Buying Guide

Filter Options for Biopharmaceutical Production

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Biopharmaceuticals are large-molecule medications created through cell-based processes. These methods differ significantly from the chemistry-based techniques used to manufacture small-molecule pharmaceuticals, also known as Active Pharmaceutical Ingredients (APIs). In both scenarios, filters are utilized at nearly every stage to safeguard the processes and ensure product quality. These filters play a crucial role in preventing contamination during the production of both sterile and non-sterile pharmaceuticals.

The right filter can protect your process and final product against harmful contaminants present as particles, bioburden, and endotoxin contamination.

Selecting the Appropriate Filter for BioPharmaceutical Applications

When selecting a filter, consider the following factors:

- Once you know the components of your process, you can identify a filter that most effectively meets your requirements.
- The type of fluid or solution undergoing filtration: raising the viscosity of the solution will necessitate a corresponding increase in the applied pressure, which will subsequently elevate the shear force acting on any bacterial cells that are present.
- Temperature: affects microbial growth and alters the surface tension of the liquid being filtered.
- Membrane Material: filter composition plays a role in charge-related attraction of particles. It should be compatible with the fluid's pH, solvents, and temperature. Selecting low-binding filters such as PES is crucial to prevent costly product loss during the filtration of proteins and biologicals.
- Pore Size: absolute 0.1 and 0.22 µm filters are the standard for sterilization processes, successfully retaining *Brevundimonas diminuta* (ATCC #19146) at a challenge concentration of 10^7 CFU per cm^2, per ASTM F838-20 standards. Filters with a pore size of 0.03 µm are validated to achieve a 7 Log Removal Value (LRV) of *Acholeplasma laidlawii* (mycoplasma).
- Filter integrity: It is essential to maintain filter integrity after sterile filtration. At Critical Process Filtration, each filter undergoes integrity testing.
- Filter Membrane Thickness: The thickness of the filter impacts the flow characteristics and influences the mechanism of particle absorption.
- Device Types: Cartridges, Capsules, and Membrane discs are available for your filtration needs.
- Connection requirements: Luer lock, hose barb, sanitary tri-clamp.
- Flow Rate & Throughput: Efficiency in processing is crucial for large-scale production.
- Extractables & Leachables (E&L): This is particularly important for sensitive biologics.
- Sterilization Compatibility: options include autoclave, gamma, and SIP (steam-in-place).
- Regulatory: Integrity-tested filters, USP Biosafety, and FDA Compliance.

Advantages of using CPF Filters and Devices

- Large product selection to cover your filtration requirements,
- High flow rates,
- Excellent retention efficiency,
- Minimal extractables,
- Reduced contamination risk,
- Variety of filter configurations,
- Proven products,
- Technical services and support,
- Short lead times,
- Competitive pricing,
- CPF will help you choose the appropriate product,
- CPF will assist with protocol development and implementation.

Filters can consist of flat membranes, pleated membranes, cartridges, and capsules. Cartridges undergo integrity testing and are available in sizes ranging from 5 to 40 inches, featuring a wide variety of membranes (PES, PTFE, PVDF, Nylon) and different configurations. These filters can be sanitized using hot water (90 °C for 30 minutes, multiple cycles, maximum 3 psi differential), steam in place (275°F for 30 minutes, over 25 cycles), and autoclaving (250°F for 30 minutes, over 25 cycles). Capsules are designed for single use, can be provided pre-sterilized and integrity tested, facilitate quick installation, and present a lower risk of contamination. They come in sizes ranging from 2 to 30 inches, with the option of Micro Capsules available for scaling and applications requiring small volumes. Their applications include sterilization of cell culture media, buffer filtration, fermentation air filtration, reagents, standards, tank venting, and final product filtration. With low extractables and compatibility for integrity testing, they comply with USP Biosafety and FDA standards, establishing them as a dependable and scalable choice for production settings.

Qualification studies have been conducted by Critical Process Filtration on the filters to establish the limits for flow rate, temperature, and pressure, as well as procedures for sterilization, integrity testing, and the written instructions and specifications for the filters.

