

Fundamentals of Tangential Flow Filtration (TFF)

Principles, Applications, and Operational Best Practices

A Comprehensive Course for Life Scientists

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COURSE AGENDA



TFF Principles

Mechanism, Flow Dynamics, and Key Process Parameters.



Hardware

System component and Membrane selection.



Applications

Concentration, Diafiltration, and Downstream implementation.



Procedures

Step-by-step operation from flushing to product recovery.

01. PRINCIPLES

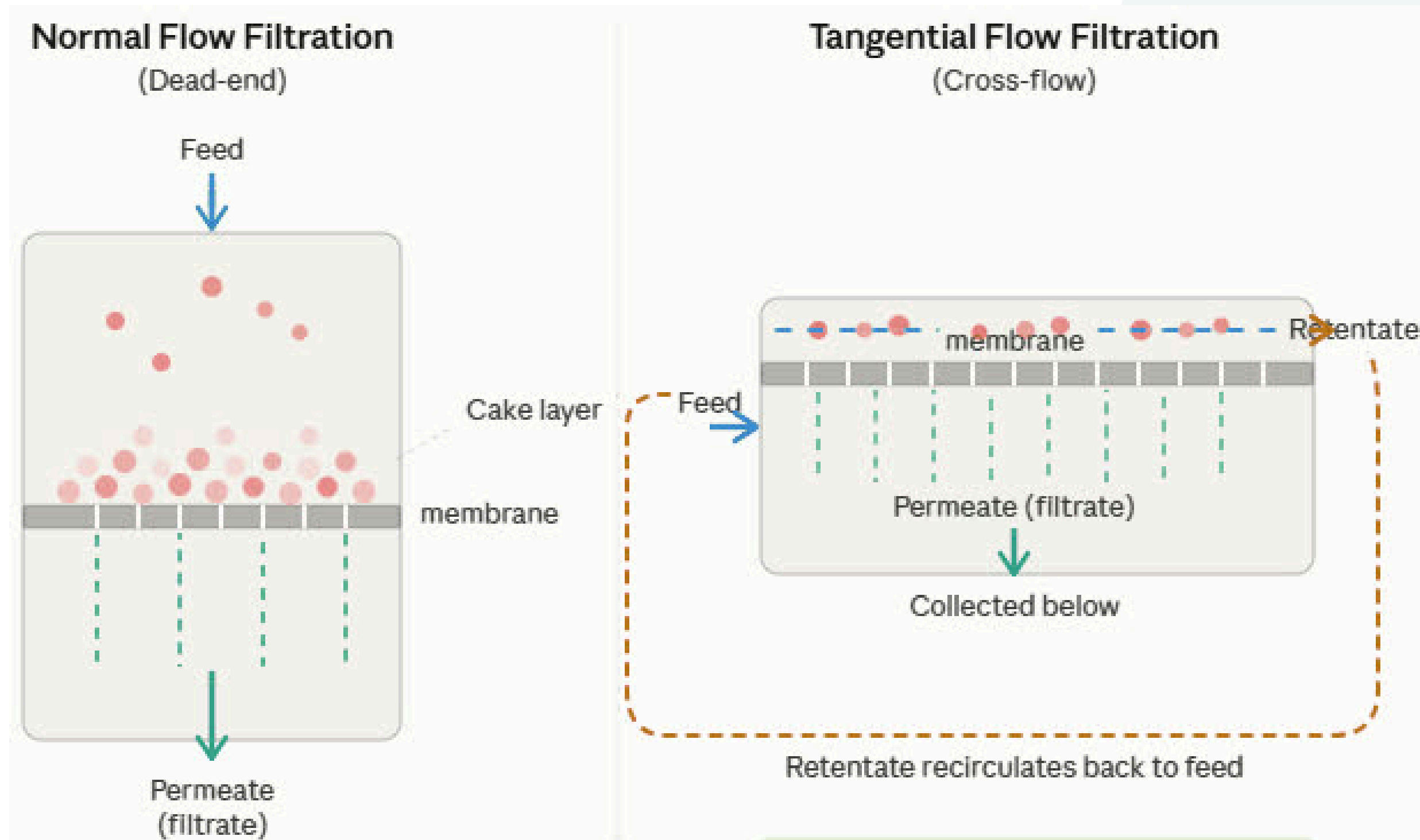
Understanding the mechanics of Tangential Flow

NORMAL FLOW VS. TANGENTIAL FLOW

The Difference is Flow Direction

- **Normal Flow (NFF):** "Dead-end" filtration where feed is perpendicular to the membrane. Leads to rapid cake formation.
- **Tangential Flow (TFF):** Feed flows parallel (tangential) to the membrane surface.
- **Sweeping Force:** The cross-flow action continuously cleans the membrane, reducing fouling.

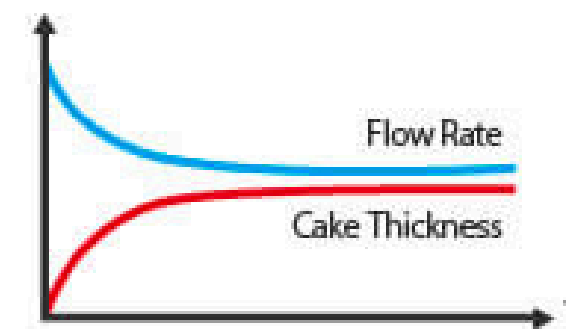
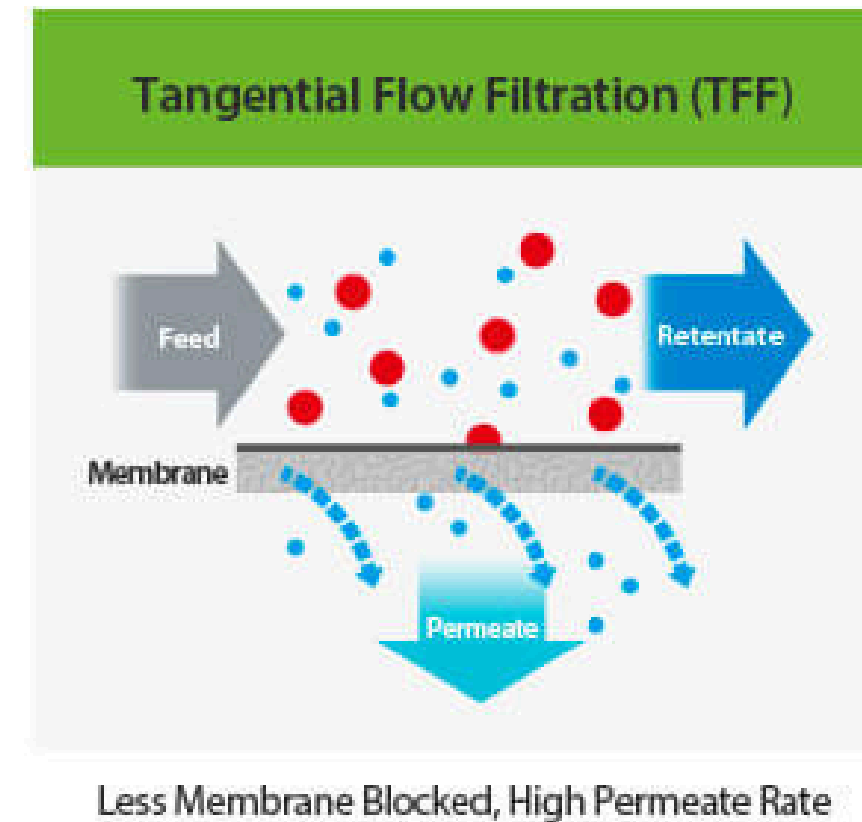
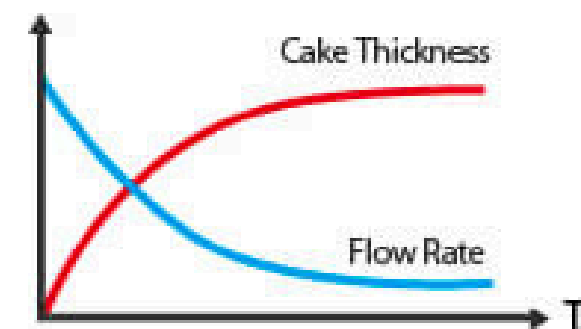
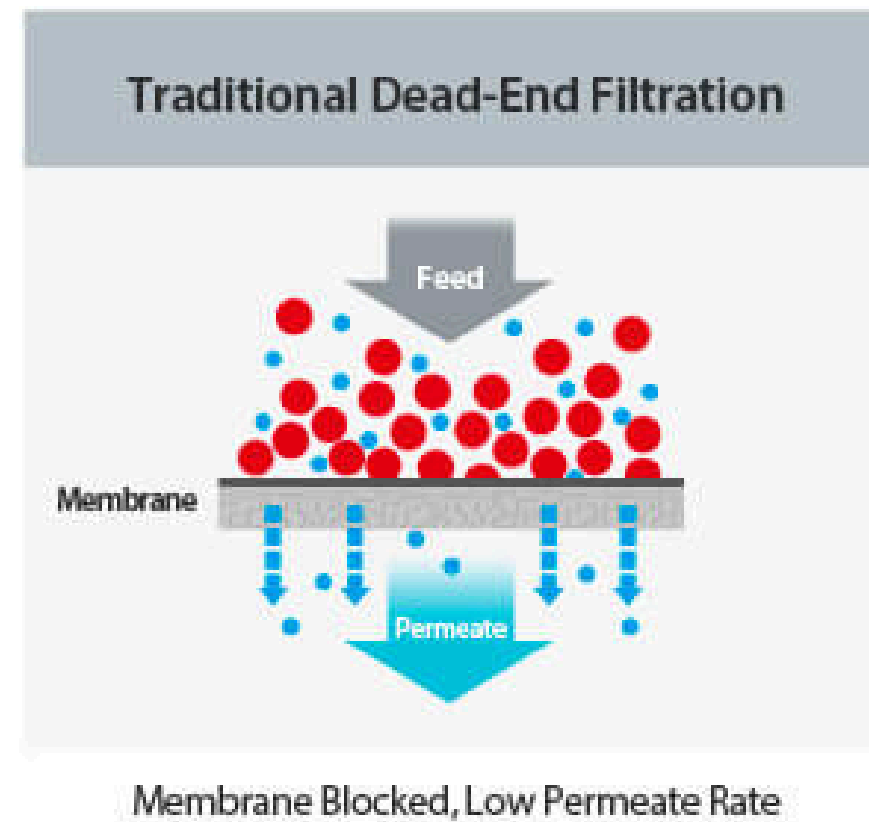
NORMAL FLOW VS. TANGENTIAL FLOW



