

## Flow-Through Technologies for a Continuous Downstream Process

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### Introduction

Biologics manufacturing is evolving rapidly, driven by significant market growth, rising cost pressures, and the increasing demand for improved yields. Companies are seeking more efficient production methods to stay competitive while meeting regulatory requirements and market demands. This poster covers two new technologies for downstream processing to achieve this goal.

- A novel flat sheet membrane cassette for single-pass tangential flow filtration (SPTFF) diafiltration (DF) with simultaneous ultrafiltration (UF) concentration
- A unique modular inflow plug flow reactor (PFR) with a narrow residence time distribution

These technologies can support process intensification and make bioprocessing more continuous.

### Pionic® Cross | Sartococon® SP

#### 1. Technology Introduction

The SPTFF inline diafiltration features three distinct flow channels formed by two functional membrane layers over an extended mixed co- and counter-current flow path, with four fluid connection points, including the diafiltration buffer inlet (Figure 1). The data illustrate buffer usage and diafiltration performance across various transmembrane pressures, permeate flux rates, and process parameters (e.g., feed concentration, feed flow rate, target diavolumes, and impurity clearance). In conclusion, it demonstrates simplified fluid connection handling and superior membrane material performance.

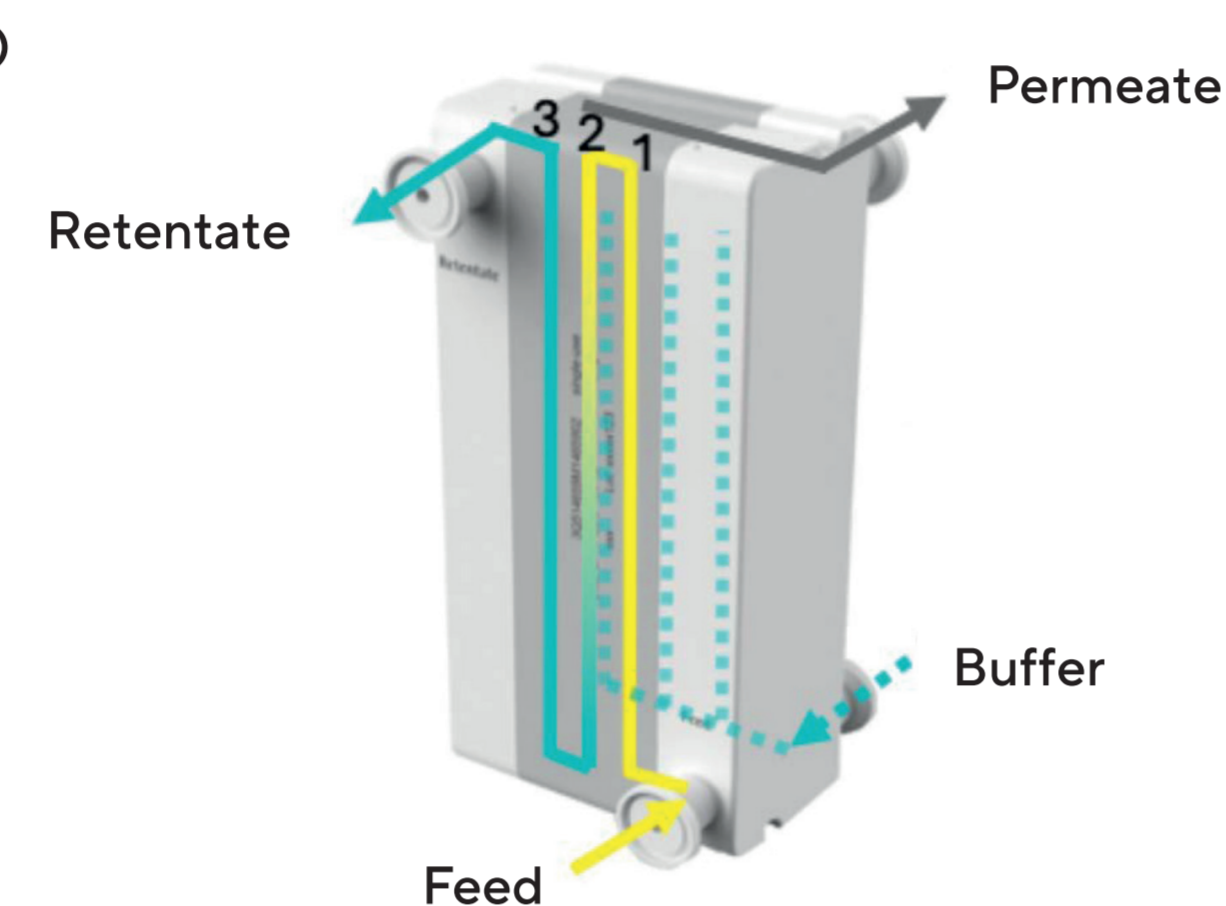


Figure 1: Illustrated Image of the Membrane Cassette In Use, With Annotations Indicating the Respective Fluid Ports