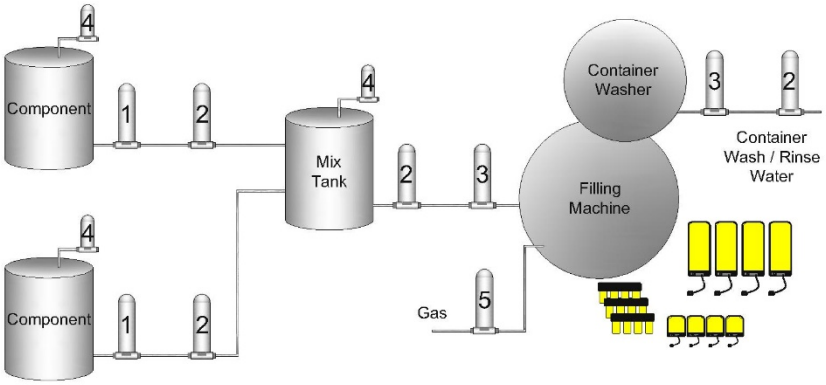
Pharmaceutical Processes

Below are simplified diagrams of certain processes that utilize cartridge or capsule filters for the creation, formulation, and packaging of biopharmaceuticals. Some of these filtration steps may be repeated within individual processes or across different processes, yet the fundamental functions and types of filter media employed remain consistent regardless of their location within the facility. The production of biopharmaceuticals is categorized into three segments: "upstream" processes, which encompass media preparation and other activities that support the bioreactor/fermenter; "downstream" processes that focus on purifying the target molecule (including buffer preparation); and formulation & filling. Filters serve various purposes in each segment. Below are concise descriptions of each function, along with options for filter media applicable to each.

Please review our application summaries and case studies for further information.

Prefiltration in Pharmaceutical Formulation and Filling

The prefiltration for the media component, buffer, or nutrient is established using 0.22 µm filters before the sterilization and filling processes. Although this step does not qualify as sterile filtration, it serves to minimize bioburden. The diagram below shows typical filtration steps in a formulation and filling process.



(1) Clarification & Prefilter,

(2) Bioburden Reduction,

(3) Sterilization Filtration,

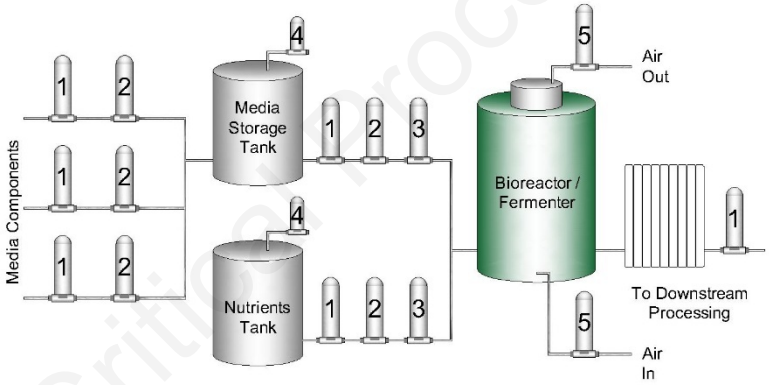
(4) Tank Vent Filtration,

(5) Process Air/Gas Filtration

Cell Culture Media Preparation

Cell culture media should be passed through a 0.22 to 0.65-micron filter to reduce microbial contaminants and particulate matter, and a 0.1 to 0.22 filter to ensure sterility, consistency, and the health of the cells.

The international standards specify <0.1 IU/mL of endotoxin contamination in cell culture water. This indicates that your water purification system must remove this endotoxin from the water utilized for your cell culture.



