Millipore®
Expert Pharm/BioPharm
Products & CTDMO Services

Application Note

Accelerating Technology Transfer of a Drug Product Tangential Flow Filtration Process Through Collaboration

This application note provides an overview of the collaboration, describes study results, and illustrates how information sharing and trust between a supplier and end-user can help achieve user requirements and accelerate process transfer.

Summary

Transferring manufacturing processes to a new site and increasing scale while incorporating newer technologies can be a complex and time-consuming activity in the lifecycle of a drug product. Close collaboration between a biomanufacturer and technology supplier can accelerate such a technology transfer while ensuring the user requirements are met. Recently, our MSAT team helped a major biomanufacturer develop performance, cleaning, and reuse data to support transfer and scale-up of a tangential flow filtration (TFF) operation **(Figure 1)** using Pellicon® 2 devices and Mobius® TFF 80 single-use system to a new manufacturing site.

Results demonstrated feasibility of higher Pellicon® 2 membrane loading and cassette reuse, addressing user requirements for performance, scalability, and process robustness. Importantly, these changes can reduce chemical and consumables costs by more than 35%.

The collaboration demonstrates how data-driven transfer and scale-up, supported by robust information sharing and mutual trust between supplier and end-user, can accelerate technology transfer, enable scalable operations that meet user requirements, while capturing meaningful cost benefits in biologics manufacturing.

MERCK

Accelerating TFF Process Transfer Optimization

Transferring manufacturing to new sites or updating existing operations can be complex and time-consuming, and often involves evaluating newer technologies, operating conditions, or systems to improve efficiency and optimize Cost of Goods (COGs).

As part of a project expanding manufacturing operations with tech transfer to a new site, a major biomanufacturer wanted to implement a single-use process designed for a TFF system at production scale, using Pellicon® 2 devices and Mobius® TFF 80 single-use system. The user requirements specification (URS) detailed a process scale up including increased membrane area and requiring higher flow rates and membrane loading. Our Manufacturing Science and Technology (MSAT) team helped optimize this scale-up to fit within the available Mobius® TFF 80 single-use system capacity. Studies executed in our M Lab™ Collaboration Center demonstrated process capability and fit, while freeing up the biomanufacturer to focus on other tech transfer objectives.

Tangential flow filtration is a critical unit operation in biologics drug product manufacturing, enabling concentration and diafiltration of the process feed stream. As commercial manufacturing scales increase, facilities may encounter operational constraints related to membrane area, skid capacity, consumable availability, and manufacturing throughput. In parallel, supply chain pressures have intensified the drive for improved membrane utilization.

Process optimization approaches include increasing membrane loading and membrane re-use within a campaign, which offer opportunities to improve facility utilization, reduce COGs, and improve operational flexibility. However, any approach must be carefully evaluated to ensure process robustness, scalability, and maintenance of critical quality attributes.

Specifically, these studies were designed to:

- Evaluate increased membrane loading
- Assess the impact of membrane re-use within a production campaign
- Assess membrane cleanability under new load conditions
- Confirm scalability of elevated load, cleaning, and re-use conditions
- Quantify potential reductions in manufacturing costs associated with membrane re-use

