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Application Note

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Sartoflow® 5000 SU for Large-Scale Single-Use Tangential Flow Filtration

Automated Ultrafiltration | Diafiltration of High-Concentration Monoclonal Antibodies

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Abstract

Commercial manufacturing of monoclonal antibodies (mAbs) requires downstream processes that achieve high product concentrations without compromising quality or efficiency. Tangential flow filtration (TFF) is a central technology for ultrafiltration and diafiltration (UF | DF), enabling buffer exchange and volume reduction prior to final formulation. This application note evaluates the performance of the Sartoflow® 5000 SU TFF system equipped with the mAb-optimized Sartocon® Q Hydrosart® 30 kDa membrane in a high-viscosity mAb UF | DF process with a particularly challenging final concentration step. A 15 g/L feed was concentrated ~15-fold to 220 g/L (viscosity of 40 cP). Pooling the main product fraction with the final flush yielded 201.4 g/L in ~30 L with 97% recovery, while aggregate levels remained unchanged. Strong performance was driven by high loading density and the powerful 4-piston recirculation pump, supporting flow rates up to 5,000 L/h. In the final concentration step, the automated switch to pressure-controlled operation and the innovative bypass mode ensured stable circulation at elevated viscosities, while the low hold-up volume supported excellent recovery. The system's compatibility with both cassette and hollow-fiber formats provides added flexibility across a wide range of TFF applications. Altogether, the Sartoflow® 5000 SU combines robustness, flexibility, and ease of use, establishing a next-generation platform for high-throughput, large-scale, sterile, single-use TFF at elevated concentrations in modern mAb manufacturing.

