Pharmaceutical Waters

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 used for the production of 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) or others. These Pharmacopeias 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. The EP only allows distillation for WFI production.

There are several USP and EP monographs for various grades of water, most of which govern water packaged for use in a location remote from where it is produced. The remainder of 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 requirements for filtration in the production of these waters.

This guide reviews USP and EP guidelines and presents a generic water purification system design, highlighting where filtration steps are utilized as the water is purified and distributed to points of use. The technical requirements for each filtration step are discussed and products manufactured by Critical Process Filtration (CPF) 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 sciences applications. As described in USP General Chapter <1231>, there are three basic grades or “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 PW 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, with efforts underway to harmonize these guidelines. Water for hemodialysis quality attributes 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.

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1 Other organizations such as the Japanese Pharmacopeia publish regulations as well, with the majority having harmonized their regulations with the USP and EP.
2 AAMI – Association for the Advancement of Medical Instrumentation
The USP and EP have adopted similar standards for the quality of Bulk Pharmaceutical Waters, as illustrated in Table 1. In addition to PW and WFI, the table also shows a grade called Highly Purified Water (HPW), as defined in EP and representing water meeting WFI specifications but produced by means other than distillation.

The exact methods for treating water to meet the standards are left intentionally flexible in both USP and EP documents. The initial assumption is that all grades of pharmaceutical water will be produced starting with a “potable water” source and using a “suitable process”. USP <1231> describes several suitable treatment processes that may be utilized to produce pharmaceutical waters. Most systems utilize a reverse osmosis process combined with deionization to produce PW. The vast majority of WFI systems utilize distillation as the final treatment process due to its widespread acceptance throughout the world.

Contact Critical Process Filtration, Inc. if you have questions regarding any information in this guide, or if you have an application not covered in this guide, by calling (603) 880-4420 or accessing our website at www.criticalprocess.com.

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Table 1 – Water Quality Specifications for Pharmaceutical Water *

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Purified Water</th>
<th>Highly Purified Water</th>
<th>Water for Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>USP Ph Eur (bulk)</td>
<td>USP Ph Eur (bulk)</td>
<td>USP Ph Eur (bulk)</td>
</tr>
<tr>
<td>TOC (ppb C)</td>
<td>500</td>
<td>500</td>
<td>NA</td>
</tr>
<tr>
<td>Conductivity @ 20ºC</td>
<td>NA</td>
<td>≤ 4.3 μS/cm</td>
<td>NA</td>
</tr>
<tr>
<td>Conductivity @ 25ºC</td>
<td>≤ 1.3 μS/cm</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nitrate (NO2)</td>
<td>NA</td>
<td>≤ 0.2 ppm</td>
<td>NA</td>
</tr>
<tr>
<td>Heavy Metals</td>
<td>NA</td>
<td>≤ 0.1 ppm</td>
<td>NA</td>
</tr>
<tr>
<td>Aerobic Bacteria</td>
<td>≤ 100 CFU/ml</td>
<td>≤ 100 CFU/ml</td>
<td>≤ 10 CFU/100ml</td>
</tr>
<tr>
<td>Bacterial Endotoxins</td>
<td>NA</td>
<td>NA</td>
<td>≤ 0.25</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
<td>≤ 0.25</td>
</tr>
</tbody>
</table>

N/A – Not an applicable requirement


1 The exception being that EP documents require distillation to produce WFI grade water.
2 Drinking water as defined by the US Environmental Protection Agency or the World Health Organization
Producing Bulk Pharmaceutical Waters

Figure 1 below is a schematic of a typical system to produce and distribute Purified Water (PW) and Water for Injection (WFI). While this schematic may not be representative of your system, it does illustrate the many locations where filtration products may be utilized. Additional system components such as Ultraviolet treatment units or ozone injection may be used for bacterial control. These additional components may impact filter selection. Contact Critical Process Filtration to discuss specifics.

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

Figure 1 – Generic Purified Water / Water for Injection System Design

A – Particle Trap Filtration
B – Carbon Fines Trap
C – Resin Trap
D – RO Prefilter
E – Tank Vent Filter
F – Bioburden Reduction/ Sterilizing Filter (Point-of-Use)
G – Bioburden Reduction/ Sterilizing Filter (Optional)
Filtration Requirements for Pharmaceutical Waters

Figure 1 shows the "typical" filter applications in a generic pharmaceutical water system. Additional filters may be required 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 bacterial removal. Filtration products located before the reverse osmosis (RO) unit reduce or remove particle contaminants while filters following the RO unit are intended to reduce or remove bacterial contaminants.

Each application shown in Figure 1 is described in detail below with recommendations for filtration products commonly used to perform a specific function.

