CRITICAL PROCESS FILTRATION, INC.

Application Summary

Filtration in Pharmaceutical Water Systems

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Water is a key ingredient used in many pharmaceutical and life sciences operations. Its uses vary widely, from equipment cleaning to a solvent to a primary ingredient in injectable drugs.

Water systems, often based on reverse osmosis and deionization, produce pure water. Additional treatment, most often distillation, further purifies the water to meet the specific requirements of the water's use. Cartridge filters are used in various parts of the process to assure process efficiency and safeguard the quality of the water.

Pharmaceutical Water Requirements

Water used to produce pharmaceutical products, whether for washing equipment, rinsing containers or as an ingredient, must meet quality requirements as dictated in standards published by the United States Pharmacopeia (USP) , Pharmacopeia Europa (EP), Japanese Pharmacopeia and others[1]. Each of these Pharmacopeia set similar standards, and efforts are underway to harmonize standards, but there are variations. For example, in the production of water for injection (WFI) grade water, the USP suggests distillation but allows for other processes. Until 2017, the EP only allowed distillation for WFI production. Due to recent discussions within the EP community regarding research on WFI technology, the EP now accepts other processes.

In addition to the formal standards, there are inspection guidelines used by various regulatory bodies. Those guidelines often discourage the use of filters for bacterial control. The argument against filters is that they may allow lax operation of systems that should be maintained in a bacteria-free state. However, many guidelines also recognize that there may be system upsets and excursions that result in bacteria in the system. For that reason, filters may be allowed as an "insurance policy" against such upsets.

There are several Pharmacopeial monographs for various grades of water. Most of the monographs govern water packaged for use in a location separate from where it is produced. This application guide focuses on the production of the two main "bulk pharmaceutical waters" produced for use on-site – Purified Water (PW) and Water for Injection (WFI) - and the filtration steps used to produce these waters.

This guide reviews USP, EP and JP standards and presents a generic water purification system design. The location of filtration steps are highlighted and the technical aspects for each filtration step discussed. Products manufactured by Critical Process Filtration are suggested for each of these steps. At the end of this guide, an overview of Critical Process Filtration filter media and devices is presented.

The USP has published monographs stating the quality requirements for water used for pharmaceutical and other life science applications. The guidelines described in USP General Chapter <1231>, outline three basic grades of "Monographed Waters": Purified Water (PW), Water for Injection (WFI) and Water for Hemodialysis. Other grades of water are identified in the monographs for specific uses and their quality attributes are based on either Purified Water or WFI. While Water for Hemodialysis is referenced in USP and EP guidelines, hemodialysis water quality requirements in the US are also governed by AAMI[2] , though efforts are underway to harmonize these

[1] Organizations in countries such as China and India publish regulations which should be considered, though most have harmonized their regulations with the USP, EP and JP.
[2] AAMI –Association for the Advancement of Medical Instrumentation

guidelines. Water for hemodialysis systems will not be covered in this guide, but many of the requirements are similar to those discussed below. Contact Critical Process Filtration if you require more specific information on filtration products for hemodialysis water systems.

The USP, EP and JP quality standards for the three main Pharmaceutical Waters are shown in Table 1 on the following page. As a note, distillation is the most common method used to produce WFI. Methods other than distillation are rarely used, but other processes have been proven to consistently produce water meeting WFI requirements.

One other item to note in the standards is that the water quality does not require sterility. There are allowable bacteria counts in both Purified Water and WFI. According to the July 1993 FDA Guide to Inspections of High Purity Water Systems, this is due to the WFI water sampling practices used. Most samples are drawn from a system in a non-sterile area, which frequently can result in sample contamination by low levels of airborne bacteria. No system operator allows bacteria counts above zero. The standard only recognizes the futility of always guaranteeing zero bacteria in sampling. However, it is also worth noting that system maintenance and the ability of bacteria to find their way into any system by numerous means can result in small excursions above zero from time to time. Addressing bacteria levels through a combination of prevention and remediation, including the use of filters, is covered later in this paper

