# Best practices for high concentration Ultrafiltration Applications

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# Overview

- Driver for high protein concentration (HPC) in Biologics.
- Challenges in processing HPC using UF.
- New UF cassette development for HPC applications.

# High Concentration Drivers for Biologics

- High patient doses required for biological products (mAbs):
  - ~1-3mg/kG (→ upto 10 mg/kg)
- Intravenous (IV) infusion – traditional delivery method
  - Issues: Infusion side effects, cost, quality of life, patient compliance

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- Subcutaneous administration (Sub-Q) preferred by patients

**Table 1 Selected drugs in development using alternative delivery[a]**

| Company (location) | Drug | Condition | Drug type | Delivery | Phase |
|---|---|---|---|---|---|
| Abbott | ABT-874 (briakinumab) | Psoriasis | Human mAb (anti-IL12/23) | SubQ | Awaiting FDA approval |
| Novartis | AIN457 (secukinumab) | Uveitis/psoriasis arthritis/MS/ rheumatoid arthritis | Human mAb (anti-IL17a) | SubQ | Phase 3/2/2/2 |
| Biogen Idec/Genentech/Roche | MabThera/Rituxan | Hodgkin's lymphoma | Chimeric mouse-human mAb (anti-CD20) | SubQ | Phase 3[b] |
| GlaxoSmithKline/Genmab (Copenhagen) | Arzerra (ofatumumab) | Rheumatoid arthritis | Human mAb (anti-CD20) | SubQ | Phase 3[b] |
| Roche | Herceptin | Breast cancer | Humanized mouse mAb (anti-HER2) | SubQ | Phase 3[b] |
| Roche | Actemra/RoActemra (tocilizumab) | Rheumatoid arthritis | Humanized mouse mAb (anti-IL6R) | SubQ | Phase 3[b] |

SubQ, subcutaneous

[a]Complete table available online. [b]FDA approved for other delivery modes and/or indications.



M.Eisenstein, v29 , # 2, Feb. 2011 Nature Biotech

# High Concentration Drivers for Biologics

- Subcutaneous injection Issues/Requirements
  - Needle phobia and pain of injection



# High Concentration Drivers for Biologics

- Subcutaneous injection Issues/Requirements
  - Needle phobia and pain of injection
    - Studies show that increasing injection vol from 0.5 ml to 1 ml increases pain significantly
    - Target injection vol < 1 ml
      - For a 2-3 mg/kg dose, for a 70 kg person → 140-210 mg dose; if injectiion vol. needs to be less than 1 ml, we are talking about a protein concentration of > 140-210 g/L

Sub-Q injections require high conc. protein formulations

# Challenges with High Concentration of Proteins

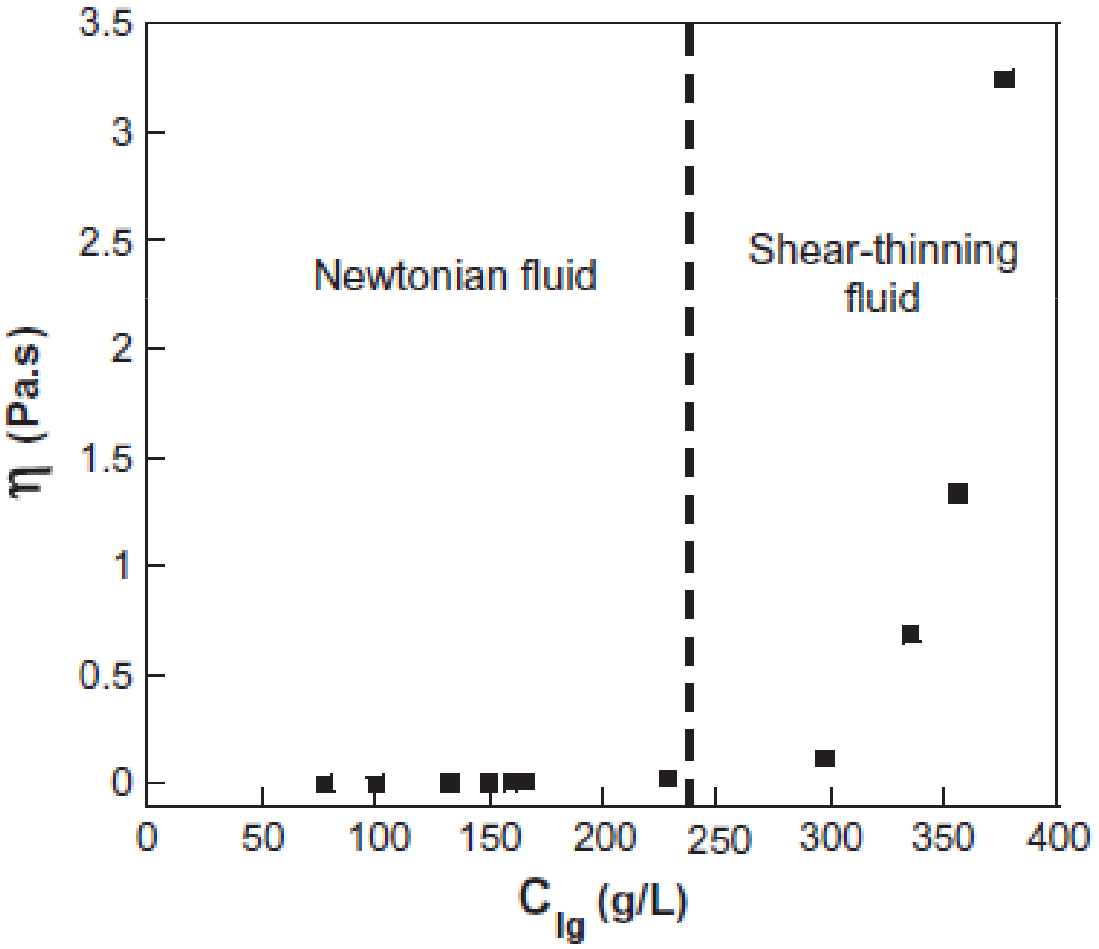
- Potentially significant changes in solution properties
  - Viscosity → mechanical processing, drug delivery
  - Osmotic Pressure → max conc in a TFF process
  - Thermodynamic properties (excluded volume, donnan) → impurity clearance in diafiltration

# Challenges with High Concentration of Proteins

- Viscosity and Osmotic effects may combine to limit the ‘Max’ achievable concentration in a TFF process
- Let’s see how?