Particle Filtration

Commonly, the initial water treatment step is coarse filtration to remove larger particulates such as sediment and silt. Figure 1 shows a multi-media (sand) filter followed by Filter A, which would remove particles released by the multi-media filter. In smaller systems, both filters may be combined into a single housing of particle filters.

Depth filtration products such as CPF Melt-Blown Polypropylene or Nano-Spun Polypropylene cartridges are commonly used for particulate removal. These products will hold a large quantity of silt or sediment before requiring replacement. Yarn wound filters are also utilized in this location, but these filters add “extractable” surfactants to the water upon installation. Additionally, the superior consistency of CPF's Melt-Blown or Nano-Spun filters ensures consistent particle removal unmatched by yarn wound filters.

Depending on the type of particles in your water supply, an economical alternative to standard depth filters are pleated media filters. Pleated filtration products, such as CPF's 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 life and greater dirt holding capacity coupled with the labor savings from reduced filter change frequency often makes pleated filters economically advantageous.

Carbon Fines Removal

The activated carbon filter shown in the diagram is typically a granular 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 Filter B has been installed to remove fine carbon particles in order to protect downstream equipment.

Depth filtration products such as CPF Melt-Blown or Nano-Spun Polypropylene Depth filters, and yarn wound 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 a great value.
Smaller systems utilize activated carbon block cartridge filters, such as CPF's ACB Activated Carbon Block filter cartridges instead of granular carbon beds. Due to their method of construction, carbon block filters do not shed carbon fines, making a downstream filter unnecessary.

**Resin Trap Filters**

There are two resin-based treatment processes illustrated in the system diagram, water softening and deionization. In both cases, the resin beads installed to treat the water will break down over time and introduce resin fines into the water supply. Filter C has been installed to remove these resin fines from the water.

Both small and larger pharmaceutical water systems will use these resin based processes. As with the previous “trap” filters, the most common filter media is melt-blown or nano-spun polypropylene, such as the CPF Melt-Blown Polypropylene or Nano-Spun Polypropylene filters, although pleated filters may be utilized for longer life and reduced replacement frequencies.

**RO Prefiltration**

Filter D in the diagram is the RO prefilter, which is present to protect the high pressure RO pump and to prevent the membranes from fouling due to particles. Protecting the RO membranes from particles is extremely important to extending the life of the membranes.

CPF's Melt-Blown Polypropylene or Nano-Spun Polypropylene filters are typically utilized to protect RO membranes. Alternatively, the use of CPF's 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.

Contact CPF for assistance in determining the best prefiltration practices for your system.

**Tank Vent Filters**

Filter E, shown in two locations in the diagram, is used to filter the air directly in contact with PW or WFI 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 particle and bacterial contamination removed.

It is critical that the filter media remain dry so that air can pass freely through it. Hydrophobic membrane such as polypropylene or PTFE is typically used because it resists wetting from water vapor.

CPF's sterilizing grade PPM or PTM cartridges or capsules are utilized for ambient temperature storage tanks. Most WFI storage tanks are maintained at elevated temperatures, requiring the use of CPF's PTM/HT high temperature PTFE membrane cartridges.

**NOTE:** Vent filters play a critical role in system design as 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.
Final Filtration and Point of Use Filtration

WFI systems utilizing distillation coupled with 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, PW systems may utilize either heat or filtration (shown as optional Filter G) as the final treatment step prior to distribution to points of use. Some systems may utilize point of use filtration, shown in the diagram as Filter F.

Due to the multitude of bacterial entry points into the system, final filtration utilizing “sterilizing grade” membrane filters is regularly utilized as the final bacterial removal process in the vast majority of ambient temperature pharmaceutical water systems. Sterilizing grade filters are typically rated to remove at least 100,000 bacterial colonies per ml without any passing through to the product side of the filter. 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 0.22 or 0.1 micron or larger in size, but coarser filters are also available. In the past, the standard has been 0.22 micron, but a few organisms, like Acholeplasma laidlawii, have been found to pass through these filters, so manufacturers have developed a finer, 0.1 micron filter to remove them.

For the removal of endotoxins (cell fragments), ultrafiltration or charge modified filter media are utilized.

CPF offers several products to meet the requirements for bioburden reduction and sterilizing grade filtration as described below.

CPF’s bioburden reduction filters include membrane filters and capsules made from asymmetric polyethersulfone (PES), polyvinylidene fluoride (PVDF) (both PES and PVDF are available in standard and high capacity grades), nylon 6,6, and blended cellulose. CPF refers to these filters as “Biopharmaceutical Grade” filters.

CPF’s sterilizing grade filters include membrane filters and capsules made from asymmetric PES; PVDF; and nylon 6,6. All are available with either a 0.1 μm or 0.22 μm pore size rating as well as larger pore sizes. CPF refers to these filters as “Pharmaceutical Grade” filters.

