

# Filter Options for Small Molecule Drug Production

## Small Molecule Drug Production

Small molecule pharmaceuticals are usually produced using a chemical process. These processes are very different from the cell-based processes used to make biopharmaceuticals (covered in a separate Selection Guide). In both cases, filters are used to protect the processes and product at almost every step.

The schematic below is a very simplified representation of the steps in the processes used to formulate and package a small molecule drug. Several of these steps may be repeated in support of individual processes or between processes, but the

basic functions and types of filters used for those functions are similar no matter where the filters are located in the facility.

There are 4 process areas where filtration is used. First is for contaminant removal in the ingredients feeding each process. Second, controlling the amount of bioburden during the process. Third, preventing environmental (airborne) contaminants from reaching the intermediate products or final product while in storage tanks or removing contaminants from any process gases that might be used. Fourth, and most critical, is sterilizing filtration of the final product just before packaging.

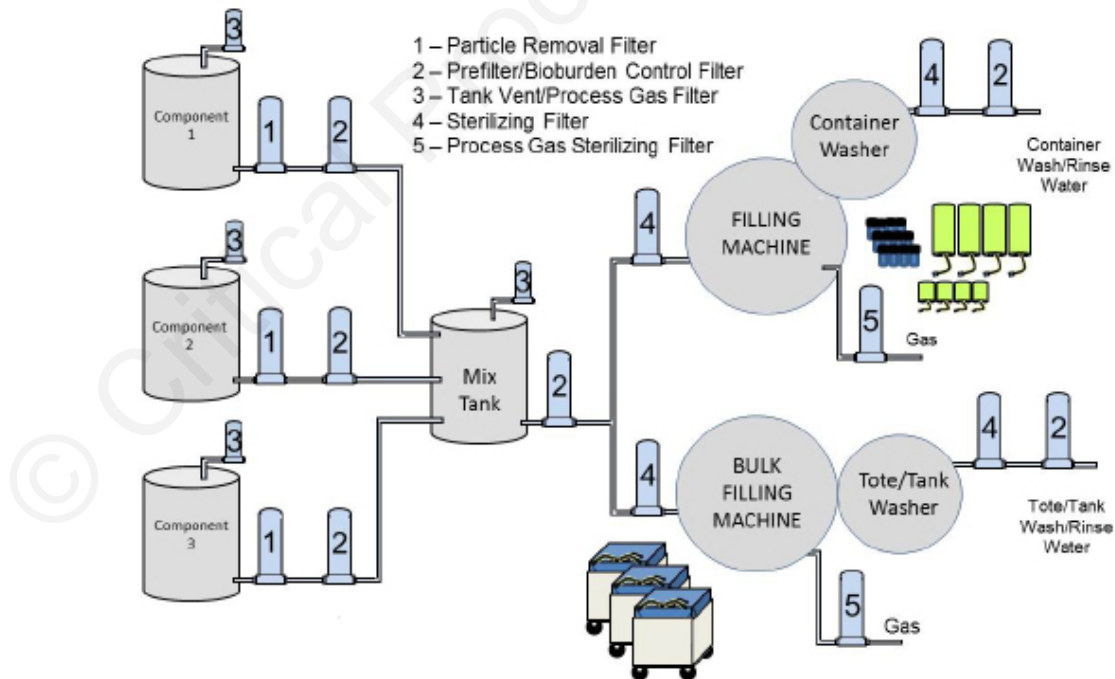


Figure 1: Filtration in Small Molecule Drug Production

## Filtering Ingredients

Ingredients feeding the manufacturing process from sources outside the direct control of plant operators are usually treated as if they contain at least some form of contamination that might harm processes and/or product quality. Even ingredients produced inside the facility are treated the same way both for consistency and to allow the possibility that outside sources may be used for the ingredients.