# Viscosity Effects

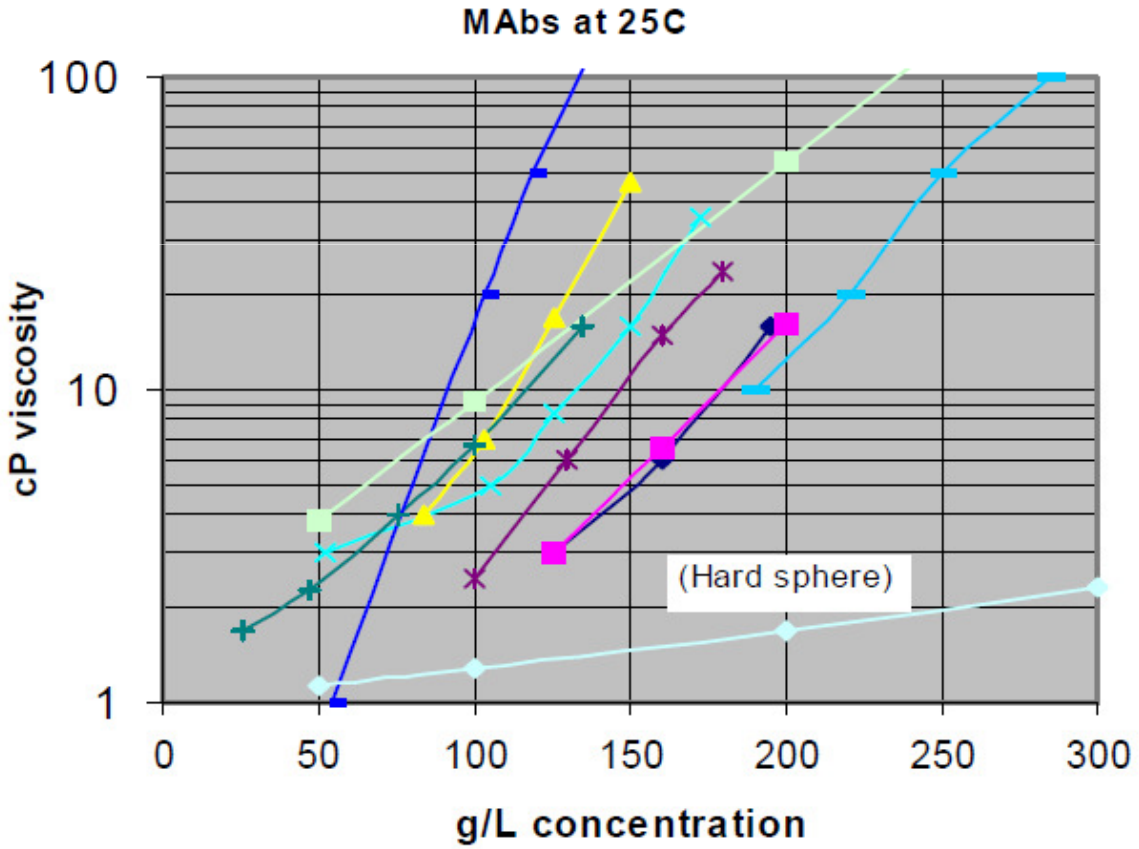
- Viscosity increases non-linearly with concentration




Burckbuchler, V., Europe an Journal of Pharmaceutics 2010

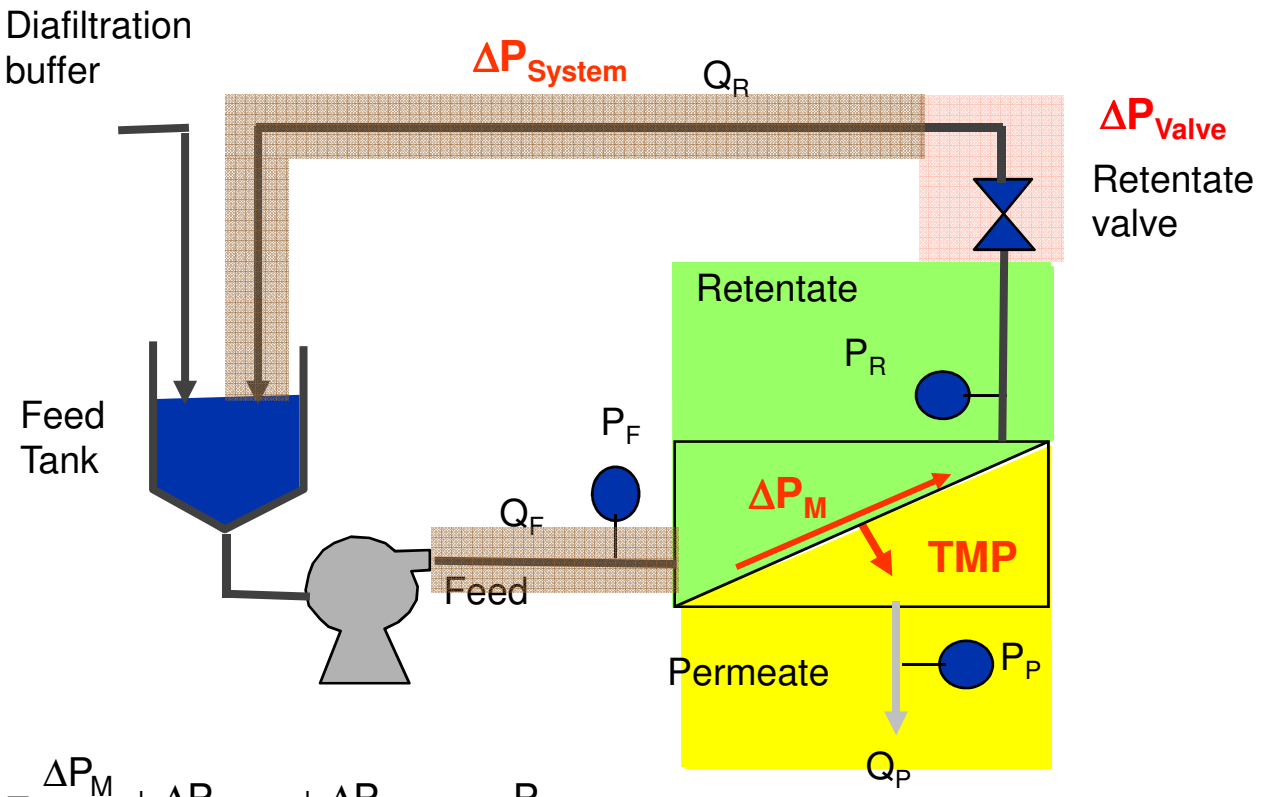
# Viscosity Effects

- Viscosity increases non-linearly with concentration
  - Varies widely with mAb type for a given concentration



