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CUNO Application Brief
The Use Of Cartridge Filtration In The Production Of Pharmaceutical Grade Water

Introduction

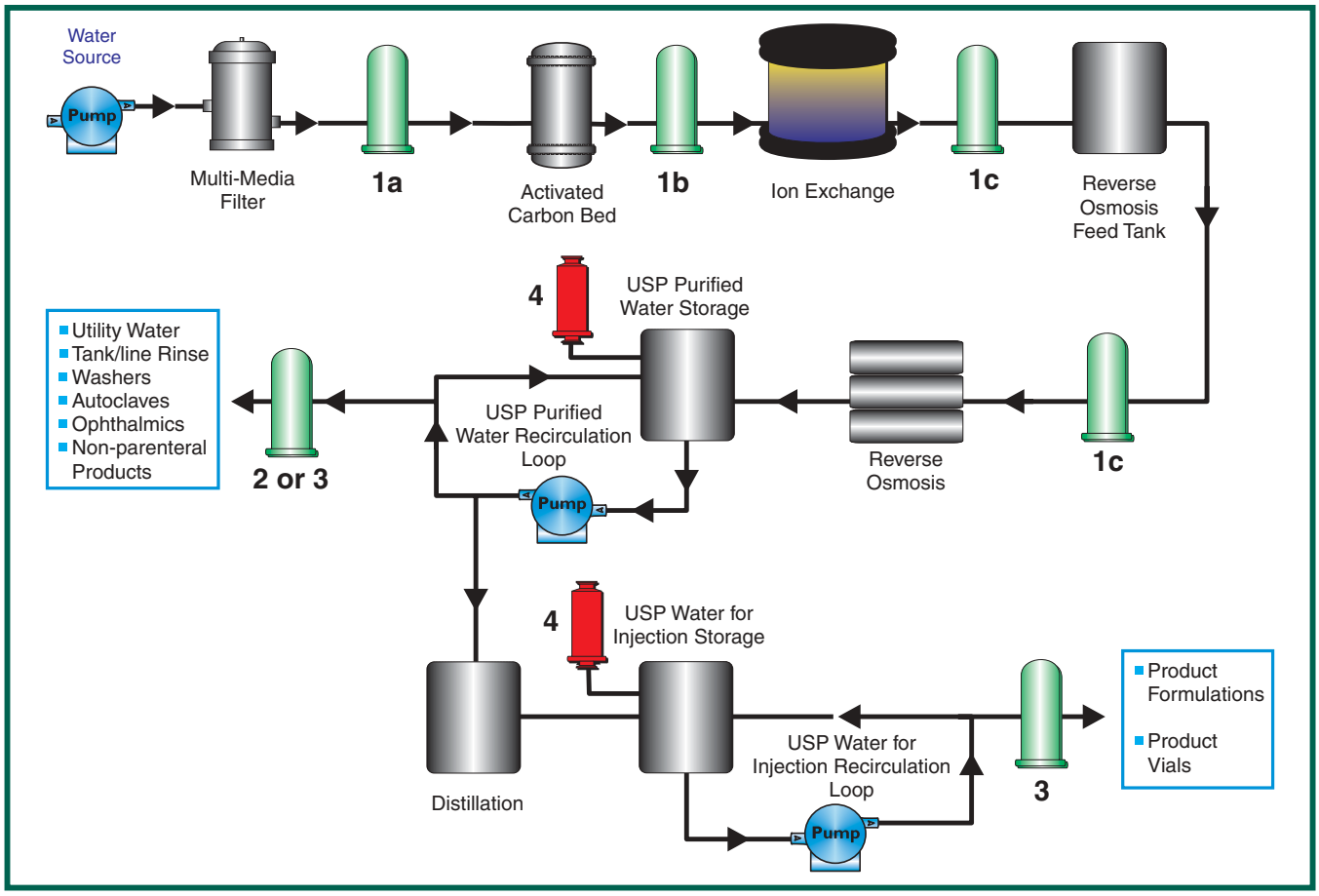
As an ingredient or solvent, water is the most frequently used component in the manufacture of virtually all pharmaceuticals. Water is a major component in many parenteral and non-perenteral drugs, and is used in numerous washing, blending, rinsing, and process steps. Pharmaceutical grade water is classified by the U.S. Pharmacopeia (USP) into 8 different categories, 5 of which are packaged water. Of the remaining three, USP Purified Water (PW) and USP Water for Injection (WFI) are considered primary or bulk waters used for most pharmaceutical water applications. USP Purified Water and Water for Injection are the primary topics of this Application Brief.