#### 2. Technology Approach

##### Buffer exchange over the entire length of the retentate channel

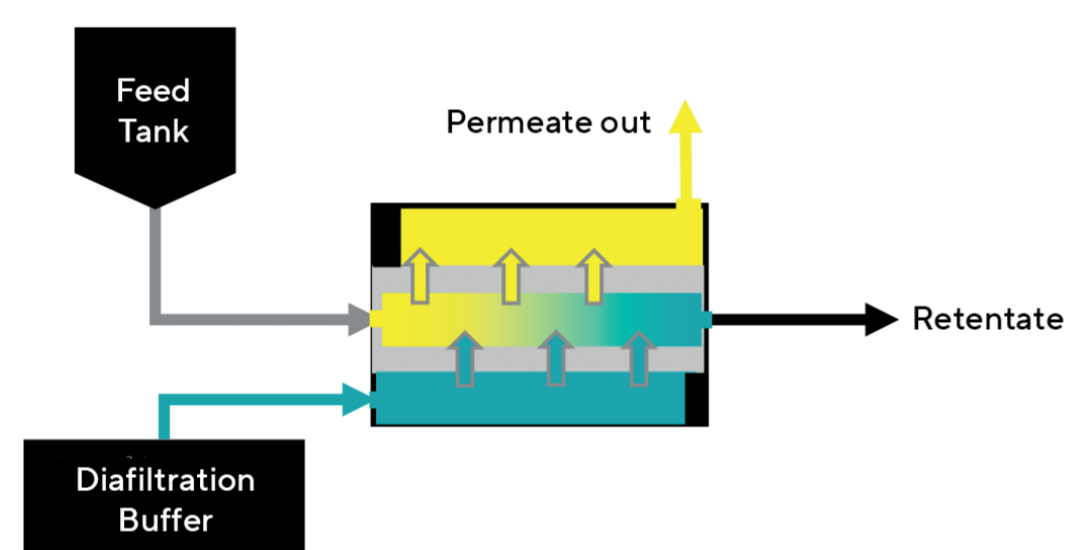
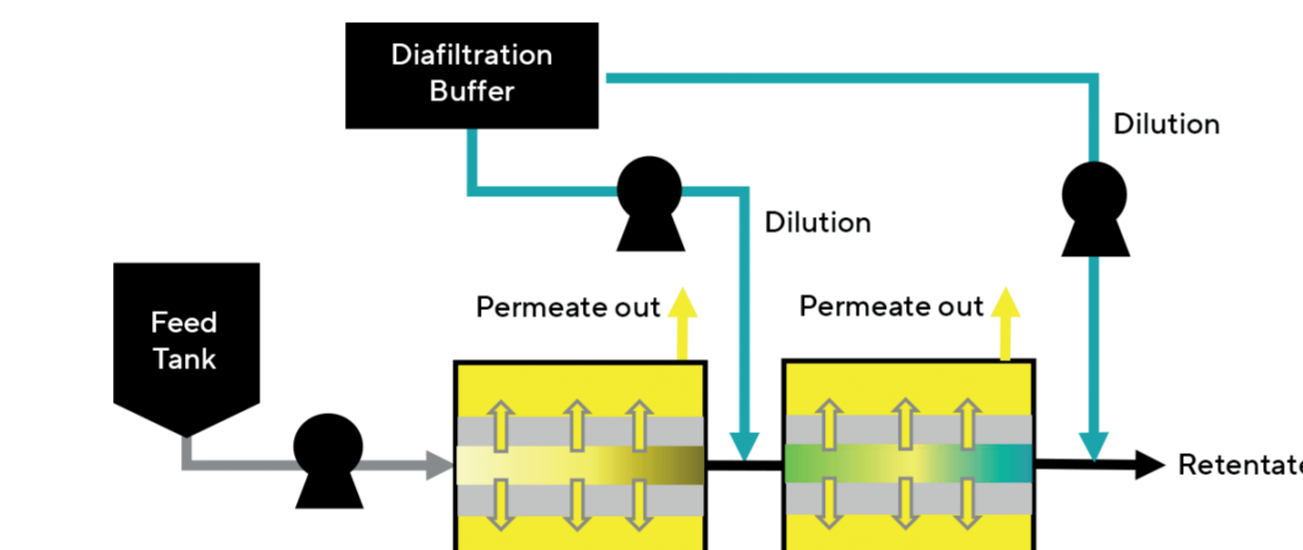


