CRITICAL PROCESS FILTRATION, INC.

Application Summary

Filtration in conjunction with Chromatography Systems

Filtration is a vital component in assuring efficient operation and maximum output of chromatography systems in purification processes. These essential processes in biotechnology usually include multiple chromatography columns - each performing a different function and separating specific components from the base solution. They are an indispensable part of the biopharmaceutical process, and the performance of each column can be enhanced through the use of an optimized filtration system.

Both inorganic and organic particles may be in the base solution, buffer solutions, and in cleaning solutions used to regenerate the columns between batches. Removing those particles helps the columns to perform at the highest level.

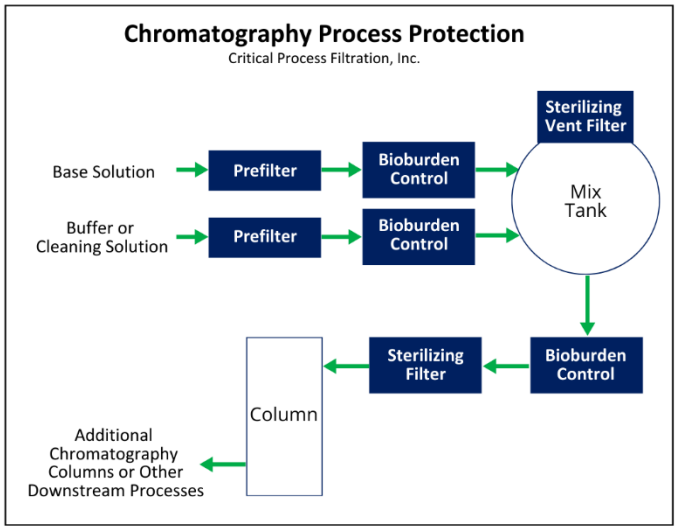

Figure 1: Chromatography Process Protection

Any of these can affect column operation through either mechanical or chemical interference. Filters help assure column performance by removing particles and organisms that clog media, block flow through the column or even cause channeling of the solution through the chromatography media.

Figure 1 represents a generic system to feed and clean a single chromatography column. If a biopharmaceutical process requires multiple columns, there will be a series of these systems employed, each requiring its own filtration.

Several possible impurities can interfere with the peak operation of columns.

- Inorganic particles in the base solution, buffer or cleaning solutions
- Organic substances from the fermentation process (lipids, DNA, etc.)
- Bacteria in the base or buffer solutions

The "base solution" noted in *Figure 1* has already been processed through initial clarification steps such as centrifugation, but is likely to contain particulates, bacteria or other organic content that could affect column operation. The solution is filtered for particles and to reduce or eliminate any bioburden. This removes particulates and bacteria that might interfere with the column before entering a mix tank.

> *The performance of each column can be enhanced through the use of an optimized filtration system.*

During normal operation, a buffer solution is often added to the base solution to facilitate the chromatography process. After the processing of a batch, an additional buffer may be used to elute the target molecule(s) from the chromatography media. Buffer solutions are mixed in a separate process. For more information on the preparation of buffer solutions, refer to the Application Summary, Filtration in Preparation of Cell Culture Media and Buffers. To assure efficient column operation, the final solution is again filtered using a particulate filter (if

necessary) and a bioburden control filter (usually a sterilizing filter in this position).

The mixing tank in the figure may not be necessary if the base solution is fed directly to the column or the base solution and buffer can be mixed using an inline mixing valve or similar system. If the system includes a mix tank, then the quality of the contents of the tank should also be protected from particles and bacteria in outside air or process gas, usually by a vent or process gas filter.

System Cleaning

Several cleaning solutions are used to regenerate chromatography columns. The solutions may be acidic (citric acid, guanidine hydrochloride) or alkaline (sodium hydroxide). The columns are regenerated to improve process economics and system efficiency. The filters in the process are commonly subjected to the same cleaning regimen as the column.

Filter compatibility with the cleaning solution is as important as filter compatibility with the base solutions and buffers. The filters may be bypassed during the cleaning process, but doing so risks cross contamination and loss of solution quality. It is best to use filters compatible with both the process solutions and cleaning agents to assure that the entire system is clear of elements that might interfere with efficient operation.

Filter Applications

Figure 1 shows typical filter types used in a chromatography system. Although only one of each filter type is shown in each process line, there may be issues unique to your process that will require additional filters. Proper filter selection and implementation will remove particulates and bioburden from process streams, optimizing chromatography column performance and product quality.

Particle Removal Filters

Prefilters are employed to remove unwanted particles that may be entrained in the ingredient feed streams. The figure shows prefilters at the point of entry for the base solution and buffer/cleaning solution. These prefilters are designed to capture larger particles that could prematurely foul bioburden reduction and sterilizing filters. They are most often used to remove inorganic particles such as undissolved powders and similar contaminants. Some large organisms, such as molds or yeasts, can also be captured by these filters.