# Viscosity Effects – TFF Processing

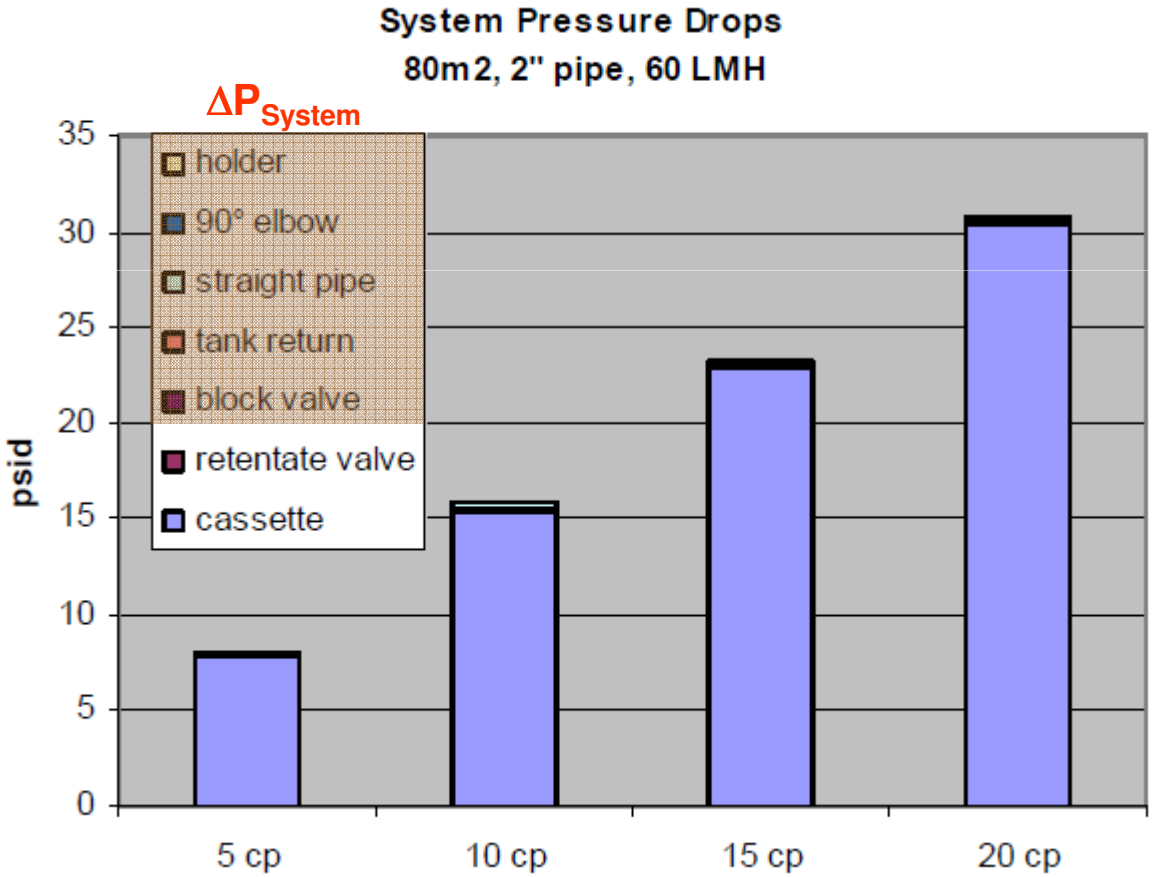
- Pressure drop in a TFF system




$$TMP = \frac{\Delta P_M}{2} + \Delta P_{Valve} + \Delta P_{System} - P_P$$

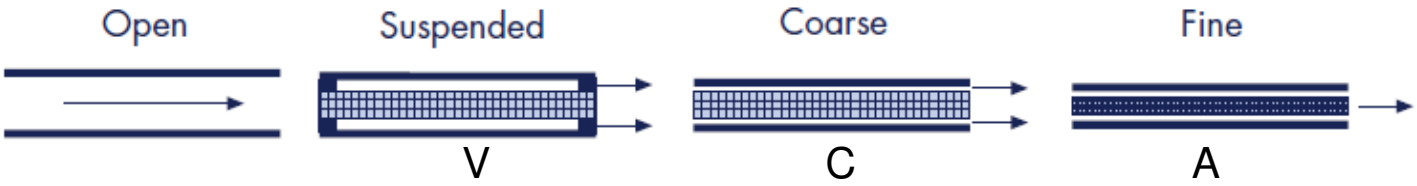
# Viscosity Effects – TFF Processing

- Pressure drop in a TFF system ↑ as viscosity ↑
  - Cassette resistance dominates for a given flow geometry



# Viscosity Effects – TFF Processing

- For a given flow, viscosity, cassette resistance determined by geometry:
  - Channel size, screen type




**A** screen “fine” - High pressure drop
**C** screen “coarse” - Medium pressure drop
**V** screen “suspended” - Very Low pressure drop

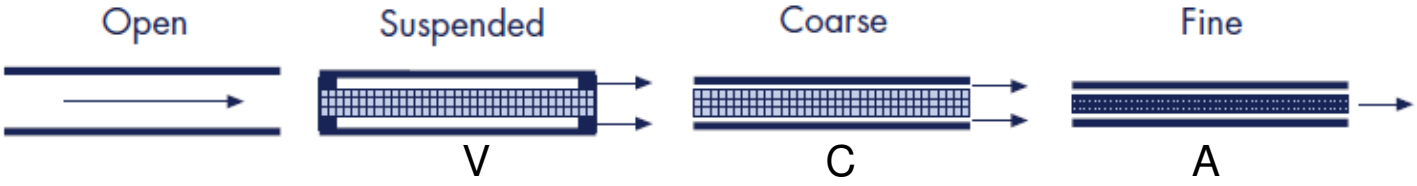
Screen variables
  - Weave pattern, wire diameter, mesh count, mesh opening, overmolding, orientation, etc.