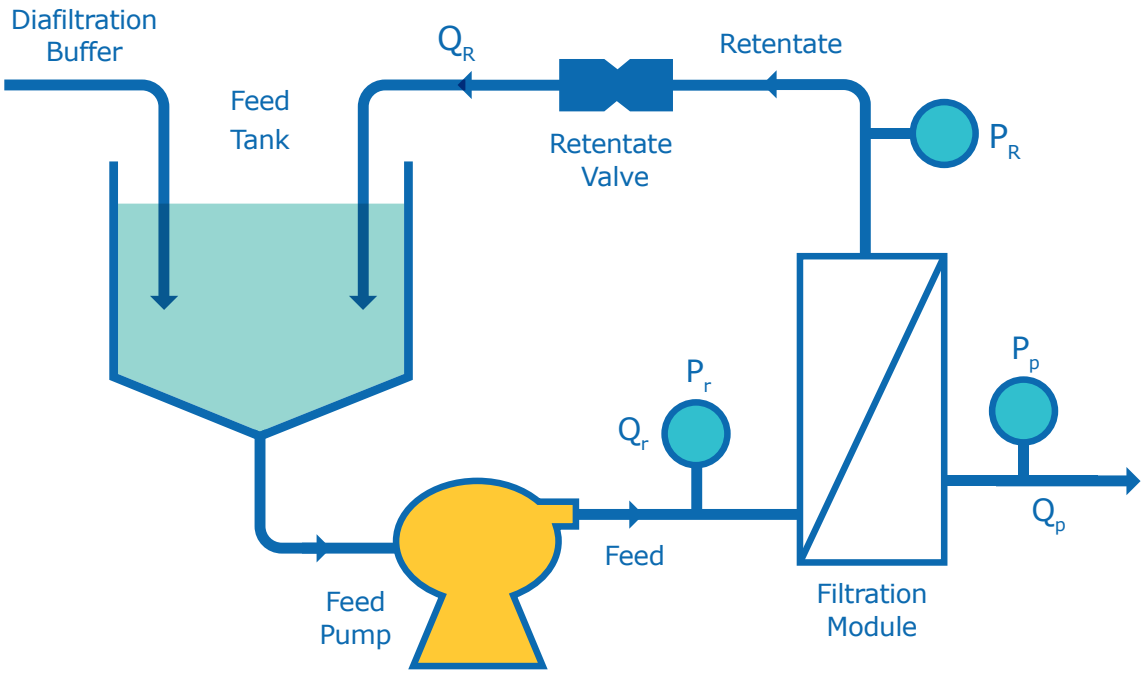

Figure 1: Diagram illustrating a TFF operation, specifically ultrafiltration and diafiltration.

Experimental Overview

Bench-scale studies were performed with process fluids supplied by the biomanufacturer and using a qualified Pellicon® 2 cassette scale down model (SDM) in the M Lab™ Collaboration Center in Burlington, MA, USA by engineers from our Manufacturing Science and Technology (MSAT) team. These M Lab™ Collaboration Centers provide a flexible space for biomanufacturers to master best practices and optimize scale-up with technical experts familiar with bioprocess applications, technologies, and products. Regular touchpoints between the biomanufacturer and MSAT team members ensured an open feedback loop. Samples collected during the studies were analyzed by the biomanufacturer using product specific analytical methods.

Three different membrane loading conditions (g/m^2) designated as low (control), middle, and high were assessed with the SDM, followed by pilot-scale confirmation studies at the biomanufacturer using the highest loading.

To evaluate membrane re-use in the SDM, membranes were subjected to repeated process cycles at each loading, followed by cleaning and sanitization which was monitored using normalized water permeability (NWP) recovery.

Results

Impact of Increased Membrane Loading

All membrane loading conditions successfully achieved the target volumetric concentration factor (VCF) **(Figure 2)**. Importantly, increased loading did not adversely affect permeability during concentration operations.

The permeability profiles observed across low, middle, and high loading conditions were comparable, demonstrating that increased membrane loading did not negatively impact ultrafiltration (UF) performance and process time requirement.

These results demonstrated that membrane capacity was not exceeded under the evaluated conditions and that the process remained within acceptable hydrodynamic operating ranges.

Diafiltration efficiency was evaluated by monitoring conductivity and pH trends during buffer exchange operations **(Figure 3)**.

All loading conditions demonstrated comparable conductivity and pH profiles throughout diafiltration, indicating equivalent buffer exchange performance across the loading ranges.

Results confirmed that higher loading conditions did not impair diafiltration effectiveness.

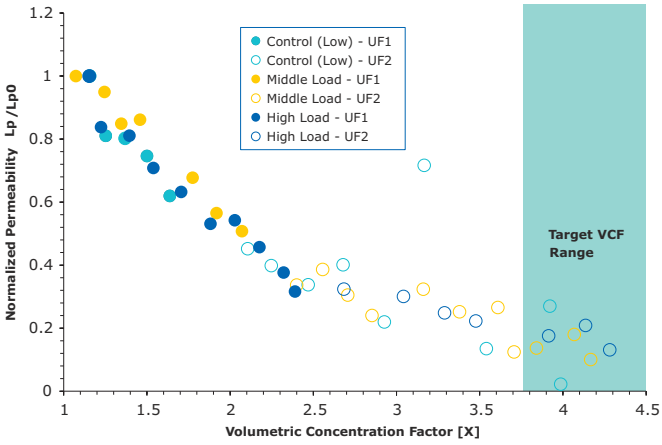

Figure 2. Normalized permeability versus volumetric concentration factor trends demonstrate comparable performance across three loading conditions during UF operations.

