Application Note

PENDOTECH
Leading Process Analytics

Advanced Filtration Solutions

For Biopharmaceutical Manufacturing

Filtration plays a vital role in the production of biopharmaceuticals, ensuring the removal of impurities, maintaining product safety, and adherence to regulatory standards throughout the complex drug development stages. However, filtration processes face challenges such as membrane fouling, pressure fluctuations, and the handling of viscous solutions, which can impact efficiency and product yield. METTLER TOLEDO Pendotech meets these challenges with advanced Normal Flow Filtration (NFF) and Tangential Flow Filtration (TFF) systems equipped with precise pressure sensors, automated controls, and real-time monitoring.

Introduction

Filtration is a critical process employed across various unit operations, such as media and buffer preparation, clarification, ultrafiltration/diafiltration and sterile filtration, throughout the manufacturing of biopharmaceuticals to remove process impurities and contaminants (particulates, viruses), and to control bioburden (1).

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Process

Biopharmaceutical manufacturing requires close monitoring at every step to produce safe, effective medicines while meeting strict regulatory standards. Filtration stands out as a fundamental element in this process, playing a critical role from the preparation of growth media and buffers to the recovery, purification, and concentration of the target biomolecules after upstream cell cultivation. It is integral across essential unit operations, including primary clarification, media and buffer preparation, pre-filtration, ultrafiltration/diafiltration (UF/DF), and sterile filtration (1).

Buffer solutions are widely used throughout biopharmaceutical manufacturing and represent a significant potential source of contamination. Impurities in buffers can introduce biological and particulate contaminants, compromising cell growth and product stability. Therefore, Normal Flow Filtration (NFF) is essential in buffer preparation, ensuring aseptic conditions that support viable cultures and consistent downstream processing. By effectively filtering buffers, NFF protects sensitive chromatography columns and ultrafiltration equipment while helping produce a contaminant-free final product (2).

During the clarification phase, NFF is generally employed as depth filtration to remove cells, cell debris, and large particulates from harvested cell culture fluid. This step is important in preparing the feed stream for downstream processes by preventing membrane fouling, protecting purification equipment, and enabling high-yield processing. Gradient-density filters efficiently trap cells and colloidal impurities within their porous structure, enhancing clarification efficiency (1).

Ultrafiltration and diafiltration (UF/DF) via Tangential Flow Filtration (TFF) are key purification steps before final drug formulation. Ultrafiltration concentrates the biologic by separating molecules by size, while diafiltration replaces the purification buffer with a formulation buffer that stabilizes the biomolecule. UF/DF achieves high product recovery rates exceeding 95%, ensuring purity by excluding aggregates and contaminants, stabilizing formulations against degradation, and meeting stringent regulatory potency requirements, a critical consideration for therapeutics where even small losses can affect dosing effectiveness. Instances such as membrane fouling due to high viscosity or improper flux can cause protein denaturation, longer processing times, and incomplete buffer exchange, thereby affecting yield and product stability. This concentration and buffer exchange process minimizes volume without compromising biological activity and removes organic and conjugation-related contaminants (3).

Sterile filtration, using 0.22 µm polyether sulfone (PES) or polyvinylidene fluoride (PVDF) membranes, provides the final barrier against bacterial contamination for heat-sensitive injectable products. As the last critical safeguard before aseptic filling, this step secures sterility assurance levels of 10^{-6}, preventing infections and endotoxin-related adverse events. Any failure in sterile filtration poses a serious risk of contamination that can lead to costly product recalls, underscoring the critical importance of maintaining effective sterile filtration. It is also necessary for ensuring patient safety and meeting regulatory compliance requirements (2).

Thus, filtration in biopharmaceutical manufacturing ensures the reliability and safety of therapeutic products. Its ability to effectively eliminate undesirable impurities at various stages supports the consistent production of high-quality biopharmaceuticals, making it a vital part of any robust bioprocessing workflow.

