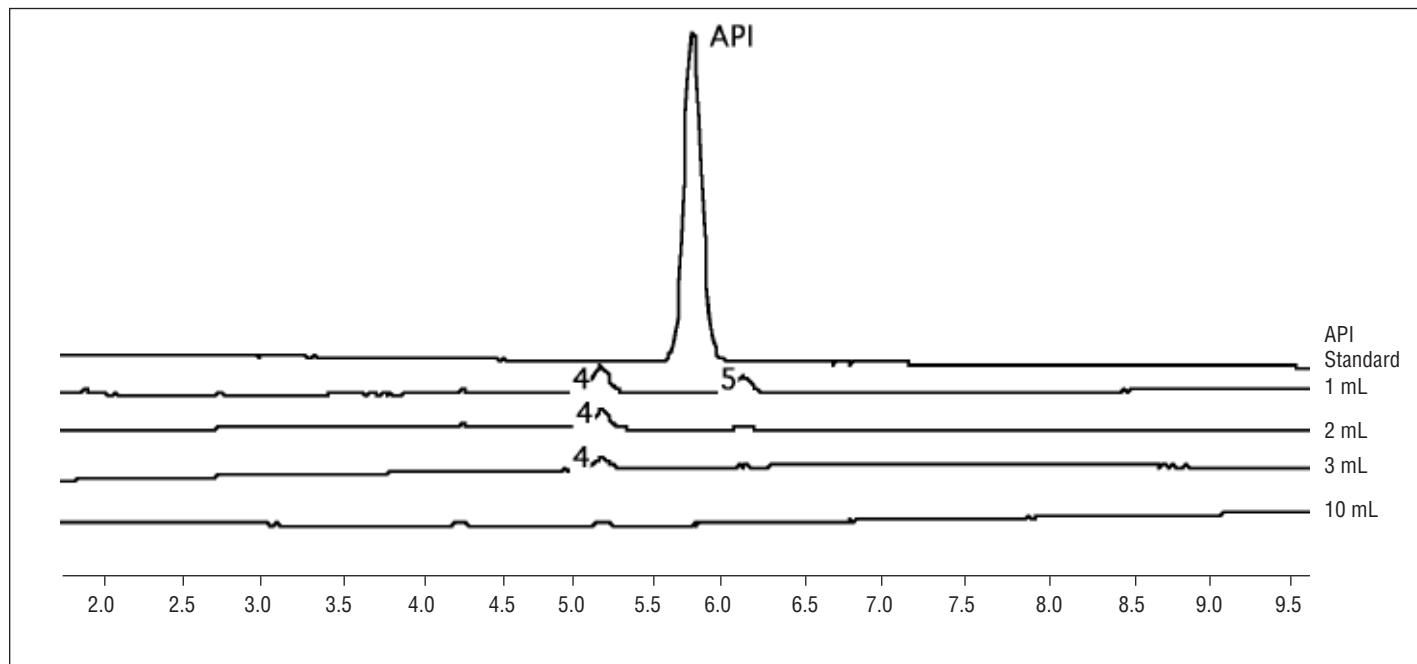
This study involves passing of the pure solvent composition (without active pharmaceutical ingredient (API)) directly through the filter and comparison of the elution profiles for each sequential 1 mL portion. It is found that a 3 mL flush volume is sufficient for the elution of possible extractables to below the interference level (equal to 0.1%). To determine an adequate flush volume, 10% Acetonitrile was pushed through an Acrodisc® PSF with GxF glass over a PVDF membrane. The sequential 1 mL filter effluent aliquots were then injected into the HPLC to determine the volume of flush required to

reduce the extractable peak(s) to an acceptable level (<0.1%). The chromatograms of the first three and the tenth 1 mL aliquots are shown in Figure 23. It is evident that the extractable peaks labeled 4 and 5 decrease considerably over the first 3 mL flush.

The same instrumentation and chromatographic conditions cited in the “Drug Binding” section of this document were followed for the flush volume determination.

### Figure 23

Filter Extractables in Consecutive 1 mL Flush Fractions (Pall GxF/PVDF, Cat # AP-4310 in 10% Acetonitrile-containing Media)



*In pharmaceuticals analysis, peaks greater than 0.1% are required to be identified. The discard volume, sufficient to reduce extractables below levels of interference with a drug purity determination, however, should be evaluated on a case-by-case basis. Changing the solvent or the filter composition may affect the required flush volume.*

## SUITABILITY OF VARIOUS FILTERS FOR SAMPLE PREPARATION IN DISSOLUTION TESTING, BASED ON DRUG BINDING

Filtration is a common method of sample preparation in dissolution testing, prior to HPLC injection. The purpose of sample filtration is to remove non-dissolved solids prior to HPLC injection. Non-dissolved solids interfere with the resulting chromatography by continuing to dissolve throughout the period of the analysis and also by plugging the HPLC column. It has already been shown that sample preparation using filtration does result in more reproducible chromatography and longer column life.

There can be potential drawbacks with filtration as a preparation for HPLC analysis in dissolution testing. The first is that the filter may adsorb active pharmaceutical ingredients (API) from the drug mixture leaving the concentration in the filtrate too low and out-of-specification (OOS).

Unwanted drug adsorption as well as the presence of possible extractables eluted from the filter during routine pharmaceutical sample analysis can be a serious problem and cause OOS results. No single analytical method can provide reliable information on comparative filter properties and the full range of extractables for all filters. Extractables have already been discussed, therefore, this study will evaluate filters for adsorption of API.