*Table 1: Selected Water Quality Specifications for Pharmaceutical Water**

Parameter	Purified Water			Water for Injection		
	USP	Ph Eur (bulk)	JP	USP	Ph Eur (bulk)	JP
TOC (ppb C)	500	500	500	500	500	500
Aerobic Bacteria	≤ 100 CFU/ml	≤ 100 CFU/ml	≤ 100 CFU/ml	≤ 10 CFU/ml	≤ 10 CFU/ml	≤ 10 CFU/ml
Bacterial Endotoxins (EU/ml or IU/ml)	NA	NA	NA	≤ 0.25	≤ 0.25	≤ 0.25

NA = Not an Applicable Requirement

* Sources – United States Pharmacopeia 40, General Chapter <1231>, United States Pharmacopoeial Convention, Inc. 12601 Twinbrook Parkway, Rockville, MD (2018); European Pharmacopoeia Edition 9 (EDQM.226. avenue de Colmar BP 907, F-67029 Strasbourg, France, 2016); Note for Guidance on Quality of Water for Pharmaceutical Use, European Agency for the Evaluation of Medicinal Products (EMEA), 7 Westferry Circus, Canary Wharf, London, E14 4HB, UK (2002); The Japanese Pharmacopoeia, Seventeenth Edition, April 1, 2016 (English Version). The Ministry of Health, Labour and Welfare, Pharmaceuticals and Medical Devices Agency. JCN 3010005007409, Shin-Kasumigaseki Building, 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan

Producing Bulk Pharmaceutical Waters

The exact methods for treating water to meet the standards are left intentionally flexible in the USP, EP and JP documents. The initial assumption is that all grades of pharmaceutical water will be produced starting with a "potable water"[1] source and using a "suitable process". USP <1231> describes several suitable treatment processes to produce pharmaceutical waters. Most systems utilize a reverse osmosis process combined with deionization to produce Purified Water. The vast majority of WFI systems utilize distillation as the final treatment process due to its widespread acceptance throughout the world. However, the majority of Pharmacopoeias are now accepting other methods to produce WFI, including double-pass reverse osmosis.

Figure 1 below is a schematic of a possible system to produce and distribute Purified Water (PW) and WFI. The system shown uses a vapor compression or multi-effect still to produce Water for Injection (WFI) from Purified Water. A system using double-pass reverse osmosis (Figure 2 on the next page) has no purified water loop or still, since the water from the 2-pass system would meet WFI standards. The location of

[1] Drinking Water as defined by the US Environmental Protection Agency or the World Health Organization

filters and their functions are essentially the same in both systems.

There are some steps in both schematics that may not be necessary based on the quality of the incoming water. However, for completeness, more steps are included at the beginning of each system to address potential incoming water quality issues. Neither figure may be representative of your system, though they do illustrate the many locations where filtration products may be utilized. Contact Critical Process Filtration to discuss specifics.

The locations of normal flow filters and their various functions are discussed in the sections below