Figure 2: Innovative Sp-Tff Three-Stage Setup for Continuous Diafiltration and Concentration Compared to Multi-Stage Dilution Approaches

##### Multi-stage dilution approach up to six separate buffer inlets



#### 3. Buffer Usage and Diafiltration Performance

In the technology landscape for single-pass diafiltration solutions, the main concept involves a multi-stage assembly with dilution and concentration intervals. Each stage needs separate tubing and measurements for buffer supply, leading to complex assembly and handling. In contrast, Sartococon® SP requires only one connection point for buffer intake, simplifying fluid handling. Additionally, Sartococon® SP offers an advantage in buffer consumption, as a six-stage dilution setup needs nearly double the buffer volume to achieve a 99.9% clearance | buffer exchange compared to conventional TFF (Table 1).

Clearance   Buffer Exchange [%]	Classic TFF [DV]	6-stage dilution [DV]
95.0	3	3.9
98.2	4	5.7
99.3	5	7.8
99.8	6	10.8
99.9	7	13.0

Table 1: Relative Diavolumes (DV) Required to Achieve Typical Clearance Levels Buffer Exchange by Classic Tff or Multistage Dilution

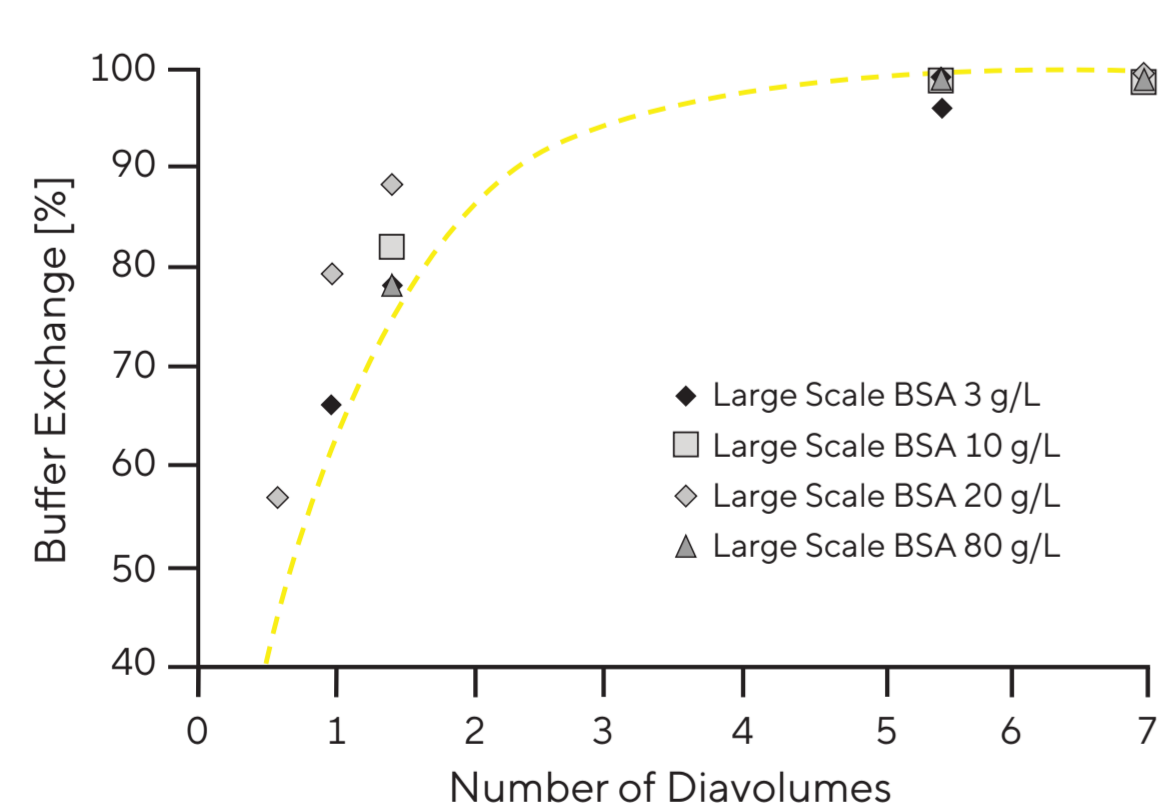


Figure 3: Buffer Exchange Relative to Diavolumes for Various Protein Concentrations Without Simultaneous Concentration, Compared to the Theoretical Values (Dotted Yellow Line) in Conventional Batch Diafiltration Processes