Depending on the particle load in the ingredient, additional prefilters may be required in series to adequately protect the bioburden control filters. This could be accomplished by installing separate filters, or by layering prefilter material within the same cartridge.

Depth filters are commonly employed for this step. Pleated filtration products, with large filtration media surface areas, can remove several times more particle contaminants than standard melt-blown or nano-spun depth filters.

Bioburden Control Filters

Filters that are designed to remove most, but not necessarily all bacteria are designated as bioburden reduction or bioburden control filters. The filter micron rating may be 0.22 µm, 0.45 µm or even 0.65 µm depending on the target organisms to be removed. These are generally used to relieve some of the burden on final, sterilizing filters.

Depending on criticality, operators may elect to employ sterilizing filters in the locations marked as bioburden control in the schematic. To decide which, several factors must be considered:

- Likelihood of bacterial contamination in the ingredient
- Level of contamination that might be encountered
- Adequacy of cleaning/sterilizing procedures for the delivery and tank system
- The burden placed on downstream sterilizing filters if a bioburden reduction filter is not employed
- How conducive is the formulation to bacterial growth?

If bacteria can easily propagate in the product, then a sterilizing filter is the best choice. If not, a less expensive bioburden reduction filter could be employed.

Sterilizing Filters

Sterilizing grade filters are rated to remove particles and bacteria that are 0.22 or 0.10 micron in size. If required, these may be used in the locations marked as bioburden control. A sterilizing filter is usually required as the final filter leading into the chromatography column.

Critical Process sterilizing grade filters have been validated for > 7-log bacteria removal following ASTM-838-15 protocols. CPF will provide a validation guide for the filter(s) chosen documenting test results for bacteria retention, and information regarding filter construction, biosafety and performance. The final choice of pore size often requires validation testing in the actual fluid to be processed.

Tank Vent and Gas Filters

Tank vent filters used to protect the solutions stored in tanks from bacterial and particulate contamination. As a tank is filled, the air inside must be allowed to escape. However, as the tank is emptied, air (or a process gas such as nitrogen) must be allowed to enter the tank to replace lost liquid volume. The filter removes particle and bacterial content from the air or gas to assure the quality of the solution. It is critical that the vent filter membrane remain dry so that air or gas can pass freely through the filter. To assure that dryness, filters are made using hydrophobic membranes, usually PTFE.

Choosing the Right Filters

The proper sequence of Prefilters and Bioburden Control filters is key to optimizing process efficiency and minimizing filtration costs. The CPF Applications Team can help identify which filters are right for you, and can provide testing support either in our Applications Lab or on site at your facility.

The filter(s) selected must be compatible with the fluid being filtered and process disinfection/sterilizing methods. The filter(s) must be capable of removing target organisms without affecting the composition or activity of the fluid being filtered.

Critical Process Filtration provides multiple filter options.

- *Membrane and Media Materials* - PES, Nylon 6,6, PVDF, PTFE, Polypropylene, Fiberglass
- *Filter Configurations* - Cartridge, Capsule, Laboratory Scale
- *Filter Function* - Sterilizing, Bioburden Reduction, Prefilters and more

Conclusion and Summary

Proper filtration of streams feeding chromatography columns is essential for process efficiency and to ensure product quality. Installation of the proper Prefilter, Bioburden Control and Sterilizing filters will ensure product sterility, guaranteeing product quality and patient safety. Critical Process Filtration supplies a wide range of filter materials and configurations allowing optimization of your filtration process while minimizing filtration costs.

Filter Options for Particle Removal, Bacteria Removal, Vent & Gas Filtration

Prefilter Options

- PPD (polypropylene pleated depth filter)
- PGD (fiberglass pleated depth filter)
- BCWPS (high capacity PES)
- GDMB, NSPD (polypropylene depth filter)

Bioburden Reduction Options (Liquid)

- BPS (PES membrane; High capacity PES prefilter layer optional)
- BNM (Nylon 6,6 membrane)
- BPVWL (PVDF membrane)

Bioburden Reduction Options (Gas)

- BTM (PTFE membrane)
- BPVWB (Hydrophobic PVDF membrane)

Sterilizing Options (Liquid)

- PPS (Dual layer PES membrane)
- DPPS (PES membrane with bioburden prefilter)
- SPS (Single layer PES membrane)
- HPPS (PES membrane with high capacity PES prefilter)
- PNM (Nylon 6,6 membrane)

Sterilizing Options (Gas)

- PTM / PTR (PTFE membrane)

For more information, or to connect with an Application Engineer, contact us here.

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