The drug product selection and product formulations in this study represent a wide variety of compounds that differ in chemical structures, ionization properties, and molecular weights and therefore differ in binding propensity. Also, a broad range of medium for the sample preparation is matrixed into the study to evaluate elution profiles of each filter. All experiments are designed based on well-characterized (validated) United States Pharmacopoeia (USP) methods.

We will demonstrate that correct selection and use of syringe filters makes the amount of API removed by the syringe filters too small to affect the HPLC determination. To do this, five drug products are each evaluated with four different syringe filters. The four different syringe filters contain three different hydrophilic polymeric membranes, plus one without glass prefilter. The five drug products represent a variety of molecular structures and chemistries and therefore are expected to demonstrate a range in adsorption to the different filter membranes.

### Experimental

There are many HPLC sample preparation filters from which to choose. Table 6 lists the four choices of hydrophilic syringe filters reviewed in this paper. The materials of construction of the filters include a glass fiber prefilter over 0.45 µm hydrophilic polypropylene (GHP), polyvinylidene fluoride (PVDF), or polyethersulfone Supor® (PES) membrane. The GHP membrane was also tested without the glass fiber prefilter. All syringe filters tested have polypropylene housings.

The drugs (API's) used in this evaluation represent a range of different functionalities and structures and should therefore

demonstrate a range of adsorption to membrane filters. As seen in Table 7, the chemical structures vary from single aromatic rings to multiple aromatic rings to a non-aromatic, polycyclic structure. Included in the study are an acid, a base, an amide, a urethane, an ester, and a lactone structure. The physical structures vary from a more flat and planar structure like that of acetaminophen to the flat but flexible structure of ibuprofen and ranitidine HCl, to the more rigid and distinct three-dimensional structure of simvastatin.

**Table 6**  
Filters Tested

ID #	Manufacturer	Product Name	Cat #	Lot #	Membrane Type	Glass Fiber Prefilter
05-04-0302	Pall Life Sciences	Acrodisc PSF	AP-4424	A224229511	Supor (PES)	YES
05-04-0303	Pall Life Sciences	Acrodisc PSF	AP-4557	A10531713	GHP	YES
05-04-0304	Pall Life Sciences	Acrodisc PSF	AP-4310	A10531121	PVDF	YES
05-04-0305	Pall Life Sciences	Acrodisc PSF	AP-4560	A10531858	GHP	NO

Membrane types:

Supor (PES) – Polyethersulfone

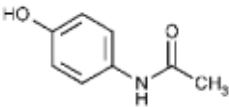
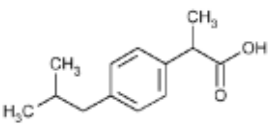
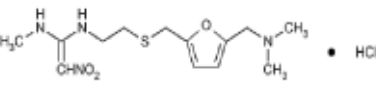
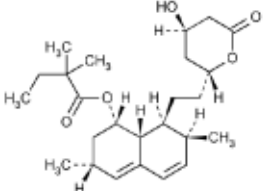
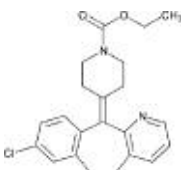
GHP – Hydrophilic polypropylene

PVDF – Hydrophilic polyvinylidene fluoride

## Experimental (continued)

**Table 7**

Pharmaceutical Products

Drug Product (Brand Name)	Molecule Type	Molecular Structure	HPLC Mobile Phase
Acetaminophen (Tylenol®) Tablets	Acetamide MW 151.16		Methanol and water (25:75)
Ibuprofen (Motrin®) Tablets	Benzeneacetic acid MW 206.28		Mixture of organic (ACN) and aqueous buffer pH 3.0 (80:20)
Ranitidine HCl (Zantac®) Tablets	Hydrochloride salt MW 350.87		Mixture of organic (Methanol) and aqueous ammonium acetate buffer (85:15) pH 7.0
Simvastatin (Zocor®) Tablets	Highly non-polar compound MW 418.57		Mixture of organic (ACN) and aqueous sodium acetate buffer pH 4.0 (80:20)
Loratadine (Claritin®) Tablets	Piperidine carboxylate MW 382.88		Mixture of organic (ACN and MeOH) and aqueous buffer (40:40:20)

## General Methodology

USP methods are intended for drug testing. Slight modifications to the sample handling in the methods are necessary for the purpose of filter comparison rather than drug testing. Well-characterized pharmaceutical samples are analyzed in duplicate and triplicate followed by statistical evaluation, which allows for increased reliability of the drawn conclusions on filter suitability.

Results are obtained by HPLC analysis with UV detector at 238 nm for Simvastatin, 243 nm for acetaminophen, 254 nm for Ibuprofen and Loratadine and 322 nm for ranitidine HCl. All calculations are performed according to each specific USP procedure against the appropriate, well-characterized (certified) corresponding USP reference standard. Label claim percentage (%LC) of each drug is calculated as ratio of the amount of drug that is found during analysis in each filtrate to the amount known (or claimed) to be present in the tested solution, and expressed as percentage. Recovery of each drug upon filtration (i.e., %LC to centrifuged) is calculated as ratio of the amount that is found during analysis in each filtrate to the amount that is found in the centrifuged sample, and expressed as percentage.