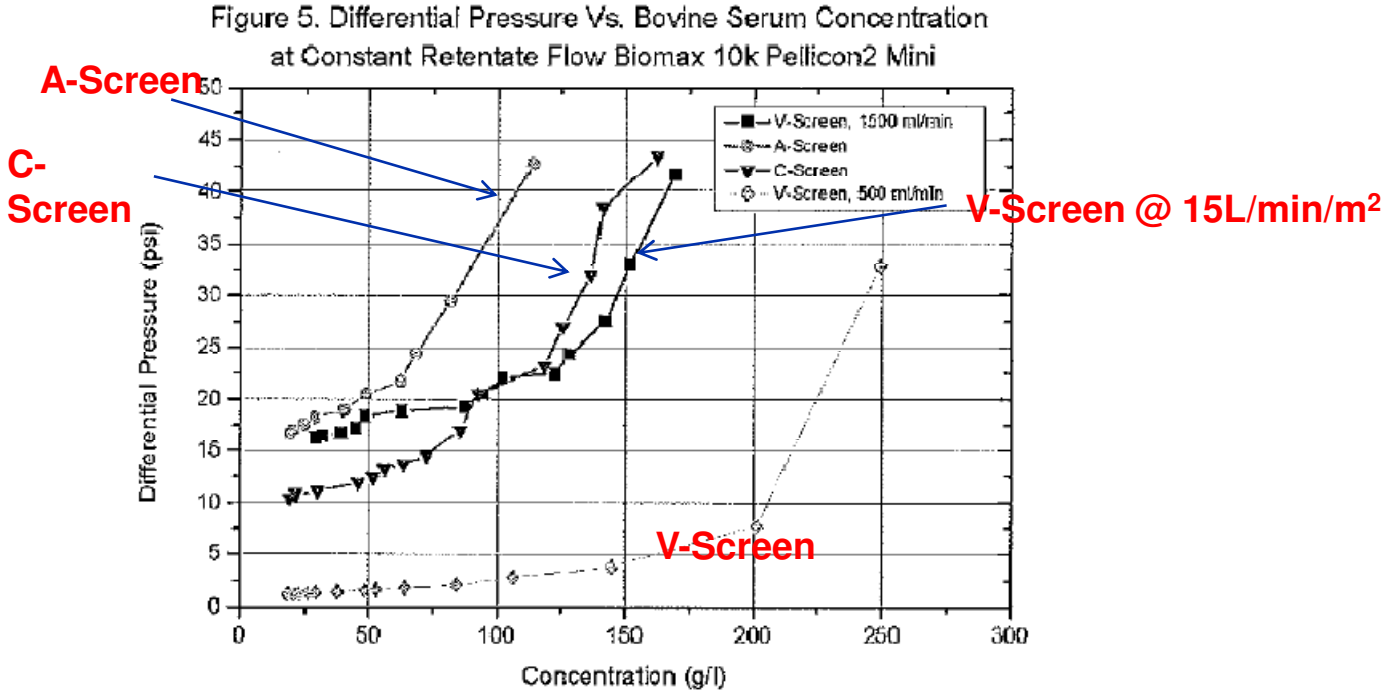


DaCosta, A., JMS 1994

# Viscosity Effects – TFF Processing

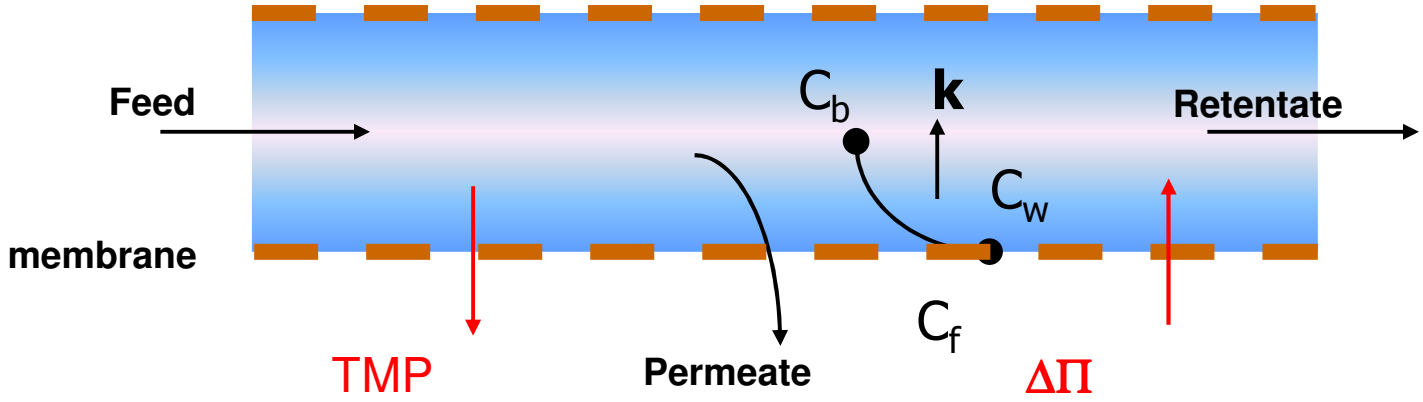
- For a given flow, viscosity, cassette resistance determined by geometry:
  - Channel size, screen type



# Osmotic Pressure Effects – TFF Processing

- Osmotic pressure resulting from concentration difference between membrane wall (Cw) and permeate (Cf≈0)




$$J = L_p(TMP - \Delta\Pi) \ldots\ldots \text{Osmotic Pressure Model}$$

- Applied TMP must be > osmotic pressure to force permeate flow
  - Modules and equipment limit maximum TMP