NORMAL FLOW VS. TANGENTIAL FLOW



https://www.tpp.ch/page/produkt/e/12_filtration_spritzenfilter.php



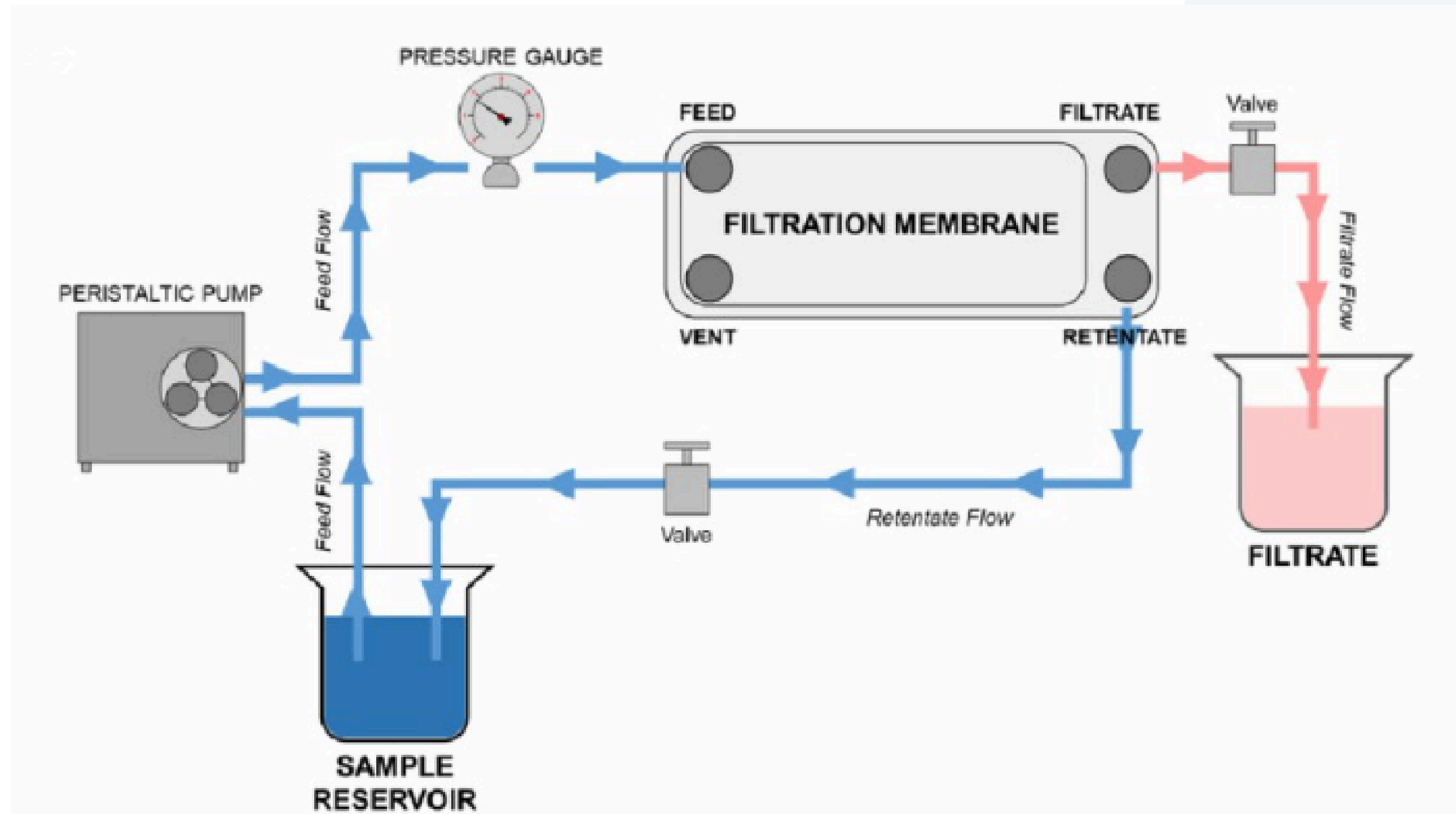
<https://www.rocker.com.tw/en/application/tangential-flow-filtration/>

WHY TFF? FLUX SUSTAINABILITY



In TFF, the cross-flow velocity maintains a high and stable permeate flux compared to dead-end filtration which clogs rapidly.

SYSTEM COMPONENTS



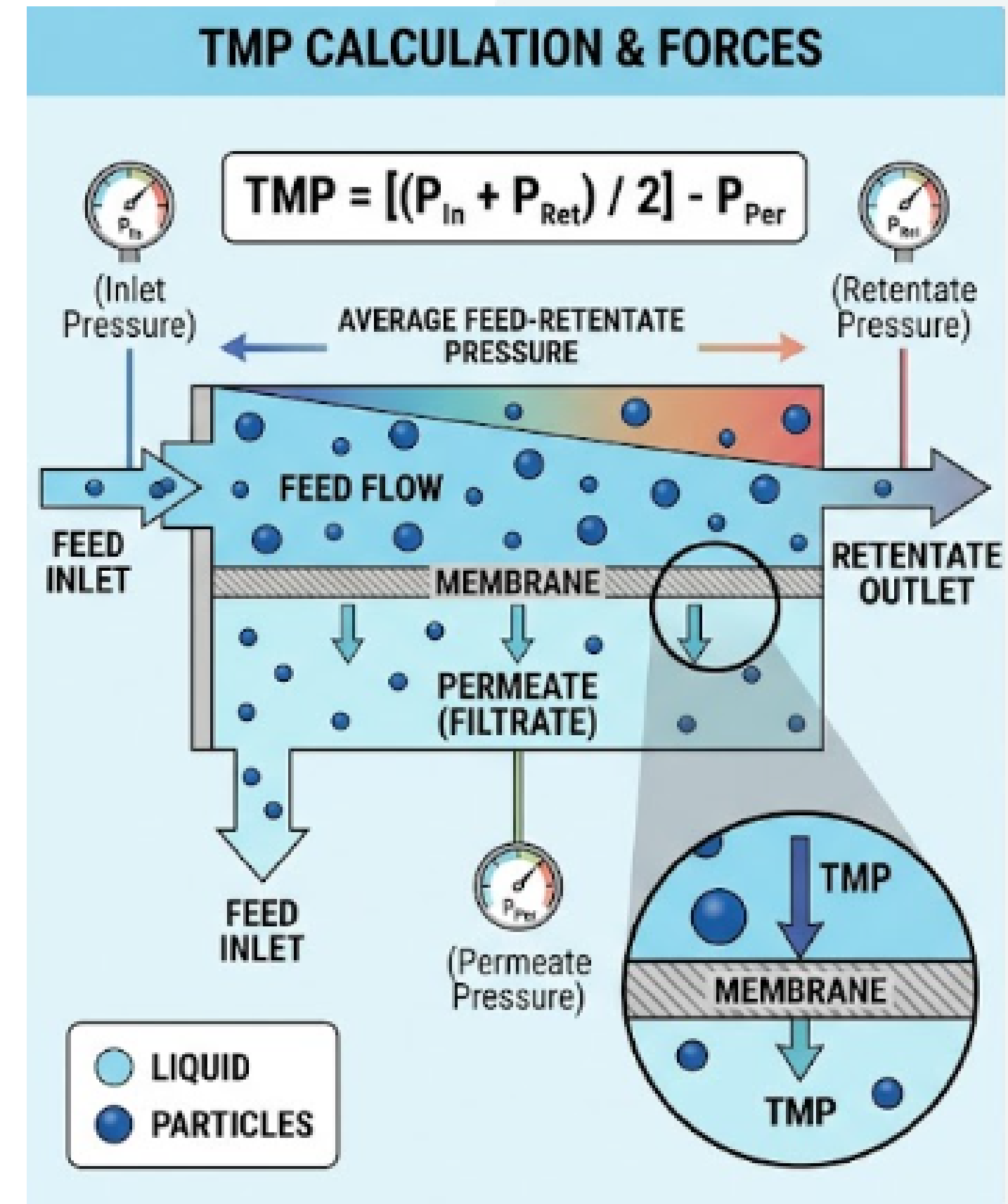
(Visan KS, et al., 2022)

SYSTEM COMPONENTS

- **Feed Pump:** Controls Cross-Flow Flux (CFF).
- **Pressure Sensors:** Monitors Feed, Retentate, and Permeate (P1, P2, P3).
- **Permeate Valve:** Regulates TMP (Transmembrane Pressure).
- **Heat Exchanger:** Protects shear-sensitive biomolecules from heat build-up.

$$TMP = \frac{(P_{\text{feed}} + P_{\text{retentate}})}{2} - P_{\text{permeate}}$$

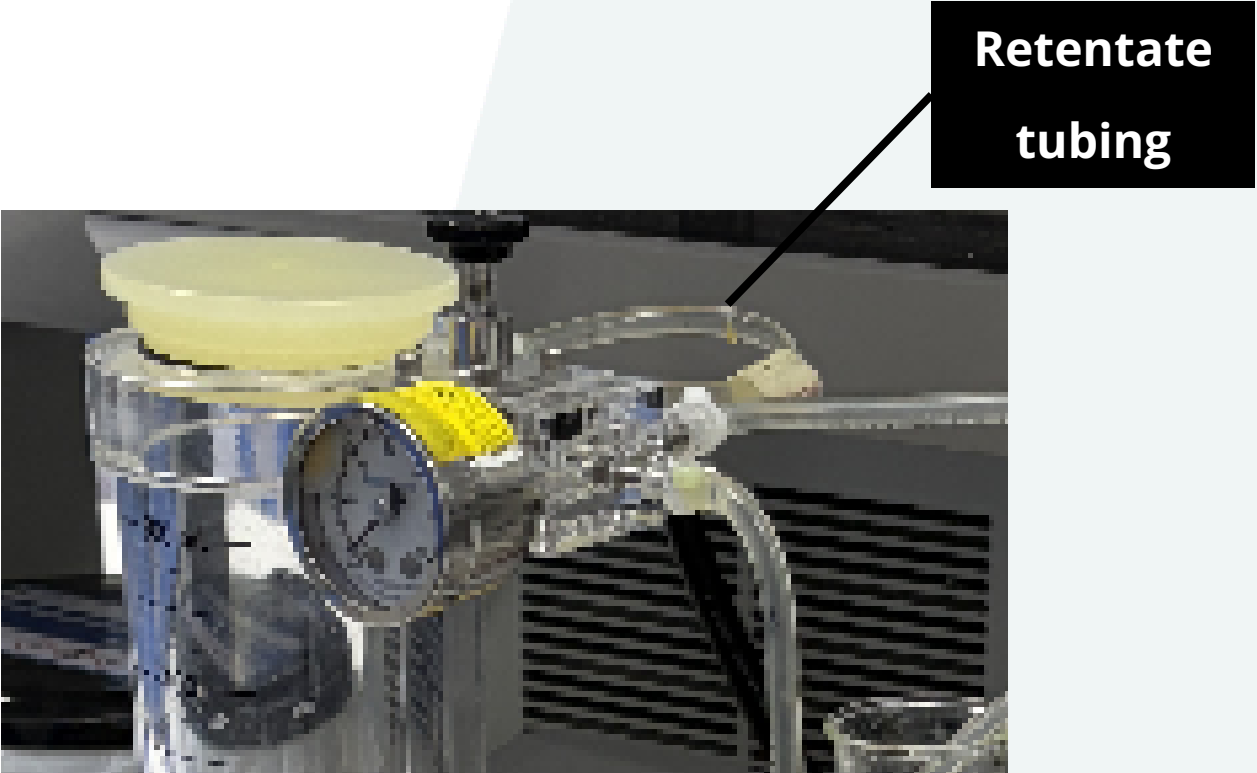
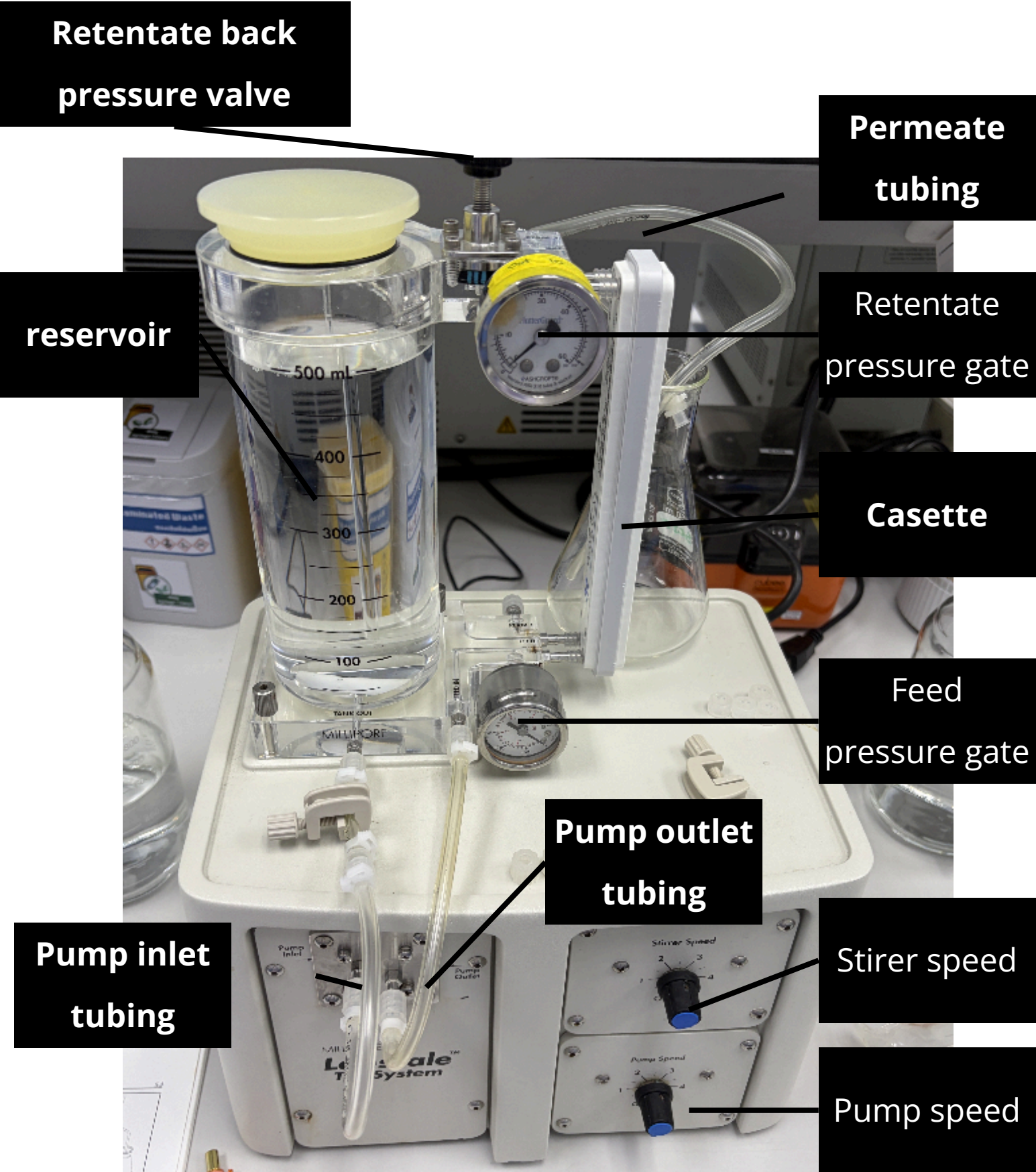
The practical operating TMP range is dependent on the membrane type; for instance, Ultrafiltration (UF) generally operates between 0.3-2.0 bar.