For more information, visit
www.sartorius.com/sartoflow-5000

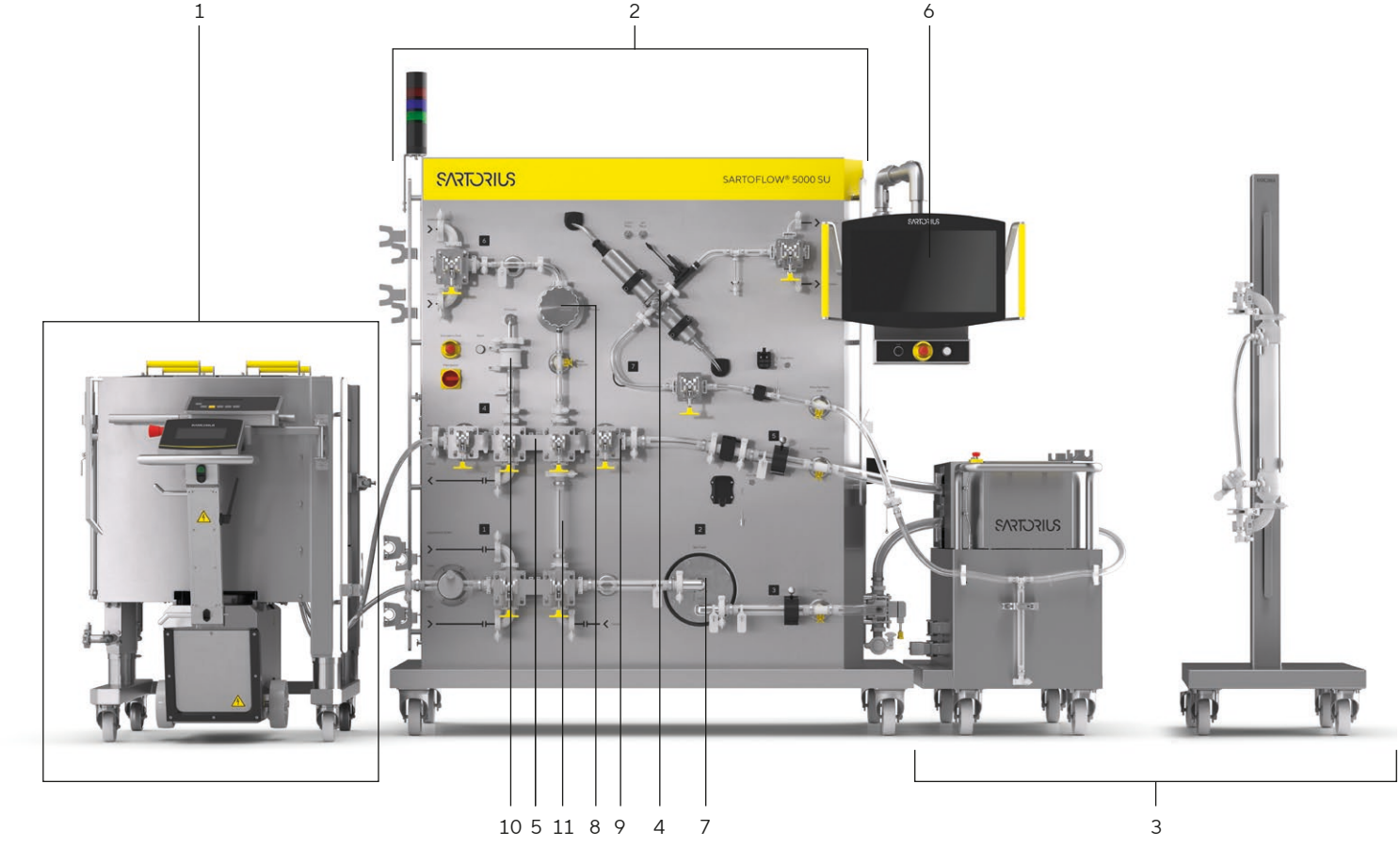
Introduction

The rising demand for high-concentration monoclonal antibody (mAb) formulations is driving innovation in commercial biopharmaceutical downstream processing. Achieving elevated protein concentrations while preserving product integrity, ensuring process efficiency, and meeting regulatory requirements calls for advanced technologies and user-friendly single-use solutions.

To address these challenges, innovative separation and concentration methods are crucial for enabling efficient downstream processing without compromising product quality. Tangential flow filtration (TFF) is a key enabling technology and has become a cornerstone of modern bioprocessing. One of its principal applications is ultrafiltration | diafiltration (UF | DF), through which buffer exchange and volume reduction are performed prior to final formulation. Sartorius has expanded its TFF portfolio with the Sartoflow® 5000 SU system, which has been developed to enhance performance and efficiency in TFF applications.

The Sartoflow® 5000 SU is a fully automated, modular single-use TFF system designed for large-scale UF, DF, and microfiltration (MF) operation. The TFF system is engineered to ensure efficient high-throughput processing even at elevated viscosities, while its low hold-up design enables maximum recovery (Figure 1).

Figure 1: The Sartoflow® 5000 SU system consists of a basic unit (2) that is combined with the recirculation tank (1) — available in different sizes — and the cassette or hollow-fiber holder trolley (3). The basic unit incorporates a 260 – 280 nm UV detector (4), multi-block valves (5), a large 22" control screen (6), a 4-piston membrane recirculation pump (7), a transfer pump (8), a transmembrane pressure valve (9), a system blowdown (10), and a bypass line (11)



Sartoflow® 5000 SU basic unit
The Sartoflow® 5000 SU system is powered by a 4-piston membrane recirculation pump, offering a scalable flow rate of up to 5,000 L/h, which ensures low-shear product handling and high process efficiency. A transfer pump supports automated feed and buffer addition for fed-batch processes as well as automated diafiltration. A membrane valve for transmembrane pressure (TMP) regulation provides precise process control, while an integrated blowdown function optimizes product recovery and maximizes yield. Multi-block valves simplify setup and dismantling by enabling easy and reliable handling.

The basic unit integrates sensor housings and electronics for accurate, real-time monitoring of pressure, flow, conductivity, and pH, while corresponding BioPAT® sensors are integrated in the single-use flow kits. A UV detector (260 – 280 nm) identifies product breakthrough for enhanced process control. The easily accessible HMI with a large 22" control screen ensures clear process visualization and convenient operation. The Sartocheck® filter integrity test system is available as an optional feature, supporting regulatory compliance and simplifying operations with automated filter integrity testing.