# How do high viscosity & osmotic pressure affect TFF processing?

- Permeate flux through a TFF membrane:
  - Is determined by excess TMP over osmotic pressure

$$J = L_p(TMP - \Delta\Pi)$$

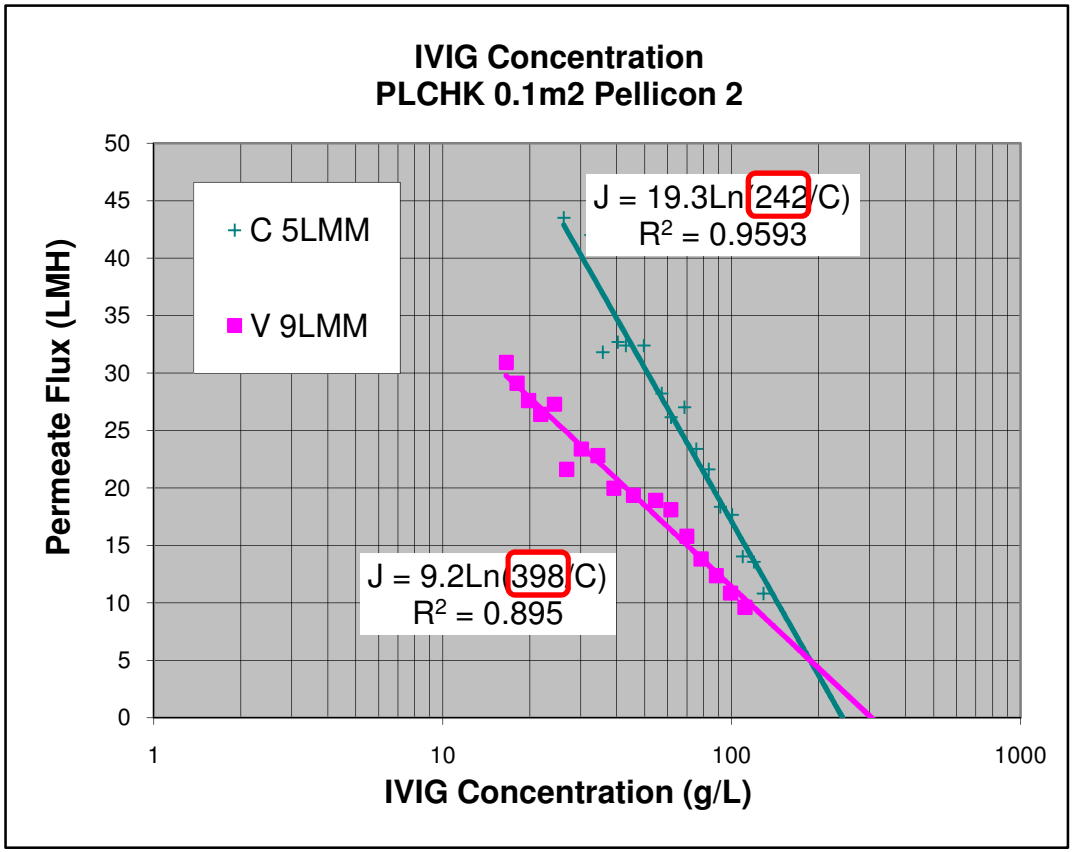
  - Depends on mass transfer coeff (flow, geom) and solute conc.

$$J = k\ln\left(\frac{C_{gel}}{C_{bulk}}\right)$$

# Example – Permeate flux vs Concentration for Tight and Open screens

- We notice that V-screen $C_{gel}$ (Open) > C-Screen $C_{gel}$ (Tight).

**398 g/L** **242 g/L**



# Inference

- High final concentrations achievable at lower feed flows and more open feed channel!
  - **Develop** a more optimum feed channel for high conc (high viscosity) apps
    - Existing C-Screen too tight, V-Screen possibly too open → optimum probably in-between
- Trade-off: lower permeate flux, larger membrane area

# High Viscosity Screen/Cassette Development

- Product need:
  - What is the right screen size?  What viscosity do we target?

# Viscosity Target – Estimation

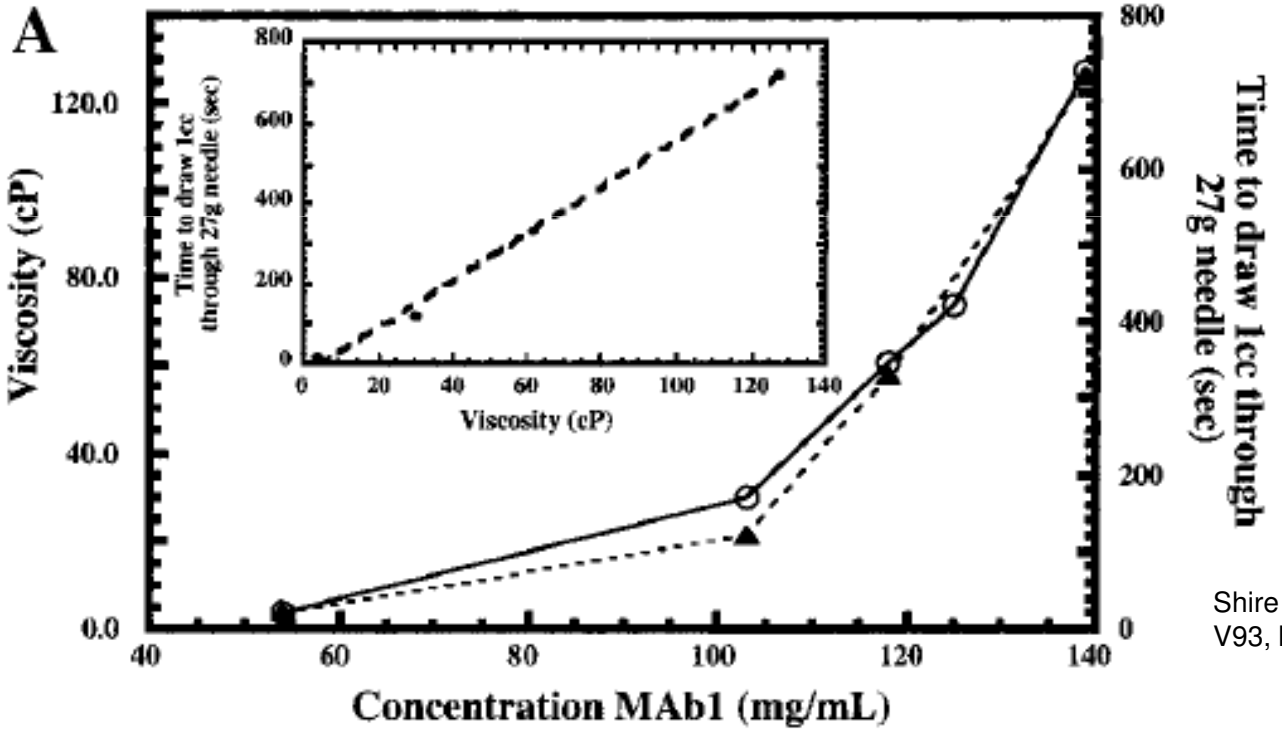
- High viscosity impacts the ability to load and deliver drug from the syringe

$$F = \frac{8Q\eta L}{R_{needle}^4} A_{syringe}$$

  - At a given force, flow (Q) is proportional to
    - fourth power of needle radius
    - Inversely to viscosity
  - If needle is too narrow
    - Require High force or Slow flow
    - Unreasonable time for patient to hold PFS during injection
      - >20 sec