For the chosen well characterized pharmaceutical products, the value of the label claim percentage (%LC) is between 98-102% for the accurately carried testing procedure. Any additional handling of the samples (e.g. filtering or centrifugation) is a source of additional error or inaccuracy. Therefore, specifications for the filtered samples are set to meet wider 97-103% interval of acceptability. This criterion is set based on the assumption that handling of the filtering process should not add more than 1% error to the sample analysis regardless of the individual filter compatibility. This assumption was validated in the filter study. The data spread (% relative standard deviation (RSD)), which is caused solely by filtration, is less than 1% for all filters (Table 15). Therefore, results outside the 97-103% interval are indicating out-of-specification results and signaling potential filter incompatibility. Each out-of-specification result (highlighted in yellow) is addressed individually in the discussion section of this report.

## General Methodology (continued)

All solvent compositions are given in Table 7. Drugs in easily soluble salt form are less adsorbed by a generally hydrophobic filter membrane and more likely to stay in solution than be attracted to a membrane. When the amount of organic component is high enough to suppress ionization (and hence solubility) of such compound, it might result in precipitation. Therefore Ranitidine Hydrochloride adsorption is studied in aqueous solutions with a low amount of organic component, to study pure adsorption effect rather than solid particle retention.

Ibuprofen and two binary mixtures with high and low Acetonitrile content are chosen to demonstrate binding of a non-polar drug in the free form to a filter membrane in different media.

## Filter Evaluation is Conducted Using the Following Methodology

The flush volume required for consistent sample analysis (flush study) is determined in three steps. A fourth and final step (filter study) is completed to verify that flush volumes are adequate. In step one, centrifuged samples of each drug are prepared in duplicate and analyzed in duplicate for average percent recovery of the active compound against the label claim. All testing follows USP methodology. Average results can be found in Table 9.

In step two; 20 mL of the sample solution are run through each filter. The 1st, 2nd, 3rd, 5th, 10th, 15th and 20th 1 mL aliquots are collected and analyzed. The drug concentration is measured after filtration. Duplicate HPLC injections of the seven 1 mL aliquots are performed for each filter, with each drug evaluated (280 samples total). The flush volume evaluation from step two is determined as sufficient when the recovery value for the filtered sample is within 97-103% of the centrifuged sample.

In step three, filtered aliquots (from step two) are compared with centrifuged samples (from step one). The recovery of each drug preparation is determined as a percentage of label claim and as a ratio of percentage of label claim to the centrifuged sample, according to USP methodologies. The average recovery of each drug with each filter is given in Tables 10-14.

In step four, triplicate sample filtrations of each drug solution with each filter are performed. The first 3 mL flush volume is discarded and subsequent 1 mL samples are collected and analyzed by HPLC in duplicate (120 samples total). The triplicate average of each filter with each drug is itemized in Table 15. Results are reported as a percentage of label claim for each drug along with the relative standard deviation found within the sample groups.

The chromatographic conditions and standards are given below and in Table 8.

### Instrumentation

- A. Hitachi (San Jose, CA, USA) HPLC systems with the following components:
- Hitachi L7200 Autosampler.
  - Hitachi L7400 UV Detector
  - Hitachi L7100 Gradient Pump.
  - Hitachi L7300 Column Oven.
  - Perkin-Elmer (Wellesley, MA, USA) 970A Interface.
  - Perkin-Elmer TotalChrom Data acquisition system and processing software.
- B. HPLC columns (as directed in each applied USP method)
- C. General laboratory equipment and Class A analytical glassware

**Table 8**  
Reagents and Reference Standards Used

Acetaminophen USP RS (lot J2C423)	Valerophenone (Reagent grade)
Ibuprofen USP RS (lot 1335508)	4-Isobutylacetophenone (Reagent grade)
Loratadine USP RS (lot GOD344)	Chloroacetic Acid (Reagent grade)
Ranitidine USP RS (lot H0B268)	Ammonium Acetate (ACS-certified Reagent)
Simvastatin USP RS (lot I0D382)	Glacial Acetic Acid (ACS-certified Reagent)
Acetonitrile (HPLC grade)	Sodium Hydroxide (ACS-certified Reagent)
Methanol (HPLC grade)	Sodium Phosphate Monobasic (ACS-certified Reagent)
DI Water suitable for HPLC	85% Phosphoric Acid (ACS-certified Reagent)
Ammonium Hydroxide (ACS certified Reagent)	Potassium Phosphate Dibasic (ACS-certified Reagent)

## Results

**Table 9**

Results Obtained for the Centrifuged Samples of Each Drug Product in Corresponding USP Method in Filter and Flush Studies.

Acetaminophen (Tylenol®)	Ibuprofen (Motrin®)	Ranitidine (Zantac®)	Loratadine (Claritin®)	Simvastatin (Zocor®)
Average %LC	Average % LC	Average % LC	Average % LC	Average % LC
101.2	100.9	100.3	97.6	100.7

Flush Study (Optimization of the filtration parameters – flush volume determination). Data from all flush studies are summarized in Tables 10-14.