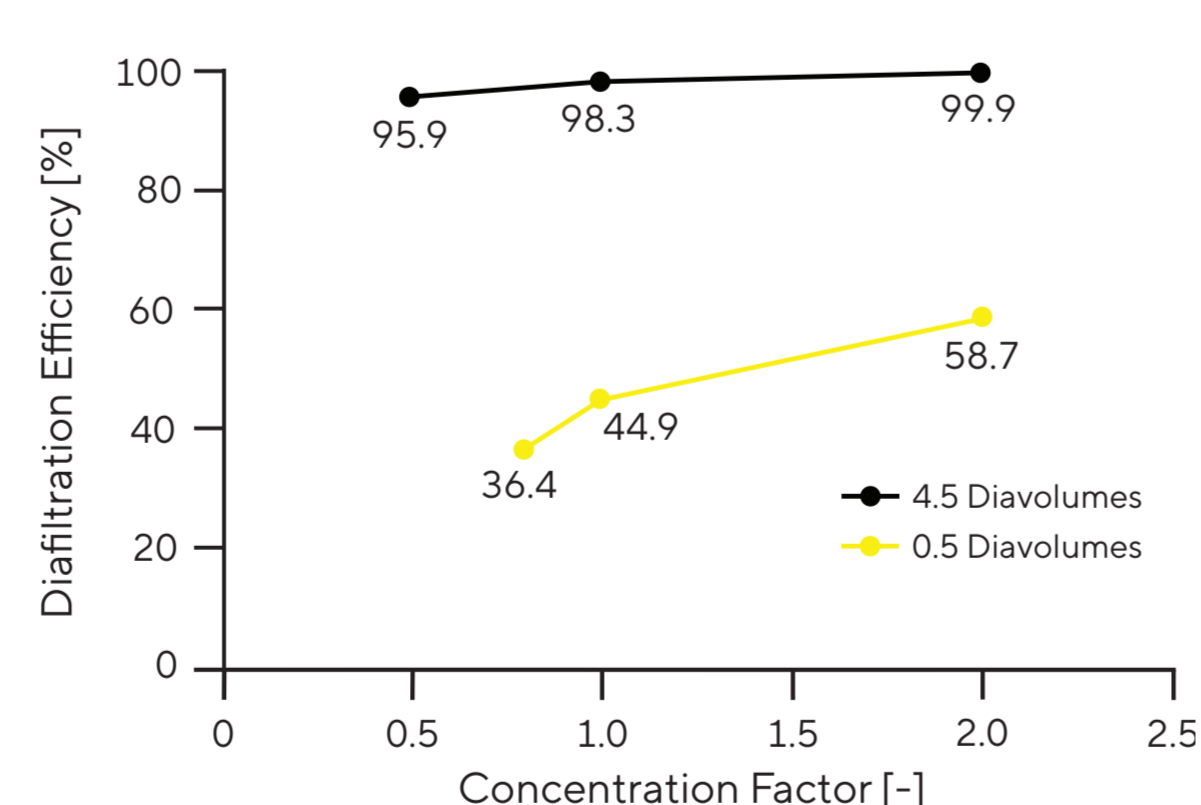


Figure 4: Influencing Diafiltration Effectiveness By Simultaneous Dilution or Concentration (CF 0.5x to 2X) at 0.5 and 4.5 Diavolumes (Buffer Flow-in to Feed Flow-in Ratio)

#### 4. Summary & Conclusion

Performance trials with albumin in phosphate buffer at concentrations up to 80 g/L confirmed that the buffer exchange process is comparable to conventional TFF diafiltration (Figure 3). Additionally, the effectiveness was increased by achieving simultaneous concentration (Feed 20 g/L) without the need for additional buffer (Figure 4). Single-pass technology plays a crucial role in process intensification through continuous processing, offering significant advantages over traditional methods. It demonstrates substantial buffer savings compared to other inline dilution and diafiltration (ILDF) techniques, highlighting its efficiency and effective buffer utilization. Ongoing performance mapping five to seven diavolumes with simultaneous concentration factors up to four is essential for optimizing and understanding the capabilities of single-pass technology in continuous processing. Further work has shown the technology being used in pure concentration mode with the reversal of flow direction in the diafiltration channel, doubling the effective filtration area relative to the ILDF mode. The next steps include expanding the portfolio of Sartococon® SP with additional module sizes (1.5 m<sup>2</sup> and 270 cm<sup>2</sup> effective filter area) and other molecular weight cut-offs to increase its flexibility and broad applicability in diverse industrial and manufacturing contexts.