# Viscosity Target – Estimation

- High viscosity impacts the ability to load and deliver drug from the syringe




Shire et al, J. of Pharm Sci, V93, NO. 6, JUNE 2004

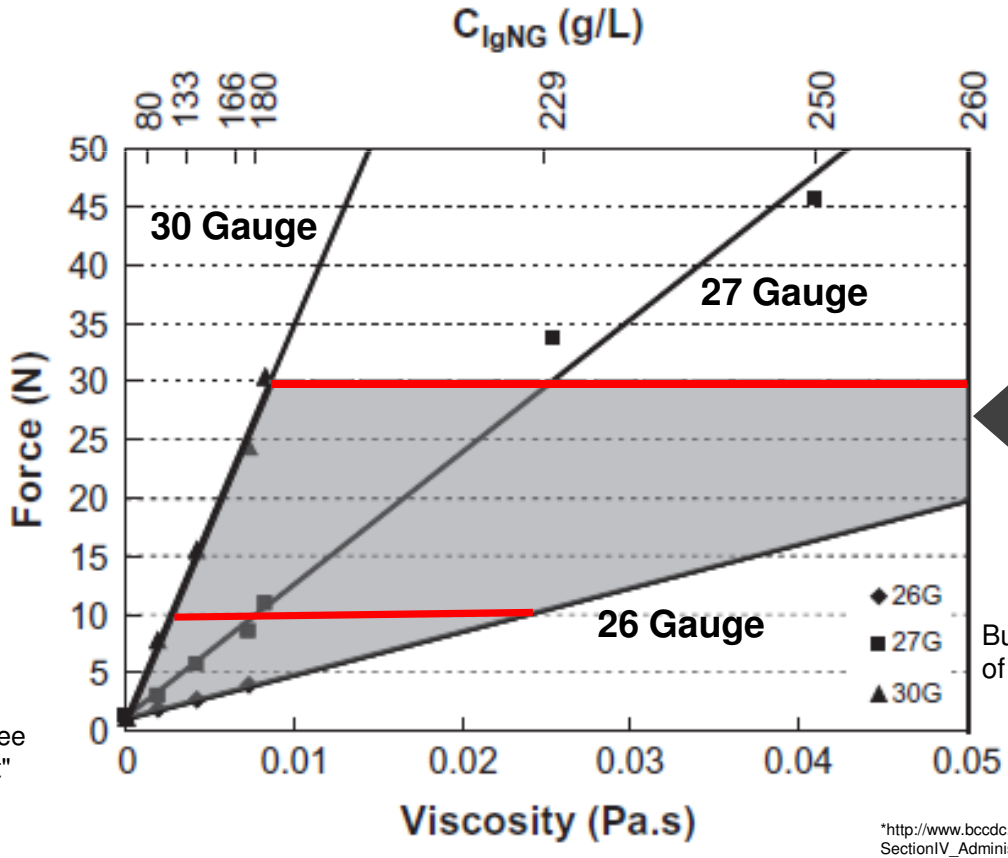
Fig A: Viscosity (solid line, open circles) and syringe (27 gauge) loading time (dashed line, solid triangles) of a monoclonal antibody as a function of concentration.

# Viscosity Target – Estimation

- High viscosity impacts the ability to load and deliver drug from the syringe
  - Manual injection force limited to 10-30 N
  - Typical sub-Q needle size range between 25-27 gauge*

| Needle Gauge | ID (mm) |
|---|---|
| 21 | 0.495 |
| 22 | 0.394 |
| 23 | 0.318 |
| 24 | 0.292 |
| 25 | 0.241 |
| 26 | 0.241 |
| 27 | 0.191 |
| 28 | 0.165 |
| 29 | 0.165 |
| 30 | 0.140 |
| 31 | 0.114 |
| 32 | 0.089 |
| 33 | 0.089 |

"http://en.wikipedia.org/wiki/Needle_gauge_comparison_chart"



