Crossflow Technology & Practical Applications

Presented by

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at

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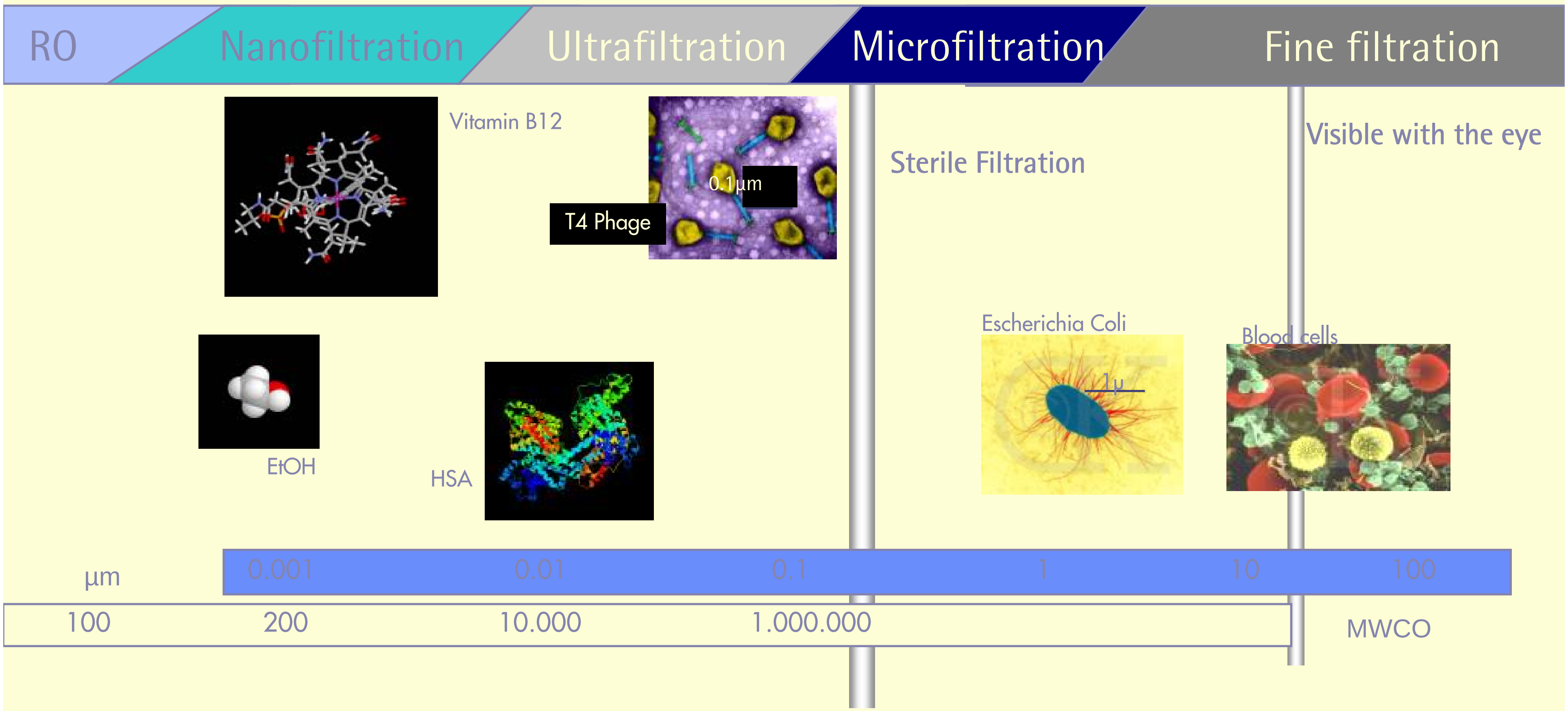
Filtration Range



Terms

- **Microfiltration (MF)**

  Pressure-driven, membrane-based separation process in which particles and dissolved macromolecules >0.1& <10 µm are retained.

- **Molecular-Weight Cutoff (MWCO)**

  The nominal measure of an ultrafiltration membrane based on a defined solute retention coefficient.

- **Nanofiltration (NF)**

  A pressure-driven membrane-based separation process in which particles and dissolved molecules smaller than 2 nm are retained.