**Table 10**

Amount of Acetaminophen in Filtered Samples

ACETAMINOPHEN (TYLENOL)									
Aliquot	GxF/Supor®*		GxF/GHP*		GxF/PVDF*		GHP*		
	Average % LC	Average % Centrifuged	Average % LC	Average % Centrifuged	Average % LC	Average % Centrifuged	Average % LC	Average % Centrifuged	
1st mL	99.9	98.7	101.4	100.2	101.9	100.6	99.6	98.4	
2nd mL	101.2	99.9	100.9	99.6	101.3	100.1	101.3	100.1	
3rd mL	101.2	99.9	101.0	99.8	100.7	99.5	101.0	99.8	
5th mL	101.9	100.6	101.2	100.0	100.7	99.5	101.3	100.0	
10th mL	102.2	100.9	100.9	99.7	101.3	100.1	101.2	99.9	
15th mL	102.0	100.8	101.1	99.8	101.5	100.2	101.4	100.1	
20th mL	101.8	100.6	101.1	99.9	100.7	99.5	101.3	100.1	

**Table 11**

Amount of Ibuprofen in Filtered Samples

IBUPROFEN (MOTRIN)									
Aliquot	GxF/Supor®*		GxF/GHP*		GxF/PVDF*		GHP*		
	Average % LC	Average % Centrifuged	Average % LC	Average % Centrifuged	Average % LC	Average % Centrifuged	Average % LC	Average % Centrifuged	
1st mL	<b>104.9</b>	<b>104.0</b>	100.6	99.8	101.3	100.4	100.6	99.7	
2nd mL	100.9	100.0	100.8	99.9	100.6	99.7	101.4	100.5	
3rd mL	101.5	100.7	100.9	100.0	100.8	100.0	100.7	99.8	
5th mL	100.7	99.8	100.6	99.8	100.8	100.0	100.5	99.6	
10th mL	100.7	99.8	100.7	99.8	100.9	100.0	100.8	99.9	
15th mL	100.9	100.0	100.5	99.6	101.1	100.2	101.4	100.5	
20th mL	100.7	99.8	100.6	99.8	100.8	99.9	101.3	100.4	

## Results (continued)

**Table 12**

Amount of Ranitidine HCl in Filtered Samples

RANITIDINE HCL (ZANTAC®)								
Aliquot	GxF/Supor®*		GxF/GHP*		GxF/PVDF*		GHP*	
	Average % LC	Average % Centrifuged	Average % LC	Average % Centrifuged	Average % LC	Average % Centrifuged	Average % LC	Average % Centrifuged
1st mL	98.9	98.6	100.8	100.5	100.8	100.5	101.1	100.7
2nd mL	101.3	100.9	101.0	100.6	100.8	100.4	101.3	100.9
3rd mL	100.6	100.3	100.5	100.2	100.6	100.3	101.0	100.7
5th mL	100.0	99.7	100.4	100.1	100.5	100.2	100.9	100.6
10th mL	101.4	101.1	100.8	100.5	100.7	100.4	101.3	101.0
15th mL	100.5	100.2	100.4	100.1	101.6	101.3	101.9	101.6
20th mL	100.4	100.0	100.6	100.3	102.2	101.9	101.3	101.0

**Table 13**

Amount of Simvastatin in Filtered Samples

SIMVASTATIN (ZOCOR®)								
Aliquot	GxF/Supor*		GxF/GHP*		GxF/PVDF*		GHP*	
	Average % LC	Average % Centrifuged	Average % LC	Average % Centrifuged	Average % LC	Average % Centrifuged	Average % LC	Average % Centrifuged
1st mL	98.6	97.9	100.7	100.0	102.1	101.4	102.5	101.8
2nd mL	100.9	100.2	100.9	100.2	102.1	101.4	102.1	101.4
3rd mL	100.7	100.0	100.6	100.0	102.5	101.8	102.1	101.4
5th mL	100.8	100.1	101.4	100.7	102.7	102.0	101.9	101.2
10th mL	100.6	99.9	102.4	101.7	102.6	101.9	102.7	102.0
15th mL	100.5	99.8	102.3	101.6	102.8	102.1	102.4	101.7
20th mL	100.6	100.0	102.7	102.0	102.1	101.4	102.4	101.7

**Table 14**

Amount of Loratadine in Filtered Samples

LORATIDINE (CLARITIN®)								
Aliquot	GxF/Supor*		GxF/GHP*		GxF/PVDF*		GHP*	
	Average % LC	Average % Centrifuged	Average % LC	Average % Centrifuged	Average % LC	Average % Centrifuged	Average % LC	Average % Centrifuged
1st mL	<b>96.1</b>	98.5	<b>95.6</b>	97.9	98.0	100.4	<b>95.2</b>	97.6
2nd mL	97.2	99.6	97.6	100.0	97.9	100.4	97.6	100.0
3rd mL	97.1	99.5	97.8	100.2	97.8	100.3	97.8	100.3
5th mL	97.6	100.0	98.0	100.4	97.9	100.4	97.8	100.2
10th mL	97.8	100.2	98.1	100.5	97.8	100.2	98.0	100.4
15th mL	97.5	99.9	98.1	100.5	97.8	100.2	98.1	100.6
20th mL	97.6	100.0	98.2	100.6	97.7	100.1	98.1	100.5

\*1 Filter ID 05-04-0302 Pall Acrodisc® PSF with glass fiber prefilter over Supor membrane, PN AP-4424 Lot A224229511

\*2 Filter ID 05-04-0303 Pall Acrodisc PSF with glass fiber prefilter over GHP membrane, PN AP-4557 Lot A10531713

\*3 Filter ID 05-04-0304 Pall Acrodisc PSF with glass fiber prefilter over PVDF membrane, PN AP-4310 Lot A10531121

\*4 Filter ID 05-04-0305 Pall Acrodisc PSF with GHP membrane, PN AP-4560 Lot A10531858

## Filter Study (Finished Pharmaceutical Product Analysis)

All tested filters perform comparably for the tested drugs and solvent compositions, and are found to be suitable for the assay of the tested drug products when a 3 mL flush volume is applied. It is noteworthy that the 3 mL discard volume is

chosen as an amount that is sufficient to ensure accuracy. Results of the triplicate determination of a label claim (%LC) and data spread (%RSD) for each drug and each filter are reported in Table 15.