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### Pionic® Spin Incubator

#### 1. Technology Introduction

The curvature design of Pionic® Spin Incubator's fluid path is optimized for high Dean numbers at low flow rates, ensuring radial mixing and narrow residence time distribution (RTD) for continuous flow-through incubation. Distinct volumes and path lengths allow operators to adjust flow rates to a minimum residence time or adapt chamber volume for a set flow rate. Expanding the flow rate range is possible by increasing volume | path length with additional plate modules or altering the plate module's inner dimensions.

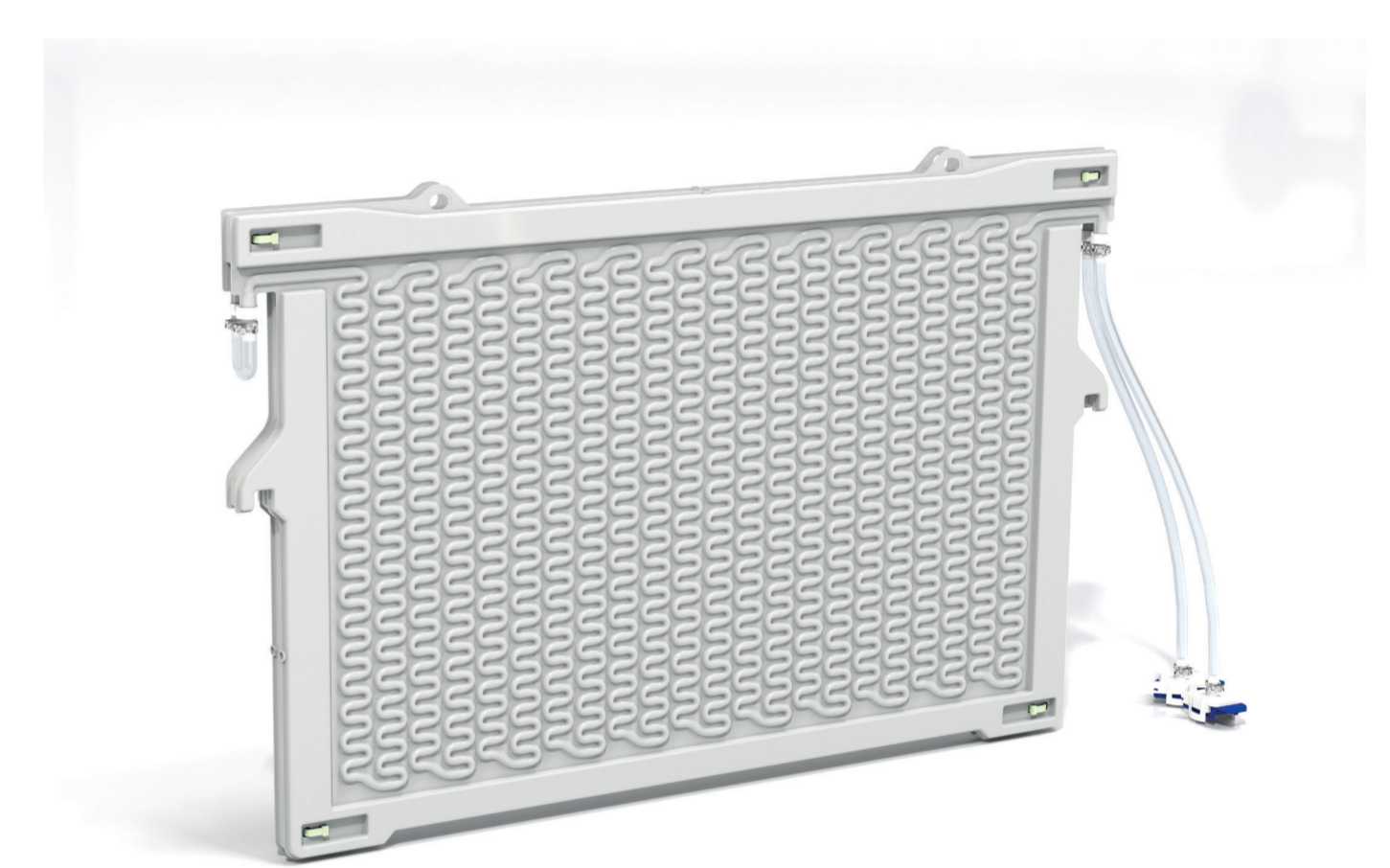


Figure 5: Pionic® Spin Incubator

#### 2. Dean Number of Pionic® Spin Incubator

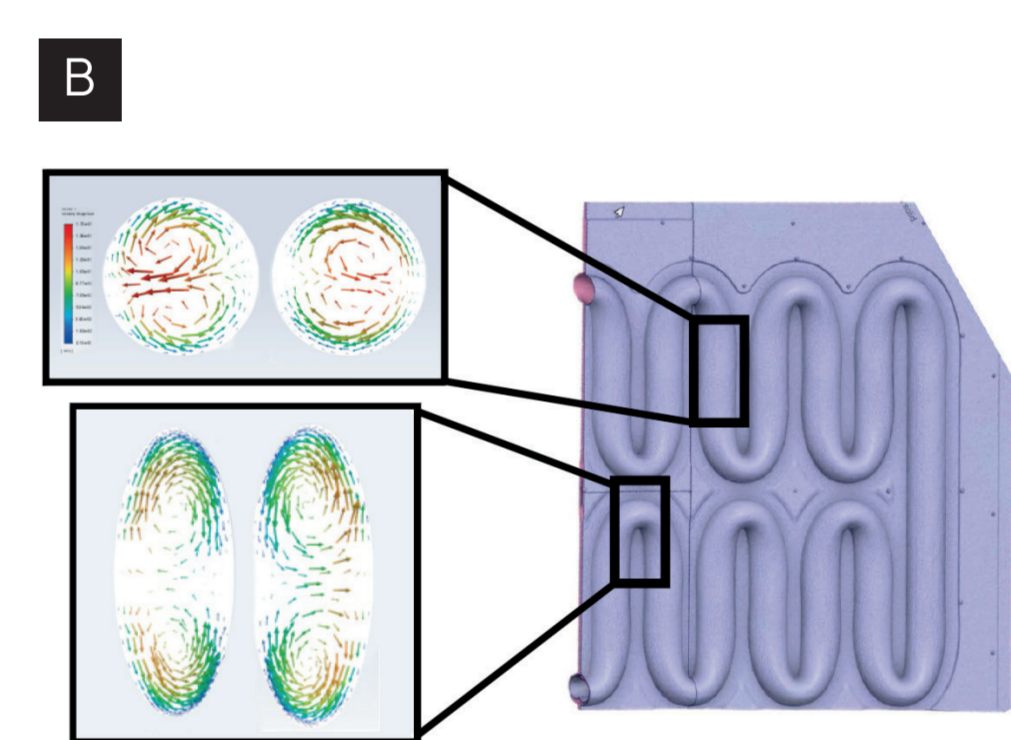
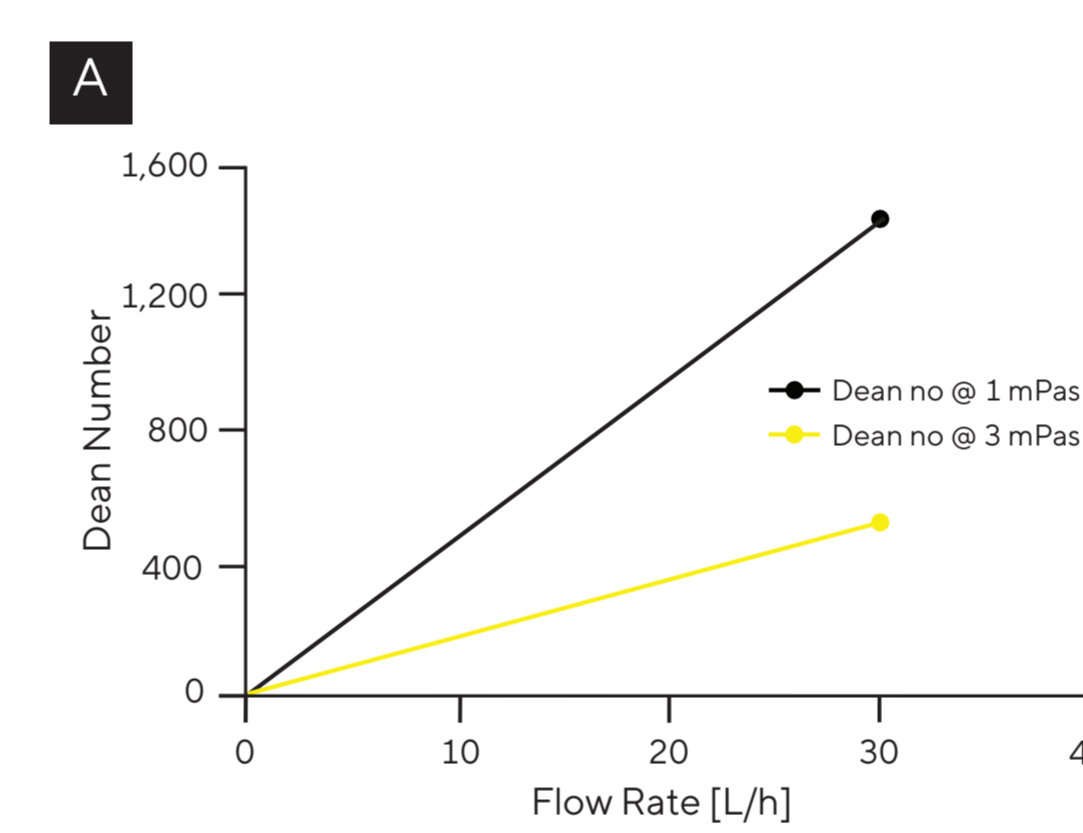