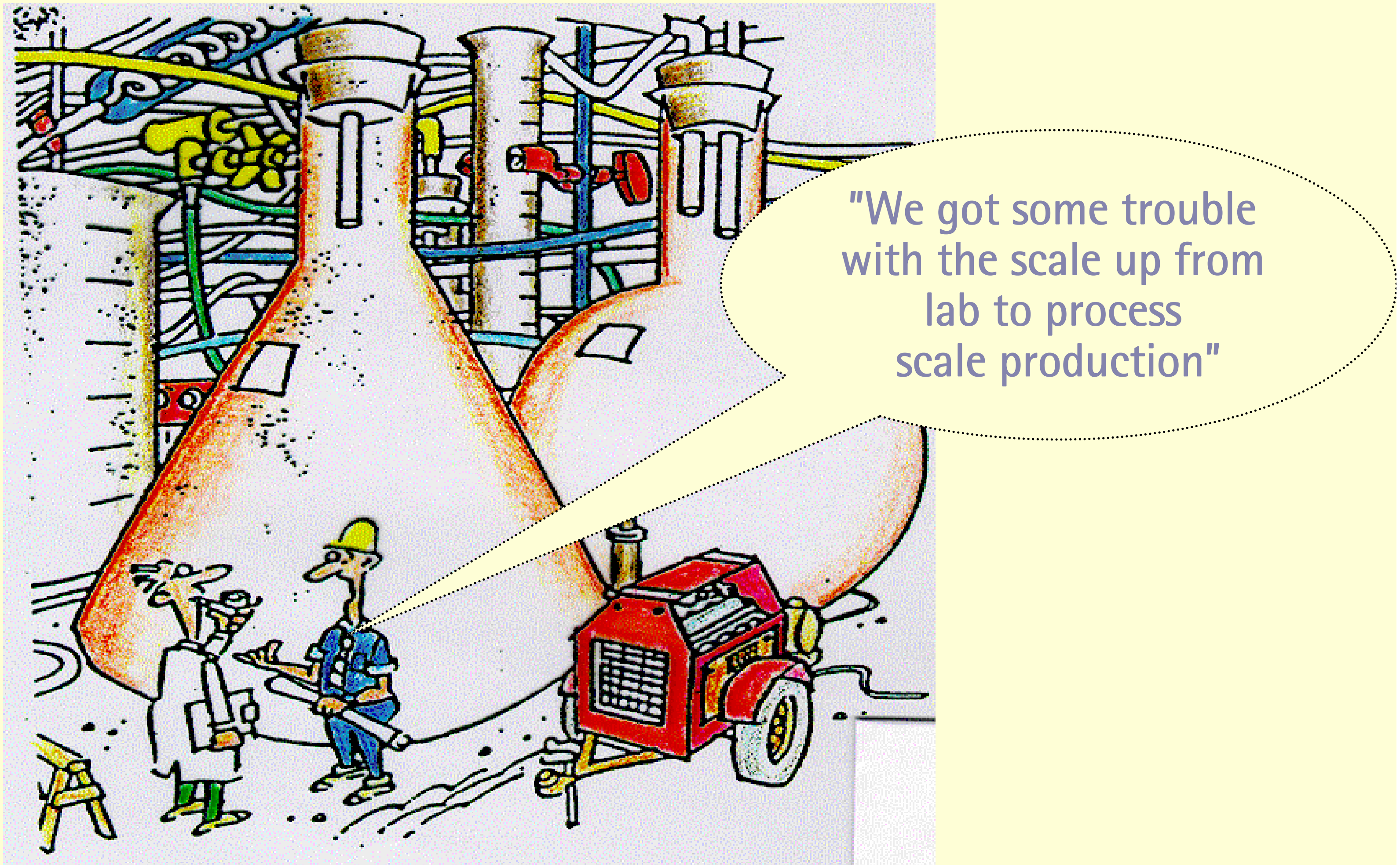
- **Reverse Osmosis (RO)**

  A membrane-based filtration process where the membrane rejects salt from solution. Pore size is not entirely meaningful for reverse-osmosis membranes, as pores are often not observable by microscopic methods. Reverse osmosis is used to desalinate water.