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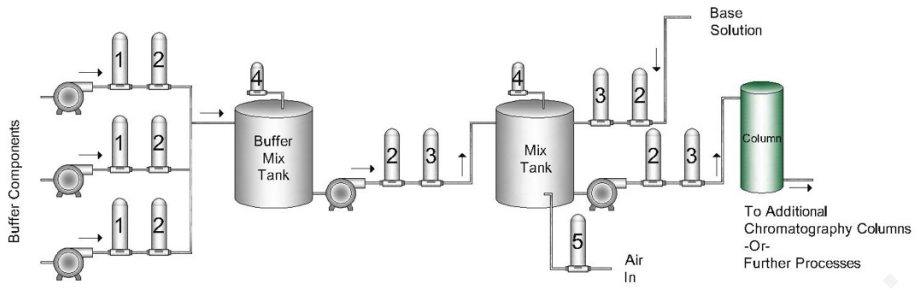
Buffer Preparation/Chromatography

The filtration process for buffer preparation necessitates choosing a filter that provides extensive chemical compatibility throughout the buffer's pH spectrum, adequate physical strength to endure sterilization methods (such as autoclaving), and high permeability to facilitate rapid flow rates for substantial buffer quantities.

Filters intended to eliminate the majority, though not all, of the bacteria (bioburden) are referred to as bioburden reduction or bioburden control filters. The micron rating of these filters can be 0.22 µm, 0.45 µm, or even 0.65 µm,

depending on the specific organisms targeted for removal. Typically, these filters are employed to lessen the load on final sterilizing filters.

In sterile applications, it is crucial to utilize a sterilizing-grade filter with confirmed bacterial retention (for instance, a pore size of 0.22 or 0.1 µm) to eliminate microbes and particulate contaminants, thereby maintaining buffer integrity and safeguarding subsequent processes.



(1) Clarification & Prefilter,

(2) Bioburden Reduction,

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(4) Tank Vent Filtration

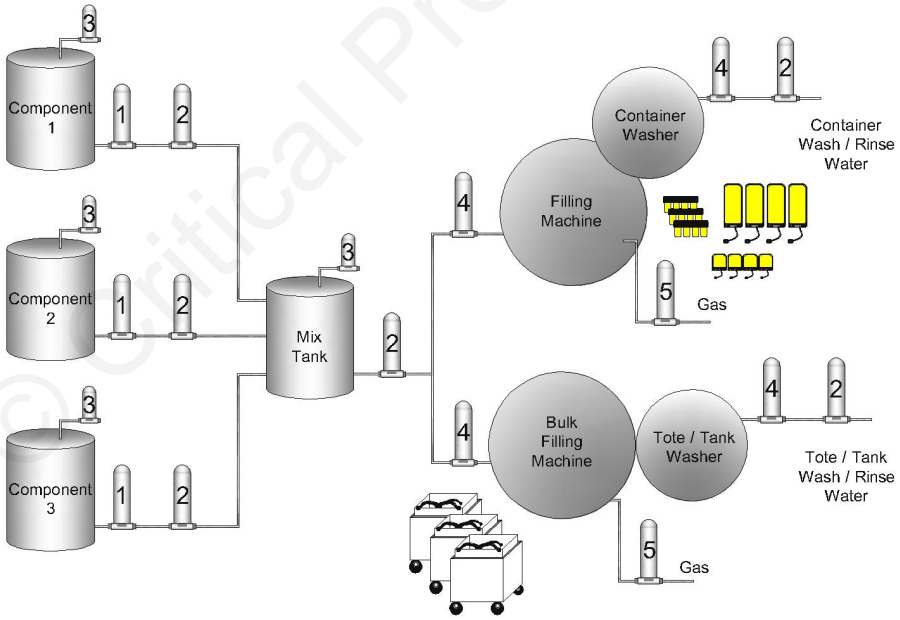
(5) Process Air/Gas Filtration

Filtration in Small Molecule Drug Production

The filtration requirements for small molecule drugs emphasize the importance of achieving high product purity and ensuring patient safety by eliminating contaminants and maintaining sterility, particularly for parenteral medications.

The pore size should be suitable for the specific contaminants being eliminated; 0.22 µm is commonly used for sterilization, whereas larger pores are designated for pre-filtration.

Selecting filter materials (such as PVDF and PES) that exhibit low protein binding and deliver the necessary durability is also important.



