CRITICAL PROCESS FILTRATION, INC.

Application Summary

Bioburden Control and Sterilizing Filtration in USP Water Systems

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People unfamiliar with water treatment may be alarmed to hear that the water used to produce pharmaceutical products can contain bacteria. As Table 1 below shows, there are limits for bacteria, but they are not 'zero'. In other words, water used in pharmaceutical production is not required to be 'sterile'.

Still, most operators of pharmaceutical water systems try to keep their systems free of bacteria. Several methods may be used to control bacteria, including filtration. This document looks at how filters may fit into the array of tools available.

*Table 1: Allowable Bacteria Content in Pharmaceutical Water**

Parameter	Purified Water (PW)		Highly Purified Water (HPW)		Water for Injection (WFI)	
	USP	Ph Eur (bulk)	USP	Ph Eur (bulk)	USP	Ph Eur (bulk)
Aerobic Bacteria	≤ 100 CFU/ml	≤ 100 CFU/ml	NA	≤ 10 CFU/ml	≤ 10 CFU/ml	≤ 10 CFU/100ml

NA – Not an applicable requirement

*Sources – United States Pharmacopeia 35, General Chapter <1231>, United States Pharmacopoeial Convention, Inc. 12601 Twinbrook Parkway, Rockville, MD (2012); European Pharmacopoeia Edition 7 (EDQM.226. avenue de Colmar BP 907, F-67029 Strasbourg, France, 2011); 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)

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 USP 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 can be designed for operation in a clean room environment that has severely reduced airborne bacteria levels, but that is often prohibitively expensive.

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 obstacles be put in place to control bacteria levels in USP water systems.

Remediation steps inhibit bacterial growth (high temperatures, high flows), 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 choice of filters based on thermal and/or chemical compatibility.

Filters in a Prevention and Remediation Process

Figure 1 on the following page shows possible components of a USP water system. Each component, including the filters, will have to be maintained during its 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 and hold the bacteria. What filters are installed will depend on the temperature of the system, any chemicals used for system disinfection, and the bacterial load.

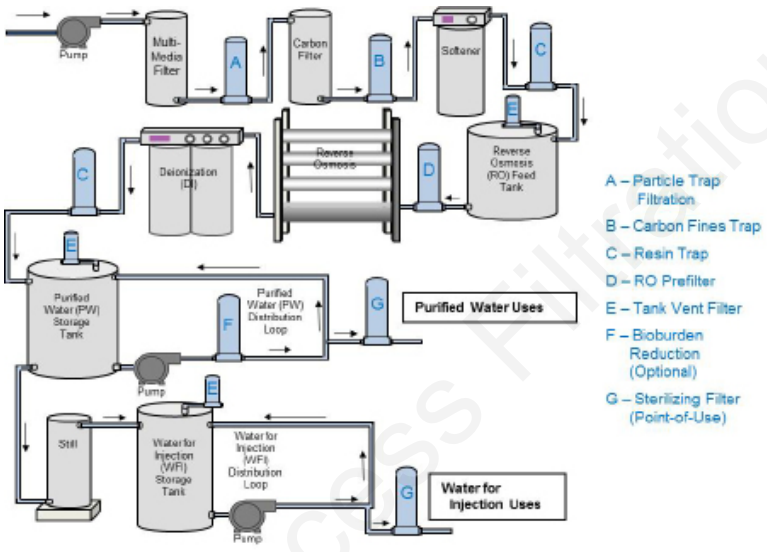

Figure 1: Filters in a USP Water System

Filter Options

Housing F shows the location of a 'bioburden reduction' filter in the distribution loop. This filter reduces or removes bacteria that might enter through open tank vents, open distribution lines or 'dead legs'. The water at this stage of the process has no chemical protection against bacteria, so any organisms that enter the system will be distributed to all parts of the facility served by the system, and could even colonize the system and form biofilms if not removed by filters or controlled by heat or chemical sanitization processes.

The two housings marked "G" are 'Point-of-Use' filters that act as the final treatment step as water is delivered to a process or machine. Most point-of-use filtration is 'sterilizing grade'. Sterilizing grade filters are rated to remove at least 106 bacteria per ml with none passing through the filter.

Tank vent filters (housings marked E) are a critical part of the 'prevention' process. They are hydrophobic membrane filters that keep airborne bacteria in the environment from entering tanks when they are emptied.

All of the filters chosen need to tolerate any chemical disinfectants used in the system (bleach, peracetic acid, etc) and also must be constructed to withstand any heat sterilization or sanitization cycles (hot water or steam).

Filter Options for Bacteria Control in Pharmaceutical Water Systems

Process Area	Filter Application	Filtration Function	Media **
Bioburden Control and Sterilizing	Bioburden Reduction	Remove most bacteria from the water stream to help meet water quality requirements	CWPS, PVWL, NM, PS
	Bacteria Removal (Sterilizing)	Remove all bacteria from the water stream	PS, NM
	Tank Vent Filtration	Prevent bacteria from entering tanks when liquid is drawn from them	PVWB, TM

**Media Codes
CWPS = High Capacity PES Membrane NM = Nylon 6,6 Membrane PS = Polyethersulfone Membrane
PVWL = High Capacity Hydrophilic PVDF Membrane PVWB = High Capacity Hydrophobic PVDF Membrane TM = PTFE Membrane

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