02. HARDWARE

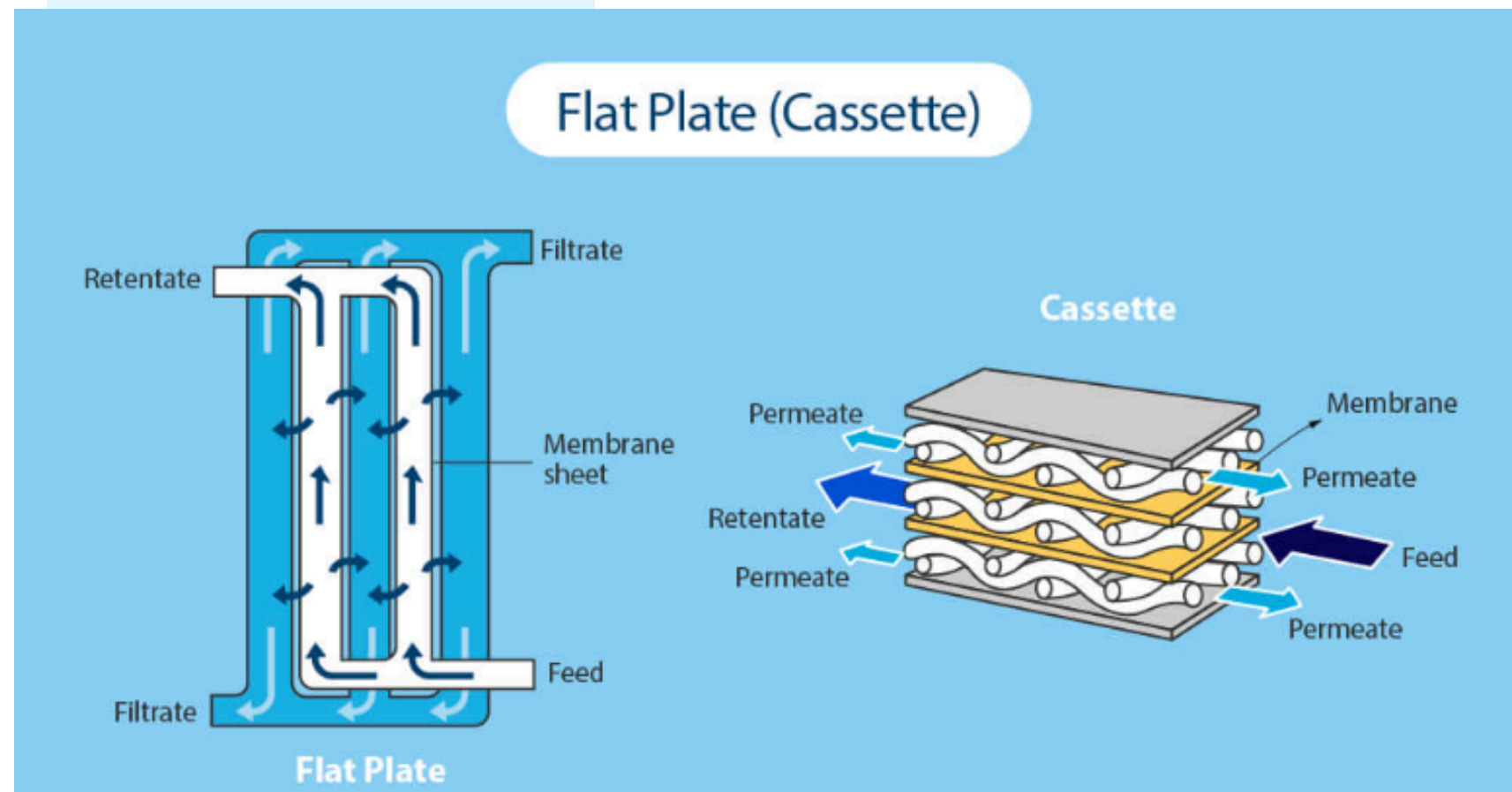
Components and Membrane Configurations

Hardware components

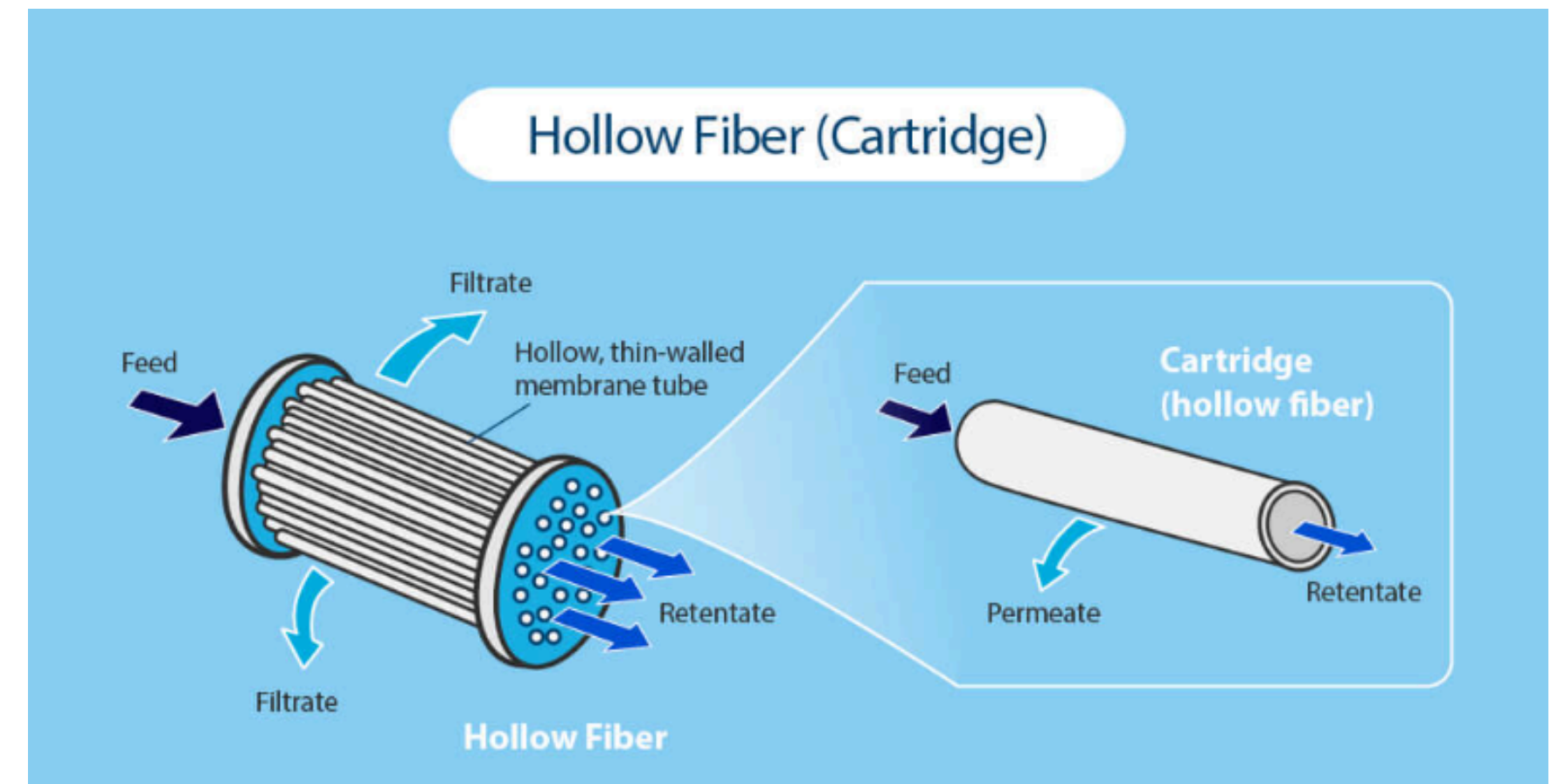


FILTER MODULE FORMATS

Cassettes vs. Hollow Fiber



Cassettes (Flat Plate): High packing density, efficient mass transfer, ideal for ultrafiltration.



Hollow Fiber: Open flow path, low shear, handles high solids and cell harvesting effectively.

