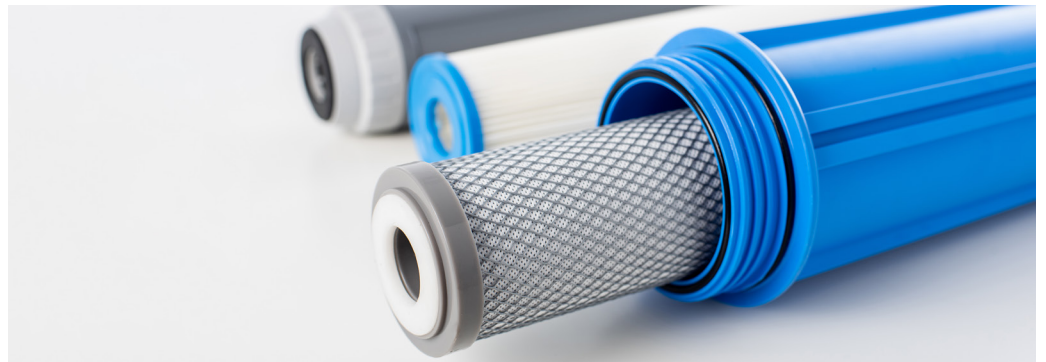


Overview of Critical Filtration Methods For Biopharmaceutical Processing

Filtration is a critical process in biopharmaceutical manufacturing, essential for meeting strict purity and safety standards across various production stages. Each filtration technology addresses specific challenges posed by complex biologics, high product viscosity, and diverse modalities, requiring scalable and robust solutions. Challenges such as fouling, filter capacity, product loss, and regulatory compliance necessitate precise process control and ongoing innovation. Advanced, integrated filtration systems with real-time monitoring, automation, and versatile configurations enhance efficiency, safety, and scalability from laboratory to pilot scales. These innovations support the evolving demands of biomanufacturing, promoting sustainability and cost-effectiveness while ensuring high-quality product outcomes.

Background

Filtration is a vital component of biopharmaceutical manufacturing, playing a key role in achieving stringent purity and safety requirements (1). A wide range of filtration technologies are applied across various production stages, from initial cell harvest clarification to final sterile filtration. These technologies must evolve to accommodate increasingly complex biologics and higher production volumes, demanding scalable and resilient solutions. As biotherapeutic modalities diversify, filtration processes face specific challenges, including managing high solution viscosity, minimizing product loss, and preserving the integrity of sensitive molecules. Continuous innovation is essential to optimize process efficiency, ensure regulatory compliance, and address sustainability and cost-effectiveness within biomanufacturing workflows.



Key Filtration Technologies and Their Roles in Biopharmaceutical Manufacturing

To effectively satisfy the diverse demands of biopharmaceutical manufacturing, it is important to understand the distinct filtration technologies available and their specific applications. Each type of filtration offers unique capabilities tailored to different process stages and challenges, enabling optimized purification and product safety throughout the manufacturing workflow. The following sections detail the primary filtration categories and their roles within bioprocessing.

Filtration technologies in biopharmaceutical manufacturing are categorized into three main types: depth filters (prefilters), membrane filters, and virus filters.

1. Depth Filters:

These are primarily used for initial clarification to remove cells and cellular debris and reduce turbidity. They are composed of non-woven media or silica reinforced with fibers, often containing cellulose fibers, diatomaceous earth, and positively charged resins to bind nucleic acids. Depth filters are used at cell harvest and prior to polishing chromatography. Normal flow filtration (NFF), which passes the fluid directly through the filter medium, is often used in conjunction with depth filters for similar clarification steps. NFF is straightforward to operate and is effective in removing larger particulates early in the process, complementing the performance of depth filtration in ensuring process clarity and protecting downstream operations.