**Table 15**

Filter Study Summary with a 3 mL Preflush

Filter ID	Filter Description	Discarded Flush Volume (mL)	Acetaminophen (Tylenol®)		Ibuprofen (Motrin®)		Ranitidine (Zantac®)		Loratadine (Claritin®)		Simvastatin (Zocor®)	
			Average %LC	%RSD	Average %LC	%RSD	Average %LC	%RSD	Average %LC	%RSD	Average %LC	%RSD
05-04-0302	Acrodisc® PSF Cat# AP-4424 Lot# A224229511 Supor® w/glass-fiber pre-filter	3 mL	100.8	0.29	99.6	0.05	99.4	0.22	98.9	0.08	101.1	0.10
05-04-0303	Acrodisc PSF Cat# AP-4557 Lot# A10531713 GHP w/glass-fiber pre-filter	3 mL	101.2	0.25	99.5	0.06	99.6	0.37	99.1	0.39	100.6	0.15
05-04-0304	Acrodisc PSF Cat# AP-4310 Lot# A10531121 PVDF w/glass-fiber pre-filter	3 mL	101.3	0.23	99.5	0.12	100.2	0.76	99.1	0.15	100.9	0.16
05-04-0305	Acrodisc PSF Cat# AP-4560 Lot# A10531858 GHP membrane	3 mL	102.2	0.68	99.4	0.02	100.0	0.37	98.9	0.08	100.6	0.20

## Discussion

All tested filters perform comparably for the tested drugs. In this study the adsorption of an active ingredient on a filter is evaluated in successive aliquots of filtrate and compared to centrifuged samples. These experiments reveal feasibility of the applied methodology and allowed for determination of the filtration conditions with the least added error of handling. Subsequently, filter performance is compared in conditions resembling routine finished product analysis at the preferred handling conditions.

The flush study demonstrates greater variations in the label claim percentage results in the first 1 mL effluent. Four out-of-specification results occur in the first 1 mL of filter eluate. The filter study demonstrates that all four Acrodisc® PSF syringe filters are appropriate for each of these drugs based on acceptable results after a 3 mL flush.

The out-of-specification result for the Ibuprofen (shown in bold in Table 11) is attributed to possible initial adsorption of the organic solvent by the filter membrane. This initial adsorption will cause the first aliquot to have an apparent concentration above the starting concentration, which causes the initial reading to be OOS, on the high side. Disposal of the first 3 mL of the effluent is the recommended resolution to allow use of this filter with this solvent system.

The out-of-specification results for the Loratadine (shown in bold in Table 14) are attributed to the inconsistency incorporated into the study design. A flush size of 3 mL is found sufficient to avoid inherent inaccuracy of the human handling and remove any potential API binding concerns.

The 3 mL discard volume is chosen as an amount that is sufficient to ensure accuracy and consistency of experimentation and environmentally responsible solvent usage. We believe that if more solvent is necessary for the analysis, the filter is not suitable for that particular application. Results of the triplicate determination of a label claim and %RSD for each drug and each filter are reported in Table 15. The results confirm that filtration does not affect the finished drug product assay numerically and all tested filters are suitable for achieving 97-103% accuracy with the data spread (precision) less than 1%.

## Conclusion

It is accepted that membrane and drug chemistry can affect the amount of adsorption of drug products in a negative manner. If the filter membrane adsorbs too much API, the results may be out-of-specification. Choosing and using filters correctly (to reduce the amount of adsorption) is critical for accurate HPLC in dissolution testing. This investigation demonstrates that Acrodisc PSF syringe filters with GHP,

*Acrodisc PSF syringe filters with GHP, PVDF, or Supor® membrane, with and without glass prefilter layers have acceptable drug binding performance*

PVDF, or Supor membrane, with and without glass prefilter layers have acceptable drug binding performance in a wide variety of API structures and chemistries. A flush volume of 3 mL is sufficient to overcome procedural variation inherent within the methodology. As can be verified from the data in Table 15, the variation that is caused solely by filtration is less than 1% for all filters in all chemistries.



## PRODUCT FEATURES

### Features and Benefits for Pall Life Sciences' Products

Feature	Benefit
Pall Life Sciences is a cGMP compliant facility and ISO 9001 certified.	Superior quality systems in place to ensure highest quality products consistently.
Acrodisc® PSF is available with single-layer or built-in multi-layered glass fiber prefilter.	Easier filtration of difficult-to-filter solutions.
Acrodisc PSF is designed for automation and Automation Certified by Caliper Life Sciences. Packaged with AutoPack™ packaging.	Provides reliable and consistent performance in automated applications. Filters can be placed directly on the Caliper Life Sciences workstations.
Acrodisc filters are designed for high operating pressures with an integral membrane seal.	Assures high retention efficiency and housing will not burst during use.
Acrodisc filters offer better retention efficiency.	Longer HPLC column life. Less HPLC maintenance. Less chromatographic interference.
Available with HPLC certification or IC certification.	More consistent chromatography with less extractable interference.
Pall Corporation is the largest membrane manufacturer in the world.	We maintain control over membrane manufacturing to assure consistent membrane with the highest quality at all times. We have 50,000 material combinations to find a solution for every customer's needs.
Pall sells products into all aspects of the drug development pipeline from discovery to delivery.	We fully understand customers' needs and requirements, and share that knowledge across divisions. We are regularly audited by the FDA, and large pharmaceutical and biotechnology companies, with no "483's" in over ten years of successful audits.

