CRITICAL PROCESS FILTRATION, INC.

Application Summary

Clarification & Prefiltration in Biopharm Formulation and Filling

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The final formulation and filling of all drug products are similar. As shown in Figure 1, active ingredients are mixed with water for injection (WFI) or another carrier and perhaps with some excipients. Then the final mixture is filtered and vials or bottles are filled. The filtration processes used vary somewhat depending on the nature of the liquids being filtered, but those processes can be generally split between 'clarification and prefiltration' and 'sterilizing filtration'.

The filtration process for biopharmaceutical products does not differ in the functions of the filters, but the nature of the products requires consideration of factors that do not apply in the filtration of APIs or small molecule drug products. For a discussion of API prefiltration, see our Application Summary on "Prefiltration in API Formulation and Filling".

Filter Functions

Clarification and prefiltration can mean many things within different processes. In some cases it may only be removing larger particles (larger than 5 µm). In other operations the removal of particles larger than 1µm might be sufficient for process efficiency and product quality. In still others, clarification and prefiltration may be defined as removing particles and some, though not all, bacteria.

This summary discusses the full range of possible functions from large particle removal to the reduction of the bacterial load in the fluid stream. In general, all of the filtration functions prior to the sterilizing filter can be considered part of the clarification and prefiltration process. With all filters used in biopharmaceutical production, the ability of the filter media to allow the protein-based product to pass without altering its characteristics is critical. No matter what filtration function, the filter cannot bind proteins or otherwise affect the content of the stream, other than removing unwanted particles or microorganisms.

The abbreviated schematic in Figure 1 shows the likely locations for clarification and prefiltration filters in a biopharmaceutical formulation and filling area. There are many possible filter configurations, but the figure indicates that the process can be completed with either a single or two-stage filter system, depending on the amount and nature of the contaminants in the stream.

A single stage system will be used if the amount of material that has to be removed is low. This could be if the process only has to remove large particles, or if the fluid entering the system has a low particle load. Two stage systems are used for more highly loaded streams (to spread that load over more filters and improve filter life) and to remove a combination of larger particles and small particles or bacteria.

The filters marked "1" in the figure are usually particle removal filters. These could be 5 micron or 1 micron rated depth filters. Filters with larger pore size ratings are efficient and cost-effective for particle removal, but they are also able to remove some microorganisms such as molds and yeasts. Using these filters to remove some bioburden will improve system efficiency.

The filters marked "2" are most often designed specifically to reduce the bioburden in the stream. Usually performed with filters having pore size ratings of 0.85 microns to 0.45 microns, they remove at least

some of the organisms in the stream. This critical process protects the sterilizing filters downstream to allow efficient batch processing and protect product quality. In the example in Figure 1, bioburden reduction is also a possible step just before product mixing, which will improve process efficiency and protect the quality of the final product.

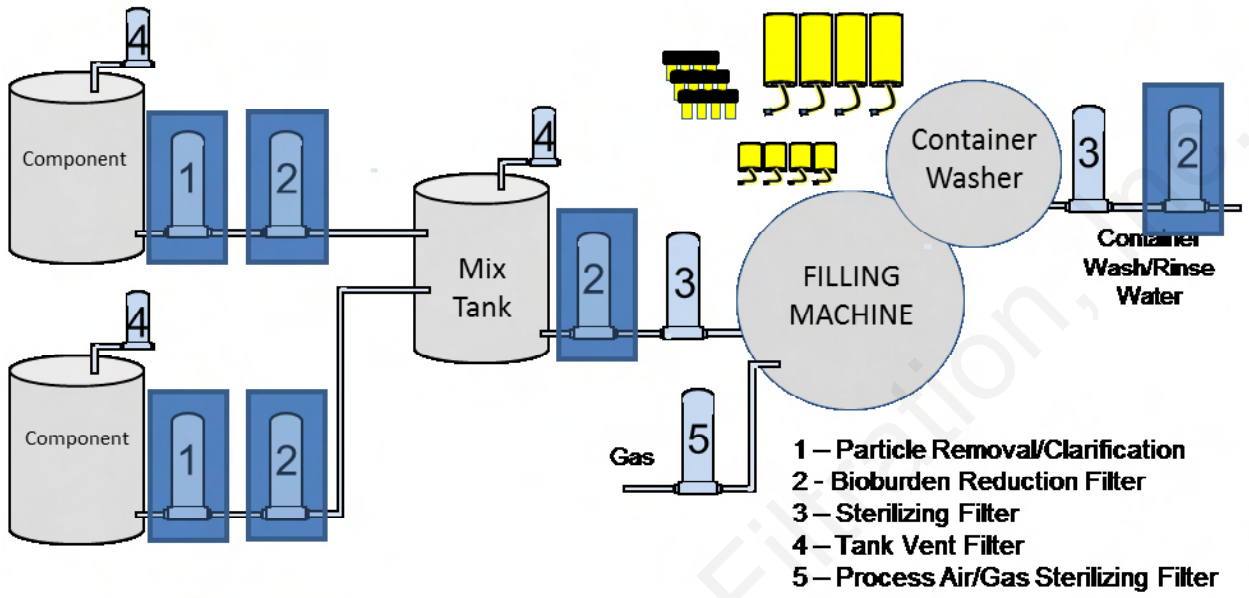

Figure 1: Filters in Biopharmaceutical Formulation & Filling

Choosing the Right Filters

Particle removal is almost always done using depth media such as melt blown polypropylene or nylon. Pleated flat sheet polypropylene or fiberglass depth filter media may also be used for particle removal, and flat sheet depth media is also capable of removing some 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 applications based on chemical compatibility.

Bioburden reduction filtration is most often performed using membrane based filters. Filters for bioburden reduction that are also low in protein binding are available 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.

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 Prefiltration in API Production

Process Area	Filter Application	Filtration Function	Media **
Clarification & Prefiltration	Particle Reduction	Reduce particulate load to protect performance of downstream water treatment processes	MB, NMMB, NS, PD, GD
	Bacteria Removal	Reduce the number of bacteria in the fluid stream – protect final filters from excessive contaminant loads	CWPS, PS, PVWL

**Media Codes

MB = Melt-Blown Polypropylene Depth Media
NS = Nano-Spun Polypropylene Depth Media
NMMB = Melt-Blown Nylon Depth Media
GD = Pleated Fiberglass Depth Media
PD = Pleated Polypropylene Depth Media
CWPS = High Capacity Polyethersulfone (PES) Membrane
PS = Polyethersulfone (PES) Membrane
PVWL = High Capacity Polyvinylidene Fluoride (PVDF) Membrane

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