Mission: control

Strategies for Effective Bioburden and Aseptic Control

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introduction

Bioburden control is an integral component of every biologics production process. Loss of control can be costly and cause significant business disruption. However, determining the appropriate bioburden control strategy can be challenging given the many different technologies available for today's biologics manufacturers.

In this series of articles, we provide information to highlight the differing objectives for bioburden control by unit operation and discuss the parameters that guide filter selection and optimization. Finally, we focus on industry trends toward intensified processing and increased implementation of single-use systems, and how they are changing expectations for sterile filtration and bioburden control.

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Vice President, Bioprocessing
MilliporeSigma

A Holistic Approach to Bioburden Control in Downstream Processing

By: Anne Leahy and Kerry Roche Lentine, MilliporeSigma

Bioburden control is key to successful drug manufacturing, and any lack of control can be disruptive and costly.[1,2] Microbial contamination can occur in the upstream or downstream process. The investigation of these bioburden excursions interrupts production schedules and diverts resources from normal operations. Then, corrective and preventative actions are investigated and developed to reduce the likelihood of a repeat occurrence. Understanding the different considerations for bioburden control in various operations and production steps can help define a strategy for successful production.

Is Control The Same Everywhere?

In upstream processes, bioburden control focuses on the sourcing and characterization of raw materials to prevent the introduction of adventitious agents into cell culture operations. These processes are typically aseptic, and cell culture media is sterile-filtered or, better yet, processed through filters that can remove either mycoplasma or adventitious virus agents. Generally, biomanufacturers that experience the pain of contamination include additional risk mitigation steps to prevent it. To complement technologies that prevent the introduction of contaminants into cell culture processes, rapid testing methods help assure contaminated pre-harvest material is not transferred into downstream processes.[2]

By contrast, most downstream operations for monoclonal antibody therapies are not considered aseptic processes and operate as "low bioburden" or "bioburden-controlled," where bioburden is present but controlled and routinely monitored. As there is no strict guidance on appropriate bioburden levels, manufacturers typically set their own control levels. The BioPhorum Operations Group (BPOG) Bioburden Working Group reported that action levels are commonly set at 1 to 10 colony-forming units per mL.[3] Later in the downstream process, stringent aseptic control is maintained before the final drug product is formulated and transferred into vials.

Assess, Mitigate, Monitor

Assess Your Risks

Effective bioburden control strategies rely on three complementary approaches: assessing bioburden, mitigating the risk of occurrence, and monitoring on an ongoing basis to assure process control.

Assessing the microbial profile of a process is the first step to evaluating risk; understanding which microbial contaminants are present and how many provides a baseline against which future operations can be benchmarked. Using industry-accepted risk assessment tools, multidisciplinary teams can use this information to brainstorm and critically evaluate all aspects of both the upstream and downstream processes to determine the potential impact of contaminants.[4] This methodical approach to risk assessment is based on recommendations from the International Council for Harmonisation document, ICH Q9.[5] A comprehensive risk analysis highlights potential problems that should be prioritized for mitigation strategies.

The risk of contamination is high in upstream processes due to the nutrient-rich environments, which are ideal for microbial proliferation. The risk is also high further downstream and closer to the final product. This is due to fewer remaining purification steps to remove microorganisms and the greater potential impact to

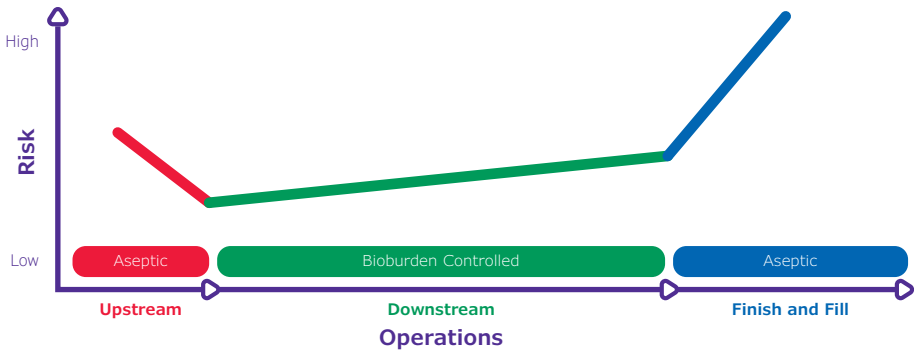

Figure 1:
The "risk hammock" created by differential risk sensitivity in biomanufacturing operations

product quality and patient safety. However, at intermediate processing steps the contamination risk is lower, as the buffers and sanitizers are less hospitable to microbes. This differential risk sensitivity throughout biomanufacturing operations has been described as a "risk hammock" and can be helpful while thinking about risk mitigation (Figure 1).

There are many potential entry routes into a downstream process for microbial contaminants: improper cleaning or sanitization, risky aseptic connections, suboptimal system design, and lapses in aseptic technique. The main types of bioburden in downstream processes are bacteria and fungi. Although control tends to focus on limiting proliferation, the consequence of proliferation in terms of microbial byproducts also needs to be considered as these can impact the quality of the biologic being produced.

Even though the risk of contamination is lower at intermediate processing steps, it is not zero. This stage presents different challenges than both upstream and terminal downstream operations. Some intermediate processing steps involve components that are reused multiple times, such as chromatography resins and tangential flow filtration devices. Typically, these components cannot be sterilized, and sanitization is the necessary option to minimize bioburden. Unfortunately, packed chromatography columns offer an ideal environment for microbial growth and biofilm formation; the Protein A column is particularly problematic as it is the first purification step, loaded with nutrient-rich material that facilitates microbial growth. This, coupled with the fact that many effective sanitizing solutions can negatively impact resin performance, makes the Protein A capture step particularly challenging for microbial control.

Mitigate The Risks

Mitigating the risk of bioburden relies on the control of materials, facility cleaning and sanitization, containment, and size-based removal of microbial contamination using filtration. Preventing microbial entry to biopharmaceutical production processes starts with the raw materials for production. Careful consideration of the origin, supplier, and supplier's quality management systems should guide selection. In addition, the supplier's characterization of the material and suggested quality level may impact handling and processing before use or even result in a change in supplier.

Sanitizers play an important role in any bioburden control strategy, particularly in the intermediate downstream processing steps where aseptic operations are not an option. Sanitization reduces but does not eliminate bioburden. Different sanitizers offer complementary mechanisms of microbial reduction that can be important in maintaining effectiveness over the life of the process. However, a disadvantage of sanitization is the increase in microbial cellular debris, such as endotoxins following treatment. For this reason, it is often beneficial to reduce bioburden by implementing containment and filtration to remove potential contaminants, rather than relying solely on sanitization for microbial kill.

Containment options such as single-use systems minimize microbial ingress, and because they are available pre-sterilized, should not contribute to process bioburden levels. Similarly, closed sampling technologies offer advantages by minimizing the risk of introducing contaminants into the product flow path.

For many operations, filtration is an excellent option for bioburden control, but only after underlying process design and operation best practices have been established and optimized. Any filter selected will also need to be compatible with the process fluid and meet performance needs in terms of bioburden control, processing efficiency, and cost.

Filtration Considerations For Bioburden Control

In upstream operations, sterilizing filters are generally used to process cell culture media and protect the bioreactor from contamination; there are no regulatory requirements for end user bacterial-retention validation on these filters. Selection of 0.1 µm sterilizing filters or virus-removal filters for processing cell culture media, rather than traditional 0.2 µm sterilizing filters, is based on processing costs, manufacturer experience, and level of risk tolerance. These are primarily business decisions based on potential impacts of contamination on production (Figure 2).