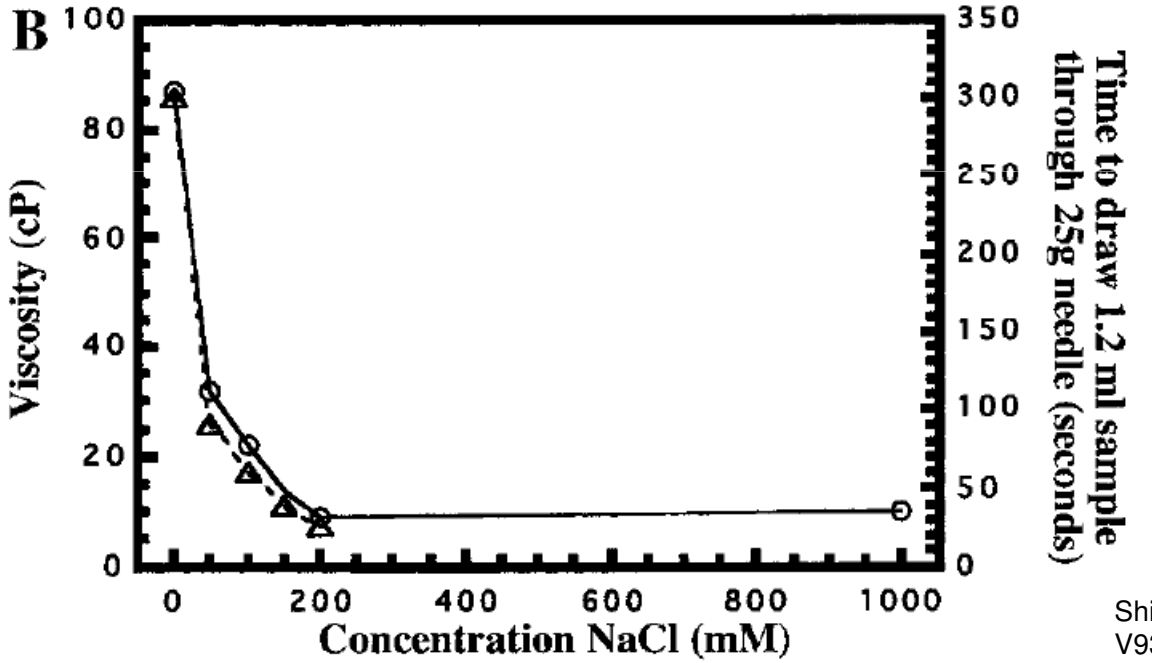

SC delivery limited by
- Viscosity ~30cp
- Needle Size
- Injection Flowrate

Burckbuchler, V., European Journal of Pharmaceutics 2010

*http://www.bccdc.ca/NR/rdonlyres/24C36473-261A-4FBD-8A41-444B3520DB64/0/SectionIV_AdministrationofBiologicalProducts_June2012_.pdf

# Other Viscosity Reduction Techniques

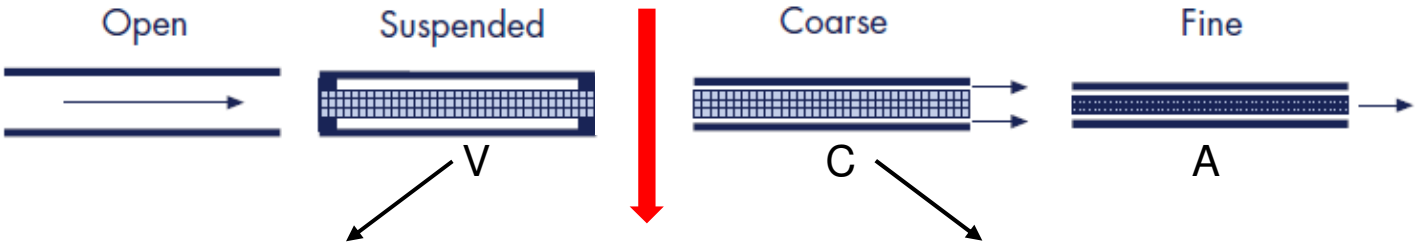
- Viscosity may be reduced by appropriate excipients
  - Ex. Addition of salt may reduce viscosity




Shire et al, J. of Pharm Sci, V93, NO. 6, JUNE 2004

**Fig: Viscosity (solid line, open circles) and syringe (25 gauge) loading time of a monoclonal antibody at 125 mg/mL as a function of NaCl concentration.**

# High Viscosity (Protein Conc) TFF Cassette




**Too Open for HC Apps**

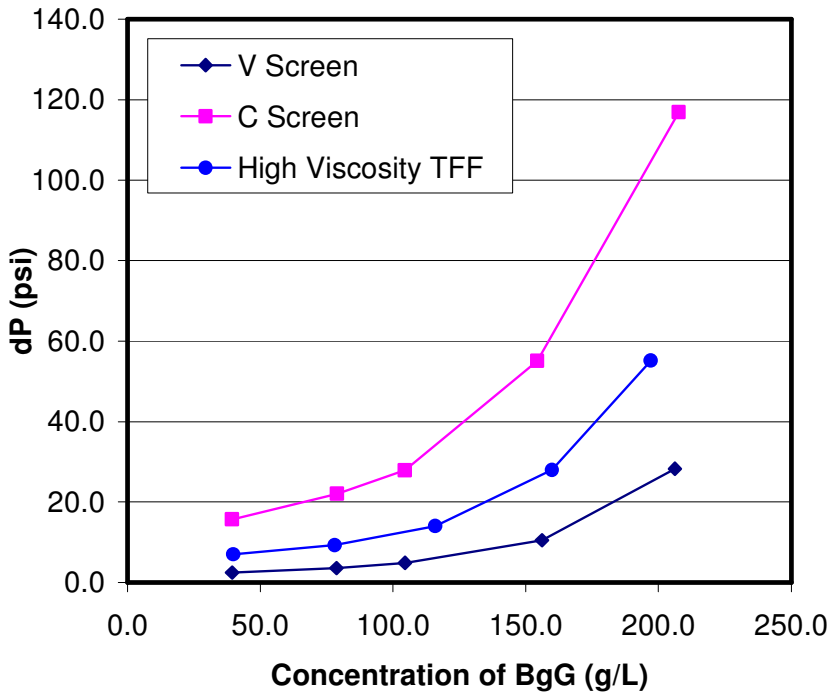
**Develop the 'Just Right' Size**

**Too tight for HC Apps**

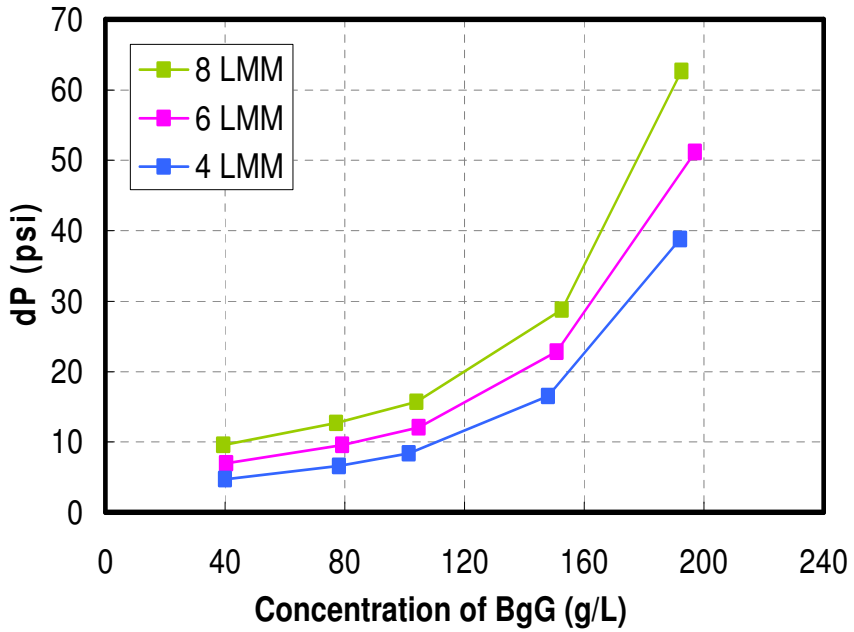
# The HV TFF Cassette – "Preview"