2. Membrane Filters:

Used to remove smaller particles, membrane filters are used for sterilizing final products, bioburden control, virus retention, concentration, and buffer exchange, utilizing precise pore sizes. Typically made of polyethersulfone (PES), these filters come as flat or pleated sheets and are employed in aseptic filtration, including 0.2 µm sterilizing-grade filters for final fill/finish and 0.1-micron variants for mycoplasma protection. They are also used for intermediate filtrations to protect downstream chromatography (3).

3. Virus Filters:

Specialized membranes, often hollow-fiber nanofilters, effectively remove adventitious and endogenous viruses due to their small pore sizes. Nanofiltration membranes are crucial in viral clearance steps for mAbs and bispecific antibodies and are adapted for viral vectors such as lentivirus (LV) and adeno-associated virus (AAV), despite filtration challenges due to size and aggregation.

Additional filtration types include vent filters to maintain tank pressure and enable integrity testing.

Each filtration type addresses specific process needs and challenges related to modality and product properties, such as higher cell density in mAbs, aggregation in bispecific antibodies, potency containment in antibody-drug conjugates (ADCs), and size/charge considerations in viral vectors and plasmid DNA. Recent advances focus on improving capacity, reducing fouling, enabling closed systems, and integrating filtration with chromatography to enhance efficiency and sustainability (2).

Challenges in Key Filtration Technologies

Depth Filters:

Depth filtration faces significant challenges due to increasing cell densities and higher impurity loads from intensified upstream processes. Traditional depth filters can experience fouling and reduced capacity, limiting throughput. Additionally, their composition, often positively charged silica media, can adsorb negatively charged viral vectors and plasmid DNA, resulting in lower product recovery (3). Overall, depth filtration in biopharma demands a comprehensive understanding, careful testing, and meticulous process control to develop a robust, scalable, and consistent filtration process.

Membrane Filters:

Membrane filtration in biopharma presents challenges in selecting and optimizing filters to process complex cell culture fluids effectively. Unlike depth filters, membranes demand precise selection of pore size, chemical compatibility, and fouling resistance, as fouling by proteins and particulates can significantly reduce throughput and filter lifespan. Key operational challenges include controlling pressure changes to prevent premature clogging, accurately sizing filters through small-scale testing for reliable scale-up and managing batch-to-batch variability. Mistakes in pressure monitoring, cleaning procedures, and scale-up calculations can negatively impact filtration efficiency and product yield. Therefore, comprehensive testing, stringent process control, and thorough validation are essential to develop a robust, scalable, and efficient membrane filtration process.

Virus Filters:

Common challenges faced by virus filters in biopharmaceutical manufacturing include balancing effective viral clearance with maintaining flow rate and product yield, and handling performance variability across molecules such as aggregation-prone bispecific antibodies. Viral vectors pose additional challenges due to size and charge. Overloading virus filters can cause pressure spikes and reduced flow, while low operating pressures, especially in continuous filtration, may impair performance. Fouling

from prefilters reduces virus retention and raises contamination risks. Optimizing buffer conditions and avoiding membrane adsorber overloading are also critical. Preventing virus carryover requires strict quality controls and segregation to avoid batch failures. Documentation and regulatory compliance remain complex, especially for emerging modalities like cell and gene therapies. Addressing these challenges needs careful planning, robust design, continuous monitoring, risk-based approaches, and early integration of viral clearance in development to ensure safety, efficacy, and compliance (4, 5).

Filtration Challenges in an Era of Process Intensification:

Other filtration components such as vent filters play a vital role in maintaining sterile conditions and tank pressure. These filters must be compatible with sterilization methods and designed to minimize contamination risks.

Overall, each filtration technology presents unique challenges driven by the complexity of bioprocesses, product-specific characteristics, and regulatory requirements. Overcoming these challenges necessitates ongoing collaboration and innovation to develop scalable, efficient, and modality-specific filtration solutions that ensure consistent, high-quality biopharmaceutical production from pilot to commercial scale.