### Materials of Construction

HPLC & IC Certified Syringe Filters

#### Housing

Pure polypropylene

#### Media

Nylon: hydrophilic nylon

PVDF: hydrophilic polyvinylidene fluoride

PTFE: hydrophobic polytetrafluoroethylene

GHP: hydrophilic polypropylene

IC: Supor®, hydrophilic polyethersulfone

Glass Fiber: hydrophilic borosilicate glass fiber

#### Fittings

Female luer lock inlet; standard male luer or minispikes outlets

## ACRODISC® PSF (25 mm Syringe Filter) PRODUCT SPECIFICATIONS

Product Numbers*	Description	Pore Size	Typical Hold-up Volume (w/air purge)	Maximum Operating Temperature	Maximum Operating Pressure	Typical Water Flow Rate
AP-4305 AP-4307 AP-4306	GxF/GHP	0.2 µm	< 200 µL	55 °C (131 °F) at 2.1 bar (210 kPa, 30 psi)	4.1 bar (410 kPa, 60 psi) at 21-24 °C (70-75 °F)	175 mL/min at 2.1 bar (210 kPa, 30 psi)
AP-4557 AP-4559 AP-4558	GxF/GHP	0.45 µm	< 200 µL	55 °C (131 °F) at 2.1 bar (210 kPa, 30 psi)	4.1 bar (410 kPa, 60 psi) at 21-24 °C (70-75 °F)	195 mL/min at 2.1 bar (210 kPa, 30 psi)
AP-4527 AP-4523 AP-4529	GxF/Glass	1 µm	< 125 µL	82 °C (180 °F) at 2.1 bar (210 kPa, 30 psi)	4.1 bar (410 kPa, 60 psi) at 21-24 °C (70-75 °F)	795 mL/min at 1.0 bar (100 kPa, 15 psi)
AP-4548 AP-4549 AP-4528	GxF/Nylon	0.45 µm	< 150 µL	55 °C (131 °F) at 2.1 bar (210 kPa, 30 psi)	4.1 bar (410 kPa, 60 psi) at 21-24 °C (70-75 °F)	215 mL/min at 2.1 bar (210 kPa, 30 psi)
AP-4301 AP-4303 AP-4302	GxF/PTFE	0.45 µm	< 125 µL	100 °C (212 °F) at 2.1 bar (210 kPa, 30 psi)	4.1 bar (410 kPa, 60 psi) at 21-24 °C (70-75 °F)	395 mL/min at 1.0 bar (100 kPa, 15 psi) (MeOH)
AP-4309 AP-4310 AP-4308	GxF/PVDF	0.45 µm	< 200 µL	82 °C (180 °F) at 2.1 bar (210 kPa, 30 psi)	4.1 bar (410 kPa, 60 psi) at 21-24 °C (70-75 °F)	144 mL/min at 2.1 bar (210 kPa, 30 psi)
AP-4364 AP-4564 AP-4566	GHP	0.2 µm	< 125 µL	55 °C (131 °F) at 2.1 bar (210 kPa, 30 psi)	4.1 bar (410 kPa, 60 psi) at 21-24 °C (70-75 °F)	215 mL/min at 2.1 bar (210 kPa, 30 psi)
AP-4357 AP-4560 AP-4562	GHP	0.45 µm	< 125 µL	55 °C (131 °F) at 2.1 bar (210 kPa, 30 psi)	4.1 bar (410 kPa, 60 psi) at 21-24 °C (70-75 °F)	300 mL/min at 2.1 bar (210 kPa, 30 psi)
AP-4587 AP-4585 AP-4785	IC (PES)	0.45 µm	< 125 µL	100 °C (212 °F) at 2.1 bar (210 kPa, 30 psi)	4.1 bar (410 kPa, 60 psi) at 21-24 °C (70-75 °F)	420 mL/min at 2.1 bar (210 kPa, 30 psi)
AP-4437 AP-4436 AP-4522	Nylon	0.2 µm	< 125 µL	55 °C (131 °F) at 2.1 bar (210 kPa, 30 psi)	4.1 bar (410 kPa, 60 psi) at 21-24 °C (70-75 °F)	115 mL/min at 2.1 bar (210 kPa, 30 psi)
AP-4517 AP-4438 AP-4502	Nylon	0.45 µm	< 125 µL	55 °C (131 °F) at 2.1 bar (210 kPa, 30 psi)	4.1 bar (410 kPa, 60 psi) at 21-24 °C (70-75 °F)	245 mL/min at 2.1 bar (210 kPa, 30 psi)
AP-4520 AP-4225 AP-4521	PTFE	0.2 µm	< 125 µL	100 °C (212 °F) at 2.1 bar (210 kPa, 30 psi)	4.1 bar (410 kPa, 60 psi) at 21-24 °C (70-75 °F)	245 mL/min at 1.0 bar (100 kPa, 15 psi) (MeOH)
AP-4518 AP-4219 AP-4501	PTFE	0.45 µm	< 125 µL	100 °C (212 °F) at 2.1 bar (210 kPa, 30 psi)	4.1 bar (410 kPa, 60 psi) at 21-24 °C (70-75 °F)	510 mL/min at 1.0 bar (100 kPa, 15 psi) (MeOH)
AP-4519 AP-4408 AP-4500	PVDF	0.45 µm	< 125 µL	82 °C (180 °F) at 2.1 bar (210 kPa, 30 psi)	4.1 bar (410 kPa, 60 psi) at 21-24 °C (70-75 °F)	144 mL/min at 2.1 bar (210 kPa, 30 psi)