MWCO SELECTION RULE

3X **Fast Processing**

<

6X **High Retention**

The Golden Rule of MWCO

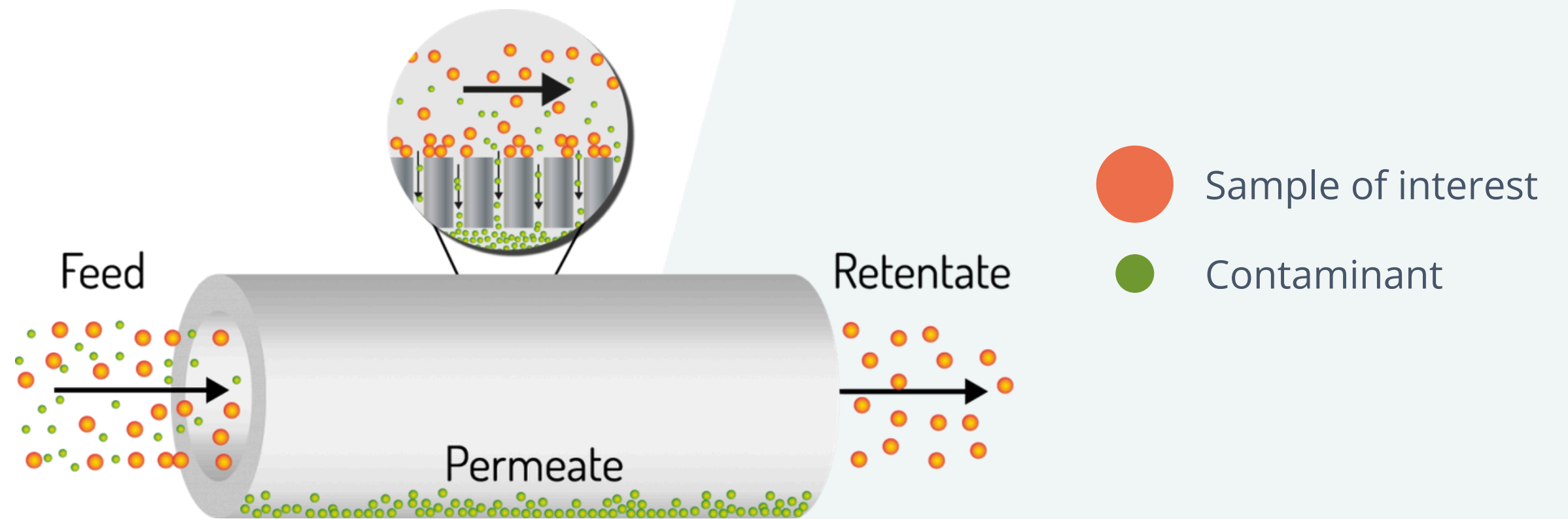
For optimal results, choose a membrane with a Molecular Weight Cut-Off (MWCO) that is **3 to 6 times smaller** than the molecular weight of your target protein.

Example

BSA 66 kDa

3x smaller = ? kDa

6x smaller = ? kDa



<https://biopharmadynamics.co.uk/blog/what-is-tangential-flow-filtration-and-how-can-it-benefit-your-process/>

FORMAT COMPARISON MATRIX

Feature	Cassette (Flat Plate)	Hollow Fiber
Shear Rate	Higher	Lower (Gentle)
Fouling Resistance	Medium	High (Open Channel)
Scaling	Linear and compact	Easy to increase length
Best for...	Proteins, mAbs, Peptides	Cells, Bacteria, Lysates

03. APPLICATIONS

Where TFF makes a difference

MARKET APPLICATION FOCUS



■ **Concentration (40%)**

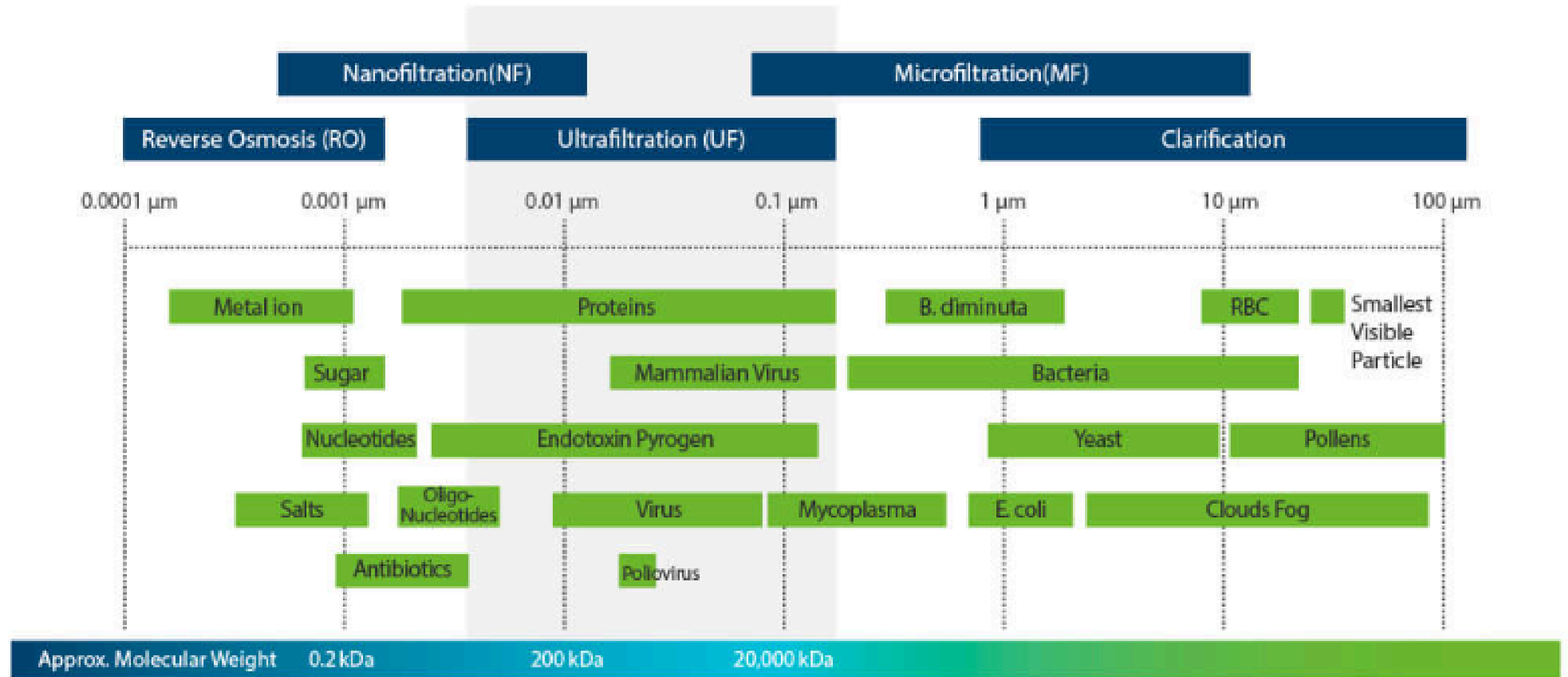
■ **Diafiltration (30%)**

■ **Clarification (30%)**

TFF is essential in downstream processing for Monoclonal Antibodies (mAbs), Vaccines, and Gene Therapy vectors like AAV/Lentivirus.