Flexible membrane configurations and batch volumes
By accommodating cassettes (including self-contained units [SCUs]) and hollow-fiber (HF) modules, the Sartoflow® 5000 SU supports two membrane configurations on a single platform, ensuring maximum flexibility for UF, DF, and MF applications. The system can be equipped with a cassette or HF trolley, with holders designed for cassette membrane areas from 4.2 – 14 m^2 (21 m^2 available on request) or 12", 24", and 41" HF modules, supporting effective filtration areas (EFAs) of up to 5 m^2. The minimal working volume is approximately 7 L (without filter module), and the largest EFAs support batch volumes of up to 2,000 L. This broad operating range enables seamless scale-up from development to large-scale manufacturing.

Configurable single-use flow kits
Gamma-irradiated single-use flow kits, featuring an intuitive interface, enable fast and easy system setup and teardown. Paired with single-use 3D Flexsafe® Pro Mixer bags, they form a complete aseptic fluid path, including pump head, process tubing, multi-block valves, connectors, bags, and advanced BioPAT® sensors for precise process control. Their configurable design ensures exceptional flexibility across various applications and supports closed-loop operation in combination with SCUs, minimizing contamination risk and ensuring consistent product quality. By eliminating cleaning and sterilization, the single-use setup reduces the risk of cross-contamination, enhances process agility, and accelerates turnaround and time to market. A leakage test of the Flexsafe® Pro Mixer bag can be performed using the optional Sartocheck®, further enhancing process safety.

Precise, gentle mixing with integrated Flexsafe® Pro Mixer
The recirculation tank incorporates the established Flexsafe® Pro Mixer technology, which automatically adjusts mixing speed to the filling level, preventing vortex formation and ensuring precise, low-shear mixing. A levitating high-torque impeller efficiently handles even high-concentration or viscous solutions while minimizing shear effects. The system supports 50, 200, and 400 L single-use 3D Flexsafe® Pro Mixer bags, designed for easy installation with optimized tubing and sensor positioning. Their smart bag design ensures smooth unfolding during filling and reliable folding during draining. Integrated sampling ports and sensors for conductivity, pH, and temperature control provide continuous real-time monitoring.

Smart process control and automation with Biobrain®
Automation and process control are powered by the robust Biobrain® platform, designed specifically for regulated upstream and downstream processes in biopharmaceutical environments. It adheres to the ISA-88 standard, organizing automation logic into control modules, equipment modules, and equipment phases to ensure precise control and flexibility. Users can monitor and control processes in real time through a modern, user-friendly interface with graphical trend presentations that support data-driven decision-making.

Materials & Methods

Biobrain® integrates seamlessly into diverse IT infrastructures via powerful OPC Unified Architecture (OPC UA) interfaces, enabling straightforward configuration of sensors, actuators, and process parameters. It prioritizes cybersecurity, supports third-party antivirus solutions, and provides regular updates to guarantee long-term reliability.

The Biobrain® platform powers Sartorius solutions across various processes, ensuring cGMP readiness and compliance with industrial standards such as GAMP 5 (Category 4), 21 CFR Part 11, and ISA-88. Built on Siemens Simatic S7-1500 PLC and WinCC OA, it provides a reliable hardware foundation with industrial interfaces for seamless integration.

The Biobrain® recipe tool supports flexible customization of process phases and recipes, enabling tailored process solutions that meet specific application needs.

Application testing under relevant process conditions
In this application note, a mAb solution with a concentration of 15 g/L was processed at a high loading density of 1,000 g/m² using the Sartoflow® 5000 SU system in combination with the new Sartocon® Q Hydrosart® 30 kDa mAb TFF module integrated into an SCU. Sartocon® Q is a new mAb-optimized TFF module that combines the strengths of the established E-Screen and ECO-Screen with an advanced Hydrosart® membrane specially developed for efficient mAb purification. The TFF process included concentration and diafiltration (UF | DF), followed by a final concentration step.

A 410 L mAb solution with a concentration of 15 g/L, purified using standard anion-exchange chromatography and polishing steps, was processed at a loading density of approximately 1,000 g/m² using the Sartoflow® 5000 SU system equipped with a Sartocon® Q Hydrosart® 30 kDa mAb membrane module (EFA 6.18 m²). Employing an SCU simplifies operation, as the cassette is delivered pre-flushed and integrity-tested, saving time, reducing preparation effort, and minimizing the risk of operator error or contamination, while enabling fast changeover between runs.