\*Product Numbers are listed per the following packaging configurations:

AutoPack™ Tubes	25/200
Standard	50/200
Bulk Bag	1000/pkg

# CHEMICAL COMPATIBILITY GUIDE

	Acetone	Acetonitrile	Acetic acid, glacial	n-Butanol	Chloroform	Dioxane	Dimethyl formamide	Dimethyl sulfoxide	Ethanol	Ethyl acetate	Ethyl ether	Freon TF	Hydrochloric acid (1N)	Hexane, dry	Methanol	Methylene chloride	Methyl ethyl ketone	N-Methylpyrrolidone	Isopropanol	Sodium hydroxide (3N)	Tetrahydrofuran	Tetrahydrofuran/water (50/50)	Toluene	Water
<b>Devices with GH Polypro (GHP) membrane (hydrophilic polypropylene)</b>																								
	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
<b>Devices with PTFE membrane (hydrophobic)</b>																								
4 mm	R*	R	R	R	L	R	R*	R*	R	R*	R	R	R	R	R	L	R*	R*	R	L	L	●	L	R
13 & 25 mm, AcroPrep™	R*	R	R	R	R	R	R*	R*	R	R*	R	R	R	R	R	R	R*	R*	R	R	R	R	R*	R
<b>Devices with PVDF membrane (hydrophilic)</b>																								
	N*	R	R	R	R	R	N*	N*	R	R*	R	R	R	R	R	N	N	R	N	N	●	R*	R	
<b>Devices with Nylon membrane (hydrophilic)</b>																								
	R*	R	N	R	R	R	R*	R*	R	R*	R	R	N	R	R	R	R*	R*	R	L	R	R	R*	R
<b>Devices with Supor® PES membrane (hydrophilic)</b>																								
	N	L	R	R	N	●	N	N	R	N	R	L	R	L	R	N	N	N	R	R	N	●	R	R
	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	L	L	●	R	R
GH Polypro	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
FP Vericef® (PVDF)	N	R	R	R	R	R	N	N	R	R	R	R	R	R	R	N	N	R	N	N	●	R	R	
Nylaflo® (Nylon)	R	R	N	R	R	R	R	R	R	R	R	N	R	R	R	R	R	R	L	R	R	R	R	
TF (PTFE)	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R

\* UV absorbance was set at 254 nm.

Test Methods: The data presented in this chart is a compilation of testing by Pall Corporation with certain chemicals, manufacturer's data, or compatibility recommendations from the *Compass Corrosion Guide*, by Kenneth M. Pruett. This data is intended to provide expected results when filtration devices are exposed to chemicals under static conditions for 48 hours at 25 °C (77 °F), unless otherwise noted. This chart is intended only as a guide. Accuracy cannot be guaranteed. Users should verify chemical compatibility with a specific filter under actual use conditions. Chemical compatibility with a specific filter, under actual use conditions, is affected by many variables, including temperature, pressure, concentration, and purity. Various chemical combinations prevent complete accuracy.

## Note:

### R = RESISTANT

No significant change was observed in flow rate or bubble point of the membrane.

### L = LIMITED RESISTANCE

Moderate changes in physical properties or dimension of the membrane were observed. The filter may be suitable for short term, non-critical use at room temperature.

### N = NOT RESISTANT

The membrane is basically unstable. In most cases, extensive shrinkage or swelling occurs. The filter may gradually weaken or partially dissolve after extended exposure.

● = INSUFFICIENT DATA Information not available. Trial testing is recommended.