The biggest issue with ingredients from outside sources is the unknown nature of the possible contamination. Even if the source of the ingredient has a spotless reputation, operators still guard against all possible scenarios. That means treating the ingredients as if they contained unwanted particles, bacteria or other microorganisms and chemical contaminants. Filters cannot normally address chemical issues, but they are a cost effective method of removing unwanted particles and microorganisms, helping process efficiency and improving product quality.

### Particle Filtration (Housings Marked 1)

Unwanted particles could be almost any size. Larger particles, those larger than 1 to 5 microns, are easily removed using depth filtration.

Depth media in cartridge filters is available in two forms. Standard depth filters are self-supporting tubes made using a polymer, most often polypropylene, though nylon is also available. The tube is formed using the melt-blown or nano-spun process.

The other form of depth filter uses pleated flat sheet media, most often made with polypropylene or fiberglass. Polypropylene is the most widely used material for water and chemical filtration, but fiberglass has better filter efficiency and generally allows higher flows and throughput than polypropylene, in most applications.

Standard depth filters will capture a range of particle sizes through the thickness of the media. Pleated media filters have the advantage of a large surface area that can hold a higher quantity of particles on that surface than the standard depth filters.

### Small Particle and Bioburden Reduction Filters (Housings Marked 2)

The next level of filtration used for ingredients is to remove smaller particles and some bacteria or other microorganisms. Most of these “bioburden control” filters are based on membranes.

The performance requirements for the filters is determined by the level of particle and microorganism purity required by the rest of the process. If the process requires only a reduced bioburden load, then a filter with pore size rating of 0.45, 0.65 or even 0.85 microns might be used, based on the expected level of contamination. However, if a process requires that an ingredient be “bacteria-free”, then the filter pore size will need to be 0.22 microns, or perhaps 0.10 microns if mycoplasma control is a requirement.

## Bioburden and Fine Particle Control During Production

All of the filtration steps prior to the final, sterilizing filters focus on particle removal and reducing or removing microorganisms. The housings marked “2” in the schematic represent filters specifically intended to reduce or remove organisms and fine particles.

Every operation has to deal with a different particle and bioburden load. Both particles and organisms can be brought into the process with outside ingredients. Some organisms may be endemic to the plant environment, like molds and yeasts, and can enter the process during mixing or be carried into the facility by personnel and introduced through normal handling of ingredients and equipment.

Depending on the nature and number of particles and organisms, operators may choose to remove most of them before the sterilizing filter or remove all of them. This critical filtration step protects processes, including the sterilizing filter, from being adversely affected by contaminants, which could unnecessarily increase costs and potentially reduce product quality.

### Choosing the Right Filter

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 particles, molds and yeasts will be filtered using pleated depth media. If the fluid contains more bacteria, which are generally smaller, 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 processes and the sterilizing filter from excessive loading and premature fouling.

## Tank Vent & Process Gas Filtration

Tank vent filters ( housings marked 3) are also critical to protecting processes and the quality of the final product. Vent filters keep particles and bacteria in the facility environment from entering tanks storage or intermediates or final product. When the tanks are emptied (and air is drawn into the tank to replace liquid volume) the tank vent filters will block bacteria and other particles from entering tanks.

Process gas, whether air or inert gas or gas to displace oxygen (like nitrogen or CO<sub>2</sub>), may also carry particles and organisms. Filters are used to remove these potential contaminants from the gas stream and protect the quality of the product.

## Choosing the Right Filter

Virtually all vent and gas filters in drug production are hydrophobic membrane with 0.22 micron pore size ratings. Other hydrophobic media and other pore sizes may be used if the filter function is only to prevent dust or other inorganic particles from entering the process or a tank, but that is rare in this industry.

An important note - tanks are not made to survive vacuum conditions. If the filter system creates an air flow restriction that results in too much vacuum as a tank is being emptied, then the tank could implode. Tanks have vacuum ratings, and most can, and should, be ordered with vacuum burst discs to prevent total tank failure. Advance planning can prevent burst disc activation or tank failure. Work with the filter supplier to install the correct size filter system and avoid excessive vacuum.