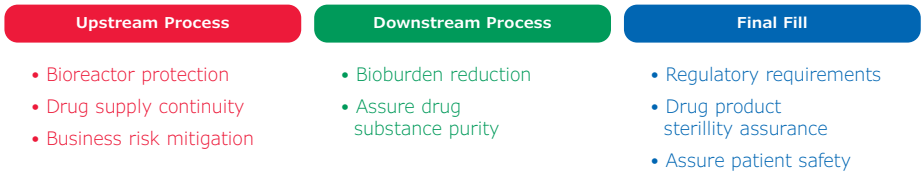

Figure 2:
The role of filters at each stage of manufacturing

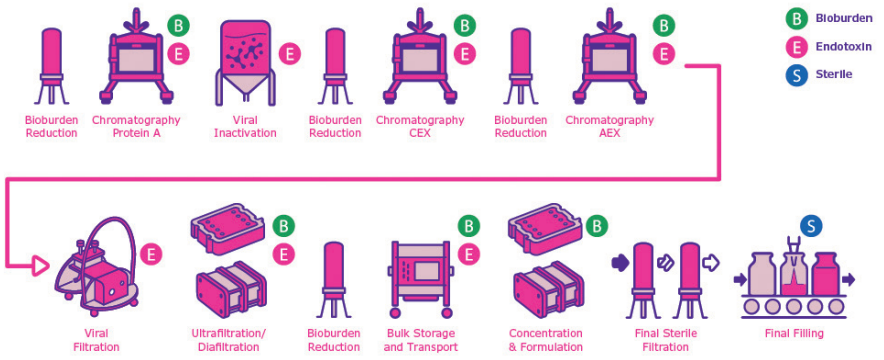

Figure 3:
Sampling plan for routine bioburden and endotoxin monitoring throughout a downstream process

For intermediate downstream operations, filtration is implemented to minimize bioburden by physically excluding microorganisms from the process. There are no regulatory requirements for end user filter validation at these steps, and although there is no universal bioburden limit, manufacturers usually set their own limits for acceptable levels at different steps. Sterilizing-grade or bioburden-reduction filters can be used in downstream operations, and, irrespective of which is used, the filter should have product-specific claims indicating the expected level of bioburden reduction. For many processes, bioburden-reduction filters present a cost-effective option for control. Understanding the specific needs of the process based upon the manufacturer's bioburden profile and the results of their risk assessment should guide filter selection.

By contrast, for the high-risk final filtration of drug product, a 0.2 µm sterilizing-grade filter validated by the filter supplier to standards, such as the ASTM F838,[6] should be used to assure safety. All global regulatory agencies provide extensive guidance on testing these filters. In addition, biomanufacturers must perform filter validation exercises to confirm sterilizing-grade performance of the filter and compatibility with their fluid stream under process conditions.

Maintain Control By Monitoring

Bioburden monitoring helps determine typical levels at different steps in downstream operations. A bioburden excursion is where bioburden exceeds an established threshold limit, and this typically results in some type of investigation. In these cases, understanding the type of contaminant can help identify the source of the problem. For example, molds and bacillus often indicate environmental contamination; *Staphylococcus* or *Propionibacterium* point to human contamination; and non-fermenting gram-negative rods, such as *Burkholderia* or *Ralstonia*, suggest contaminated water systems or raw materials with high water content as the contamination source. Even with contaminant identification, investigations still need to include detailed analysis of the system, materials, and operations to confidently establish route of ingress and appropriate corrective actions.

Risk assessments usually guide where samples are collected throughout the process for routine monitoring and which tests will be performed (Figure 3). Detailed plans define acceptable levels of bioburden, address how bioburden excursions or adverse trends will be investigated, and evaluate potential impacts to the safety of the drug product. Balancing the needs for bioburden safety with sampling and testing is always a challenge and relies on a risk analysis to identify the appropriate strategy for each process.

Bioburden excursions are a real risk to the manufacturing process—a lack of control can be disruptive and costly. Effective control relies on process understanding and a comprehensive mitigation plan. Understanding the process needs can help integrate the various elements of a bioburden control strategy to assure safe drug production.

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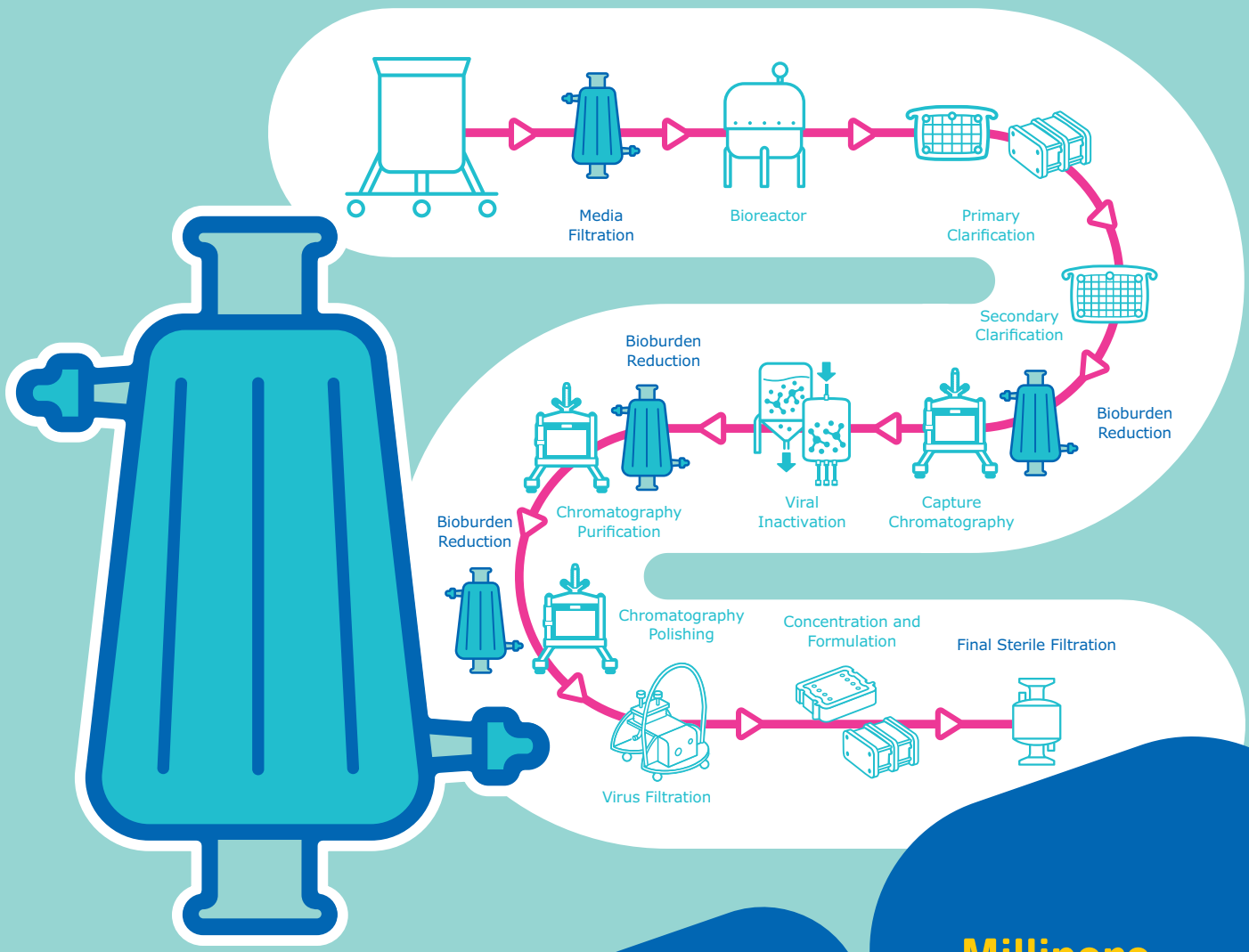

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Selecting Filters to Address Your Bioburden Challenges

By: Stephanie Ferrante and David Beattie, MilliporeSigma

Biologics development and manufacturing is inherently complex and challenging. Compounding this is the added pressure to be first to market in a highly competitive healthcare landscape, where delays can put the success of a product and company at risk. The implication for process development engineers is that they are tasked with rapidly designing a purification process for a drug product that meets safety and quality standards for human use.

In the growing market of biologics, the sterile filtration of liquids is a key component of many operations. This step is vital to minimizing microbial contamination and ensuring product safety and integrity. Preventing microbial contamination in upstream processes reduces the risk of bioreactor contamination and subsequent business disruption. Selecting the right filter for downstream processes can significantly impact operational efficiency and cost. Understanding the different criteria for optimum filter selection helps narrow the options and streamlines product selection.

Technological innovations have opened the doors to many new approaches to drug development. Progress has also been made in the development of improved technologies for producing and manufacturing biologics. Advances in membrane technology and device design have resulted in new options for sterile filtration. Rather than a traditional one-size-fits-all sterilizing filter, more specialized filters have been developed for optimum performance in specific unit operations or with particular fluid streams.

Opportunities to consider and evaluate new filters most often occur in either the early stages of process development with a new molecule, or after approval when there is a change to production processes. By choosing a filter that best fits the goals of the process, it is likely to be reliable, sustainable, and scalable for the life of the drug product.