The types and quality of the water are closely regulated in major pharmaceutical producing regions by similar, although not identical, standards: European Pharmacopeia – EP, Japanese Pharmacopeia – JP, and the United States Pharmacopeia – USP. The industry is working to "harmonize" these standards so that a single standard will be available in the future. Differences in the Pharmacopeias can impact how a pharmaceutical manufacturer constructs and operates their water systems. For instance, the EP does not allow the use of reverse osmosis (RO) for WFI production, nor does it recognize the U.S. EPA drinking water standard as a basis for raw water entering a system. The discussion in this brief is applicable to waters produced under all three Pharmacopeias, although some variation in filter selection may be required to meet specific local regulations.

This Application Brief will address the applications where cartridge filters are employed to make bulk pharmaceutical grade water (PW and WFI), as well as the benefits derived from their use. These include:

- Removal of particulate that would contaminate the system and foul downstream processing equipment.
- Elimination of contaminating microorganisms, particularly smaller Pseudomonades commonly found in water systems.
- Reduction of bacterial endotoxins (pyrogens) with charge modified membrane filters.
- Protection of storage tanks during draw-down with hydrophobic sterile vent filters.

The Process



The schematic above is for explanatory purposes and does not necessarily reflect the design of any single USP water system. Equipment depicted will vary depending on the nature of the raw water source, intended use of the water, and local regulations. For simplicity, additional equipment not depicted in this schematic, but commonly found in water systems, include: Continuous Electrodeionization (CEDI), Ultra Violet light, and Ozone injectors. These devices are commonly used as complimentary technologies to cartridge particle and membrane filters.

Important cartridge filtration points consist of the following:

1.a., b, & c. Particle removal

2. Removal of bacteria

3. Endotoxin control, removal of bacteria

4. Sterile hydrophobic tank vent

WFI source water is fed from recirculating PW source and becomes WFI after distillation (common) or RO filtration (less common in the US, Japan; prohibited in Europe) or Ultrafiltration (Japan only). WFI is then distributed at hot or ambient temperatures.

Although not as common in the United States, sterilizing grade membrane filters can be used downstream of WFI or PW holding tanks in the distribution network to ensure bacteria removal. Charge modified filters can also provide enhanced removal of pyrogens in the water as well. More commonly, these distribution loops are designed to minimize bacterial potential without the use of membrane filters through turbulent flow pipe design and recirculation of hot (80°C) water and/or sanitizing chemicals.

The Problems

The primary objectives of a pharmaceutical grade bulk water system are that the system be successfully validated and that it consistently produces water in compliance with USP 24. Loss of compliance can result in the loss of product to market. Five basic groups of contaminants are present in water: particulate matter, ionic material, colloids, microorganism and bacterial endotoxins.

Particulate matter, silt, dirt, rust, organic debris and other suspended matter, are non-soluble suspended solids. They are typically indicative of the source water, but can also be generated within a water purification system by equipment such as multimedia filters, carbon beds and ion exchange beds. High particle levels contaminate downstream piping and equipment, diminishing product quality. They can also contribute to the fouling of RO membranes, increasing cleaning cycles and even premature replacement of the membranes. The Silt Density Index (SDI) is recommended by most RO manufacturers to evaluate the quality of the feed water to ensure proper protection of the RO membranes. RO manufacturer's typically recommend a SDI <5.

Ionic material, dissolved compounds that produce cations and anions, are typically removed with water softening equipment, reverse osmosis (RO) membranes, and/or ion exchange beds. The level of the ionic material in the water determines the purity of the water, with standards listed in the USP for each water type.