## Final Sterilizing Filtration

Bacteria removal, or sterilizing, is the most critical filter application in all pharmaceutical operations. It is the final filter most products see before packaging. However, sterilizing filtration may be used to protect any process that would be harmed by the presence of bacteria. In almost all systems, multiple filter steps are used to assure the reliable, successful performance of this critical function.

The filtration steps prior to the final, sterilizing filter are discussed above. The goals of these steps vary according to the product and process, but the most critical function of prefilters is to protect the sterilizing filters from premature fouling by bacteria or other particles. The “final” filtration system often includes both prefilter(s) and a sterilizing filter.

## Understanding Sterilizing Filters

When a filter is supplied as a “sterilizing grade” filter, it is expected to remove all bacteria, molds and yeasts so that the resulting fluid is “bacteria-free”. In the pharmaceutical industry, this is considered “sterile”. The filters are made to comply with pharmaceutical industry standards. The most important of these is ASTM F838-05 - “Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration”. That test challenges the

filter to remove at least 100,000 bacteria per ml without any passing through to the product side of the filter. Filters supplied as sterilizing grade are almost always shipped with a “Certificate of Compliance” showing that the filter has been tested using a non-destructive method (integrity test) to assure its quality and state that it will retain bacteria as long as it is installed correctly and remains “integral”. Most suppliers also provide a “Validation Guide” in support of the performance claim.

### Choosing the Right Filter

All sterilizing grade filters are membrane-based filters with 0.22 or 0.1 micron pore size ratings. Many users install 0.22 micron filters that pass the ASTM test. However, a few organisms, such as mycoplasma and *Acholeplasma laidlawii*, have been found to pass

through these filters under extreme circumstances. After that test result was found, manufacturers developed finer, 0.1 micron membrane filters to allow removal of these smaller organisms, even though their occurrence in actual operating conditions is quite rare.

## Filter Options

The filters chosen must be compatible with the fluid being filtered. The particles and 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 as in flat disc form for laboratory scale testing.

### Filter Options for Small Molecule Drug Production

Process Area	Filter Application	Filtration Function	Media **
Ingredient Filtration	Particle Removal and Bioburden Reduction	Removal of larger particles and some larger organisms (molds, yeasts) to protect downstream processes and safeguard product quality	MB, NS, NMMB, GD, PD
Small Particle & Bioburden Control	Small Particle Removal and Bacteria Reduction	Remove smaller particles (smaller than 1 micron) and reduce/remove organisms. Protect downstream processes. In final filtration systems, protect sterilizing filters from premature fouling by bacteria	PS, NM, PVWL, CWPS
Tank Vent & Process Gas Filtration	Particle & Organism Removal from Air and Process Gasses	Prevent bacteria and fine particles in plant atmosphere from contaminating intermediates or product while being held in tanks. Block particles or organisms carried in process gases from reaching processes or product	TM, PM, PVWB
Sterilizing Filtration		Remove all bacteria and other cell-based organisms from process fluids or product. May remove mycoplasma. May remove larger viruses.	PS, NM

#### \*\*Media Codes

MB = Polypropylene Melt Blown Media  
 GD = Fiberglass Pleated Depth Media  
 PVWB = High Capacity Hydrophobic PVDF Membrane  
 NM = Nylon 6,6 Membrane