Considerations for Filter Selection

There are many filtration options available for today's biologics manufacturers, and the following considerations can help narrow down choices: filter compatibility, retention requirements, fluid stream characteristics, filter format and scale-up needs (Figure 1).

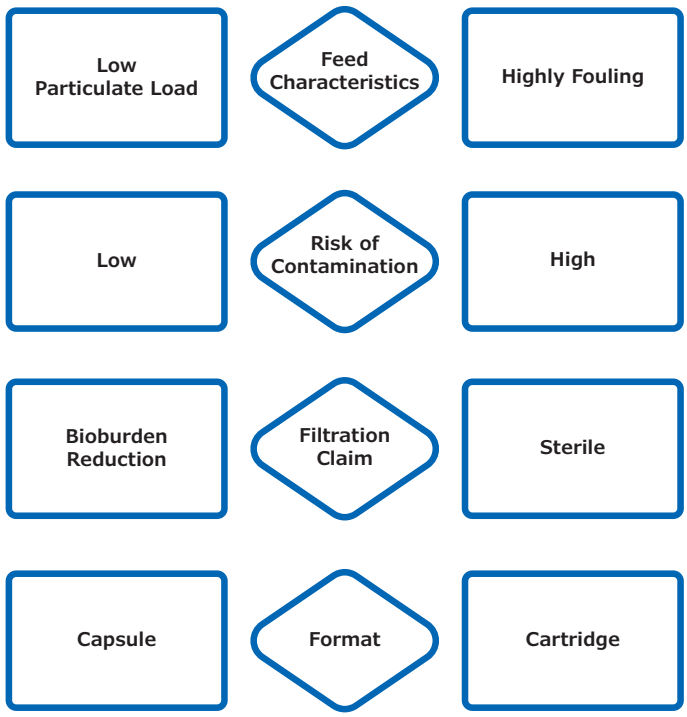


Figure 1:
Criteria for Filter Selection

Compatibility

The first and, perhaps, most important parameter to consider when selecting a filter is its chemical compatibility with the fluid stream. This is very important for fluid streams that have a very high or very low pH or contain solvents and/or surfactants. Performing a chemical compatibility assessment ensures the membrane selected will not be chemically altered and/or potentially shed particles when exposed

to a specific fluid stream. Another compatibility consideration is the potential for binding of the product or a component of the product to the membrane. For example, if the fluid stream is a monoclonal antibody, a low-protein binding membrane should be selected to minimize product loss. Similarly, if the product to be processed contains a preservative, it is important to minimize binding of the preservative or other active ingredient in the fluid stream to the membrane.

Microbial Retention

When selecting filters, it is important to understand the goal of the filtration at each process step. There are filters that are designed to remove particulates and reduce bioburden (bioburden reduction), filters to completely remove bacteria (sterilizing filters), and filters designed to remove mycoplasma and reduce the levels of adventitious virus. Figure 2 illustrates the various operations in a monoclonal antibody (mAb) production process including where sterilizing filters might be implemented.

Bioburden reduction

As purification processes can span several days, there is always a risk of microbial ingress to the system, which can challenge the integrity of any manufacturing process. Filters that offer bioburden reduction can be implemented at multiple points throughout manufacturing processes to reduce this risk. Many downstream purification operations are not sterile operations, and bioburden reduction filters may be sufficient to minimize the risks of microbial contamination. Examples of operations include buffer filtration or filtration of process streams before chromatography operations. Bioburden reduction filters do not provide the same sterility assurance levels as sterilizing filters, but they are generally less expensive and can be an effective option for many operations.

Sterilization

Complete sterilization is required at a few critical steps in biomanufacturing processes, such as the filtration of cell culture media before the bioreactor and the final sterile filtration step prior to filling. Regulatory expectations for sterilizing-grade filters are outlined in the FDA Aseptic Processing Guidelines[1] as well as ASTM® standards[2] that define a sterilizing-grade filter as one that, when challenged with the bacterium *Brevundimonas diminuta* at a minimum concentration of 10^7 colony forming units (CFU) per cm^2 of filter surface area, will produce a sterile effluent. Currently, sterilizing-grade filters usually have a rated pore size of 0.2 µm or smaller, but it is important to note that

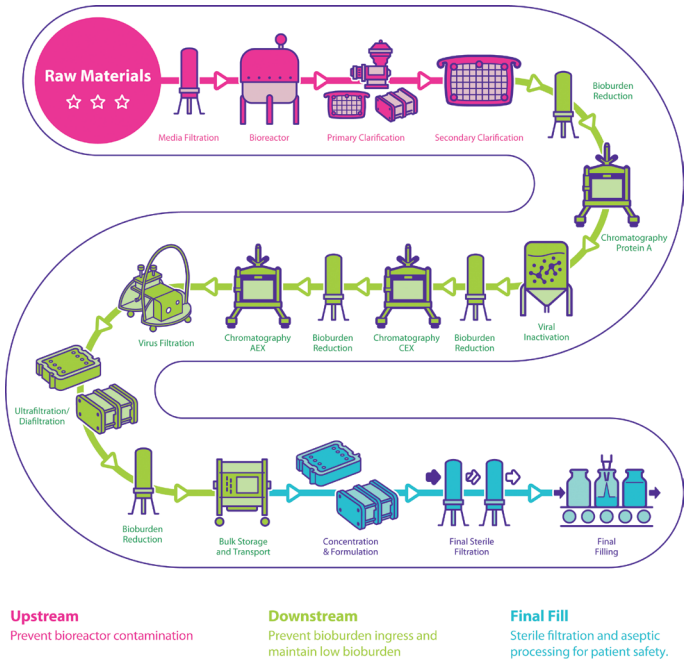


Figure 2:
mAb Production Process Operations Including Sterilizing Filtration Steps.

not every 0.2 µm filter is a true sterilizing-grade filter. Clarification filters, prefilters, as well as bioburden reduction filters, can all have 0.2 µm ratings, yet they are not always sterilizing grade. All sterilizing-grade filters should be supplied with a certificate of quality that shows the membrane meets bacterial-retention testing requirements outlined in ASTM® standards.[2]

Mycoplasma and virus removal

Sterile filtration of cell culture media and supplements presents different challenges than the sterile filtration of process intermediates, buffers, or final drug product. Raw materials in some cell culture media and supplements can contain mycoplasma contaminants in addition to bacteria. Mycoplasmas, which lack a cell wall, are the simplest and smallest self-replicating prokaryotes that gives them the ability to pass through a 0.2 µm sterilizing-grade filter. For this reason, sterilizing-grade filters with a 0.1 µm pore size rating, which, in some cases, have been validated to retain mycoplasma, are often selected for cell culture media applications.

Similarly, raw materials in cell culture media and feeds are susceptible to adventitious virus contamination, and virus removal filters have been developed to efficiently

process these materials. These upstream virus filters reduce the risk of a potential bioreactor contamination, which could have a significant business impact in terms of production interruption and reduced drug availability. Both the 0.1 µm pore size sterilizing filter, and the virus filter for cell culture media and feeds, are specifically designed for 'protecting the bioreactor' and would not be efficient options for downstream filtration.

Understanding the contamination risks and the processing and application needs of different operations helps define the appropriate filter requirements.

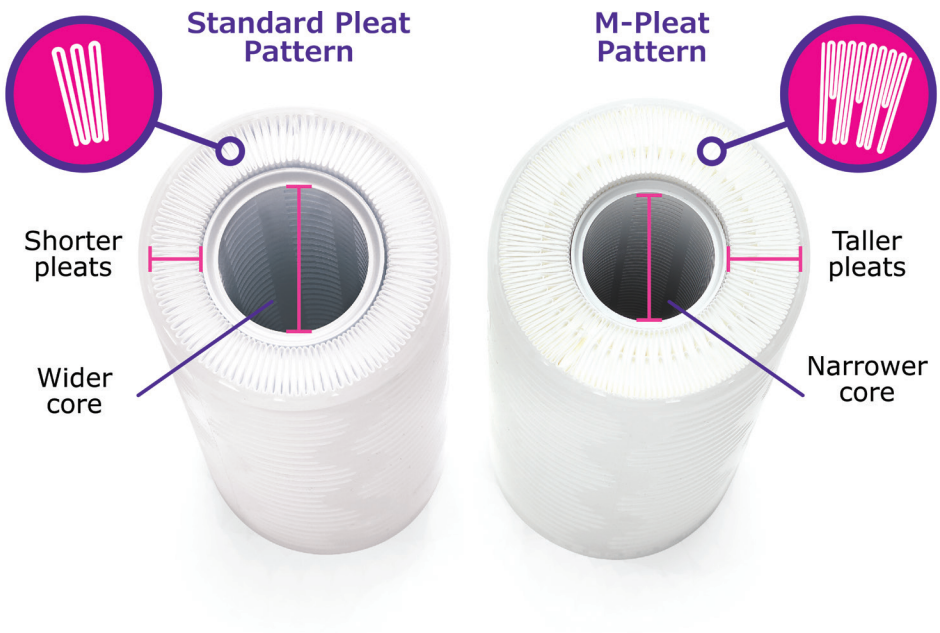
Fluid Stream: Does it Impact Selection?