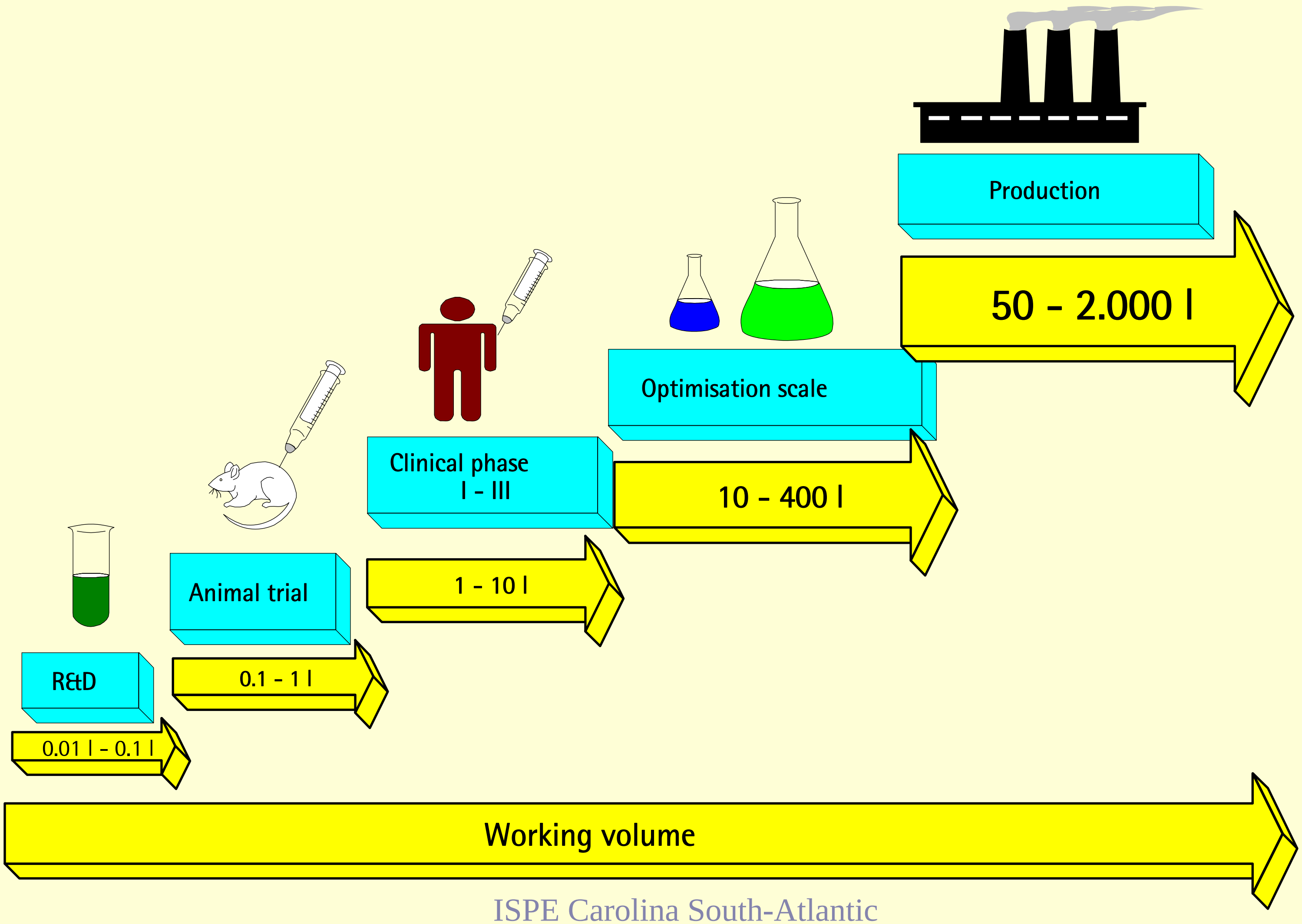
- **Ultrafiltration (UF)**

  Pressure-driven membrane-based separation process in which a semi-permeable membrane is used to retain high molecular weight solutes while low molecular weight solutes are allowed to pass through the membrane.

Scale - Up


"We got some trouble with the scale up from lab to process scale production"

Scale - Up



Production
50 - 2.000 l
Optimisation scale
10 - 400 l
Clinical phase
I - III
1 - 10 l
Animal trial
0.1 - 1 l
R&D
0.01 l - 0.1 l
Working volume

Scale - Up

Example for Scale-up calculation :

<u>Small Scale trial result:</u>
is 5,2 litre per Cassette (0.1m²) per hour

↓

<u>Factor to Full Size Cassette:</u>
5,2 x 5 = 26 litre per Cassette per hour

↓

<u>Factor to m^2:</u>
5,2 x 7,1 = 3,692 litre per m^2 per hour

Scale - Up

General requirement :

- Temperature
- Product / Product concentration
- Transmembrane Pressure (TMP)
- Crossflow velocity
- 3 Trials for verification

Typical LS BioProcess Train

Application of the Technology

Concentration

Diafiltration

Fractionation

Application of UF

Concentration

Concentration using CF/TFF is the process by which the solute concentration is increased by decreasing the solution volume.

$$\frac{C}{C_o} = CF^{(1-S)}$$

Where,

C is the concentration of the solute at the given instance,

Co is the concentration of the solute initially and

S is the observed sieving factor or ratio of the filtrate concentration to the feed concentration of the target species.

- **Concentrate**
  The concentrated feed solution after removal of filtered liquid through the membrane and into the filtrate. [Synonym: retentate solution]
- **Concentration Factor**
  The ratio of the concentration of a component "i" in the retentate to the concentration of the same component in the feed.
- **Concentration Polarization**
  A phenomenon that describes the rate of solute of particle transport in the bulk solution adjacent to the membrane.