Colloids, typically larger than ions but smaller than particulate matter, offer a special challenge to water system filtration design. Colloids can be organic in nature, or of silica, iron, or aluminum, and typically exhibit a negative charge. Colloids can prematurely foul RO membranes, resulting in increased cleaning/maintenance costs, and form deposits in distillation equipment. In the latter case, these depositions can result in liquid carryover, potentially contaminating the product water with pyrogens.

Numerous microorganisms (viable bacteria, non-viable bacteria, biofilms, algae, viruses, cysts) exist in raw water supplies depending on the source and the nutrients available. Although disinfection chemicals (chlorine, chloramine) are commonly used, bacteria are extremely flexible in adapting to low nutrient environmental conditions and can establish micro-niches where they thrive and continue to be a source of system contamination.

Bacterial endotoxins (outer membranes of disrupted gram-negative bacteria) are also present in water and must be eliminated. Also known as pyrogens, endotoxins can activate the body's defense mechanisms if they enter the bloodstream, resulting in elevated body temperature and even death.

USP 24 (formerly USP 23) eliminated individual standards for ion and metal levels in favor of conductivity and Total Organic Carbon (TOC) standards for both WFI and PW. WFI is also required to have an endotoxin level of less than 0.25 EU/ml. Recommended action levels are listed in Table 1.

Table 1. - Recommended Action Levels

Parameter	Units	USP 24 WFI	USP 24 PW
Total Organic Carbon	µg/l, ppb	500	500
Conductivity	µS/cm, Stage 1	<1.3 online	<1.3 online
Resistivity	Megohm-cm	0.77	0.77
Endotoxin	EU/ml	0.25	NA
Bacteria	CFU/l	100	100,000

The CUNO Solution

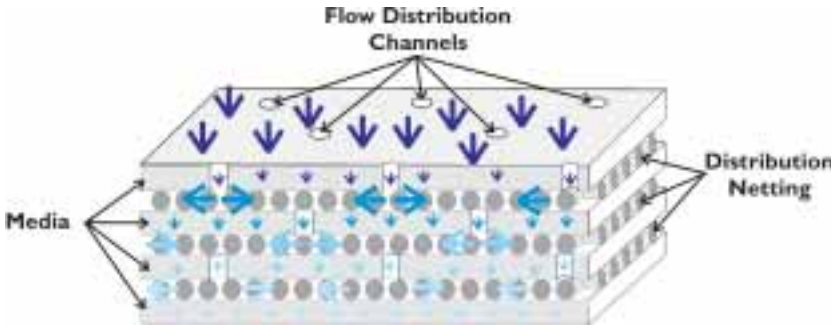
CUNO has developed a wide array of particle and membrane based filters for use in pharmaceutical water systems. Broadly speaking, they can be grouped into two categories, particle filters and membrane filters. Membrane filters can further be divided into non-charge modified membranes and membranes that have been chemically modified to exhibit a positive charge on the membrane surface. The latter aids in adsorption of negatively charged contaminant, particularly bacterial endotoxin. Additionally, hydrophobic membranes, typically constructed with PTFE material (Teflon®) are used to provide sterile vent filtration on storage tanks.

Particle Filters

Particle filters are required in pharmaceutical water systems to prevent raw water contaminants such as silt, rust, and larger organic debris from contaminating the system. Larger colloids can also be removed with particle filters. Smaller water systems can use disposable cartridge filters, while larger systems employ multimedia or sand filters. Cartridge filters are also important in retaining particles generated from other separations steps such as multimedia filters, carbon towers and ion-exchange beds. Cartridge filters prevent particles released from this equipment from contaminating downstream processes. Additionally, particle filters are required as prefilters to RO membranes and in some cases, as prefilters to cartridge membrane filters.

The CUNO PolyNet® PB filter was developed for use in particle removal in water systems. PolyNet filter construction combines a unique polypropylene filter media with fluid distribution netting to form multiple layers. Critically positioned media flow channels allow greater movement of fluid from layer to layer (Figure 2.). Three distinct media sections, made from multiple media/netting layers, are combined to form a filter cartridge (Figure 3). The outer and middle sections contain multiple layers of interleaved filter media and fluid distribution netting. Within each media layer, a portion of the fluid travels through the media while the balance of fluid is delivered directly to the next distribution layer through the flow channels. The fluid distribution netting provides longitudinal and latitudinal flow paths to evenly distribute fluid flow across the surface of each successive filter media layer.