## Pressure drop vs Concentration & Xflow:

At 8 L/min/m$^2$ cross flow rate




HV TFF Cassette –Cross Flow Effects

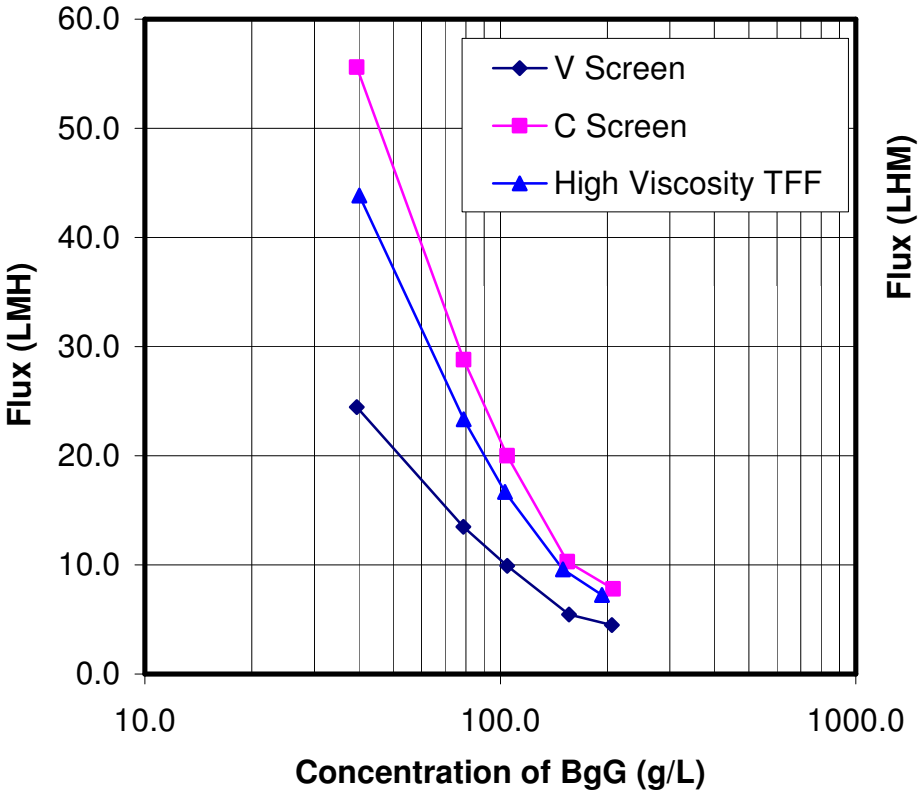



HV Cassette screen ('D' Screen) $\Delta P$ ~ 50% of C screen $\Delta P$ $\Delta P = K\mu J_F$

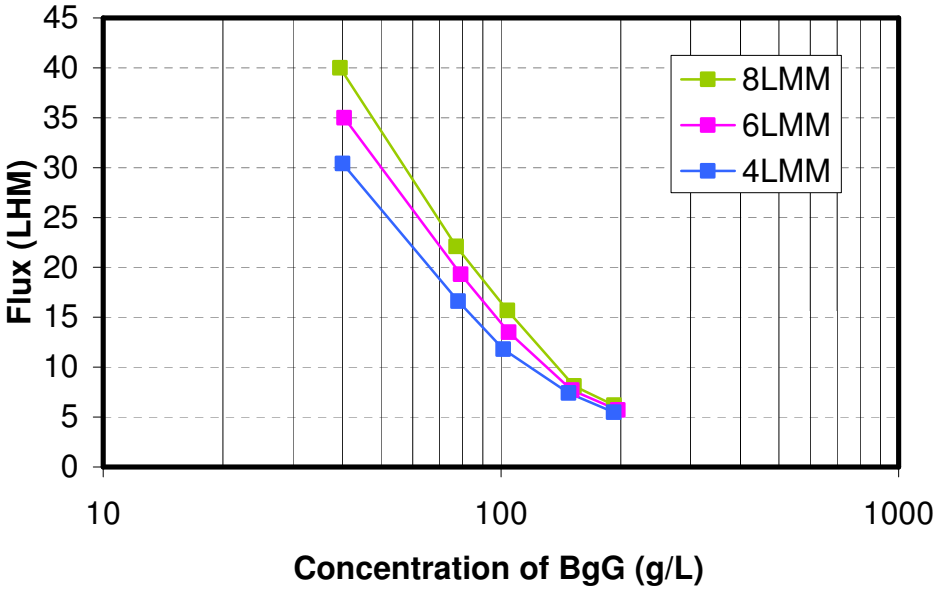
# The HV TFF Cassette – "Preview"

## Flux vs. Concentration & Xflow:

At 8 L/min/m$^2$ cross flow rate




HV TFF Cassette –Cross Flow Effects




HV Cassette (D) screen J~ 80% of C screen J

## Slide 26

**M6** do you think talking about D-screen is OK and people may ask about the launch time
M176127, 20-09-2013

# HV Cassette – Performance Summary

| Product Attribute | Performance Outcome |
|---|---|
| Final viscosity | > 25 cP |
| Feed channel ΔP-water | 2-6 psi |
| Feed channel ΔP-mAb | 50% of C screen<br>at ≥ 25 cP |
| Mass transfer k* | ≥ 150% of V-screen<br>≥ 80% of C-screen |
| Membrane Area | ≈ 0.5 X of V-Screen$^{\perp}$<br>≈ 1.2 X of C-Screen$^{\perp}$ |

•Mass transfer coefficient is compared at the same cross flow rate.
$^{\perp}$At 8 L/min/m$^2$ cross flow rate

- Enables the TFF process to optimally get to high protein concentrations required for Subcutaneous drug delivery

# Thank You!


## Acknowledgements

Herb Lutz

Joseph Parrella

Bala Raghunath