The entire UF | DF process, from setup to cleanroom dismantling, was guided by a pre-defined recipe in the Biobrain® recipe tool. Target process parameters were a final concentration of 200 g/L at approximately 30 L, with a high viscosity, while maintaining mAb integrity and enabling rapid and efficient processing.

To evaluate process performance with respect to efficient mAb concentration and product integrity, mAb and aggregate titers (high molecular weight species [HMWS] and low molecular weight species [LMWS]) were quantified in feed and TFF output samples by size-exclusion high-performance liquid chromatography (SE-HPLC) using an ultra-high-performance liquid chromatography system.

Results

Process preparation

Guided by the Biobrain® recipe tool, the system setup was completed in under 1 hour. This included the following steps:

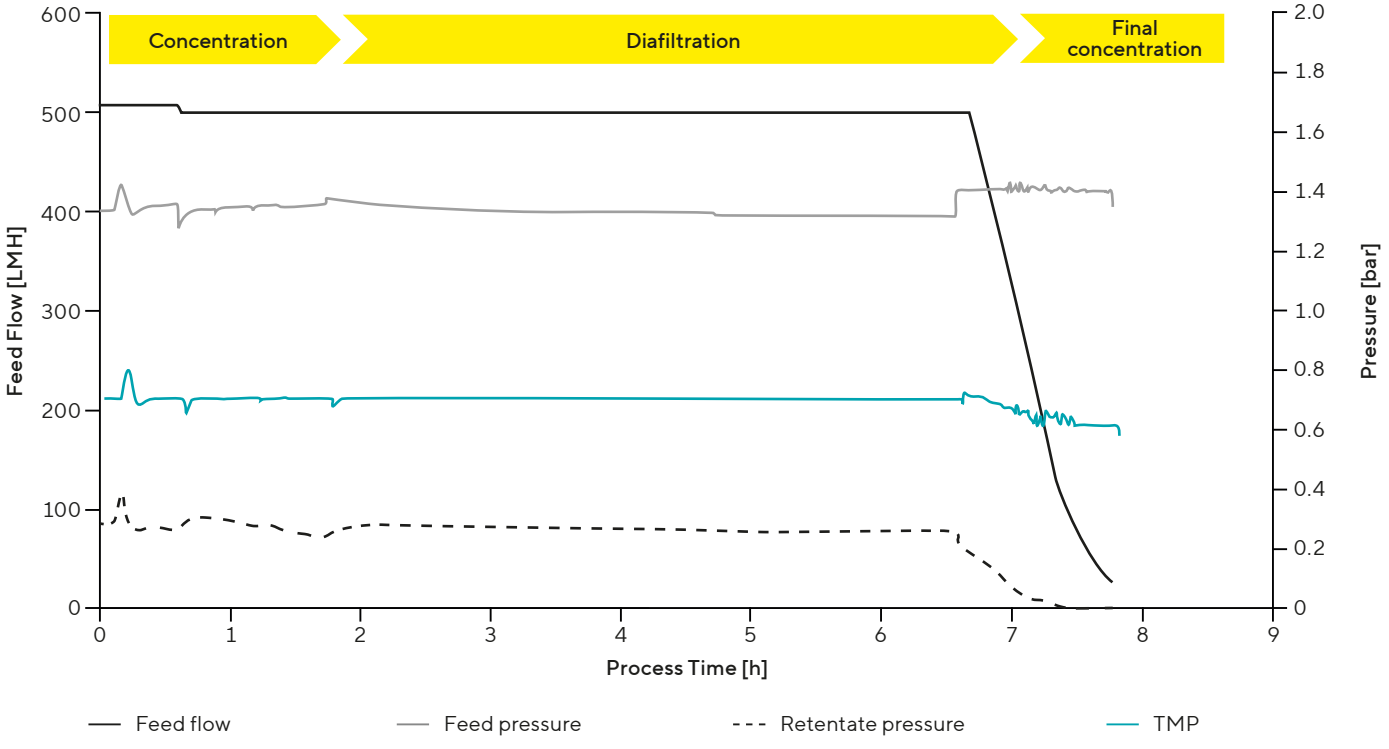
- Connecting the feed and diafiltration buffer vessels
- Installing the single-use 3D Flexsafe® Pro Mixer bag (200 L) into the recirculation tank
- Integrating the pre-assembled single-use flow kit and the Sartocon® Q SCU into the Sartoflow® 5000 SU system
- Performing automated sensor calibration

The TFF system was then flushed with 62 L of reverse osmosis water (10 L/m²), followed by equilibration with 10 L buffer.