(1) Particle Removal Filter,

(2) Prefilter/Bioburden Control Filter,

(3) Tank Vent/Process Gas Filter,

(4) Sterilizing Filter,

(5) Process Gas Sterilizing Filter.

Production Purified Water and Water for Injection System Design (Distillation)

PPD, PGD, and BCWPS serve as prefilters commonly utilized in the early phases of WFI/PW production to eliminate coarse particles from the incoming water source. They may also assist in removing particles that could potentially cause premature fouling of the RO system.

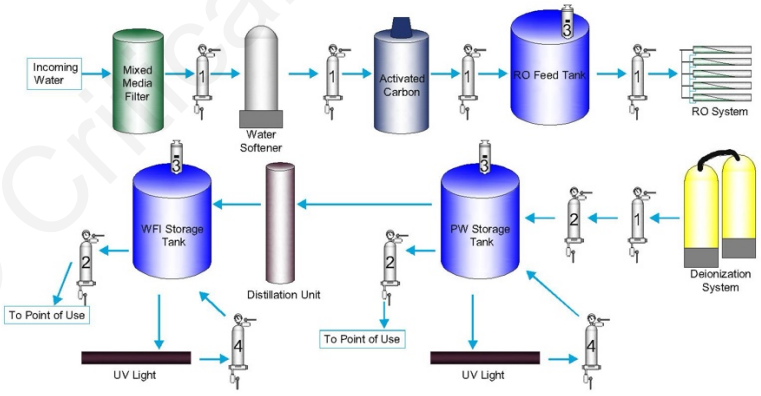
Bioburden reduction filters suitable for water treatment include BPS, BNM, and BPVWL, while for gas, BRM and BPVWB are applicable. It is crucial to sterilize the water using PPS filters. A sterilizing filter is typically installed at point-of-use outlets to provide a final level of assurance.

To safeguard the storage of PW and to generate WFI, an endotoxin removal filter is utilized to ensure the water complies with the specified limits, employing a positively charged filter such as PPC to eliminate endotoxin. All tanks must be isolated from the environment during the filling and draining processes. Gas sterilization can be achieved through PRT filters.

Specifications for Purified Water and Water for Injection

Test	Specification
Total Organic Carbon	500 ppb
Conductivity	<1.3 S/cm at 25°C
Bioburden	100 CFU/ml for PW, 10 CFU/ml for WFI
Endotoxin	0.25 EU/ml

These diagrams may not align perfectly with your specific process, as each water treatment process varies. Depending on the quality and origin of the incoming water, your system might need fewer steps before the RO system. If there is an uncommon substance that needs to be eliminated, a unique filtration step may be necessary. These diagrams are provided to demonstrate the locations and types of cartridge filters that can be utilized in a pharmaceutical water system.



(1) Particle Filter,

(2) Bioburden Reduction,

(3) Tank Vent Filtration,

(4) Endotoxin Filter

Support for Designing Your System

If you are looking to enhance efficiency and reduce the overall costs of your current filtration system, we are here to assist. The application team at Critical Process Filtration can assess your existing system and provide suggestions that minimize your risks while ensuring that your purification goals are achieved.