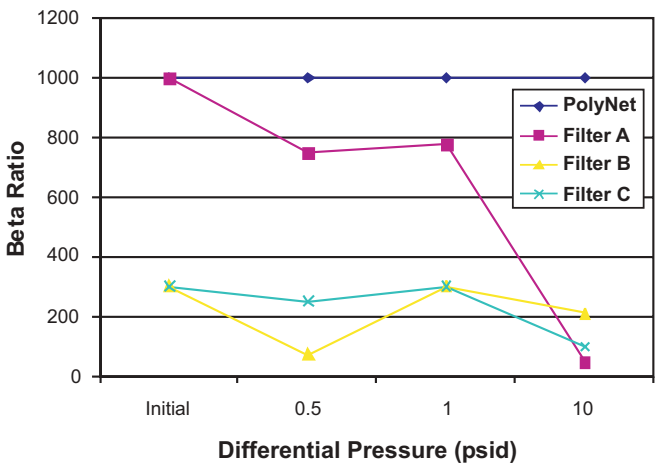
Figure 2 -PolyNet filter media cross-section.



Of particular importance to particle removal is maintaining an absolute retention of particles over the life of the filter. Compressible filters (string wound or polypropylene melt-blown) can unload previously retained particles as differential pressure builds across the filter over time, diminishing their performance (Graph 1). PolyNet filter cartridges do not exhibit this effect and provide consistent retention of trapped particles, resulting in more reliable performance and protection of downstream equipment.

Figure 3 - Cut-away of the PolyNet filter cartridge showing the three sections

Graph 1. - Beta Ratio Comparisons of 20 micron Filters



Filter A: polypropylene gradient pore structure melt-blown filter with core
Filter B: polypropylene graded density structure melt-blown filter without core
Filter C: cotton string-wound filter (10 micron nominally rated)

In Figure 1. the following PolyNet PB filters are recommended:

Table 2. - PolyNet PB Filter Recommendations

Location	Purpose	Filter Recommendation
1.a.	Particulate (silt, sand) removal	PolyNet PB 40 µm
1.b.	Particulate (silt, sand, carbon fines) removal	PolyNet PB 20 µm
1.c.	Particulate removal, Pre RO protection	PolyNet PB 20 mm – 10 µm

Membrane Filters – Bioburden Control

CUNO LifeASSURE® PB filters offer an effective means to remove bacteria and other microorganisms from pharmaceutical water systems. In order to assess the bacterial retention capability of different pore size LifeASSURE PB filters, a series of bacteria challenge experiments were conducted. The results of the tests with *B. diminuta* (one of the smallest bacteria identified, and used to assess sterilizing grade filters) are shown in Table 3. The results show that the average log reduction value (LRV) with 0.2 µm rated LifeASSURE filters was 7.3 and for the 0.45 µm rated filters the average LRV was 3.5. Based on these LRVs, LifeASSURE PB filters will provide a high level of assurance that significant levels of bacteria are removed from pharmaceutical water production systems where complementary bioburden control measures (U.V., R.O. Distillation) are also employed.

Table 3 - *B. diminuta* Retention Results

Sample Filter	Pre-Challenge DFT	Total Challenge CFU	Challenge Level CFU/cm^2	Post-Challenge DFT	LRV
LifeASSURE PLA020, 0.2 micron, 10-inch cartridge					
98J017-04-0023	Pass	1.8×10^{11}	1.7×10^{7}	Pass	8.00
98J017-04-0048	Pass	2.4×10^{11}	2.2×10^{7}	Pass	5.93
98J017-04-0066	Pass	3.0×10^{11}	2.8×10^{7}	Pass	7.69
98G111-05-0052	Pass	2.3×10^{11}	2.2×10^{7}	Pass	7.58
98G111-03-0088	Pass	5.3×10^{11}	5.0×10^{7}	Pass	7.34
98G111-03-0095	Pass	1.5×10^{11}	1.4×10^{7}	Pass	7.29
LifeASSURE PLA045, 0.45 micron, 10-inch cartridge					
98H028-06-0023	Pass	2.7×10^{11}	2.5×10^{7}	Pass	3.93
98H028-07-0094	Pass	1.3×10^{11}	1.2×10^{7}	Pass	3.47
99E043-04-0097	Pass	1.5×10^{11}	1.4×10^{7}	Pass	3.22
99E043-04-0101	Pass	3.5×10^{11}	3.3×10^{7}	Pass	4.69
98F089-03-0165	Pass	1.7×10^{11}	1.6×10^{7}	Pass	2.32
98F089-03-0174	Pass	3.2×10^{11}	3.0×10^{7}	Pass	3.39