Aside from the level of microorganism retention required, the complexity of the fluid stream influences filter selection. Fluid streams can be generally classified as non-plugging or plugging.

If processing a non-plugging stream, such as a buffer or water, a filter designed for high-flux processing is generally recommended. These filters can efficiently process a large volume of non-plugging liquid through a small area of membrane, resulting in a small filter footprint. To predict the process-scale filter size, most filter manufacturers provide water flow curves along with other buffer sizing tools.

For processing plugging or viscous streams, like cell culture media, filters designed to maintain flux while retaining particulates are recommended and process-scale performance is best predicted by running a trial using a small-scale filtration tool. For these challenging streams, high-capacity filters that contain integrated prefilters can be used to remove particulates and protect the downstream sterilizing filter from plugging. An alternative might be a high-area filter where membrane is configured in an "M pleat pattern" resulting in more membrane area in the same size filter, reducing filter footprint as compared to standard area filters (Picture 1).

Not considering the type of fluid stream being filtered could have consequences. Incorrect sizing can result in oversizing, which results in paying for more filter area than necessary, as well as increasing the amount of unrecovered product trapped in the membrane (hold up). Conversely, under-sizing filters can result in the filter plugging before the filtration is finished. Ideally, manufacturers should use the lowest filtration area that meets their process needs. Not only will this reduce costs, but it will also result in less hold-up volume, ultimately resulting in higher product yield.



Picture 1:
Pleat Patterns of Standard and High Area Filters (M-Pleat Pattern)

Filter Formats and Device Scale

Independent of the considerations outlined above, but no less important, is the format of the filter. There are two main formats available: cartridge filters, used in stainless-steel housings, and stand-alone single-use capsule filters. The choice of cartridge or capsule is largely driven by the manufacturing plant and setup. Cartridge filters have traditionally been used in biologics manufacturing; however, more manufacturers have moved away from stainless steel and are implementing single-use technologies to increase manufacturing flexibility and efficiency.

In addition to the choice of cartridges or capsules, it is important to consider future needs. The filter selected should be available in the sizes needed for current processes and also in sizes that enable scaled-up production in the future. In general, considering the long-term goals of a project early may prevent having to redevelop the filtration process later, potentially saving valuable resources and mitigating the risks associated with design changes.

Today, filters are selected to meet the needs of different biologics manufacturers, applications, and process steps. An experienced filter supplier can be a partner that helps identify the most suitable sterile filtration products to maximize the efficiency of your operation, assure successful validation of performance, and provide supporting product documentation to streamline regulatory filing.

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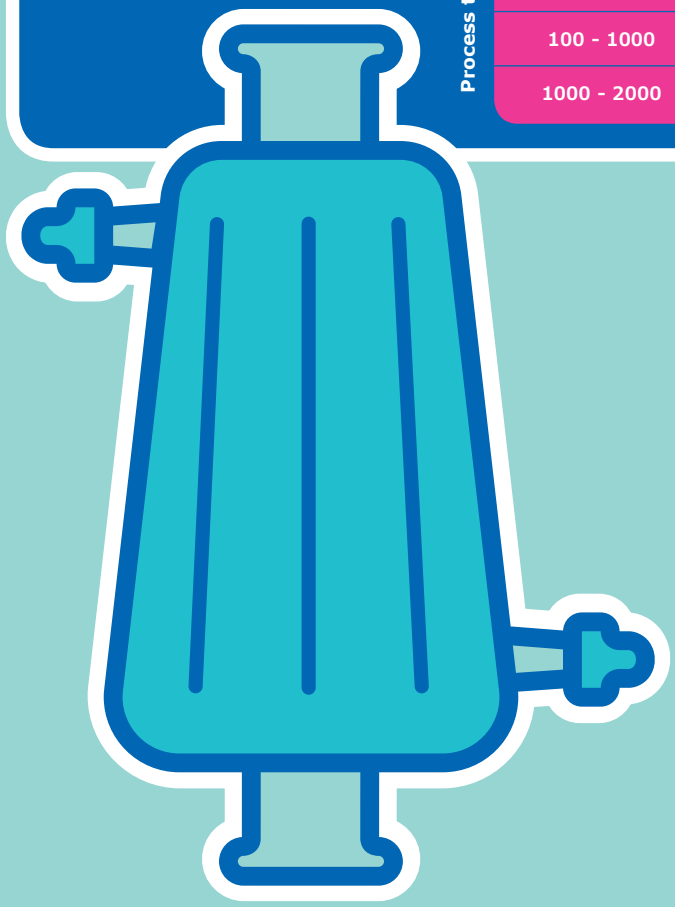
Filter recommendation example

Process time: 1 hour

Batch Volume (L)	Mycoplasma and Bacterial Retention	Virus, Mycoplasma and Bacterial Retention
	Millipore Express® SHR-P (0.5/0.1 µm) filters	Viresolve® Barrier filters
< 100	Opticap® XL 3 KHVEG03TT3	0.15 m^2 VBKG015TC1
100 - 1000	Opticap® XL 10 KHVEG10TT1	1.0 m^2 VBKG100TC1
1000 - 2000	Opticap® XL 10 KHVEG10TT1	2 x 1.0 m^2 VBKG100TC1



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Maximizing the Performance And Efficiency Of Your Sterilizing-Grade Filtration

By: Kimberly Steffen and Sal Giglia, MilliporeSigma

For biomanufacturers, sterility assurance is a critical part of any process. To achieve this goal, sterilizing-grade filters have traditionally been used at multiple points in purification processes. However, as science and technology have advanced, so have the filtration options. Instead of the one-size-fits-all sterilizing-grade filter, you can now design a filtration train tailored to the specific needs of your application or unit operation. Selecting the right filter is the first step in reaping the benefits of today's filters; optimizing their performance efficiency is key to maximizing the benefits for the lifetime of your process.

Being able to depend on this performance efficiency means having confidence that your filters will always be able to reach a defined throughput or capacity in the set process time and, at the same time, provide the expected levels of microbial retention. Delivering this performance relies on your filter supplier having highly-controlled membrane manufacturing processes. Ideally, the filter supplier will also have a sound understanding of the fundamental mechanisms of filtration to provide guidance on both filter selection and how to maximize filter performance under your process conditions.

Optimizing the performance of sterilizing filters in a process is often shaped by the facility fit, which might constrain the operating conditions. For example, existing equipment may limit the process to either constant flow or constant pressure operations; in these cases, filtration processes can be designed and optimized to accommodate these limitations. Similarly, the scale of production or facility setup will determine whether cartridge filters must be used in stainless-steel housings or whether the process can accommodate a more flexible single-use system. These types of decisions influence multiple aspects of process design and optimization.

Key Considerations for Optimizing Filter Performance

The best time to select and optimize performance of a new filter is in the early stages of process development, before production of Phase 1 clinical material. Several considerations will guide selection, but most important is confirming the filter meets performance targets under the process operating conditions. Although filters are designed to accommodate a wide range of operating conditions, such as pressure, pH, temperature, flow rate, duration, and different sterilization methods, individual process conditions can have a significant impact on the efficiency of the operation. The key considerations when assessing filter performance under different operating conditions include microbial retention, permeability, and filter throughput capacity (Figure 1).[1]

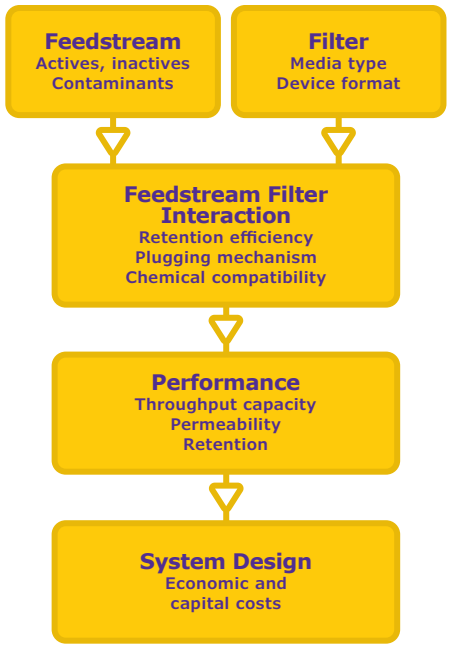

Figure 1:
Considerations for assessing filter performance

Regardless of your filtration goals, new filter technologies offer improvements in operation, efficiency, and cost.