Figure 6 – CPF offers a full line of hydrophilic membrane-based cartridge and capsule filters for bioburden reduction and sterilizing filtration in water systems.
Biofilm and Bacterial Grow-Through Considerations

The USP standards for PW and WFI do not require them to be sterile, but that is the goal of almost all system operators. To achieve that goal, operators must deal with biofilms. This is a controversial area in the operation of pharmaceutical water systems, but virtually everyone believes that biofilm formation is inevitable, and 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 “expert” opinions on the best ways to control biofilm, there seems to be a consensus that they can and do occur in several parts of pharmaceutical water systems. USP Chapter <1231> mentions biofilms in the sections on activated carbon, softeners, and distribution systems. The European Medicines Agency (EMEA) published a “Reflection Paper” in March 2008 outlining why it considered double-pass RO inadequate for the production of WFI, citing biofilm concerns as a major factor in their determination.

Almost all water system operation 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 inevitable. That is why the use of final or point-of-use filters is important. These filters assure the quality of the processes that use PW 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 recent 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.

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.

Critical Process Filtration’s WPS filters are made using symmetric PES membrane. This membrane is characterized by the critical pore sizes being constant through its entire thickness. Filters made using asymmetric membranes are designed with an extremely thin critical pore size layer. Using WPS filters 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 PW or WFI in your process.

Contact CPF for more information.

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2 Jornitz MW, Meltzer TH “Grow-Throught and Penetration of the 0.2/0.22 ‘Sterilizing’ Membranes”, (Pharmaceutical Technology - Mar 2, 2006), accessed on PharmTech.com – Aug 2012
All Critical Process Filtration filter media discussed in this guide are available in cartridge and capsule configurations. Cartridges are available in 5", 10", 20", 30" and 40" nominal lengths. Capsules are available in 2", 5", 10", 20" and 30" nominal lengths. All flat sheet depth media and membranes are available in disc filter format in 13mm, 25mm, 47mm, 90mm and 142mm diameters.

## Filter Media Options for Pharmaceutical Water System Applications

<table>
<thead>
<tr>
<th>Process Area</th>
<th>Filter Application</th>
<th>Filter Function</th>
<th>Critical Process Media*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prefiltration</strong></td>
<td>Particulate Reduction</td>
<td>Reduce particulate load to protect performance of downstream water treatment processes</td>
<td>MB, NS, PD</td>
</tr>
<tr>
<td></td>
<td>Carbon Fines Removal</td>
<td>Remove carbon fines to protect downstream processes</td>
<td>MB, NS [ACB for Small Systems]</td>
</tr>
<tr>
<td></td>
<td>Resin Trap</td>
<td>Protect downstream processes from resin fragments that might foul media or membranes</td>
<td>MB, NS</td>
</tr>
<tr>
<td></td>
<td>RO Prefiltration</td>
<td>Remove particulates that might prematurely foul membrane or interfere with membrane performance</td>
<td>MB, NS, PD</td>
</tr>
<tr>
<td><strong>Bioburden Control and Sterilizing</strong></td>
<td>Bioburden Reduction</td>
<td>Remove most bacteria from the water stream to help meet water quality requirements</td>
<td>BC, CWPS, PVWL, NM, PS</td>
</tr>
<tr>
<td></td>
<td>Bacteria Removal</td>
<td>Remove all bacteria from the water stream</td>
<td>PS, NM</td>
</tr>
<tr>
<td></td>
<td>Tank Vent Filtration</td>
<td>Prevent bacteria and particulates from entering tanks when water is drawn from the tanks. Protect water quality</td>
<td>PVWB, TM</td>
</tr>
</tbody>
</table>

*Media Codes
ACB = Activated Carbon Block
GD - Fiberglass Depth Media
NS - Nano-Spun Polypropylene Depth Media
PVWB = High Capacity Hydrophobic PVDF Membrane
BC = High Capacity Blended Cellulose Membrane
MB - Melt-Blown Polypropylene Media
PD - Pleated Polypropylene Depth Media
PVWL = High Capacity Hydrophilic PVDF Membrane
CWPS = High Capacity PES Membrane
NM = Nylon 6,6 Membrane
PS = Polyethersulfone Membrane
TM – PTFE Membrane

### Housings

Critical Process Filtration can provide housings for all cartridge filters. Sanitary housings are available for 1, 3, 6, 8, 12 and 21 cartridges from 10" to 40" long.

Visit our website at [www.criticalprocess.com](http://www.criticalprocess.com) or contact Critical Process Filtration for more information, application assistance and access to datasheets for all of our products.