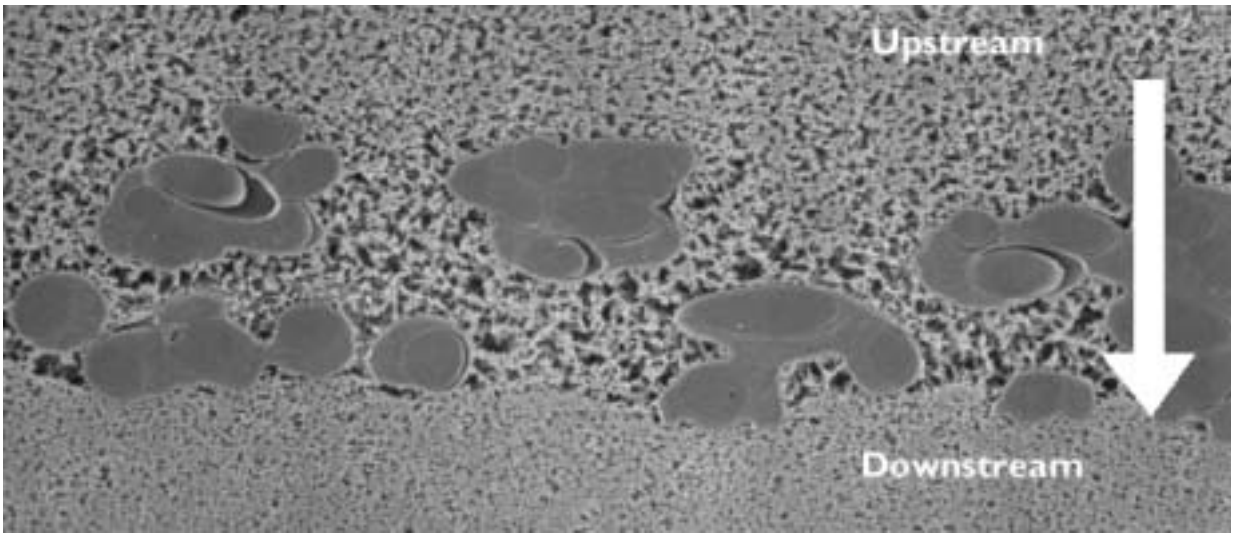
LifeASSURE PB filters also provide superior contaminant capacity for long service life. LifeASSURE PB filters are constructed with Nylon 6,6 membrane produced by a patented process called FlexN™ technology. The FlexN process of membrane casting results in a multi-zone pore structure contained within a single continuous membrane layer. The structure of the membrane is shown in Figure 4. The multi-zone membrane structure contains open pores for prefiltration and tighter pores for controlled particle and bacteria retention.

In Figure 1. the following LifeASSURE PB filters are recommended:

Table 4. - LifeASSURE PB Filter Recommendation

Location	Purpose	Filter Recommendation
2 (or 1.c.)	Bacteria removal	LifeASSURE PB 0.2 µm

Figure 4. - LifeASSURE PB Multi-Zone Pore Structure



Membrane Filters – Absolute Bacteria Retention and Pyrogen Reduction

For the highest level of sterility assurance, CUNO Zetapor® 020SP grade 0.2 µm absolute rated filters are recommended. Zetapor 020SP sterilizing grade filters are validated for absolute retention of *B. diminuta* at challenge levels in excess of 10^7 organisms per cm^2 of filter area.

