CRITICAL PROCESS FILTRATION, INC.

Application Summary

Removing Bacteria in Biopharmaceutical Formulation & Filling Systems

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In general, all pharmaceutical operations, whether for small molecule products or biopharmaceuticals, use both 'prevention' and 'remediation' processes to control system contamination. The names are apt for processes that prevent the introduction of contaminants into a system and for the processes that remove the contamination issue when it happens (remediation). Barriers, including filters, are in place in almost all pharmaceutical operations to prevent bacteria from entering the operation. However, since it is almost impossible to prevent all bacteria from entering a system, filters are used to 'remediate' the bacterial contamination, removing organisms and protecting product quality and patient safety.

Bacteria removal, or sterilizing, is the most critical filter application in biopharmaceutical production and is the final filter most products see before packaging. However, in almost all systems, multiple filters are used to block bacteria from either entering the system or migrating downstream from their entry point.

Sources of Bacteria

Every biopharmaceutical operation must deal with different bacteria. Because the process itself is based on microorganisms, one of the first upstream process filtration steps is the harvesting of the cells or the removal of the cells from the process stream. There are also upstream processes such as growth media preparation that use filters to reduce or remove microorganisms that might contaminate those solutions. See the companion Application Guide, "Filtration in Preparation of Cell Culture Media and Buffers" for more information on those applications.

Numerous organisms exist in every environment and surround every facility. Barriers that will prevent them from entering the process include the garb worn by plant personnel and cleaning procedures like hand washing. Preventive measures also include using filters to block bacteria from entering storage and mix tanks. However, as mentioned above, preventive measures are rarely, if ever, 100% effective, so operators wisely use remediation steps, including filters, to remove microorganisms from the production stream.

Filter Functions

The abbreviated schematic in Figure 1 shows possible locations for the filters that contribute to both the prevention of bacterial contamination and the removal of bacteria that may elude the preventive measures. There are many possible filter configurations, but these show the basic functions performed by filters in the prevention and remediation scheme.

Depending on the nature and number of organisms, operators may choose to remove most or all of them before the sterilizing filter. The critical bioburden control filtration step protects processes as well as protecting sterilizing filters from being prematurely fouled by organisms. Fouled sterilizing filters will disrupt batch processing, unnecessarily increasing costs and reducing product quality.

The combination of bioburden control filter location and process economics will help determine the performance required from any particular filter. For example, bioburden control upstream of mixing and

storage may not require complete removal of all organisms, but operators may determine that keeping the system 'bacteria-free' necessitates the use of more costly filters that can remove all bacteria. This determination is made at each stage of bioburden control.

No matter the system configuration, removing at least some of the organisms present before they reach the sterilizing filter is a critical process. As mentioned above, protecting the critical sterilizing filters from premature fouling protects both product quality and process economics.

Vent and process gas filters are also critical barriers to bacteria entering the system from the environment. Usually membrane filters, these hydrophobic filters prevent bacteria from being drawn into a tank as the liquid is removed or remove bacteria from gases used when oxygen contact will affect product characteristics, protecting system integrity and product quality.

Figure 1 - Bacteria Removal Filters in Biopharmaceutical Formulation & Filling

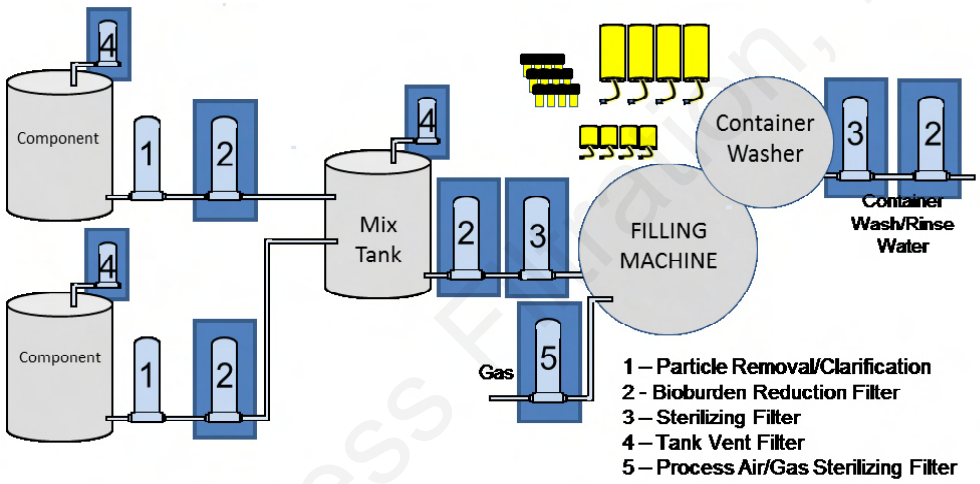

Figure 1: System Removing Bacteria in Biopharmaceutical Formulation & Filling Systems

Choosing the Right Filters

Almost all bioburden reduction filtration is performed by membrane based filters, though some large organisms like molds and yeasts may be removed by high efficiency pleated depth media filters.

Cartridge filters using pleated flat sheet media, most often made with polypropylene or fiberglass, can remove organisms as small as 1 micron in size. That can include most molds and yeasts as well as spores such as Bacillus subtilis. Fiberglass flat sheet depth media has better filter efficiency and generally allows higher flows than polypropylene depth media, though polypropylene may be a better choice in some chemical filtration applications.

Membrane filters for bioburden reduction are available in a number materials with pore size ratings of anywhere from 0.85 microns to 0.22 microns. The nature of the fluid being filtered and the size and number of organisms will dictate the filter material and pore size.

Generally, a stream with a high load of molds and yeasts will be filtered using pleated depth media. If the fluid contains more bacteria, then a sub-micron rated membrane filter with either a 0.65 micron or 0.45 micron pore size, will remove most of the organisms. It is important to identify the number and size of the organisms to be sure that enough will be removed to protect the sterilizing filter from excessive loading and premature fouling.

Sterilizing filters all have pore size ratings of either 0.22 microns or 0.10 microns. The 0.10 micron filters are used in applications where the liquid may contain

mycoplasma or organisms smaller than almost all bacteria.

Filter Options

The filters chosen must be compatible with the fluid being filtered. The organisms targeted for removal also need to be considered. Finally, assure that the filters are designed to function after whatever disinfection or sterilization process will be used.

Critical Process Filtration has several filter options, as shown in the table below. These filters are available as cartridge filters and disposable capsule filters as well is in flat disc form for laboratory scale testing.

Filter Media Options for Bioburden Control and Sterilizing Filtration in API Formulation & Filling

Process Area	Filter Application	Filtration Function	Media **
Bioburden control and Sterilizing	Large Organisms Removal	Remove particles and larger organisms like yeasts and molds	GD, PD
	Bioburden Reduction	Remove most bacteria from the water stream to help meet water quality requirements	CWPS, PVWL, PS
	Bacteria Removal	Remove all bacteria from the water stream	PS
	Tank Vent Filtration	Prevent bacteria from entering tanks when liquid is drawn from them	PVWB, TM

**Media Codes

GD = Pleated Fiberglass Depth Media PD = Pleated Polypropylene Depth Media CWPS = High Capacity PES Membrane
PS = Polyethersulfone Membrane PVWB = High Capacity Hydrophobic PVDF Membrane PVWL = High Capacity Hydrophilic PVDF Membrane
TM = PTFE Membrane

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