Microbial Retention

Microbial retention by the membrane is based on the principle of size exclusion. The membrane pores must be smaller than the microorganisms to be retained. Regardless of the operating conditions, retention must be consistent throughout the entire filtration process. Typically, microbial retention under the process-specific conditions is confirmed by the biomanufacturer during validation of filter performance. Performing a filter integrity test after use confirms the filter meets a defined specification for retention assurance and links the conditions of filter operation to the validation of filter performance.[2]

Permeability

Permeability is flux per unit pressure and determines how quickly and efficiently a filter can process a fluid stream. Changes in permeability impact the duration of the filtration step. For non-plugging fluid streams, such as buffers, specialized filters with high permeability can quickly process a large volume of fluid with a small amount of membrane area. For plugging fluid streams, such as cell culture media, high permeability filters are less useful, as the membrane plugs quickly. Filtration of these streams often relies on membranes that have lower permeability, but a higher capacity for particulates.

Filter Throughput Capacity

Throughput capacity determines how much fluid can be processed before the filter is plugged to the point where it is no longer useful. The symmetry and morphology of the membrane in the filter greatly impacts the throughput capacity. Symmetric membranes have pores of uniform size throughout the depth of the membrane, and while they may provide excellent microorganism retention and reasonable throughput for non-plugging streams, when challenged with a more fouling fluid stream, the microorganism-retentive pores may foul prematurely with particulates. Asymmetric membranes have a gradation of pore sizes through the depth of the membrane, enabling the larger pores at the upstream side of the membrane to trap and retain particulates while allowing the smaller microorganism-retentive pores deeper in the membrane to remain open for fluid passage. The gradation of pore size is the reason asymmetric membranes generally allow higher throughput capacity with fouling streams than symmetric membranes.

Prefilters: A Cost-Effective Solution To Reduce Your Sterile Filtration Cost

Prefilters can significantly improve the overall performance of a filtration train by removing unwanted particles before the fluid stream reaches the sterilizing-grade filter. By reducing the particle load prior to the sterile filtration step, manufacturers can reduce the amount of sterilizing-grade membrane required. As prefilters are less expensive than sterilizing-grade filters, implementing prefiltration can result in significant cost savings.

However, designing a filter train that includes prefilters can be complicated, as you must determine the optimal prefilter-to-sterilizing-filter-area ratio for maximum efficiency. Oversizing the filtration area means the filter train is more expensive than it needs to be, and undersizing risks incomplete batch processing in the expected time. While a prefilter affects the performance of the sterilizing filter, the sterilizing filter can also affect the performance of the prefilter by restricting fluid flow through the prefilter. This complexity is increased when thinking about the different sizes of particulates in fluid streams and how these impact membrane pore fouling (Figure 2).

Fouling Mechanism	Physical Concept	
Cake filtration	Formation of a surface deposit	
Intermediate blocking	Pore blocking + surface deposit	
Standard blocking	Pore constriction	
Complete blocking	Pore blocking	
Adsorption	Particle-surface attraction	

Figure 2:
Different Fouling Mechanisms for Membrane Filters

Behavior Modeling for Prefilter And Final Filter Configurations

Descriptions of filtration mechanisms and the factors that affect flux and throughput capacity have been published.[2,3,4] Technical experts at MilliporeSigma used this information to develop proprietary modeling software that can be used to predict filter performance. Filters are run under constant pressure, recording the volume processed as a function of time, and the data generated is used to predict filter volumetric loading capacities using the modeling software. These models can also be used to predict loading capacities using data generated from trials run under constant flow conditions. The modeling software determines which filtration mechanism or mechanisms best describe the observed filtration behavior, resulting in more accurate and reliable filter sizing.

Characterizing and predicting performance from filtration trains that include prefilters and sterilizing-grade filters adds additional complexity. Yet, with some modifications in trial setup, the modeling software can be used to predict the optimum number of prefilters needed upstream of a sterilizing filter to process a fluid stream within the target time and the batch volume. In general, additional prefilter area results in increased throughput capacity. Depending on some considerations, such as the respective costs of the prefilter and sterilizing-grade filter, there can be limited benefit in additional prefilter area (see Figure 3). The MilliporeSigma predictive models can incorporate pricing information to identify the most cost-effective solution for the process conditions.

MilliporeSigma offers technical support in streamlining trial design to minimize the amount of effort and volume of fluid needed for trials. These technical experts can also help process trial results into an optimized filtration train design to minimize cost, footprint, or some combination of these, to maximize filtration efficiency. Most importantly, this approach to predicting filtration performance has been empirically verified using different filters and feed streams.

The main purpose of these small-scale trials is prediction of process-scale performance, which relies on good scaling in filtration performance between small and process-scale devices. Reliable filter manufacturers will have data for their filters in one or more process streams demonstrating good scalability.

Assuring Filter Performance

Although filter selection and an optimized filter train are essential to maximizing the efficiency of throughput capacity performance, the most important aspect of any sterile filtration operation is making sure the filter is integral. Integrity testing assures the filter has performed as expected and prevented passage of bacteria.

There are two types of integrity tests to assure filter performance. A ***pre-use integrity test*** confirms the filter is correctly installed and there was no damage from shipping or installation. The pre-use test is widely recommended, though required only in certain geographies. End users who distribute their drugs globally should keep this in mind when deciding on a testing strategy. ***Post-use integrity testing*** is performed after processing to ensure the filter was not damaged during use. This is a regulatory requirement in the United States and most other geographies.

Integrity testing specifications are filter-specific and should correlate

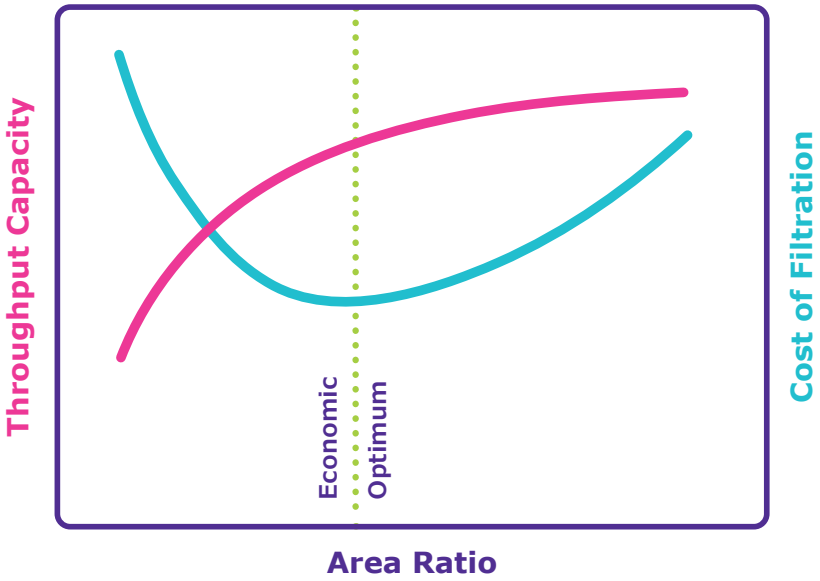

Figure 3:
Throughput Performance and Filtration Costs with Increasing Prefilter Area

to bacterial retention performance. Each filter product, and sometimes different formats of the same product, will have different integrity test values. In general, for small-area filters, a bubble point test is recommended; for higher-area filters, diffusion testing is preferred. Because sterilizing-grade filters have different wetting guidelines, it is important that the correct conditions for the specific filter are followed, as the bubble point and the diffusion tests rely on a fully wet filter membrane. To confidently assure filter performance, check the test guidance from your filter manufacturer.

Regardless of your filtration goals, new filter technologies offer improvements in operation, efficiency, and cost. However, filter selection and optimization can be complex, especially in the early stages of process design where multiple filters may need to be selected. Partnering with a supplier that has experience and deep understanding of membrane and filter design can help streamline the design and sizing of a filtration system that delivers the performance and safety assurance needed for producing biopharmaceuticals for patients.