Figure 6: (A) The Dean Number ( $de$ ) Describes Vorticity in a Circularly Curved Pipe ( $De = F$  (Flow Velocity, Pipe Geometry, And Dynamic Viscosity)) With an Increased Flow Rate (Dean Number Should Be  $> 100$ ); Rtd Is Narrowed but Significant Pressure Increase Occurs. (B) the Incubator Design Shows Further Improved Rtd

#### 3. Process Flow Range Coverage

The product line of Pionic® Spin Incubators will consist of 14 devices, each covering a range of flow rates to ensure minimum residence time (RT), low pressure drop, and narrow RTD.

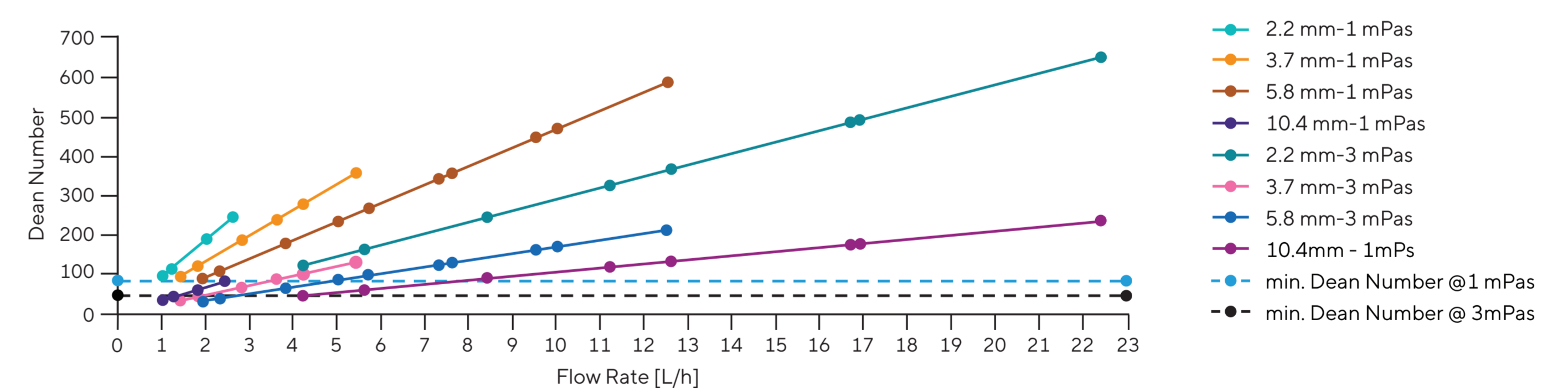


Figure 7: Pionic® Spin Incubator Portfolio Range. Each Product's Recommended High and Low Flow Rates At Various Viscosities Are Displayed. The Black Line Marks the Desired Dean Number (Or Higher) for Adequate Radial Mixing

#### 4. Residence Time Distribution

Characterization of the incubation chamber with a 2% acetone tracer ( $c_0$ ) signal at different flow rates for one device volume.