Zetapor 020SP filters are also useful for removal of endotoxins from water. The filter is constructed with a double layer of positively charge modified Nylon 6,6 membrane. The fixed pore structure provides absolute retention of *B. diminuta* via size exclusion mechanisms, while the positive surface charge provides enhanced retention of smaller negatively charged particles such as endotoxin by electrokinetic mechanisms. Endotoxins are lipopolysaccharide fragments of Gram negative bacteria cell walls. These molecules must be removed per the specifications in the USP WFI (< 0.25 EU/ml). It is also highly desirable that USP PW be controlled for endotoxins as well, since their presence indicates bacterial contamination and can comprise product quality.

Table 5 shows the results of experiments designed to evaluate the efficiency of endotoxin removal by Zetapor 020SP filters, LifeASSURE PB (non-charge modified) filters and a Millipore Durapore (non-charge modified) filter.

Table 5. - Endotoxin Removal

Filter Type	Challenge Solution	Endotoxin Challenge Concentration (EU/ml)	Total Endotoxin Challenge (EU)	Percent Endotoxin Removal
CUNO Zetapor 0.20 micron	SWFI*	600	1.2×10^6	99.98%
	Buffer **	600	1.2×10^6	83.46%
CUNO Zetapor 0.20 micron	SWFI*	600	1.2×10^6	100.0 %
	Buffer **	900	1.8×10^6	98.73%
CUNO LifeASSURE 0.20 micron	SWFI*	600	1.2×10^6	26.67%
	Buffer **	512	1.0×10^6	2.87%
Millipore Durapore® 0.22 micron	SWFI*	600	1.2×10^6	0.00%
	Buffer **	600	1.2×10^6	0.00%

*SWFI: sterile water for injection ** Buffer: 0.1 M Potassium phosphate, pH 7.0

Durapore is a tradmark of Millipore Corp.

The results show the highest level of endotoxin removal by the Zetapor® 020SP filters – significantly higher than the non-charge modified filters tested. The enhanced endotoxin removal by positive charge is based on electrokinetic interaction between the membrane surface and the endotoxin molecules.

In Figure 1. the following Zetapor 020SP filters are recommended:

Table 6. - Zetapor 020SP filter Recommendation

Location	Purpose	Filter Recommendation
2 or 3	Bacteria removal, endotoxin control	Zetapor 020SP 0.2 µm

Tank Vent Filters

Hydrophobic sterilizing grade filters are commonly used to provide sterile venting of WFI and PW storage tanks, and prevent bacterial contamination during draw-off of water. Nitrogen blanketing systems can also be used in conjunction with these filters, further eliminating a potential source of contamination. Special attention should be given to proper sizing of the filter system, matching the filter's ability to the maximum draw-off rate of the tank. Improper sizing can result in a vacuum and tank deformation.

CUNO Microfluor® 020FP hydrophilic membrane filters were designed to provide sterile air/gas service for tank vent applications. Made with rugged PTFE membrane, Microfluor 020FP filters provide high per cartridge flow rates allowing the use of smaller vent assemblies. The cartridges are repeatedly steam sterilizable.

In Figure 1. the following Microfluor 020FP filters are recommended:

Table 7. - Microfluor 020FP filters are recommendation

Location	Purpose	Filter Recommendation
4	Sterile hydrophobic tank vent	Microfluor 020FP 0.2 µm

Conclusion

Water is the most widely used ingredient in the production of pharmaceuticals. As such, great attention is paid to the proper design, performance, and validation of PW and WFI systems. Of key importance is the placement and performance of cartridge filters and their role in maintaining compliance to local Pharmacopoeia standards, and decreasing overall maintenance and production costs as well as limiting system down-time.

This Application Brief addressed the applications where cartridge filters are employed to make bulk pharmaceutical grade water (PW and WFI), as well as the benefits derived from their use. These include:

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- Reduction of bacterial endotoxins (pyrogens).
- Protection of storage tanks during draw-down with hydrophobic sterile vent filters.

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Additional CUNO Literature:	
PolyNet Particle Filters	LITCPN1
Microfluor Hydrophobic Vent Filters	LITMRFP1
LifeASSURE PB Bioburden Reduction Filters	LITCLAPB1
Zetapor 020SP Sterilizing Grade Filters	LITCZR020SP
ZWC/ZWB Sanitary Filter Housings	LITZRH106

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