UF | DF and final concentration

The complete sequence of UF, DF, and final concentration was accomplished in under 8 hours, ensuring fast and efficient processing. Real-time monitoring covered feed pressure (Pin), retentate pressure (Pout), TMP, UV absorbance, conductivity, pH, and temperature. To prevent vortex formation in the recirculation bag, the Biobrain® operating software automatically adjusted the speed of the Flexsafe® Pro Mixer according to the bag's filling level. The feed was concentrated 5-fold to a final concentration of 75 g/L at a constant feed flow rate of 500 LMH, while the TMP was set to 0.7 bar.

Figure 2: Process parameters of the UF | DF run followed by final concentration using the Sartoflow® 5000 SU system equipped with a Sartocon® Q Hydrosart® 30 kDa mAb cassette in an SCU



Note. UF (5-fold concentration to 75 g/L) and DF were conducted under flow-controlled conditions at 500 LMH (black line), with the TMP remaining stable at ~0.7 bar (blue line). The diafiltration phase diagram data were expanded by two diavolumes, based on average process parameters during the DF, to represent a full 7 × DF process. During the final concentration phase at high viscosity (3-fold concentration from 6.5 h onwards, reaching 220 g/L), the system automatically switched to pressure-controlled mode (Pin = 1.4 bar, gray line), during which the TMP was kept at 0.7 bar, ensuring stable crossflow despite challenging conditions.

Once concentration was achieved, DF was performed with a buffer volume equivalent to five times the retentate volume under the same operating conditions (flow-controlled at 500 LMH; Figure 2). The diafiltration step was concluded after five diafiltration volumes, when the pH and conductivity of were reached. This was already sufficient for buffer exchange requirements, demonstrating the high efficiency of the TFF system. This strong performance can be attributed to the excellent mixing capabilities of the Flexsafe® Pro Mixer — particularly the design of the mixing bag — as well as to the Sartoflow® 5000 SU system, which integrates zero-dead-leg valves to minimize hold-up and ensure complete flushing of all product-contact surfaces.

Following DF, the Sartoflow® 5000 SU system automatically switched from flow-controlled to pressure-controlled operation (Pin = 1.4 bar) for the final concentration step (from ~6.5 hours onwards), as indicated by the drop in feed flow and the corresponding rise in Pin (Figure 2). This switching strategy ensured a constant TMP during the process, while minimizing fouling and the formation of a gel layer. The low recirculation volume of the system enables concentration to exceptionally high product levels.

Product recovery

After the UF | DF process was completed, the concentrated mAb was recovered from the system in three steps. First, the recirculation vessel was hydrostatically emptied using the 4-piston membrane recirculation pump. Residual product in the Sartocon® Q cassette and the tubing was then automatically removed by blowdown with sterile compressed air. Finally, the low hold-up volume of the flow kit enabled recirculation with minimal buffer, supporting efficient product recovery from both the membrane and the flow path.

Post-process handling and documentation

Dismantling of the flow kit, the SCU, and the Flexsafe® Pro Mixer bag was completed in ~15 minutes. A GMP-compliant batch record was automatically generated and exported, further reducing operational effort and ensuring regulatory compliance.

Analytical results

Analytical results from SE-HPLC of the TFF output confirmed the high efficiency of the process in terms of concentration, volume reduction (weight recovered), and mAb recovery. Table 1 summarizes these results, categorized into contributions from hydrostatic pump emptying and system blowdown, the final buffer flush, and the pooled product after combining both fractions.

Table 1: Overview of obtained weight, concentration, and recovery of the concentrated mAb after UF | DF and harvest.