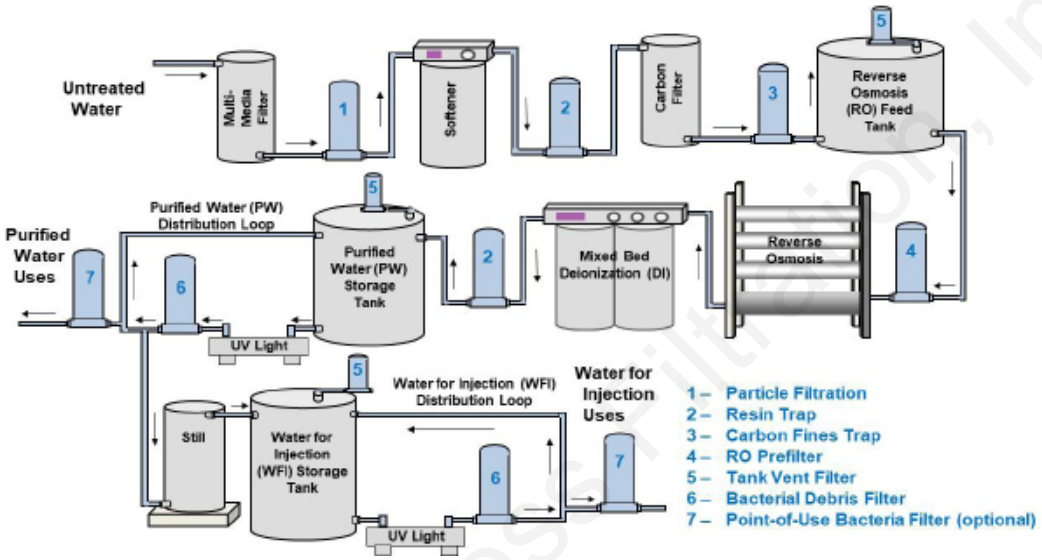

Figure 1: Purified Water/Water for Injection from Distillation System Design

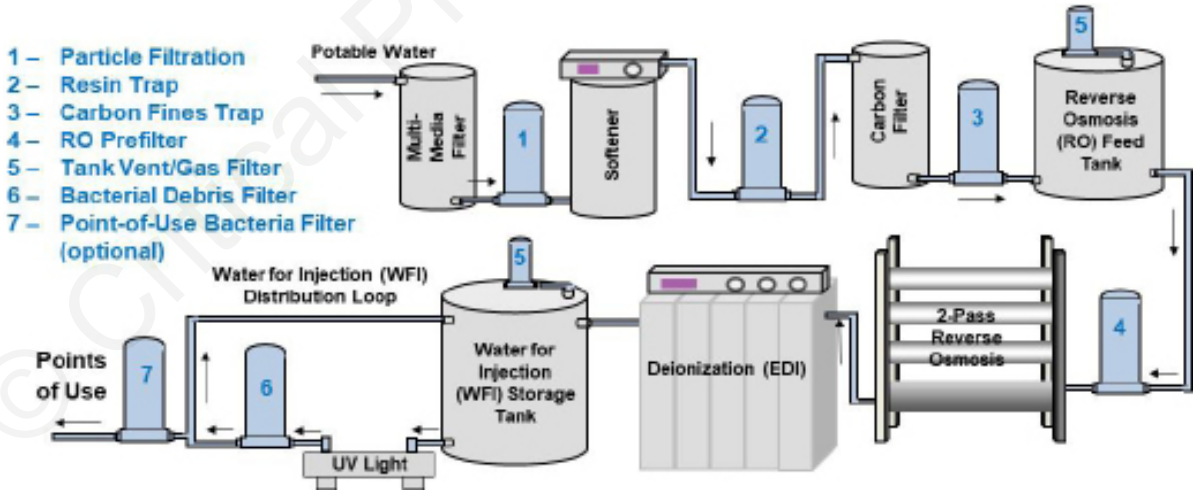

Figure 2: Water for Injection System 2-Pass RO Design

Prevention and Remediation

Most of the time, the old saying, "An ounce of prevention is worth a pound of cure" is true. Preventing an unwanted event is usually easier than repairing whatever damage is done if the event occurs. However, in virtually all water systems, including pharmaceutical water systems, it is safe to assume that BOTH prevention and remediation are needed to control bacteria.

For our purposes, we will define prevention as not allowing bacteria to enter a system. The only way to do that is to design the system using components that are operated with a minimum of maintenance. Any maintenance activities that require opening system components will expose the interior to the atmosphere and allow bacteria to enter. Though rare, some systems have been designed for operation in a clean room environment that has severely reduced airborne bacteria levels, but that is prohibitively expensive for most operators.

As you can tell, it is almost impossible to totally prevent bacteria from entering a system. Therefore, remediation steps are needed. Some may call these steps prevention – because they are designed to prevent the bacteria from rising to unacceptable levels. What they are called doesn't matter. What matters is that multiple barriers be put in place to control bacteria levels in pharmaceutical water systems.

Remediation steps inhibit bacterial growth (high temperatures, ozone injection), kill bacteria (system sanitizing or disinfection with heat or chemicals) or physically remove bacteria (filtration). We will focus on filtration, but the other methods used may impact the decision to use filters at all, or the choice of filters based on thermal and/or chemical compatibility.

Filters in a Prevention and Remediation Process

The filters shown in Figure 1 on the previous page are possible components of a pharmaceutical water system. All components, including the filters, will have to be maintained during the system's service life. Installing components that require minimal maintenance, including an optimized filter system, reduces the opportunity for bacteria to enter the system (prevention). But each component WILL be opened, and bacteria WILL enter the system. Therefore, filters are in place to capture the bacteria. What filters are installed will depend on the temperature of the system, any chemicals used for system disinfection, and the likely bacterial load.