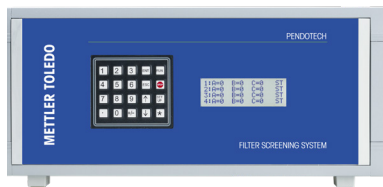
The biopharmaceutical industry is experiencing significant demands driven by process intensification, characterized by higher production titers and more complex therapeutic modalities, which strain traditional filtration systems. These challenges span technical, modality-specific, regulatory, and operational dimensions.

Addressing these multiple challenges requires ongoing innovation, collaboration across technology providers, manufacturers, and regulators, and a keen focus on process intensification.

METTLER TOLEDO Pendotech Solutions

Normal Flow Filter Screening System

The METTLER TOLEDO Pendotech Filter Screening System provides an effective solution for optimizing NFF processes, a type of depth filtration in which fluid passes directly through a porous filter medium to remove larger particles such as cells and debris during clarification. This system enables volume-throughput studies under constant flow or pressure conditions and supports up to four parallel filtration trains, each equipped with up to three pressure sensors. It is compatible with Pendotech Pressure Sensors featuring luer fittings, as well as larger sanitary flange or barb sensors. The user-friendly graphical interface (GUI) simplifies interaction, while integration with up to four independent pumps enables automated, unattended operation. Pumps automatically stop once volume targets are reached or if alarms—such as high pressure or delta pressure—are triggered, ensuring safety. Additionally, the system allows simultaneous execution of four constant-pressure experiments via its scale input functionality, providing enhanced flexibility and precise control during screening.



Tangential Flow Filtration System

The Tangential Flow Filtration system utilizes METTLER TOLEDO Pendotech sensors to monitor pressure and transmembrane pressure (TMP), along with integrated sensors for conductivity, pH, and temperature to maintain process integrity. The membrane filters in TFF feature specific pore sizes designed to retain biomolecules while allowing smaller solutes to pass. Housed in a robust stainless steel enclosure, the system integrates seamlessly with scales and pumps. It includes an intuitive GUI that supports touchscreen and mouse operation, remote access, and real-time error notifications. It provides precise retentate flow control through flow meters and

DeltaP regulation via built-in software algorithms that set the DeltaP setpoint. Additionally, two external input channels enable the incorporation of other process parameters. Configurable alarms deliver email and text alerts for prompt updates. Overall, the system ensures reliable, safe, and efficient automation across various operational scales, enhancing both process efficiency and data management in TFF applications.



Virus-Depth Filtration System

Depth filters serve as prefilters to remove larger contaminants, thereby protecting downstream virus filters. The integrated Automated Virus Depth Filtration System incorporates METTLER TOLEDO Pendotech single-use sensors for monitoring pressure, temperature, and conductivity, alongside automated valve and pump control via an intuitive PC-based graphical interface. Designed for laboratory and pilot-scale applications, this system streamlines workflows by automating critical steps such as filter cleaning and endpoint management, minimizing manual intervention while enabling real-time data collection and trending with Excel-compatible logging. It supports cleaning both prefilters and virus filters, filtration processes that utilize air detection and filtrate scale endpoints, as well as recovery operations. Optional functionalities include automated valve selection and precise pump regulation via delta-pressure control. Compatible with benchtop and Pilot Cart setups, the system offers flexible integration with various pumps, scales, and Pendotech single-use sensors, boosting operational efficiency and adaptability across a wide range of processes.



Conclusion

Filtration plays an essential and continuously advancing role in biopharmaceutical manufacturing, addressing the growing complexity and scale of biologic production. Various filtration technologies, including depth filters, membrane filters, virus filters, and tangential flow filtration, each fulfill specific needs to overcome challenges related to product properties, process intensification, and regulatory requirements. METTLER TOLEDO Pendotech provides sophisticated, integrated filtration systems that improve process control, automation, and data management. These solutions boost operational efficiency, ensure safety, and support scalable workflows that meet the high standards of modern biomanufacturing. Continued innovation and collaboration remain key to developing robust, modality-specific filtration technologies that meet the evolving demands of the biopharmaceutical industry while enhancing sustainability and cost-effectiveness.

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