	Weight recovered [kg]	Concentration [g/L]	Yield [%]
Recovery with pump blowdown	24.8	221.6	89.9
Buffer flush	4.6	110.9	6.8
Pool	29.4	201.4	96.7

The main product fraction, obtained by pump-driven hydrostatic emptying and system blowdown, reached a concentration of ~220 g/L at a weight of 24.8 kg, corresponding to a robust recovery of 89.9%. The low hold-up volume design together with the bypass mode enabled a final buffer flush with minimal buffer volume, yielding 4.6 kg at ~110 g/L (6.8% recovery). Pooling both fractions resulted in an excellent overall recovery of ~97%, with a final concentration of ~201 g/L at a weight of 29.4 kg. This result highlights the precise process control, as the target concentration and volume of 200 g/L in 30 L were met nearly exactly. In addition, aggregate analysis revealed no increase in HMWS or LMWS, confirming preservation of product quality.

In summary, these analytical results demonstrate the robust performance of the Sartoflow® 5000 SU system, combined with the mAb-optimized Sartocon® Q membrane, enabling gentle yet highly efficient processing, even at high viscosities.

Discussion

The novel Sartoflow® 5000 SU system, equipped with the new mAb-optimized 6.18 m² Sartocon® Q Hydrosart® 30 kDa SCU, demonstrated exceptional performance in a high-viscosity mAb UF | DF process at a high loading density of ~1,000 g/m². A 15 g/L mAb feed solution (410 L) was concentrated ~15-fold to 220 g/L, corresponding to a very high viscosity of 40 cP. Pooling the main product fraction with material obtained from the final buffer flush resulted in a final concentration of 201.4 g/L in ~30 L, with an excellent overall recovery of 97%. The combination of a low hold-up volume and bypass mode allowed a minimal buffer flush, reducing dilution of the final product. Aggregate analysis confirmed that HMWS and LMWS levels remained unchanged throughout processing, underlining the gentle nature of the operation and the preservation of product quality.

Operating at such high loading density is a key requirement for efficient large-scale manufacturing, as it maximizes membrane productivity while minimizing footprint and resource use. Combined with scalable flow rates of up to 5,000 L/h delivered by the 4-piston membrane recirculation pump, this ensures that the Sartoflow® 5000 SU system is ideally suited for large-scale UF | DF operations in commercial biomanufacturing.

Beyond supporting large-scale operations, the ability to deliver highly concentrated mAbs is another critical need in commercial production, requiring stable and robust processing. A key factor in this context is the Sartoflow® 5000 SU system's automated transition from flow to pressure-controlled mode. This switch prevents fouling and gel layer formation and maintains stable performance at a constant TMP as viscosity increases. The novel bypass mode further enhances robustness at elevated product concentrations by maintaining stable retentate circulation. Additionally, the Flexsafe® Pro Mixer reliably secures homogeneity in the recirculation vessel. Its filling-level-dependent mixing speed prevents vortex formation, thereby safeguarding product integrity and supporting optimal diafiltration efficiency with minimal product loss.

Alongside technical features, user-friendliness across software and single-use components is essential for production efficiency. The Sartoflow® 5000 SU facilitates easy handling through the Biobrain® platform and optimized design of single-use components. The Biobrain® platform provides a modern, user-friendly interface for process control and documentation, ensuring GMP compliance and facilitating regulatory audits. The integrated Biobrain® recipe tool allows flexible customization of process phases and protocols, ensuring tailored process solutions. Together with configurable pre-assembled single-use flow kits and single-use 3D Flexsafe® Pro Mixer bags (50, 200, and 400 L), these features streamline workflows, minimize contamination risk and operator error, and reduce overall workload. This ease of use was clearly demonstrated in the present study, where the complete UF | DF run, including setup and cleanroom dismantling, was accomplished in just 10 hours, underlining the system's ability to reduce operational complexity and accelerate time to market while safeguarding process safety, regulatory compliance, and product integrity.

Conclusion

With the innovative Sartoflow® 5000 SU system, Sartorius offers a fully automated, modular, closed-loop, single-use TFF solution for UF, DF, and MF applications, designed for robust and reliable operation from clinical to commercial scale. Configurable single-use flow kits and single-use recirculation bags from 50 – 400 L, a scalable flow rate of up to 5,000 L/h, and support for multiple membrane configurations with EFAs of up to 14 m^2 provide maximum flexibility. In addition, the system demonstrates robust performance in processing highly concentrated mAbs, ensuring stable operation even at elevated viscosities and delivering excellent product recovery and integrity. Altogether, these features position the Sartoflow® 5000 SU as an outstanding next-generation platform for large-scale single-use TFF in modern bioprocessing.

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