APPLICATIONS



<https://www.rock.com.tw/en/application/tangential-flow-filtration/>

04. PROCEDURES

Operational Step-by-Step Guide

STANDARD OPERATING WORKFLOW



Flushing

Remove storage solutions



Integrity Test

Check for leaks/faults



Equilibration

Precondition with buffer



Processing

Conc. & Diafiltration



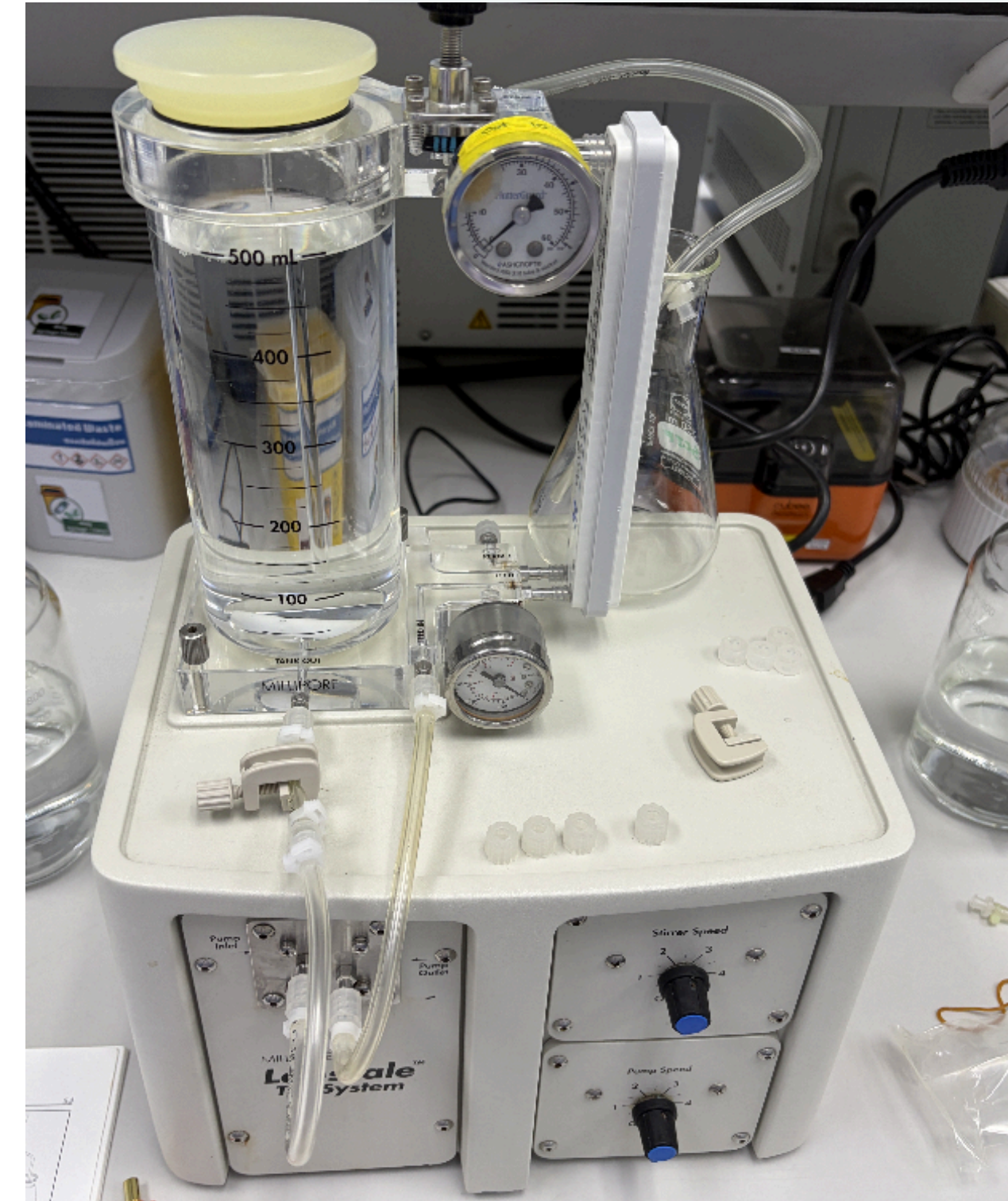
Recovery

Maximize yield

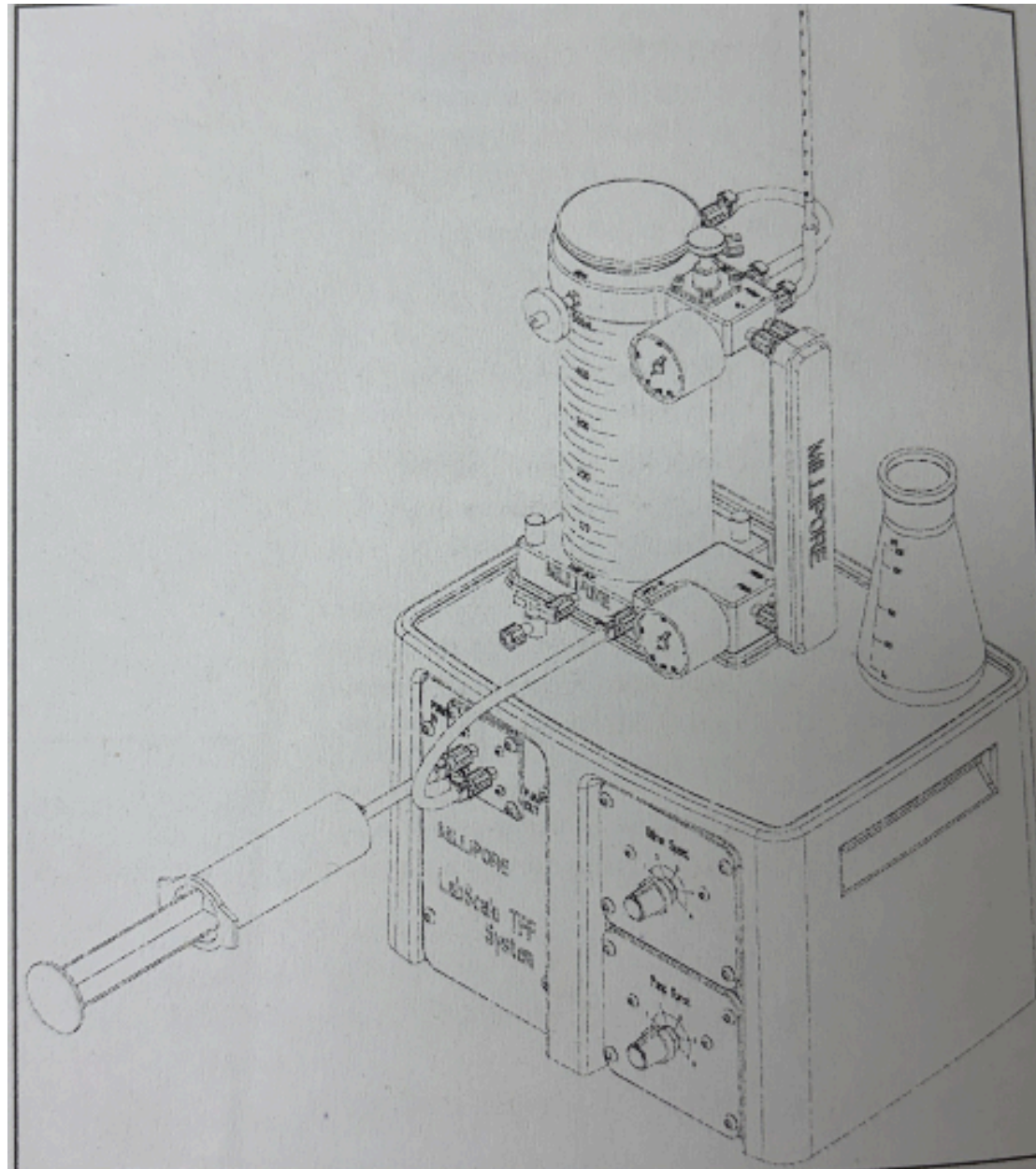
SETUP: FLUSHING

1. Flushing & Draining

- Remove storage fluids (Glycerol/Sodium Azide).
- Flush with DI water until pH/conductivity matches.
- Ensures no residues contaminate your product.



SETUP: TESTING



Integrity

Each unit exhibited air flow through the membrane less than or equal to 3 cc/min at 30 psig (2.1 bar) inlet pressure.

2. Integrity Testing

- **Air Diffusion Test:** Measures gas flow through wetted membrane.
- Ensures there are no membrane defects or bypass leaks.
- Crucial for validation and regulatory compliance.

PROCESSING: CONCENTRATION MODE

Volumetric Concentration Factor (VCF)

The goal is to reduce the bulk volume while retaining the target protein.

$$\text{VCF} = \frac{V_{\text{initial}}}{V_{\text{final}}}$$

Monitor permeate flow rate and TMP throughout the process to prevent gel layer formation.

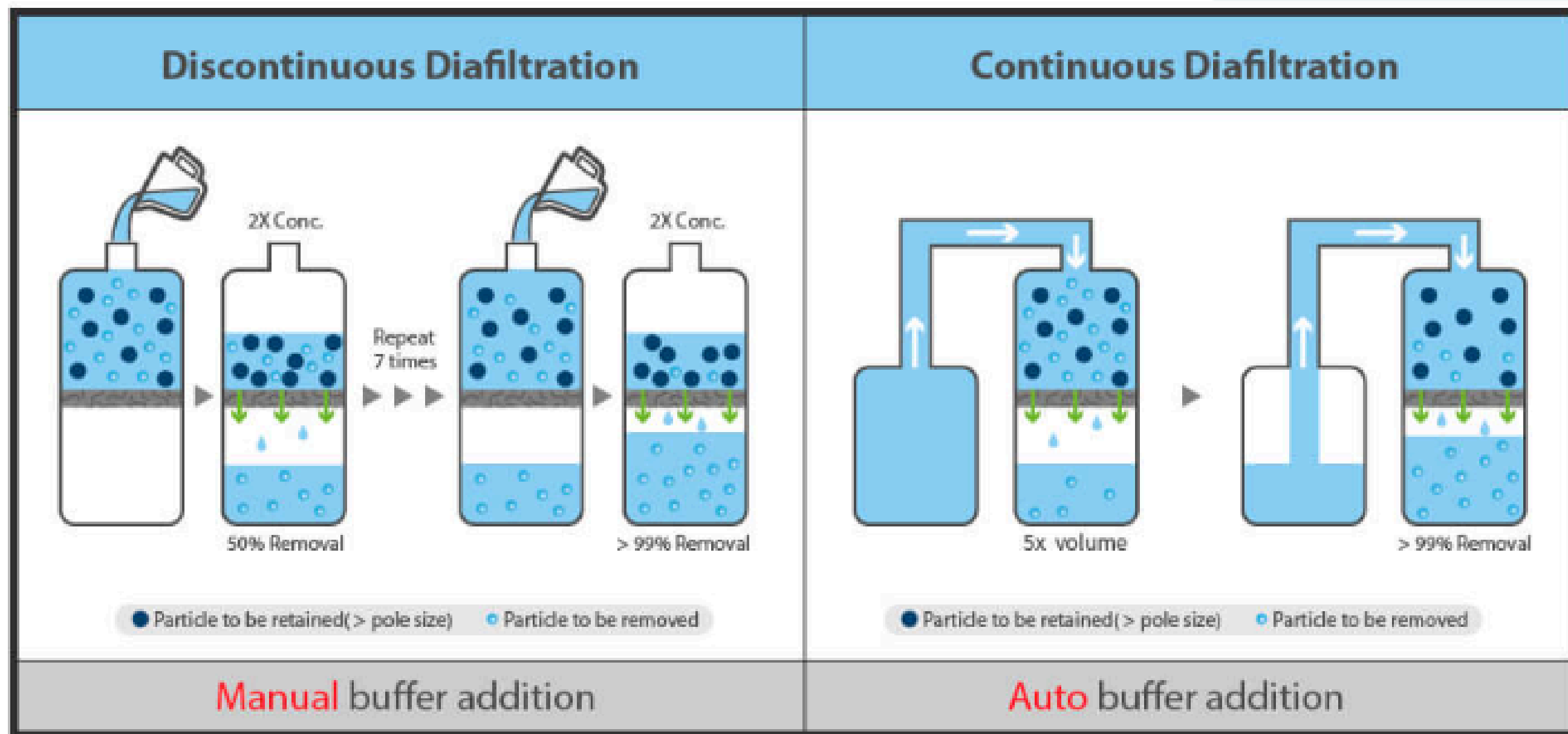
PROCESSING: DIAFILTRATION MODE



Buffer Exchange (Desalting)

- **Continuous DF:** Buffer is added at the same rate as permeate removal (Constant Volume).
- **Efficiency:** 5 Diavolumes (DV) typically achieves >99% impurity removal.
- **Why?** To exchange buffer for the next purification step or final formulation.

PROCESSING: DIAFILTRATION MODE



FINAL STEPS: RECOVERY & DRAINING



Draining

Ensure the feed tank is fully empty and pumps have pushed remaining liquid through.



Buffer Flush

Small volume buffer wash to recover protein adsorbed to the membrane surface.

CONCLUSION

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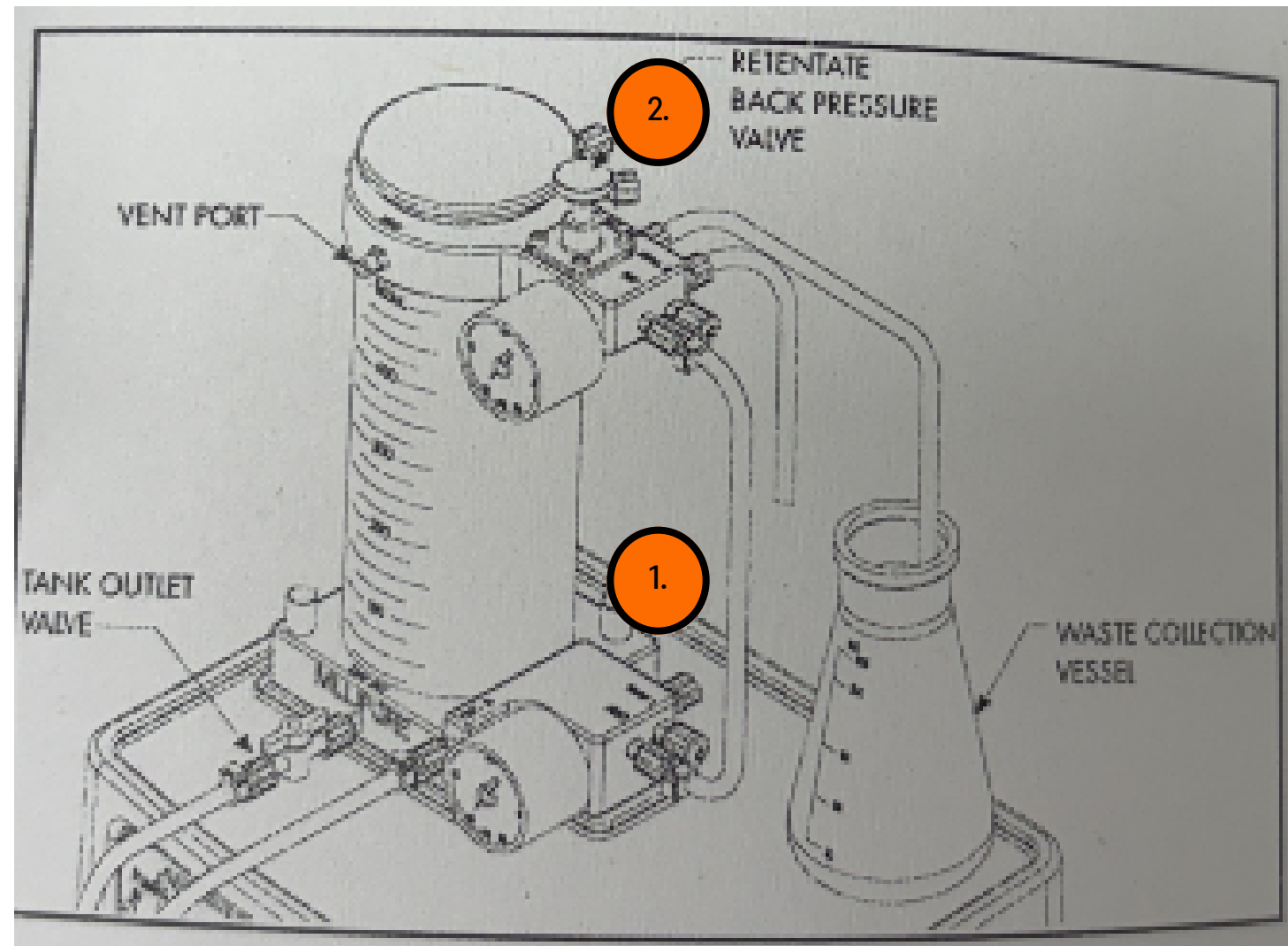
"Success in TFF is a balance of correct hardware selection and disciplined operational procedures."