Filter Options for Biopharmaceutical Applications

Filter Application	Filtration Function	Features and Benefits	Pore Size	Media*
Sterilization Filtration				
Sterilization Assurance	Ensure 100% bacterial retention. This filter consists of two identical, hydrophilic membranes.	✓ Delivers high flow and throughput across a wide pH range. ✓ Low binding characteristics for filtering liquids with preservatives and proteins that can absorb to the media.	0.03 to 1.2 µm	PPS
Targeted bacteria retention	The bioburden reduction prefilter and the sterilizing grade final filter each come in several pore sizes to meet unique requirements for your application.	✓ Prefilter retains large amounts of bacteria and other particulates, which can extend the life of the final filter, reduce changeouts, and ultimately lower costs. ✓ Low binding characteristics, well-suited for filtering products with preservatives and protein solutions that can absorb to the media.	Prefilter pore sizes: 0.1 to 1.2 µm Final layer pore sizes: 0.03 to 0.65 µm	DPPS
Sterilization fluids with high particle loads	This dual-layer filter has an integrated, high-capacity prefilter and an asymmetric PES final filter. This dual-layer model reduces multiple filtrations into a single step.	✓ Delivers high flow across a wide pH range. ✓ Low binding characteristics for filtering liquids with preservatives and proteins that can absorb to the media. ✓ Integrated prefilter saves space by eliminating a separate prefilter/housing. ✓ Prefilter extends the life of the final filter.	0.22/0.1, 0.5/0.22, 0.8/0.22 µm	HPPS
Sterilization & Endotoxin removal	Consists of a double-layer sterilizing membrane for stringent bacteria retention; the filter has been positively charged to remove any gram-negative bacteria debris.	✓ Removes negatively charged biological contaminants. ✓ Highest available charge capacity. ✓ Typically exhibits > 3 log removal of endotoxin. ✓ Double-layer configuration provides high overall capacity and greater assurance against bacteria and endotoxin.	0.03, 0.1, 0.22, 0.45 µm	PPC
Sterilization of water, solvents, and aqueous liquids	PNM represents a series of pharmaceutical-grade Nylon 6,6 membrane sterilizing filters.	✓ Designed for optimal flow, high retention, and chemical compatibility. ✓ Flushed to remove manufacturing residues and minimize extractables.	0.10 to 0.65 µm	PNM

Bioburden Reduction				
Bioburden reduction, non-sterilizing	Reduce microorganisms in aqueous liquids when sterilization is not required. These hydrophilic filters are available in single and dual-layer configurations with a choice of pore sizes for each layer to provide the right level of reduction.	✓ Delivers high flow across a wide pH range. ✓ Low binding characteristics for filtering liquids with preservatives and proteins that can absorb to the media. ✓ An optional integrated prefilter saves space by eliminating a separate prefilter and housing. ✓ Prefilter extends the life of the final filter.	Prefilter pore sizes: 0.22 to 1.0 µm Final layer pore sizes: 0.03 to 1.2 µm	BPS
Clarification & Prefiltration				
High particle loads	CPF's high-capacity PES membrane excels at protecting downstream filters. With its low binding characteristics, BCWPS filters are used for the clarification and prefiltration of products with high protein and preservatives. Membrane prefilters, such as the BCWPS, offer greater retention than a depth filter.	✓ High contamination holding capacity. ✓ Delivers high flow across a wide pH range. ✓ Low binding characteristics for filtering liquids with preservatives and proteins that can absorb to the media. ✓ Dual-layer option saves space by eliminating a separate prefilter and housing. ✓ Optimized to protect sterilizing final filters.	Prefilter pore sizes: 0.22 to 1.0 µm Final layer pore sizes: 0.1 to 1.0 µm	BCWPS
High flow and particle removal	Made with pleated fiberglass depth media for the clarification and prefiltration of aqueous liquids.	✓ High flow rates. ✓ High contaminant holding capacity. ✓ Designed to meet FDA requirements ✓ Rated at 99% retention at the indicated pore size.	0.22 to 5 µm	PGD
Fine particles in water, solvents, and chemicals	Constructed with pleated polypropylene depth media, versatile filters offering broad chemical compatibility and high retention of fine particles in a variety of fluids used in pharmaceutical applications.	✓ Superior retention and downstream protection filters. ✓ Rated at 99.9% efficiency at the indicated pore size. ✓ Designed for high capacity and long life.	0.10 to 100 µm	PPD
Heavy solids and contamination	Constructed with high-loft pleated polypropylene depth media, combining superior filtration capacity with retention of fine particles.	✓ Superior retention of high particle concentration for final product filtration. ✓ Provides long life and high throughput. ✓ Protects downstream filters.	0.10 to 10 µm	HLP