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Industry Trends Changing Sterile Filtration

By: Randy Wilkins and Matt Daley, MilliporeSigma

According to a recent report from the Tufts Center for the Study of Drug Development, the total price tag for bringing a new drug to market can be up to $2.7 billion.[1] While development costs are high, keeping costs low during commercial production while delivering products that are safe for human use are key components of market success.

Over the past decade, there have been major improvements in process understanding that have resulted in more efficient processes that meet market demands for high-volume, blockbuster therapies. Improvements have also been made in the efficiency of small-volume, microscale processes to the point where patient-specific therapies are a reality. To help meet the needs of both large- and small-scale processes, suppliers of sterilizing-grade filters have developed new products and technologies and, in some cases, optimized existing products by creating new sizes or formats. Although the fundamental function of sterilizing-grade filters is to control bioburden and provide sterility assurance, there are many more filtration product offerings today that can improve efficiency and expand flexibility in process design.

Industry trends toward intensified processing and increased implementation of single-use systems are changing approaches to sterile filtration and bioburden control in biomanufacturing processes. These trends have adjusted expectations for both suppliers and biomanufacturers.

The Move to Process Efficiency and Intensified Processing

Process efficiency means different things, depending on your perspective. For upstream processes, it may be more productive cell culture processes or increased confidence in more reliable, uninterrupted production. High-profile bioreactor contamination events that resulted in plant shutdowns and disruptions in drug supply highlighted the criticality of raw material sourcing and comprehensive risk analysis for cell culture media components. Filter suppliers met this need for improved microbial retention with specialized filters that not only provide sterilizing-grade performance but also remove other high-risk microbial contaminants, such as mycoplasma and adventitious virus.

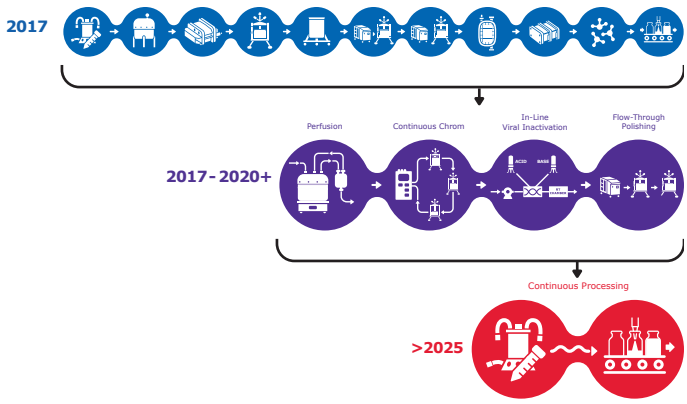

Figure 1:
Manufacturing processes are evolving from today's batch operations to the intensified connected operations of the future

These filters, containing membrane with smaller pore sizes than the traditional 0.2 µm sterilizing-grade membrane, are now routinely used to reduce the risk of bioreactor contamination and consequent production interruptions. These complex bioreactor feeds often contain a high concentration of components that would plug traditional sterilizing-grade filters. High-capacity filters that maintain flux in the presence of filter-fouling components have been developed to efficiently process these fluid streams. Additional flexibility is achieved by implementation of high-area filters that offer a large area of high-capacity membrane in a small filter footprint. These types of innovations can improve process economics and facility fit.

For downstream operations, process efficiency may mean higher yield, faster processing, or higher loadings on individual unit operations. Purification challenges

are being met by modifying traditional downstream operations from batch to intensified operations with either hybrid systems of batch and flow-through operations or fully continuous flow-through operations (Figure 1). Although purification operations are often a focus for improved efficiency, as existing processes are modified or new processes are developed, sterile filtration operations are also often reviewed for potential efficiency improvements.

Traditionally, sterilizing-grade filters have been used at multiple points in downstream processes. Prefilters, with their generally lower costs than sterilizing-grade filters, are increasingly being implemented to extend the life of sterilizing-grade filters and reduce the overall costs of filtration. In some cases, prefilters with bioburden reduction claims can be used as stand-alone filters and offer a lower-cost alternative to sterilizing filters for bioburden control at intermediate process steps, such as column protection. These types of filters may also be appropriate for processing buffers where bioburden control, rather than sterility, is the objective. Risk analysis tools can help understand the needs for bioburden reduction or sterile filtration at different process steps and will guide selection of both the appropriate filter type and its performance requirements.

In addition to the filtration devices or technologies, suppliers are thinking about ease of use in integrated system flow paths. Design features on filters are being modified to improve the user experience, minimize operator errors, and increase connectivity. In addition, suppliers are developing technologies to simplify digital integration of their products into biomanufacturing operations. New scannable labels afford simpler inventory management, easier ordering, and more direct access to supplier information as well as expanded options for increased connectivity to automation and electronic data management systems. As these features become more widely available, today's manufacturers have many more options for sterile filtration than the one-size-fits-all sterile filter of a decade ago.

The Rise of Single-Use Technology

Extensive work over the last two decades has resulted in significant increases in cell culture productivity, with molecule titers up to 10g/L from fed-batch processes.[2] These higher-yield processes have enabled a 2-liter bioreactor using a more efficient process to generate the same quantity of material as a 20-liter stainless-steel bioreactor operating under traditional conditions. Increased productivity opens the opportunity of using single-use technology for manufacturing. Single-use technology offers many advantages over traditional stainless-steel operations: minimized cleaning, resulting in reduced labor, material, and utility costs, and significantly improved operational flexibility. These benefits, together with the reduced up-front costs, are driving the rapid adoption of single-use technology across the industry.[3]

The flexibility of single-use systems is particularly attractive in the final sterilizing filtration of the drug product. Single-use offers clear advantages in final filtration by reducing the risks of product contamination and offering increased efficiency for process changeover as compared to traditional operations. Specialized sterilizing-grade filters have been developed for final filtration; these filters have a novel design format that reduces hold-up volume and maximizes product recovery. Other modifications to the filter housing make these filters easier to use and easier to integrate into

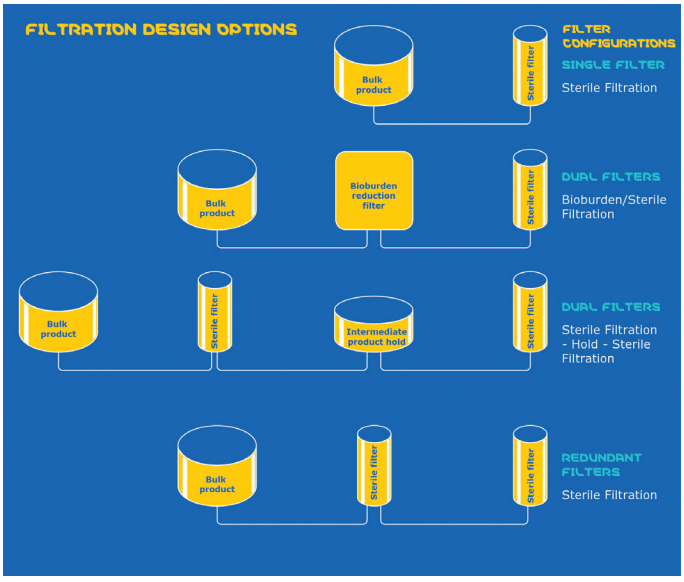

Figure 2:
Different filter configurations for final sterile filtration of purified drug product.

single-use systems. For final filtration of highly-purified, concentrated drug product, filters such as these that offer sterilizing-grade performance combined with features that simplify operation and reduce operator errors offer many benefits to biomanufacturers.

Yet implementing single-use does not come without challenges for biomanufacturers. Specifically, the polymer components in these systems increase the possibility of potential interactions with the drug substance as compared to the standard stainless steel. These polymers increase the risk of extractables and leachables as well as particulates, which can interact with the product and affect its quality, safety, and efficacy. Suppliers are expected to provide comprehensive information on the system components, with details on materials of construction and well-characterized extractable and leachable profiles according to industry standards, such as BPOG and USP 665. This information is used by biomanufacturers to develop risk assessments and documentation to meet regulatory expectations for single-use implementation.[3]

The complexity of requirements to assure suitability of single-use system components for biomanufacturing has resulted in a much closer relationship between manufacturers and their suppliers, as manufacturers leverage the supplier's expertise, experience, and technical know-how to help meet their needs.