Filtration Applications for Pharmaceutical Waters

The "typical" filter applications shown in the generic pharmaceutical water systems represented in Figures 1 and 2 are not the only filters that may be required. Additional filters may be used if the source water contains unique substances which could cause premature filter plugging or premature fouling of RO membranes if not addressed. Contact the Critical Process Filtration's technical support team to discuss any unique requirements.

The use of filtration products in pharmaceutical water systems generally falls into two categories, particle filtration and bacteria reduction/removal. Filtration products located before the reverse osmosis (RO) unit reduce or remove particle contaminants while most filters following the RO unit are intended to reduce or remove bacterial contaminants.

Each filter application shown is described in some detail below with recommendations for filtration products commonly used to perform each function.

Particle Filtration

The initial water treatment step is coarse filtration to remove larger particulates such as sediment and silt. The figures show a sand or multi-media filter followed by a filter which would remove particles that pass through or are released by the multi-media filter. In smaller systems, both filters may be combined into a single step (Housing 1) for sediment and particle removal. The typical pore size rating of these filters is 5 micron.

Depth filtration products such as Critical Process Filtration's Melt-Blown Polypropylene or Nano-Spun Polypropylene cartridges are commonly used for particulate removal. These products can capture a

large quantity of silt or sediment before requiring replacement. Yarn wound filters are utilized by some system manufacturers, but wound filters often add "extractable" surfactants to the water upon installation. Yarn wound filters are also susceptible to channeling, which allows water to pass unfiltered through the media. The superior consistency of Melt-Blown or Nano-Spun filters ensures consistent particle removal unmatched by yarn wound filters.

Depending on the type and number of particles in your water supply, an economical alternative to standard depth filters are pleated media filters. Pleated filtration products, such as the Critical Process Filtration Pleated Polypropylene Depth filters, can remove several times more sediment and silt than melt-blown or nano-spun filters. While pleated filters generally cost more, the increased service life and greater dirt holding capacity coupled with the labor savings from lower filter change frequency can make pleated filters economical.

Resin Trap Filters

There are two resin-based treatment processes illustrated in the system diagrams, water softening and mixed bed deionization. In both cases, the resin beads installed to treat the water may break down as the resins age and introduce resin fines into the water. Filters in housings marked "2" have been installed to remove these resin fines from the water. Note: some 2-pass RO systems may use mixed bed DI instead of electro-deionization. Such systems would also have a resin trap filter after the DI step.

Both small and larger pharmaceutical water systems will use these resin based processes. As with the previous particle filters, the most common filter media is melt-blown or nano-spun polypropylene, such as the Critical Process Filtration Melt-Blown Polypropylene or Nano-Spun Polypropylene filters, although pleated filters may be utilized for longer life and reduced replacement frequency. As with particle filters, the typical pore size rating is 5 micron.

Carbon Fines Removal

The activated carbon filter shown in the diagram is typically a granular activated carbon filter that removes chlorine, chloramine, and other dissolved organic materials from the water supply. This protects downstream treatment components, particularly RO membranes, from oxidation. Unfortunately, all carbon filters produce carbon fines, and the filter marked "3" is installed to remove fine carbon particles in order to protect downstream equipment.

Depth filtration products such as Critical Process Filtration's Melt-Blown or Nano-Spun Polypropylene Depth filters, and yarn would filters are the most commonly used products for carbon fines removal, with the same limitations mentioned above for yarn wound filters. Pleated filters may also be utilized in this location, with their high dirt holding capacity providing value. Filter pore size ratings are usually 3 to 5 microns.

Smaller systems utilize activated carbon block cartridge filters, such as ACB Activated Carbon Block filter cartridges from Critical Process Filtration instead of granular carbon beds. Due to their method of construction, carbon block filters do not shed carbon fines after a short initial rinse, making a downstream filter unnecessary.

RO Prefiltration

Filter 4 in the diagrams is the RO prefilter, which is critical to protecting the high pressure RO pump and preventing the membranes from premature fouling due to particles. Protecting the RO membranes from particles is extremely important. Particles larger than 3 to 5 microns can quickly reduce the efficiency of the membranes.