— Downstream Processing Principles

Q&A

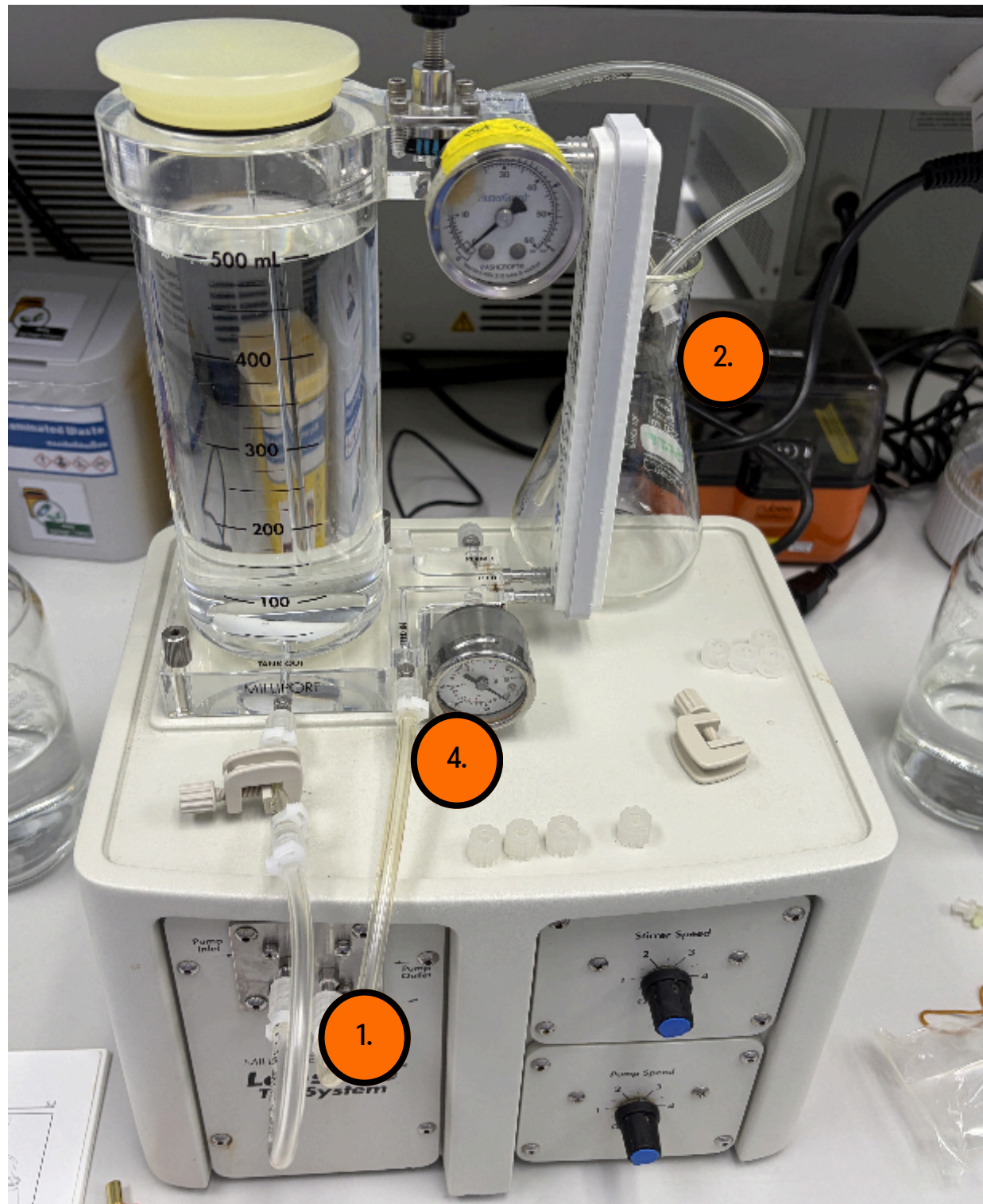
Thank you for your attention!

Cleaning



1. Install cleaning tube at device port.
2. Disconnect Ret IN tubing place in container.
3. Open retentate valve (counter clock wise).
4. Pour in 500 ml of 0.1 N NaOH.
5. Turn pump on - set pump speed to 2.
6. Continue until the level in reservoir drop to 250 mL.
7. Reconnect Ret IN tubing and recirculate for 15 min.

Drainning

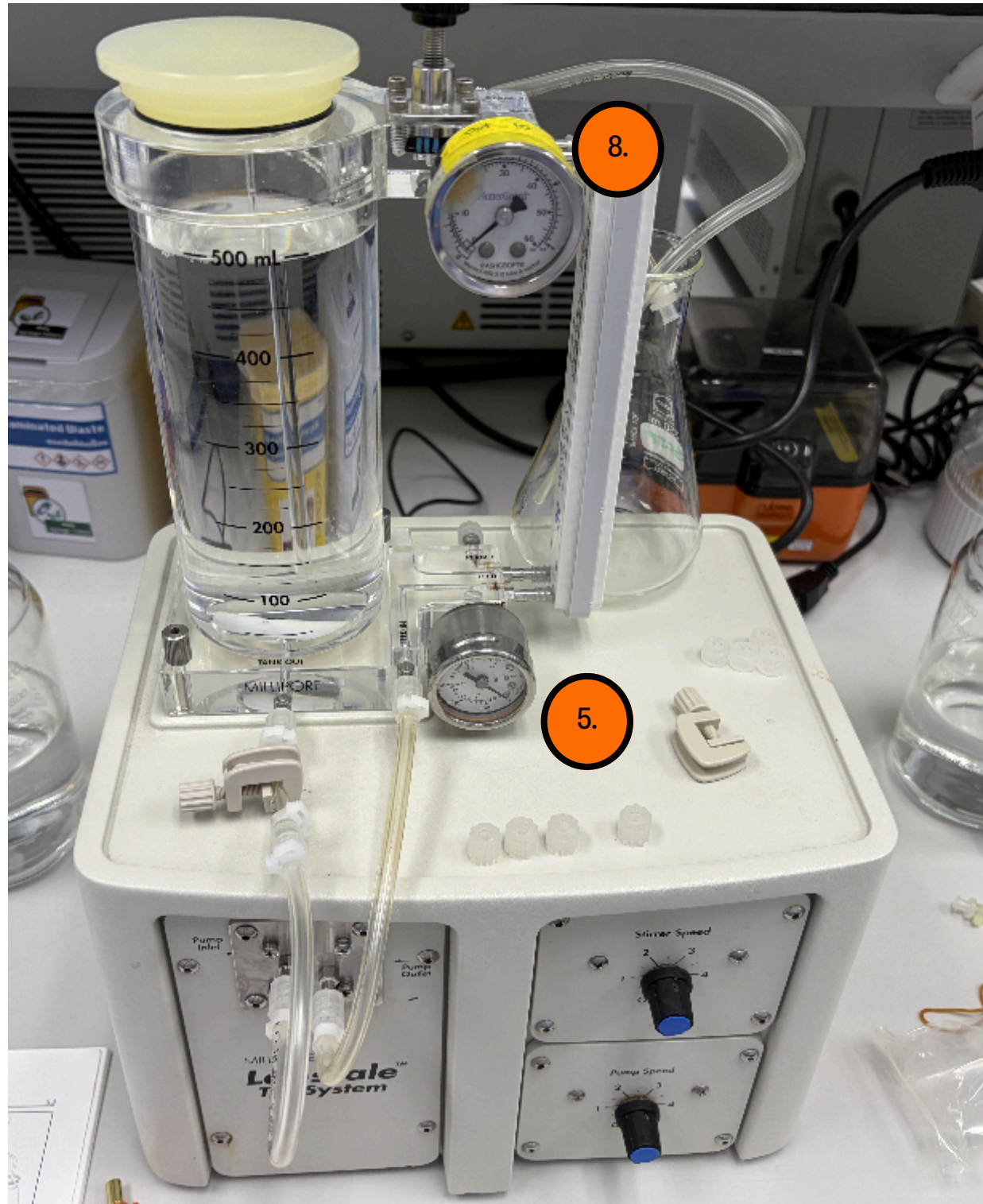


1. Disconnect pump out tubing from pump outlet port and place in container.
2. Disconnect Retentate tubing from RET IN port (If additional drainage is required a syringe can be placed on the end of retentate tube and blow out).
3. Replace retentate tube. Reconnect pump outlet tubing.
4. Disconnect pump outlet tubing from feed in port and place in collection vessel.
5. Turn pump on to drain reservoir.
6. Reconnect pump outlet to the feed in port.