Meeting Evolving Industry and Regulatory Expectations

As processing systems have evolved, there has been increased focus on integrity testing and filtration system design, particularly around the final sterilizing filtration before filling. Regulatory requirements, risk profile, facility fit, and costs are all considerations that affect the final filtration system design. These systems can include single or dual filters where one or both may deliver sterilizing-grade performance (Figure 2). Although a single sterilizing-grade filter will provide sterility assurance, redundant filtration reduces the risk of compromising sterility and of having to discard a batch of processed drug product should the single sterilizing-grade filter fail integrity testing.

FDA aseptic processing guidelines recommend a pre-use integrity test of sterilizing-grade filters but do not specify if it should be done before or after sterilization.[4] By contrast, EU Annex 1 guidelines for Manufacture of Sterile Medicinal Products state that "the integrity of the sterilized filter should be verified before use."[5] This pre-use, post-sterilization integrity test (PUPSIT) presents challenges for biomanufacturers, as they may have to perform a potentially intrusive integrity test after a filter is sterilized, without compromising sterility downstream of the filter. The difficulty is magnified in systems where two sterilizing-grade filters are connected in series and must both be integrity tested before use. The lack of a global harmonized position on PUPSIT makes it difficult for manufacturers trying to design processes that comply with global regulatory expectations.[6]

Irrespective of their position on the risks and benefits of PUPSIT, it is important filter suppliers support their customers' needs by designing and validating systems that minimize the risks of PUPSIT. Specialized barrier filters containing hydrophilic and hydrophobic membrane layers offer opportunities for simplified system design by enabling filter flushing with water and subsequent blow-down with air (Figure 3). However, even with these filters, verifying filter integrity post sterilization in a redundant filtration train remains a challenge for many biologics manufacturers. There is no one common design for a single-use, final-filling system, and designs are based on each user's risk analysis. A robust system design requires extensive knowledge and understanding of the drug product, operating conditions, filter performance, and regulatory requirements.

Suppliers are designing new products for use in biopharmaceutical production processes, with features that maintain sterility while simplifying operations and improving digital integration. Biologics manufacturers

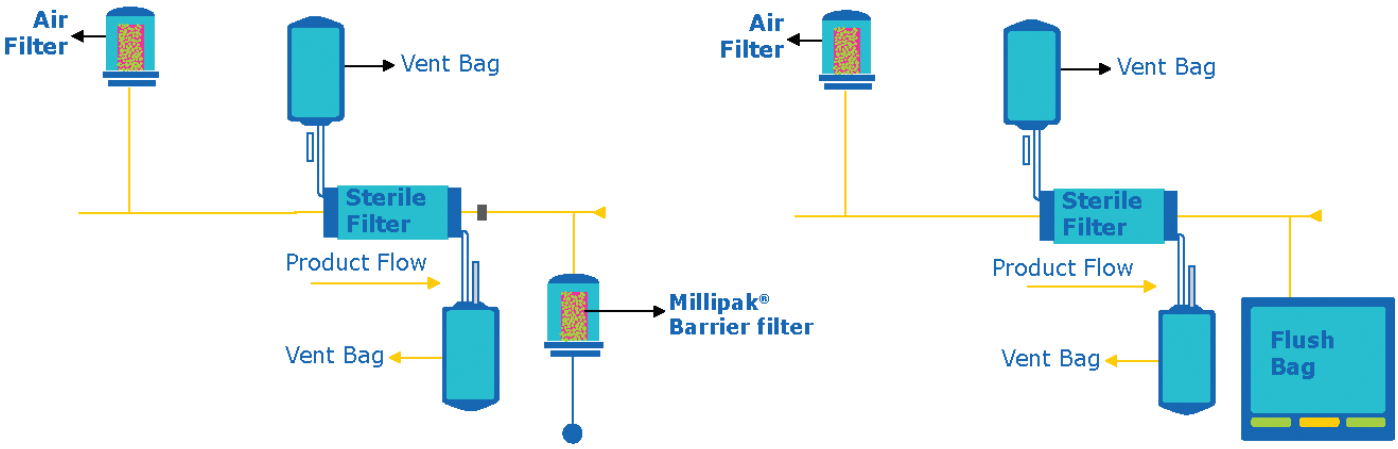

Figure 3:
Possible configurations for in-line integrity testing using a barrier filter, such as Millipak® Barrier filter (left), or a flush bag (right)

have many decisions to make when identifying the appropriate filters for a process and when designing and validating the filtration system. Collaborating with a supplier with experience in both filtration technology and single-use systems can provide confidence as they work together to maximize the efficiency and improve the economics of drug production.

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Mark Blanchard
Research Fellow
MilliporeSigma

White Paper

Minimizing Sterile Filtration Risk through Quality by Design

Controlling bioburden throughout biomanufacturing processes is critical to assuring drug products are safe for human use. To ensure products are free from microbial contamination, multiple filtration steps are implemented across the biomanufacturing process (Figure 1). The final sterilizing filtration prior to filling is especially critical, and filtration performance should be confirmed according to industry standards and test criteria. Other steps in the downstream process, such as the filtration of buffers used in chromatography and TFF applications, are less critical; a filter designed for bioburden reduction may provide a sufficient level of risk mitigation against potential bioburden issues for these applications.

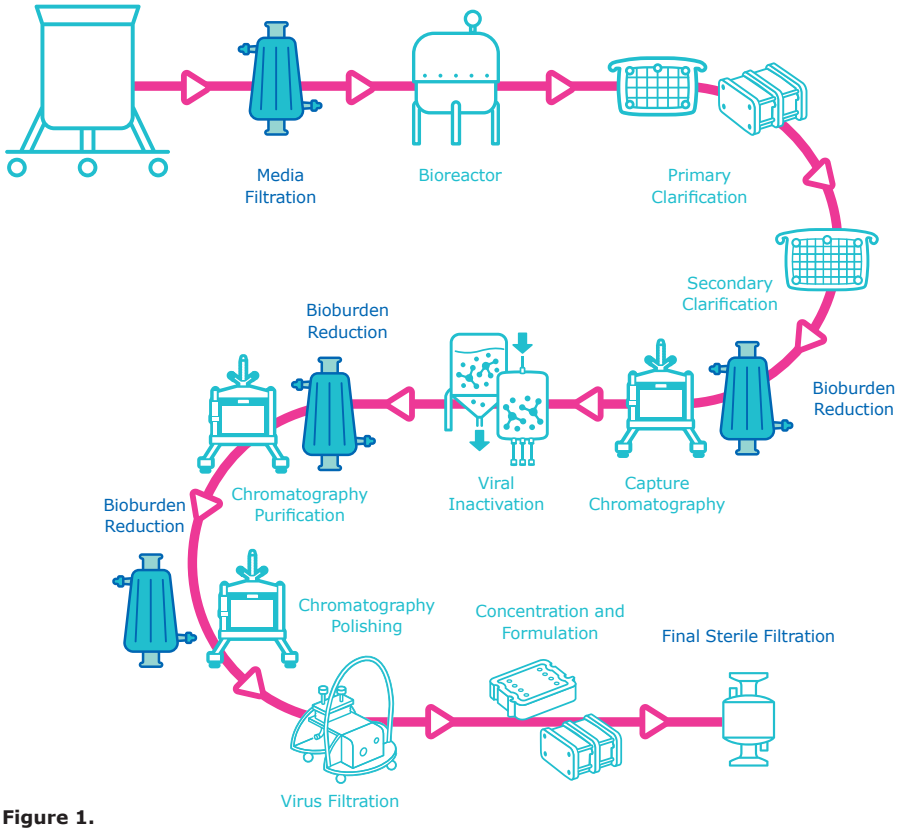


Figure 1.

Sterilizing-grade filtration is used at multiple points in the biomanufacturing process to minimize the risk of contamination from microbes.

To achieve a robust sterile filtration process, drug manufacturers should follow industry best practices and regulatory guidelines. For final filtration and other critical steps, filter efficacy must be validated under worst-case processing conditions, and the chosen integrity test must use specifications that are consistent with data generated during validation.

US FDA aseptic processing guidelines require a sterilizing filter to "reproducibly remove all viable microorganisms from the process stream, producing a sterile effluent" (1). For products that are not terminally sterilized, EMA guidelines state that solutions or liquids "can be filtered through a sterile filter of nominal pore size of 0.22 µm or less, with [a filter] with at least equivalent microorganism retaining properties" (2). In brief, all microorganisms must be removed and the microorganism retention properties of the filter must be well defined.