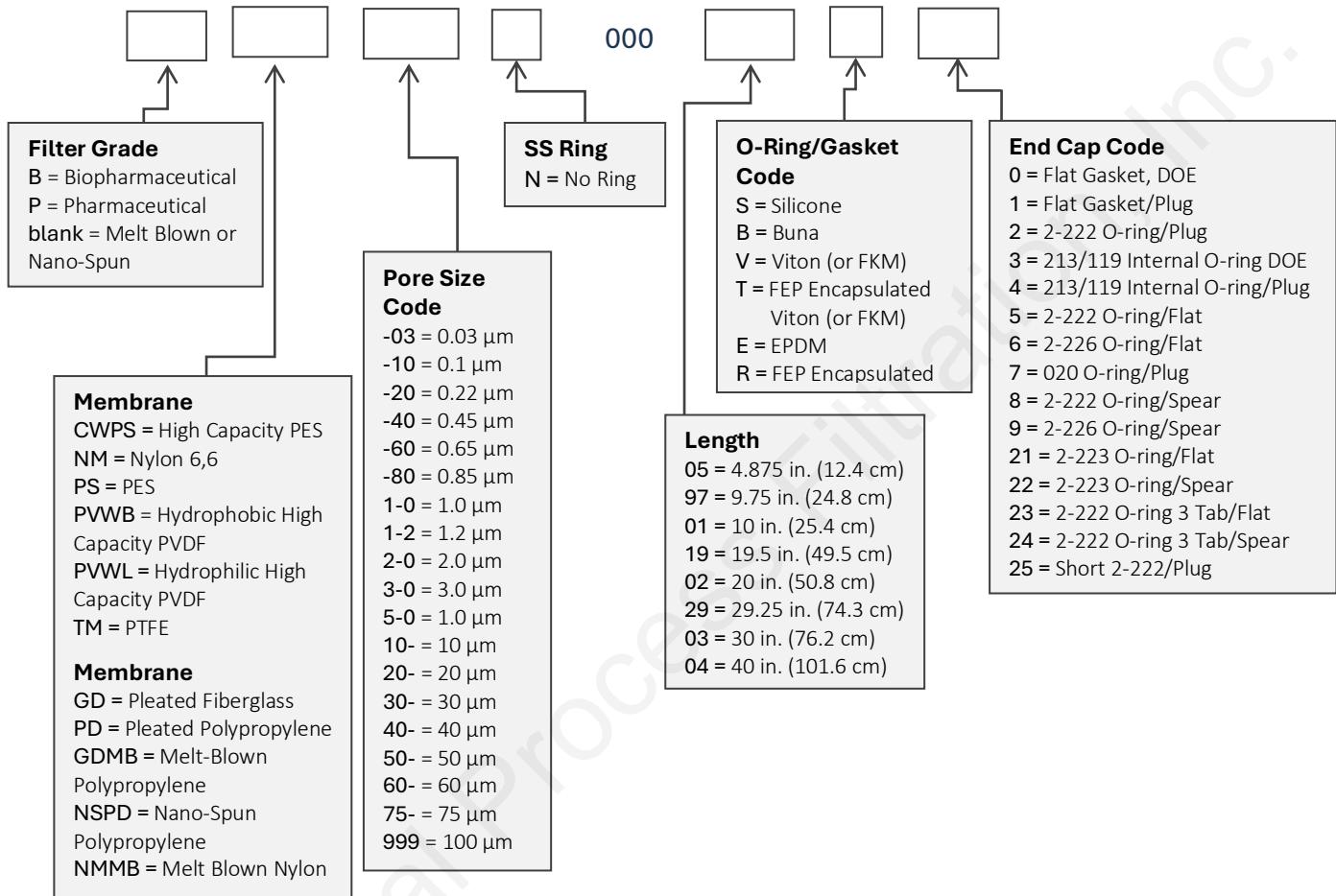
NS = Nano-Spun Polypropylene Media  
 PD = Polypropylene Pleated Depth Media  
 PVWL = High Capacity Hydrophilic (PVDF) Membrane  
 PM = Polypropylene Membrane

NMMB = Nylon Melt Blown Media  
 CWPS = High Capacity Polyethersulfone Membrane  
 PS = Polyethersulfone (PES) Membrane  
 TM = PTFE Membrane

Contact [Critical Process Filtration](#) for help determining the best filter options for you.

## 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.



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One Chestnut Street  
 Nashua, NH 03060  
 603.880.4420  
 FAX: 603.880.4536

[CriticalProcess.com](http://CriticalProcess.com)

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