The Critical Process Filtration Melt-Blown Polypropylene or Nano-Spun Polypropylene filters rated at 5 microns are typically utilized to protect RO membranes. Alternatively, the use of Pleated Polypropylene Depth filters will reduce the number of filter elements needed (due to lower pressure drops and higher flows) and may reduce change frequency because of their higher dirt holding capacity. Though melt-blown or nano-spun cartridges may each cost less than a pleated cartridge, the pleated filters may be desirable due to the lower the number of filters and potentially longer filter life.

Tank Vent Prefilters

Filter housings marked 5, shown in multiple locations in the diagrams, contain elements to filter the air or process gas (such as nitrogen) directly in contact with RO feed water, Purified Water or WFI in storage tanks, protecting the water from bacterial and particulate contamination. As a tank is filled, the air inside must be allowed to escape. Conversely, as the tank is emptied, air (or a process gas such as nitrogen) must be allowed to enter the tank to replace lost liquid volume. The air or gas entering the tank must have particles and bacteria removed or the water will become contaminated. Because these filters are expected to remove bacteria, the pore size ratings are usually 0.2/0.22 or 0.10 microns. They may also be designated as "sterilizing grade".

It is critical that the tank filter media remain dry so that air or gas can pass freely through it. If the pores of the membrane are filled with water, then air flow will be blocked and a vacuum will develop inside a tank being emptied. (Tanks, like thin aluminum soda cans, are built to remain stable when pressurized, but easily crush if even a small vacuum develops.) Hydrophobic membrane such as PTFE is typically used because it resists wetting from water vapor and reduces the risk of tank failure.

Critical Process Filtration sterilizing grade PTM filters are utilized for ambient temperature storage tanks. Most WFI storage tanks are maintained at elevated temperatures, requiring the use of high temperature PTFE membrane cartridges (model PTM/HT), often in steam jacketed housings to maintain heat levels and prevent vapor from condensing within the membrane pores.

NOTE: Vent filters play a critical role in system design. Tanks that are not specifically designed for vacuum conditions are very susceptible to collapse if subjected to a vacuum. It is critical to properly size the vent filter to allow for ample air flow at the maximum draw down rate of the storage tank. Improper sizing can result in permanent tank damage.

Bacteria Filtration

WFI systems utilizing storage and distribution systems kept at elevated temperatures need no additional filtration since the water has been rendered sterile and is maintained in a sterile state with heat. However, some systems may install a UV light to kill any stray bacteria that can enter the system (as previously discussed). Filters marked "6" are shown as barriers to bacterial cell debris moving down the distribution system to points of use. Some system operators may choose to also utilize point-of-use filtration as their final insurance against bacterial excursions. They are shown in the diagrams as Filter 7. Bacterial debris filters could be either bioburden reduction filters or sterilizing grade filters, depending on the level or debris removal desired. Final filters, if used, are usually "sterilizing grade" filters.

Sterilizing grade filters must pass the ASTM International F838-05 "Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration". That test proves that the filters will remove at least 100,000 bacterial colonies per cm2 of membrane surface area without any passing through to the product side of the filters. Filters not meeting this removal criteria are considered "bioburden reduction filters" rather than "sterilizing grade filters". Typical sterilizing grade filters utilized in pharmaceutical water systems are rated to remove particles and bacteria that are 0.2/0.22 or 0.1 micron or larger in size. Bioburden reduction filters may be rated with the same pore sizes, but larger pore sizes are also used.

Critical Process Filtration offers several products to meet the requirements for bioburden reduction and sterilizing grade filtration. Critical Process Filtration's bioburden reduction filters include membrane filters made from symmetric or asymmetric polyethersulfone (PES), polyvinylidene fluoride (PVDF), and nylon 6,6. Critical Process Filtration refers to these filters as "Biopharmaceutical Grade" filters.

Critical Process Filtration's sterilizing grade and bioburden reduction filters include membrane filters made from asymmetric PES and nylon 6,6. Both are available with either a 0.1 µm or 0.22 µm pore size rating as well as larger pore sizes. Critical Process Filtration refers to these filters as "Pharmaceutical Grade" or "Biopharmaceutical Grade" filters.

Biofilm and Bacterial Grow-Through Considerations

As mentioned above, the standards for Purified Water and Water for Injection do not require them to be sterile, but sterility is the goal of all system operators. To achieve that goal, operators may have to deal with biofilms. This is a controversial area in the operation of pharmaceutical water systems, but virtually everyone believes that biofilm formation is possible. Almost everyone also agrees that biofilm formation must be halted very early in the process, or control quickly becomes very difficult.