The Role of Your Filter Supplier

Although meeting regulatory and industry requirements is the responsibility of the drug manufacturer, filter suppliers play a critical role.

Filter suppliers must show that a sterilizing filter meets the requirements of the FDA Aseptic Processing Guidelines and other regulations. These requirements define a sterilizing-grade filter as

a filter which, when challenged with the bacterium *Brevundimonas diminuta* at a minimum concentration of 10^7 colony forming units (CFU) per cm^2 of filter surface area, will produce a sterile effluent.

Caution should be used when evaluating filters that claim to be sterilizing because a number of historical approaches do not meet current minimum requirements. A nominal 0.2 µm filter size rating itself does not ensure sterile filtrate. The bacterial log reduction value (LRV) provides a good starting point, but it does not directly ensure that filtrate will be sterile.

The minimum requirement is reflected in ASTM® F838, which states that a filter must successfully retain all bacteria through the standard challenge test (3). Ideally, a filter will be validated with a defined safety margin above that minimum. A quantitative safety margin ensures low risk of failure. Drug manufacturers should ensure that the sterilizing grade filter they choose meets this requirement.

Because sterilizing filters occupy critical control points in downstream purification processes, it is important to know how consistent and reliable a sterilizing filter will be beyond the minimum standard. Filters must be designed with a quantifiably high safety margin for bacterial retention and minimum loss of flow or processing time efficiency. Evidence of design conformance should be available from your filter manufacturer, and the risk of a filter being out of specification must be low.

Applying QbD to Filter Design

At MilliporeSigma, we design and manufacture filtration system components to provide high assurance of sterility for aseptic processes by applying principles of Quality by Design (QbD) to the process.

QbD is a science- and risk-based approach for process development and manufacturing. The approach starts with definition of clinically-relevant product attributes followed by design and implementation of a process to consistently deliver quality product. FDA's emphasis on QbD is based on the recognition that increased testing does not necessarily improve product quality. Instead, quality should be built into the product from the beginning, based on knowledge of its characteristics and a thorough understanding of the process by which it is manufactured.

FDA's initiative on QbD embodies key principles:

- The product is designed to meet patient requirements
- The process is designed to consistently meet product critical quality attributes
- The impact of product components and process parameters on product quality is understood
- Critical sources of process variability are identified and controlled
- The process is continually monitored and updated to assure consistent quality over time

Consistent with those principles, a "design space" (the combination and interaction of input variables and process parameters that have demonstrated quality assurance) is defined and validated (4). From that, a "control space" for on-going filter manufacturing is developed. For sterilizing filters, this is applied to three areas:

- Membrane design and validation during which membranes are developed with a quantified safety margin
- Device design and validation during which retention performance is verified
- Manufacturing process control of critical process attributes (CPAs), during which continuous conformance to the design principles is monitored and ensured

The Design Space

Designing a filter for sterility assurance begins with developing a manufacturing process within a well understood design space. The process begins with manufacturing a series of membrane samples with different membrane bubble points. Bubble point is the minimum pressure required to force an air bubble through the largest membrane pore. The membrane bubble point is inversely proportional to the size of the pores. Pore size is one of the primary membrane characteristics that define retention based on size exclusion.

Bacterial retention testing is conducted on the membrane bubble point series to measure organisms in the filtrate using a standard ASTM® test method. A membrane is defined as "fully retentive" if there are no bacteria downstream following a challenge of $>10^7$ CFUs *Brevundimonas diminuta* per square centimeter of membrane area. This organism is small in size and for most applications, represents a worst-case scenario.

Bacterial retention increases with increasing bubble points, resulting in higher sterility assurance (Figure 2). For sterilizing filters, sterility assurance of >99.9% at 10^7 CFU/cm^2 is desired. The safety margin comes from log (CFU) = −3. With that margin, zero CFU are expected 999 times out of 1000 tests.

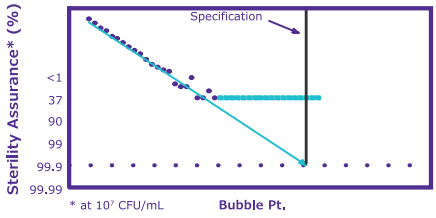


Figure 2.

Filter specification set with high capability retention at ASTM® F838 conditions

- Retention assurance >99.9% at 10^7 CFU/cm^2
- Using log (CFU) vs. bubble point, the specification is established with a safety margin
- When log (CFU) = -3, average CFU is zero with 99.9% confidence

The Control Space

Once that safety margin has been established, we set a manufacturing range (the QbD control space) well above the sterility assurance specification. The range must also be beyond the potential

measurement error for bubble point testing and the manufacturing capability must be high, Figure 3.

Within those safety margins, filter membranes are routinely manufactured with >99.99% sterility assurance under ASTM® conditions at a bacterial challenge load of 10^7 CFU/cm^2.

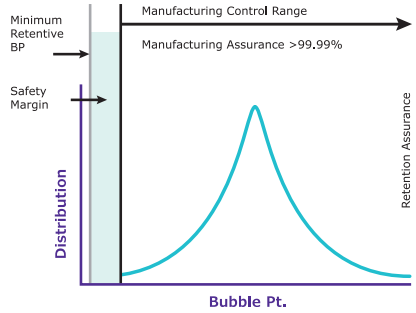


Figure 3.

Our sterilizing-grade membranes are manufactured with >99.99% sterility assurance at a bacterial challenge load of 10^7/cm^2.

All membrane rolls at MilliporeSigma are bubble point tested during manufacturing to ensure they meet this standard and membrane manufacturing process is adjusted in real time, if necessary. In addition, ASTM® bacterial retention performance is verified for each membrane lot (Figure 4A).

Filter Device Manufacturing

To effectively support a sterile process, a membrane must be coupled with a complete device manufacturing process. For this process, all sterilizing grade devices are 100% integrity tested during manufacturing (Figure 4B). Bacterial retention performance is verified on samples from each lot of devices followed by a full panel of tests for endotoxins, extractables, flow rate, hydraulic stress, and resistance change after sterilization (Figure 4C).

Final Validation

Filter validation confirms the filtration device provides sterilizing performance under the user's process conditions. Process conditions to be validated include temperature, pressure, filtration time, bioburden profile and quantity, and any conditions that may adversely affect filter materials or filtration properties (e.g., sterilization condition). The validation evaluates the filter under worst case processing conditions.

Our Commitment to Customers

Sterilizing filtration is a critical control point in biomanufacturing. A capable filter and thorough validation at worst case filter and process conditions can provide confidence in sterility assurance. We design sterilizing grade filters to meet regulatory and industry requirements and assure sterility by following a scientifically-based process to develop, validate, and control critical design properties (Table 1). Our membranes are designed with a high and well-characterized safety margin for bacterial retention, with further safety margin, control and monitoring provided during manufacturing.

We understand the critical importance of aseptic processing to the success of our pharmaceutical customers and patient safety. With more than fifty years of experience and expertise in sterile filtration and industry leading products, our membranes have processed billions of sterile doses.

STERILITY ASSURED. No one does more to assure sterility and compliance
End-User Validation and Testing
Device Lot Release Tests
Device 100% In-Process Integrity Test
Membrane Lot Release Tests
Membrane and Device Product Design and Process Validation

Table 1.

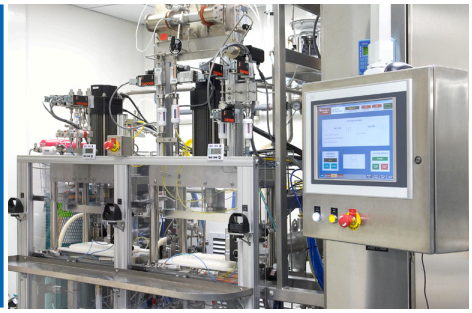
Elements of MilliporeSigma's comprehensive quality program to minimize sterile filtration risk and assure compliance.

Figure 4.

Ongoing process monitoring includes membrane lot release testing (A), in-process integrity testing (B) and device lot release testing (C).

A.

B.



C.

Membrane Lot Release Testing

- ASTM® Retention tested
- Endotoxin tested
- Integrity tested
- Application based tests

In-Process Integrity Testing

- 100% device testing (proprietary high sensitivity test)

Device Lot Release Testing

- ASTM® Retention tested
- Endotoxin tested
- Thermal stress tests
- Hydraulic stress tests
- Integrity lot tests
- Application based lot tests

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