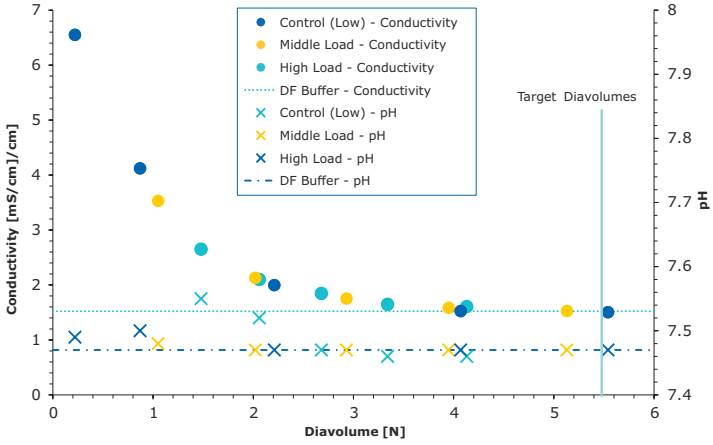

Figure 3. pH and conductivity trends demonstrate comparable buffer exchange during diafiltration across the three loading conditions.

Evaluation of Membrane Re-Use

Membrane re-use studies assessed reproducibility and scalability during a campaign.

No meaningful trends in permeability decline were observed across membrane re-use cycles **(Figure 4)**. Furthermore, permeability behavior between pilot-scale and bench-scale membranes was comparable.

These findings demonstrate excellent process scale-up, reproducibility, and support re-use of the TFF membrane.

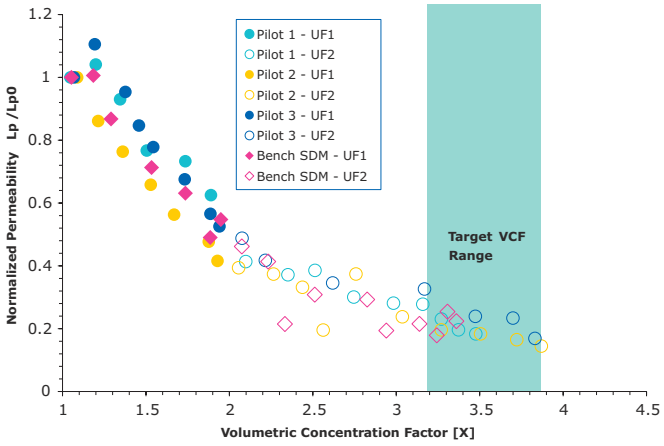

Figure 4. Normalized permeability versus volumetric concentration factor trends demonstrate reproducibility and scalability of membrane reuse.

Pressure profiles were monitored throughout concentration to ensure the process remained within equipment and membrane operating limits. Feed pressure and pressure drop behavior remained comparable across re-use runs **(Figure 5)**.

The bench-scale device flow rate was adjusted later in the UF2[1] step to maintain a pressure of 30 psi due to constraints of the SDM. However, the trends before the flow rate reduction were like the pilot-scale system demonstrating the feasibility of scale-up. The pressure drop with the bench-scale device was lower than the pilot scale system, but the rate of change throughout concentration was similar.

These results demonstrate that the feed pressure was within at-scale system limitations while achieving the target final concentration range.

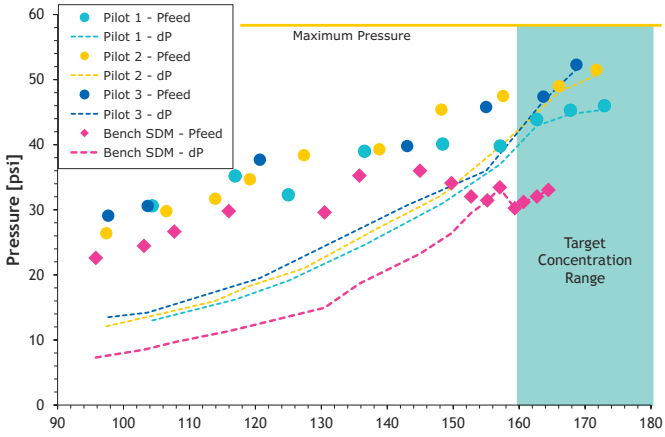

Figure 5. Pressure vs. Concentration trends for UF2 pilot and SDM runs show comparable feed pressure and device pressure drop demonstrating scalability and consistency in re-use.

1. UF2 is the second or final ultrafiltration step. This is because the optimum diafiltration point is often at an intermediate concentration between $C_{initial}$ and C_{final}.

Membrane Cleaning and Sanitization Optimization

A key consideration for membrane and device re-use is the effectiveness of cleaning and sanitization procedures and includes evaluating carryover (TOC, total protein, residuals), bioburden, process consistency (run to run pressure and flux), and NWP trending.

To evaluate cleaning performance, total organic carbon (TOC) testing was performed on both retentate and permeate lines after target conductivity was reached to ensure proper clearance of the cleaning solution and material. All TOC measurements remained below 1 ppm, confirming effective clearance of process materials and cleaning agents (data not shown).