While there are many opinions on the best ways to control biofilm, there seems to be a consensus that they can and do occur in parts of pharmaceutical water systems. USP Chapter <1231> mentions biofilms throughout the chapter. The European Medicines Agency (EMEA) published a "Reflection Paper" in March 2008 that, among other subjects, discussed biofilm as a concern in some water systems.

Almost all pharmaceutical water system operating procedures include treatment by heat, chemical sanitization or both to control the levels of bacteria in components and piping. However, the presence of bacteria is considered by some to be inevitable. That is why point-of-use filters may be important. These filters can be a final barrier (a combination of the prevention and remediation mentioned earlier), and assure the quality of the processes that use Purified Water or WFI by preventing bacteria in the system from reaching those processes.

Bacteria Grow-Through – Choosing filters for water systems should also consider the phenomenon of bacterial grow-through. Some studies[1,2] have discussed how bacteria can grow through severely confined spaces, including filter pores much smaller than the bacteria. The amount of time required depends on a number of factors from the organism itself to temperature, fluid contents, flow rates and other system conditions. What is clear is that many different bacteria are capable of penetrating a filter membrane, if given the time to do so, though some evidence indicates that certain filters with 0.1µm pore size ratings may resist bacteria grow-through. When qualifying filters for bacteria removal, testing should be done to determine if the filters allow grow-through, and the time required for the grow-through to occur. This will determine the effective life of the filter in the system.

As might be expected, the longer the distance that a bacteria has to travel through a restricted space, the more time is required. Therefore, the thicker the "critical layer" of filter pores, the more resistance to penetration due to grow-through. For that reason, some operators prefer symmetric membrane designs (same size pore through the thickness of the membrane) rather than the widely used asymmetric pore design (very thin layer of smaller pore sizes).

Critical Process Filtration's WPS and EPS filters are made using symmetric PES membrane. This membrane is characterized by the critical pore sizes being a consistent size throughout its thickness. Using WPS or EPS filters with pore sizes smaller than 0.22µm can help extend the effective life of the filters in point-of-use applications for bacteria removal or sterilizing filtration. That increases the time that the filters can assure the quality of the Purified Water or WFI in your process.

[1] Mannik J, Driessen R, Galajda P, Keymer JE, Dekker C (2009) "Bacterial growth and motility in sub-micron constrictions". Proc Natl Acad Sci USA 106(35):14861–14866
[2] Jornitz MW, Meltzer TH "Grow-Through and Penetration of the 0.2/0.22 'Sterilizing' Membranes", (Pharmaceutical Technology - Mar 2,

Filter Media Options for Pharmaceutical Water System Applications

Process Area	Filter Application	Filtration Function	Media **	Typical Pore Sizes
Prefiltration	Particle Reduction	Reduce particulate load to protect performance of downstream water treatment processes	MB, NS, PD	5 to 10µm
	Carbon Fines Removal	Remove carbon fines to protect downstream processes	MB, NS [ACB for Small Systems]	3 to 5µm
	Resin Trap	Protect downstream processes from resin fragments that might foul media or membranes	MB, NS	3 to 5µm
	RO Prefiltration	Remove particulates that might prematurely foul membrane or interfere with membrane performance	MB, NS, PD	1 to 5µm
Bioburden Control and Sterilizing	Bioburden Reduction	Remove most bacteria from the water stream to help meet water quality requirements	CWPS, PVWL, NM, PS	0.22 to 0.45µm
	Bacteria Removal (Sterilizing)	Remove all bacteria from the water stream	PS, NM	0.10 to 0.22µm
	Tank Vent Filtration	Prevent bacteria and particulates from entering tanks when water is drawn from the tanks. Protect water quality	TM, TM/HT	0.22µm

**Media Codes

ACB = Activated Carbon Block
MB = Melt-Blown Polypropylene Media
NS = Nanospun Polypropylene Depth Media
PD = Pleated Polypropylene Depth Media
CWPS = High Capacity PES Membrane
NM = Nylon 6,6 Membrane
PS = Polyethersulfone Membrane
PVWB = High Capacity Hydrophobic PVDF Membrane
PVWL = High Capacity Hydrophilic PVDF Membrane
TM = PTFE Membrane

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