Flush system using water

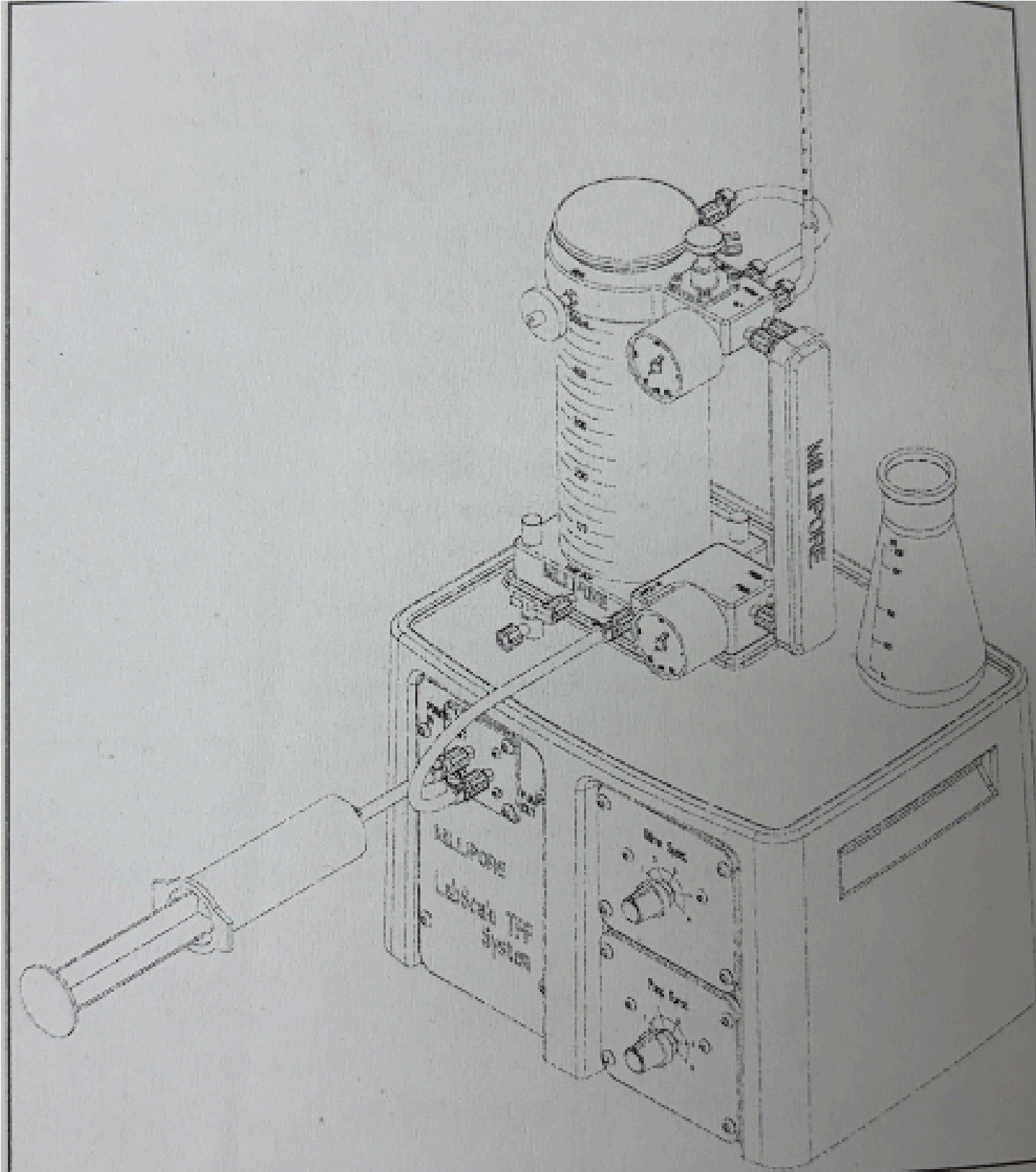
**repeating step using
Purified water**

Install Pellicon XL device



1. Install Pellicon XL device by press device firmly on the port.
2. Disconnect Ret IN tubing place in container.
3. Open retentate valve (counter clock wise).
4. Pour in 500 ml of purified water.
5. Turn pump on untill feed pressure gage reach 20 psi.
6. Continue untill level in the reservoir drop to 350 mL Turn pump off.
7. Reconect Ret IN tubing and Turn pump on untill feed pressure gage reach 20 psi.
8. Adjust retentate valve untill retentate pressure gage reads 10 psi.
9. Adjust pump speed to acheive 30 psi feed pressure and 10 psi retentate pressure.
10. Continue untill level of reservoir drop to 50 mL.
11. Repeat drain step.

Integrity testing

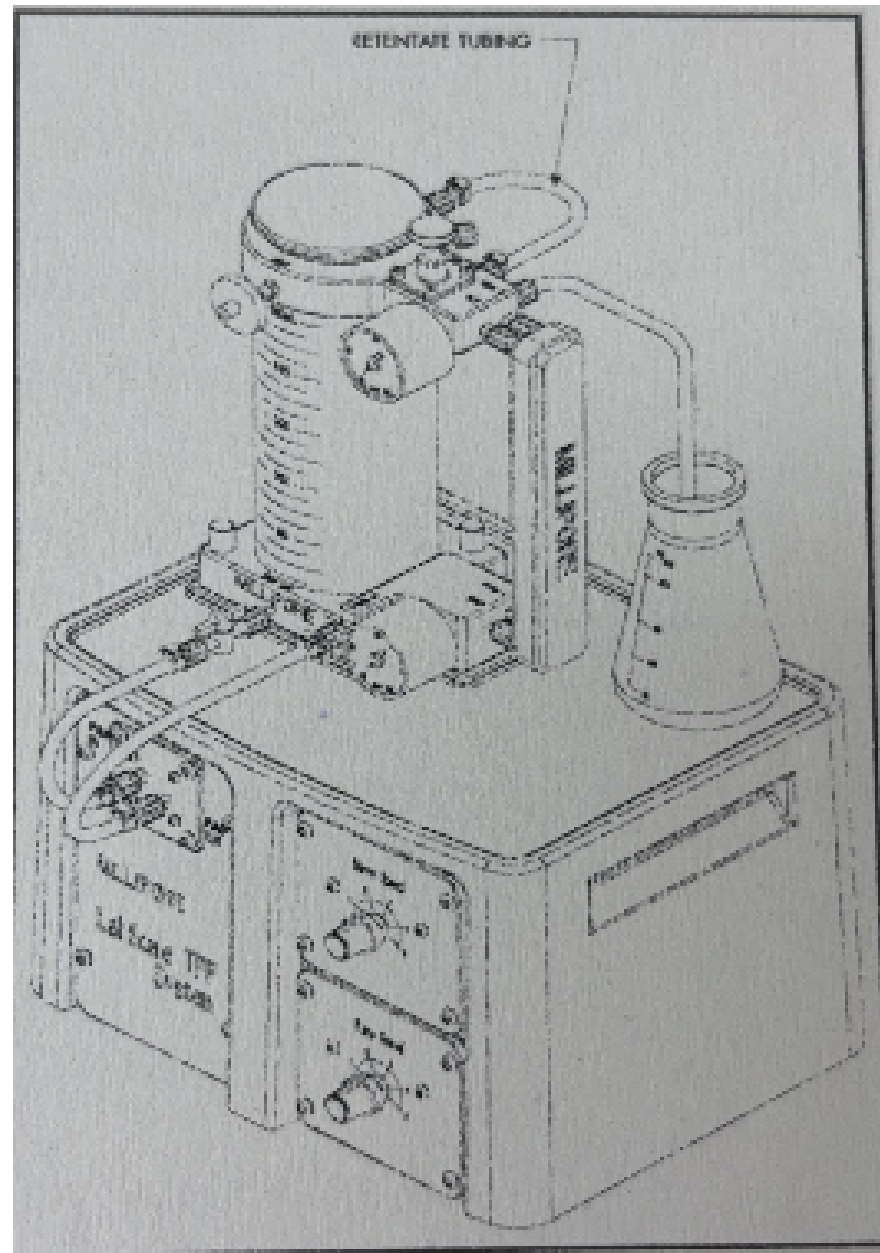


Integrity

Each unit exhibited air flow through the membrane less than or equal to 3 cc/min at 30 psig (2.1 bar) inlet pressure.

1. Close retentate valve and disconnect pump inlet tubing from pump outlet valve.
2. Insert syringe in the end of pump inlet tubing.
3. Injecting air until feed pressure gauge reach 30 psi.
4. add 0.1 ml water to 1 ml pipette.
5. insert bottom of pipette in to the end of permeate tubing.
6. Measure air flow for 30 sec and multiply by 2 to calculate air flow (mL/min).

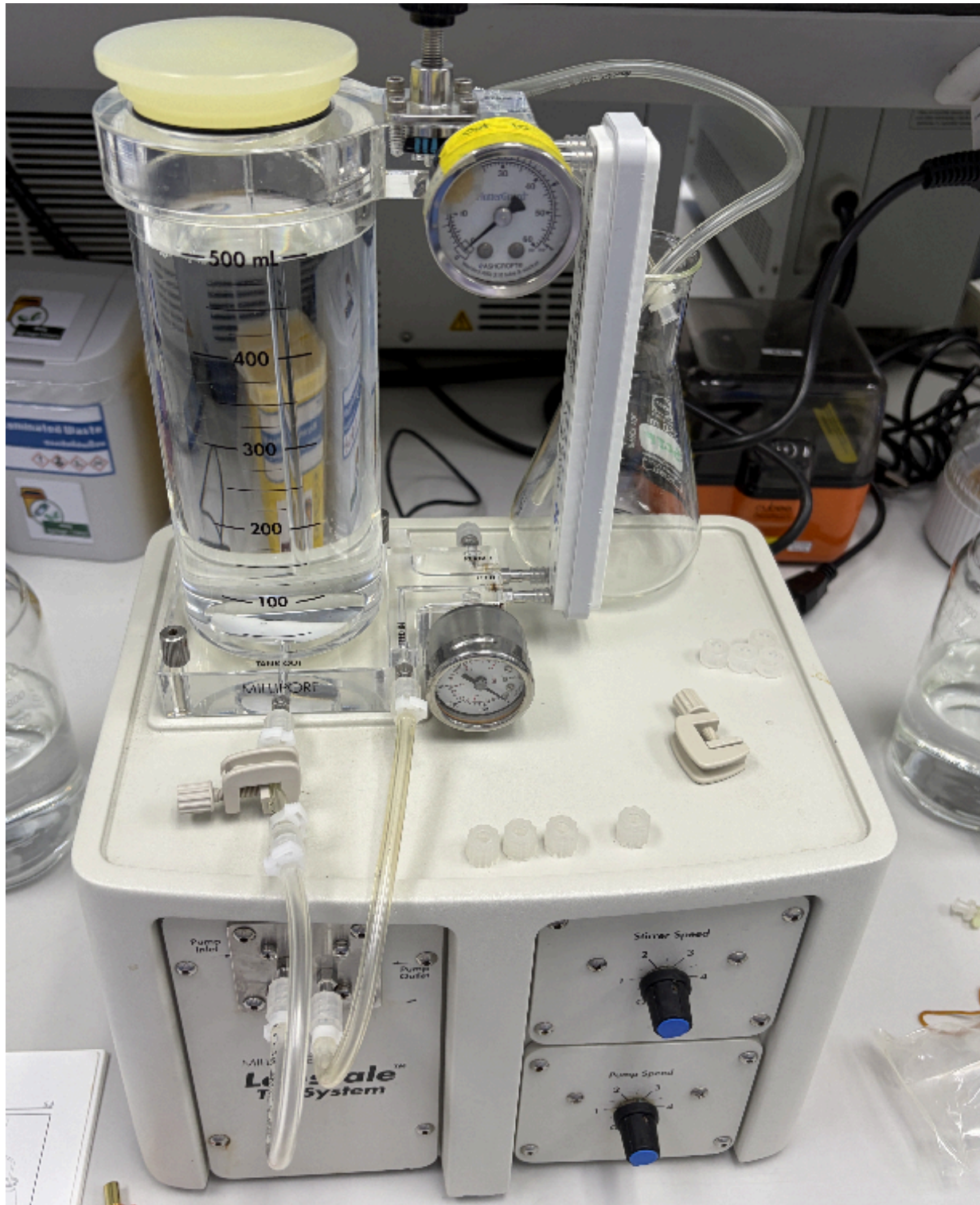
Preconditioning



1. Fill reservoir with 50 mL of appropriate buffer.
2. Turn pump speed until pressure gauge reads 20 psi.
3. Continue until the level of reservoir drops to the bottom of stir bar well. Turn pump off.
4. Disconnect permeate tubing and drain residual to container.
5. Reconnect the permeate tubing.