Table 1 demonstrates the cleanability of the membranes, as measured by NWP. The original sanitization solution resulted in low NWP recovery after completion of the targeted number of cycles on the membrane. An optimized cleaning chemistry was evaluated which improved NWP recovery after the targeted number of cycles, suggesting that membrane reuse could be achieved using this new cleaning solution.

Experiment	Final Run NWP Recovery %
SDM Control	40.7
SDM Middle Loading	42.7
SDM High Loading	49.3
Pilot-scale High Loding with Optimized Cleaning Chemistry	87.7

Table 1. NWP recovery following membrane reuse for the targeted number of cycles. NWP recovery was greatly enhanced and achieved acceptable levels when the new cleaning solution chemistry was used.

Economic and Sustainability Considerations

An economic assessment was performed to compare single-use and multi-use membrane strategies. The analysis considered membrane costs, buffer consumption, chemicals, and labor requirements.

The multi-use membrane approach revealed substantial annual cost savings relative to the single-use operation with overall COGs and labor reductions estimated at more than 35%.

These findings highlight the importance of balancing process performance with operational economics when redesigning TFF manufacturing operations.

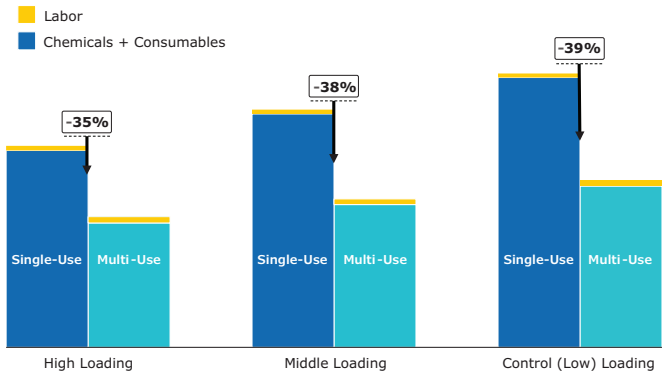

Figure 6. Annual cost of goods and labor savings for a multi-use strategy versus single use.

Conclusions

These studies highlight the benefits of close collaboration between our MSAT team and a major biomanufacturer looking to perform a technology transfer, scale-up their operation, and introduce a SU-TFF system at a new manufacturing site. They demonstrated process capability and fit within Mobius® TFF 80 single-use system operating parameters, thus satisfying their URS.

The technical results demonstrated that higher Pellicon® 2 membrane loading and membrane re-use could be successful in a biologics drug product TFF operation without compromising performance, scalability, or overall process robustness. Implementing this strategy will meaningfully reduce manufacturing costs.

Key technical findings

Increased Membrane Loading: Across all loading conditions evaluated, target volumetric concentration factors were consistently achieved while permeability was maintained during both ultrafiltration and diafiltration operations, using Pellicon® 2 devices. Higher loading did not adversely affect pressure profiles, conductivity trends, or pH equilibration during buffer exchange, indicating that the process remained well-controlled even under intensified operating conditions.

Membrane Re-use: Across multiple re-use cycles, strong process reproducibility and operational consistency were observed. Permeability trends remained stable throughout repeated membrane use, with no meaningful evidence of performance degradation. Strong agreement between laboratory-scale and pilot-scale systems confirmed scalability, a critical element for commercial implementation.

Optimized Sanitization: Membrane sanitization conditions were identified that substantially improved NWP recovery following repeated membrane use. These modified sanitization conditions more effectively removed residual fouling materials and improved restoration of membrane performance highlighting the importance of cleaning chemistry as a key enabler for successful membrane re-use.

Confirmed Process Fit: These studies helped satisfy requirements in the URS by confirming that higher loading did not impact process performance and therefore the process would fit on the Mobius® TFF 80 single-use system.

Beyond technical feasibility, the study demonstrated meaningful economic benefits associated with multi-use membrane operations which could reduce the annual COGs by more than 35%. These savings can become particularly significant in large-scale manufacturing settings where membrane replacement and consumables costs represent substantial operational expenses.

Additional studies assessing operations below maximum loading and pressure thresholds, membrane lifetime studies and assessing additional cleaning strategies could be helpful for commercial implementation, and offer future collaboration opportunities between the MSAT team and biomanufacturers.

For additional information
please visit **SigmaAldrich.com**

Merck KGaA
Frankfurter Strasse 250
64293 Darmstadt
Germany

Millipore®
Expert Pharm/BioPharm
Products & CTDMO Services

Lit. No. MK_AN14578EN Ver. 1.0
8/2026