## REFERENCES

- Azopharma Contract Pharmaceutical Services, Filter Evaluation Study Report Number R050T18B, (October 2005) (Internal Pall Report)
- B. Pearce and W.L. Thomas, *Anal. Chem.*, 44, 1107 (1972).
- Ding W. and Scheer L., Syringe Filter Efficiency and the Effect of Filtration on HPLC Column Life, European Biopharmaceutical Review, p. 60, (2004).
- D. Parriott, A Practical Guide to HPLC Detection (Academic Press Inc, 1993).
- F.M. Rabel, *J. Chromatogr. Sci.*, 18, 222 (1980).
- H. Spaans, H. Terol, and A. Onderwater, *J. Chromatogr. Sci.*, 14, 246 (1976).
- J.A. Dean, Analytical Chemistry Handbook, McGraw-Hill, Inc. (1995).
- J.G. Nikely and D.A. Ventura, *Anal. Chem.*, 51, 1585 (1979).
- J. Merrill, *American Laboratory*, 19 (10), 74 (1987).
- Jones Chromatography Manual, Lakewood, CO, (1995).
- J.W. Dolan and L.R. Snyder, Troubleshooting LC Systems, Humana Press Clifton, NJ, (1989).
- Lindenberg M., Wiegand C., Dressman B., Comparison of the Adsorption of Several Drugs to Typical Filter Materials, Dissolution Technologies, (2005).
- L.R. Snyder, J.J. Kirkland, and J.L. Glajch, Practical HPLC Method Development, 2nd Edition, John Wiley & Sons, Inc. (1997).
- L.V. Berry and B.L. Karger, *Anal. Chem.*, 45, 819A (1973).
- R.W. Yost, L.S. Ettre, and R.D. Conlon, Practical Liquid Chromatography. An Introduction, Perkin-Elmer, Norwalk, (1980).
- W.W. Yau, J.J. Kirkland, and D.D. Bly, Modern Size-Exclusion Liquid Chromatography, Wiley, New York, (1979).
- M.L. Mayer, *LC. GC*, 14 (10), 902 (1996).
- M.L. Mayer, *American Laboratory*, 29 (1), 1 (1997).
- M. Martin, G. Blu, C. Eon, and G. Guiochon, *J. Chromatogr. Sci.*, 112, 399 (1975).
- P. Achener, S.R. Abbott, and R.L. Stevenson, *J. Chromatogr. Sci.*, 130, 29 (1977).
- R.E. Jentoft and T.H. Gouw, *J. Chromatogr. Sci.*, 14, 246 (1976).
- R.E. Majors, *LC..GC*, 13 (5), 364 (1995).
- R.M. Cassidy and R.W. Frei, *Anal. Chem.*, 44, 2250 (1972).
- R.W. Yost, L.S. Ettre, and R.D. Conlon, Practical Liquid Chromatography. An Introduction, Perkin-Elmer, Norwalk, (1980).
- Snyder L.R., Kirkland J.J. and Glajch J.L., Practical HPLC Method Development, 2nd Edition, John Wiley & Sons, Inc. (1997).
- USP 28 – NF 23, page 1702, 1704 (Ranitidine Hydrochloride Monograph).  
Pharmacopeial Forum: Volume Number 30(6), page 2033.
- USP 28 – NF 23, page 1770, 1771 (Simvastatin Monograph).  
Pharmacopeial Forum: Volume Number 30(5), page 1647.  
Pharmacopeial Forum: Volume Number 29(2), page 437.
- The Waters Chromatography Handbook, Milford, MA (1993 - 1994).
- T.W. Smuts, D.J. Solms, F.A. Van Niekerk, and V. Petorius, *J. Chromatogr. Sci.*, 7, 24 (1969).
- USP 28 – NF 23, page 16, 17, 19 (Acetaminophen Monograph).  
Pharmacopeial Forum: Volume Number 27(3), page 2494, 2495.
- USP 28 – NF 23, page 991, 993 (Ibuprofen Monograph).  
Pharmacopeial Forum: Volume Number 27(4), page 2740.
- USP 28 – NF 23, page 1149, 1151 (Loratadine Monograph)  
USP 28 – NF 23 Supplement: No. 2, page 3500.  
Pharmacopeial Forum: Volume Number 30(6), page 2011.  
Pharmacopeial Forum: Volume Number 29(4), page 1045.
- V.R. Meyer, 2nd Edition, Practical HPLC, John Wiley and Sons LTD, (1994).
- W.W. Yau, J.J. Kirkland, and D.D. Bly, Modern Size-Exclusion Liquid Chromatography, Wiley, New York, (1979).



Life Sciences

**Pall Life Sciences**  
600 South Wagner Road  
Ann Arbor, MI 48103-9019 USA

800.521.1520 toll free in USA  
734.665.0651 phone  
734.913.6114 fax

**Australia** – Lane Cove, NSW

Tel: 02 9424-3000  
1800 635-082 (in Australia)  
Fax: 02 9428-5610

**Austria** – Wien

Tel: 00 1 49 192 0  
Fax: 00 1 49 192 400

**Canada** – Ontario

Tel: 905-542-0330  
800-263-5910 (in Canada)  
Fax: 905-542-0331

**Canada** – Québec

Tel: 514-332-7255  
800-435-6268 (in Canada)  
Fax: 514-332-0996  
800-808-6268 (in Canada)

**China** – P. R., Beijing

Tel: 86-10-8458 4010  
Fax: 86-10-8458 4001

**France** – St. Germain-en-Laye

Tel: 01 30 61 39 92  
Fax: 01 30 61 58 01

Lab-FR@pall.com

**Germany** – Dreieich

Tel: 06103-307 333  
Fax: 06103-307 399

Lab-DE@pall.com

**India** – Mumbai

Tel: 91 (0) 22 55995555  
Fax: 91(0) 22 55995556

**Italy** – Milano

Tel: 02 47 79 61  
Fax: 02-47796 394  
or 02-4122 985

**Japan** – Tokyo

Tel: 03-6901-5800  
Fax: 03-5322-2134

**Korea** – Seoul

Tel: 82-2-560-7871  
Fax: 82-2-560-7822

**Malaysia** – Selangor

Tel: +60 3 5569 4892  
Fax: +60 3 5569 4896

**New Zealand** – Hamilton

Tel: +64 7 957 9510  
Fax: +64 7 957 9513

**Poland** – Warszawa

Tel: 22 510 2100  
Fax: 22 510 2101

**Russia** – Moscow

Tel: 5 01 787 76 14  
Fax: 5 01 787 76 15

**Singapore**

Tel: (65) 389-6500  
Fax: (65) 389-6501

**South Africa** –

Johannesburg  
Tel: +27-11-2662300  
Fax: +27-11-3253243

**Spain** – Madrid

Tel: 91-657-9876  
Fax: 91-657-9836

**Sweden** – Lund

Tel: (0)46 158400  
Fax: (0)46 320781

**Switzerland** – Basel

Tel: 061-638 39 00  
Fax: 061-638 39 40

**Taiwan** – Taipei

Tel: 886 2 2545 5991  
Fax: 886 2 2545 5990

**Thailand** – Bangkok


Tel: 66 2937 1055  
Fax: 66 2937 1066

**United Kingdom** –

Farlington  
Tel: 02392 302600  
Fax: 02392 302601  
Lab-UK@europe.pall.com

Visit us on the Web at [www.pall.com/lab](http://www.pall.com/lab)

E-mail us at [Lab@pall.com](mailto:Lab@pall.com)

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