Concentration

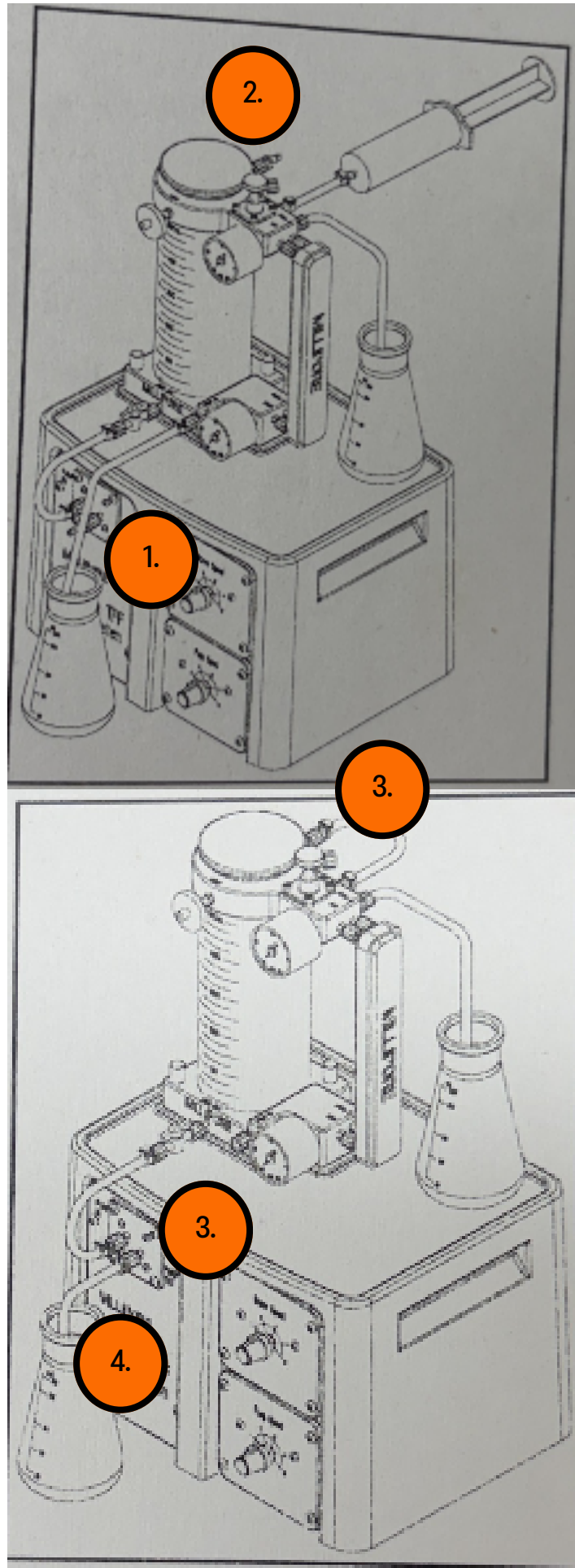
1. Fill reservoir with sample (100 ml for demonstration)
2. Turn pump on until feed pressure gage reach 20 psi.
3. Adjust retentate valve until retentate pressure gauge reads 10 psi.
4. Adjust pump speed to achieve 30 psi feed pressure and 10 psi retentate pressure.
5. Continue processing until the desired volume is reached (25 mL for demonstration)



Diafiltration

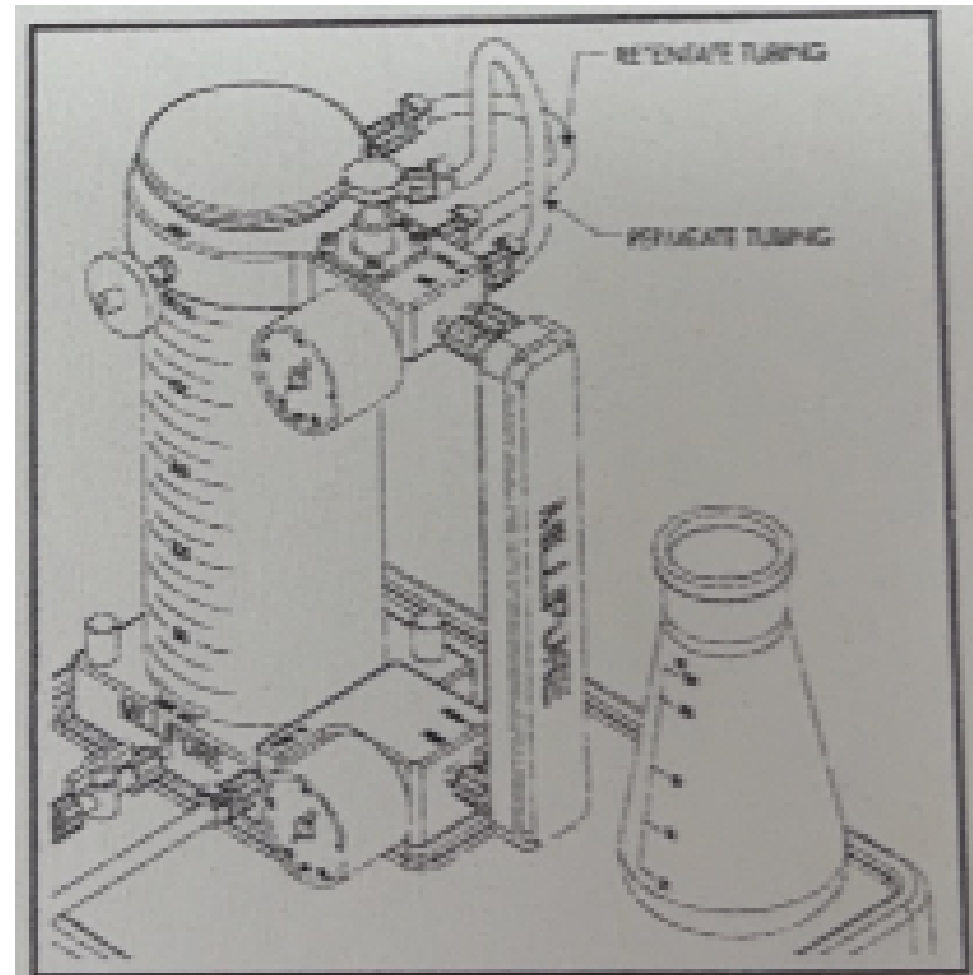
1. Connect tubing to DIA/RECIRC port and place other end of tubing to vessel of appropriate buffer.
2. Plug vent port.

Product recovery



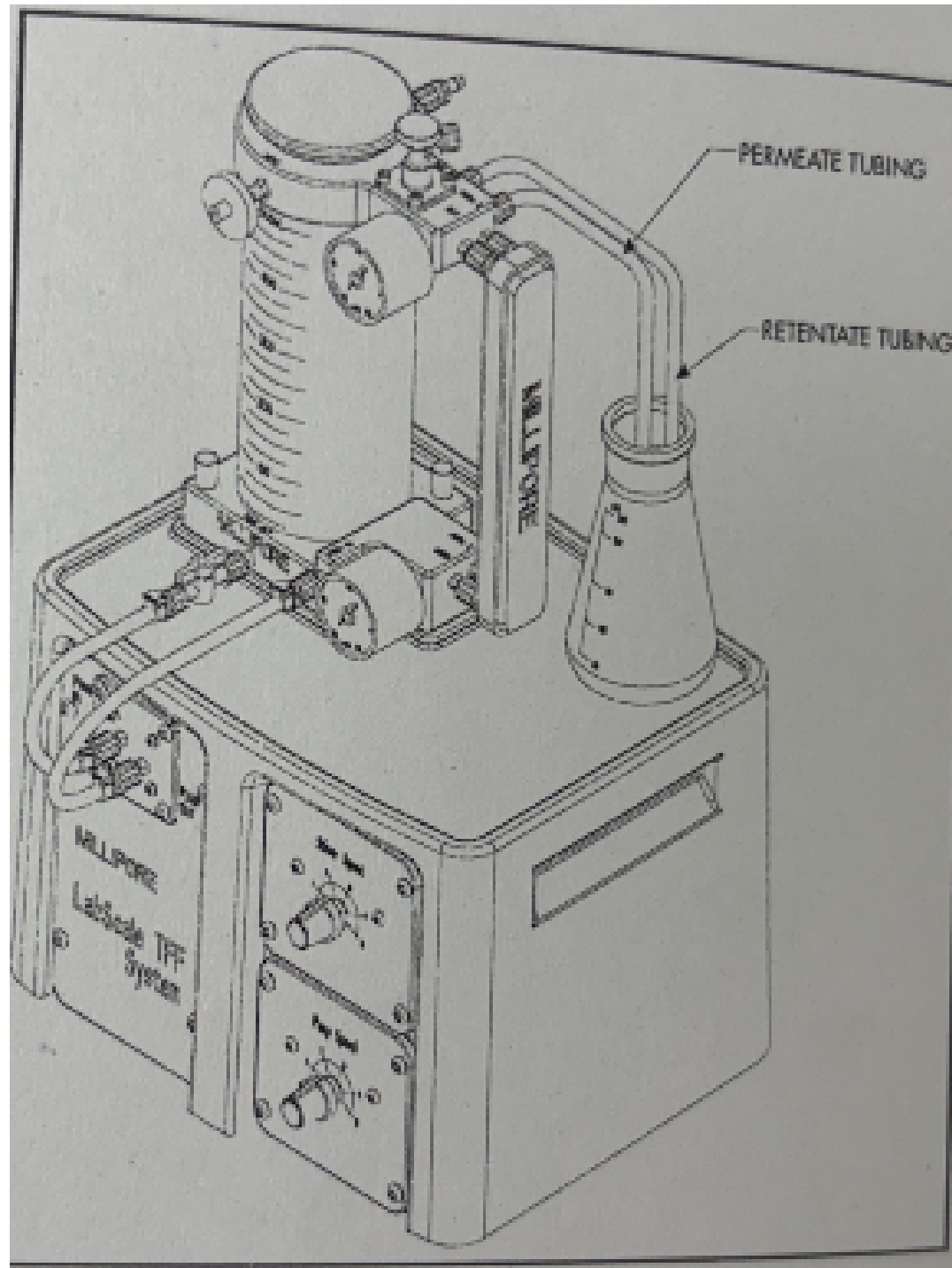
1. Disconnect pump out tubing from pump outlet port and place in container.
2. Disconnect Retentate tubing from RET IN port (If additional drainage is required a syringe can be placed on the end of retentate tube).
3. Replace retentate tube. Reconnect pump outlet tubing.
4. Disconnect pump outlet tubing from feed in port and place in collection vessel.
5. Turn pump on to drain reservoir.
6. Reconnect pumpoutlet to the feed in port.

Clean system



1. Disconnect Ret IN tubing place in container.
2. Open retentate valve (counter clock wise).
3. Pour in 500 ml of 0.1N NaOH.
4. Turn pump on untill feed pressure gage reach 20 psi.
5. Continue untill level in the reservoir drop to 250 mL Turn pump off.
6. Reconect Ret IN tubing/permeate tubing to DIA/RECIRC port and Turn pump on untill feed pressure gage reach 20 psi.
7. Adjust retentate valve untill retentate pressure gage reads 10 psi.
8. Adjust pump speed to acheive 30 psi feed pressure and 10 psi retentate pressure.
9. Recirculate 30 mins.
10. Repeat drain step.

Flushing system after cleaning



1. Disconnect Ret IN tubing place in container.
2. Open retentate valve (counter clock wise).
3. Pour in 500 ml of DI water
4. Turn pump on untill feed pressure gage reach 20 psi.
5. Continue untill level in the reservoir drop to 350 mL
Turn pump off.
6. Reconect Ret IN tubing/permeate tubing to DIA/RECIRC port and Turn pump on untill feed pressure gage reach 20 psi.
7. Adjust retentate valve untill retentate pressure gage reads 10 psi.
8. Adjust pump speed to acheive 30 psi feed pressure and 10 psi retentate pressure.
9. Continue untill level of reservoir drop to 50 mL.
10. Repeat drain step.

THANK YOU