- At 2.6 L/h
  - minRT: 1%  $c_0$  was reached after 30 min
  - maxRT: 99%  $c_0$  was reached after 37 min
- At 1.8 L/h
  - minRT: 1%  $c_0$  was reached after 41 min
  - maxRT: 99%  $c_0$  was reached after 55 min

Reducing the laminar flow rate decreases Dean numbers, resulting in a broader residence time distribution.

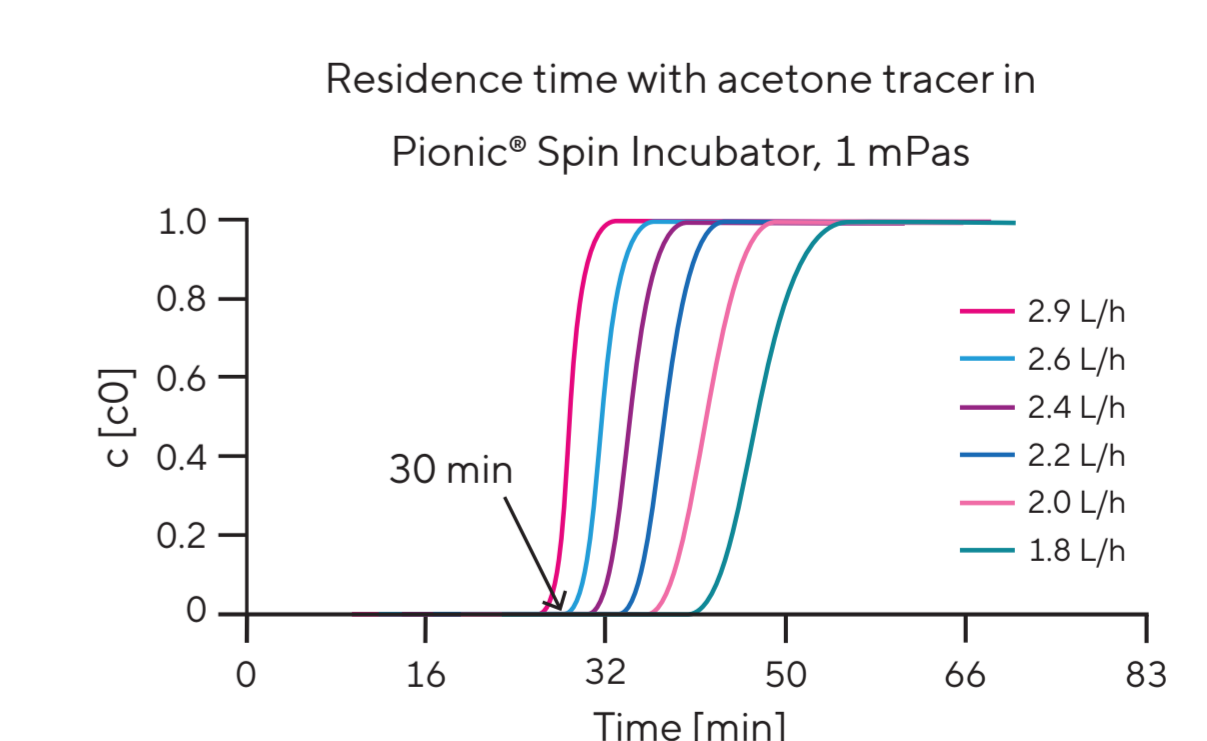


Figure 8: Acetone Curves for One Incubator Size at Different Flow Rates

#### 5. Summary & Conclusion

These data demonstrate the performance of the first device in their the product line for Pionic® Spin, supporting a continuous process flow stream of 1 to 22 L/h (16 to 300 mL/min). In addition to a narrow residence time distribution and reliable minimal residence time, the following features are highlighted:

- Pre-irradiated with sterile connectors for easy setup within Pionic® Spin System and Flowkit
- Designed for easy decontamination and disposal, using non-PFAS materials selected for sustainability
- Constructed for low pressure drop, the two-plate device has a pressure drop of about 10 mbar at 2 L/h
- Low weight and reduced material consumption at high inner volumes, e.g., an incubator volume of 1,400 mL with a device weight of 1,234 g, resulting in a lightweight, easy-to-handle product (720 × 450 × 30 mm)
- Industrially manufactured with a tight tolerance in lot-to-lot variance of incubator volume (+/- 7.5 mL) and residence time distribution (+/- 20 sec)