Endotoxin				
Endotoxin removal	Consists of a double-layer sterilizing membrane designated for effective bacteria retention, it is positively charged to remove any debris from gram-negative bacteria.	✓ Removes negatively charged biological contaminants. ✓ Offers the highest charge capacity available. ✓ Typically exhibits > 3 log removal of endotoxin. ✓ The double-layer configuration provides higher overall capacity and provides greater assurance of bacteria and endotoxin removal compared to a single-layer SPC filter.	0.03, 0.1, 0.22, and 0.45 µm	PPC
Endotoxin removal	Consists of a positively charged Nylon 6,6 membrane designed for filtering both aqueous and non-aqueous liquids that contain negatively charged contaminants.	✓ Removes negatively charged biological contaminants. ✓ Offers extensive chemical compatibility. ✓ Provides high flow and throughput.	0.1, 0.22, 0.45, and 0.65 µm	PNC
Tank Vent & Process Gas Filtration				
Sterilization of process gas applications and tank vents	Hydrophobic sterilizing filters made with a PTFE membrane to capture microorganisms as air/gas enters the tank. Likewise, as air/gas is released from the tank, the PTR filter protects operators and the environment in the surrounding workspace.	✓ High air flow and low pressure drops. ✓ Individually integrity tested using the water intrusion method. ✓ 25+ steam sterilization cycles.	0.22 µm	PTR
Sterilization of gases and non-aqueous liquids.	Constructed using Polytetrafluoroethylene (PTFE) membrane.	✓ Hydrophobic filters are resistant to wetting from airborne water droplets, which makes them ideal for air and gas applications. ✓ They exhibit a wide range of chemical compatibility. ✓ These filters are particularly effective with aggressive solvents and various non-aqueous liquids.	0.10 to 5 µm	PTM

**Media Codes

PPS, DPPS, HPPS, BPS, PPC, DPPC, GPC, BCWPS = Polyethersulfone (PES)

D, as in DPPC, consists of two layers of membrane

H, as in HPPS, includes a high-capacity prefilter along with an asymmetric final filter.

PTR = PTFE

PGD = Fiberglass

PPD, HLP, Polypro Depth

If you are in search of a sterilization filter, here are some key characteristics of the media to consider:

Characteristic	Positively Charged PES	PES	PTFE	PVDF
Aqueous sterile filtration	Excellent	Excellent	Pre-wetting	Excellent
Extractables	Extremely low	Extremely low	Extremely low	Very low
Hydrophobicity	No	No	Excellent	Moderate
Regulatory	Yes	Yes	Yes	Yes
Sterilization compatibility	Excellent	Excellent	Excellent	Excellent
Solvent Resistance	No	No	Excellent	Excellent

Membrane filter pore sizes according to application:

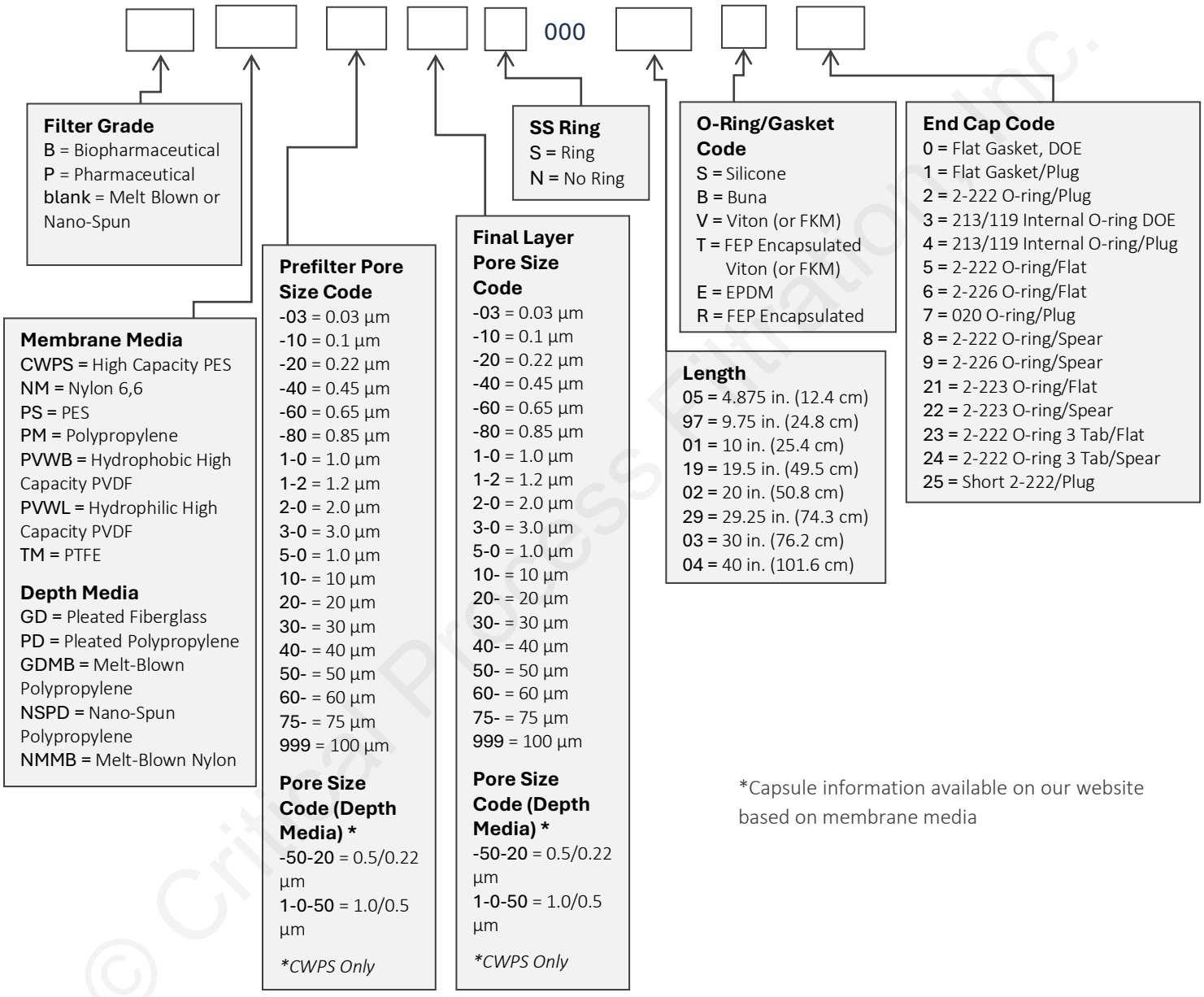
Membrane Filter Ratings	
Rating	Application
0.03 µm	Mycoplasma removal
0.2 µm/0.22 µm	Sterilization (bacterial)
0.45 µm	Clarification, Prefiltration, Bioburden reduction
1-5 µm	Clarification, Prefiltration, particle removal

A quick recommendation for the selection of cartridges and capsules based on the application

Application	Filter type
Alcohol, ethers, and hydrocarbon filtration in formulation steps	PTFE filter
Bacterial retention in vaccine processing	0.1 µm PES filter
Buffer	0.22 µm PES or 0.22 µm PVDF
Clarification of cell culture before protein purification	PES filter
DNA, PCR preparations	0.22 µm Nylon
Fermentation air filtration	PTFE filter
Final sterile filtration of drug substance	0.1 µm PES filter
Endotoxin Removal in Process Water and WFI	0.03 to 0.45 µm Positively charged PES or Nylon filter
High particle removal	Depth filter
Particle removal before chromatography columns	Depth filter
Sterile gas filtration (N_2, CO_2, compressed air)	PTFE filter
Sterilization of cell culture media	0.1 µm PES
Venting tanks (WFI/bioreactors)	PTFE filter
Viral filtration	0.1 µm PES
WFI sterility	0.1 µm PES

Ordering Information

*Cartridge order numbers have several variables, from grade to media and pore size to end cap type. For example, Pharmaceutical Grade, Polyethersulfone Membrane, 0.22 Micron Rating, with SS Support Ring, 20" Length, Silicone O-Rings, 2-226 O-Ring/Spear End Cap Configuration = PPS-20S00002S9.



*Capsule information available on our website based on membrane media

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