Challenges

Filtration processes in biopharmaceutical manufacturing face several challenges that can affect system performance. In NFF, membrane clogging caused by accumulated cells and debris on the filter surface can reduce flow rates and decrease filtration efficiency. To counter this, a positive pressure gradient is applied to drive the feed solution through the membrane, overcoming hydraulic resistance and maintaining flow. However, fluctuations in applied pressure can greatly affect filtration outcomes. Insufficient pressure lowers flow rates and prolongs filtration time, while excessive pressure risks membrane damage, resulting in decreased filtration effectiveness and product yield. Therefore, maintaining stable and appropriate pressure is vital for optimal filtration performance and product recovery.

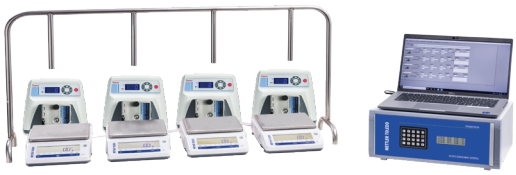
Highly concentrated drug formulations commonly exhibit increased viscosity due to protein aggregation, posing challenges for TFF systems. Elevated viscosity leads to higher back pressure, reduced membrane permeability, membrane fouling, and longer processing times. Variations in transmembrane pressure (TMP) can also cause membrane damage, potentially compromising product quality.

Continuous pressure monitoring during NFF and TFF is crucial for early detection of pressure deviations or clogging. METTLER TOLEDO Pendotech's NFF and TFF systems feature advanced pressure sensors that provide real-time system pressure data. This enables timely adjustments to maintain optimal TMP and membrane integrity, securing efficient filtration and reliable production of high-quality biopharmaceutical products.

Solutions by METTLER TOLEDO Pendotech

Normal Flow Filtration Screening System

METTLER TOLEDO Pendotech's Filter Screening System is a valuable tool for optimizing normal flow filtration processes. The system is designed to conduct volume-throughput studies at constant flow or constant pressure. It allows up to four trains to operate in parallel, with up to three pressure measurements per train. Pendotech Pressure Sensors, featuring luer fittings for direct connection to filter test devices, or larger sensors equipped with sanitary flanges or barbs, are available for use. A graphical user interface (GUI) streamlines user interaction with the process. The system interfaces with up to four pumps for independent control of each pump, and automation allows for unattended operation, such as individual pumps shutting off when a volume target is reached or an alarm occurs. Alarms for high pressure in each train and elevated differential pressures across each filter will automatically shut off the pump for that specific train. The system can also run four parallel constant-pressure experiments using scale input functionality.



Tangential Flow Filtration System

The Tangential Flow Filtration system uses METTLER TOLEDO Pendotech sensors for precise pressure and TMP measurement, supported by built-in conductivity, pH, and temperature sensors to maintain process integrity. The stainless steel system integrates seamlessly with scales and pumps, and features an intuitive GUI for touchscreen or mouse operation, remote access, and error alerts.

TMP monitoring tracks the pressure difference across the membrane, helping to optimize filtration efficiency and extend membrane life. DeltaP control is managed through the software's built-in algorithms by inputting the DeltaP setpoint. It provides retentate flow control through flow meters, which are fundamental for accurate measurement despite changes in viscosity. Additionally, the system includes a Filtrate Flow Meter input on the back panel for filtrate flow measurement, flux calculation, and total flow monitoring, optimized for clean, filtered materials with relatively consistent viscosity.

Additionally, two external input channels enable integration of additional process parameters. Its configurable alarms provide email and text notifications for prompt alerts. The system ensures reliable, safe, and streamlined automation across wide operational scales, raising efficiency and data management in TFF processes.

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Conclusion

Filtration is a fundamental and crucial process in biopharmaceutical manufacturing, key for ensuring product purity, safety, and consistent quality throughout complex manufacturing. By effectively managing impurities and safeguarding microbial contamination at multiple stages, filtration supports the integrity and efficacy of therapeutic products while meeting rigorous regulatory standards. METTLER TOLEDO Pendotech provides cutting-edge filtration solutions, including a Normal Flow Filter Screening system and Tangential Flow Filtration system, featuring accurate pressure sensors, automated control mechanisms, and comprehensive real-time monitoring. These capabilities enable proactive issue detection, optimal process conditions, and seamless integration with manufacturing controls. They improve filtration efficiency, boost product yields, and strengthen operational reliability. Leveraging METTLER TOLEDO Pendotech's innovative tools ensures robust filtration processes that uphold the highest standards of biopharmaceutical manufacturing.

References

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