Application of UF

Diafiltration (Continuous and Discontinuous)

Buffer exchange

The convective elimination of permeable solutes by the addition of fresh solvent to the retentate

$$\frac{C}{C_o} = e^{-NS}$$

Where,

C is the concentration of the solute at the given instance,

Co is the concentration of the solute initially

N is the number of diavolumes (defined as the ratio of the volume of the total diafiltration buffer added to that of the retentate in the system)

Diavolume (DV)

Applications of UF

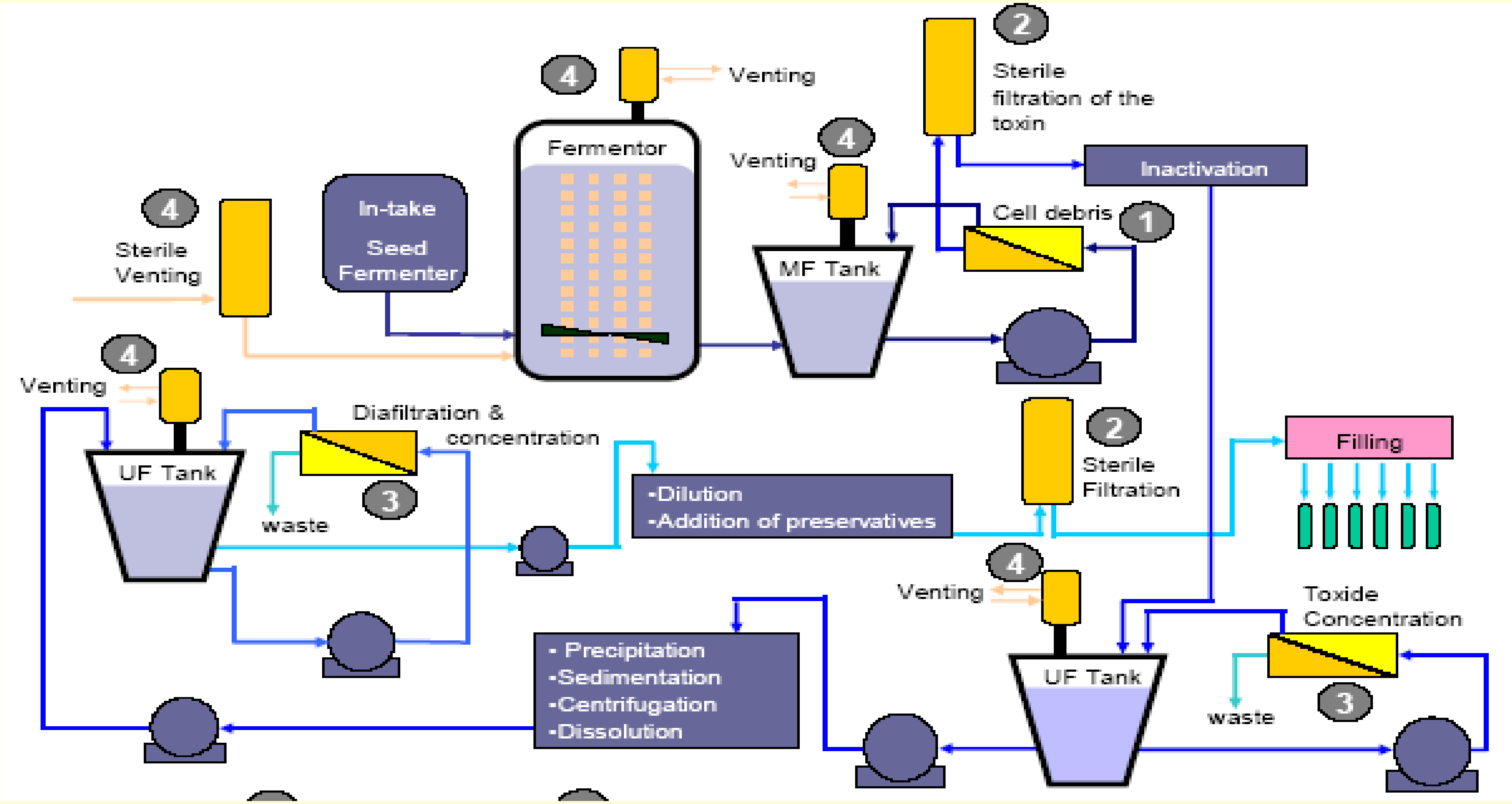
Fractionation

Separating the target protein from contaminating proteins, protein fractions, protein aggregates, and pyrogens from solutions.

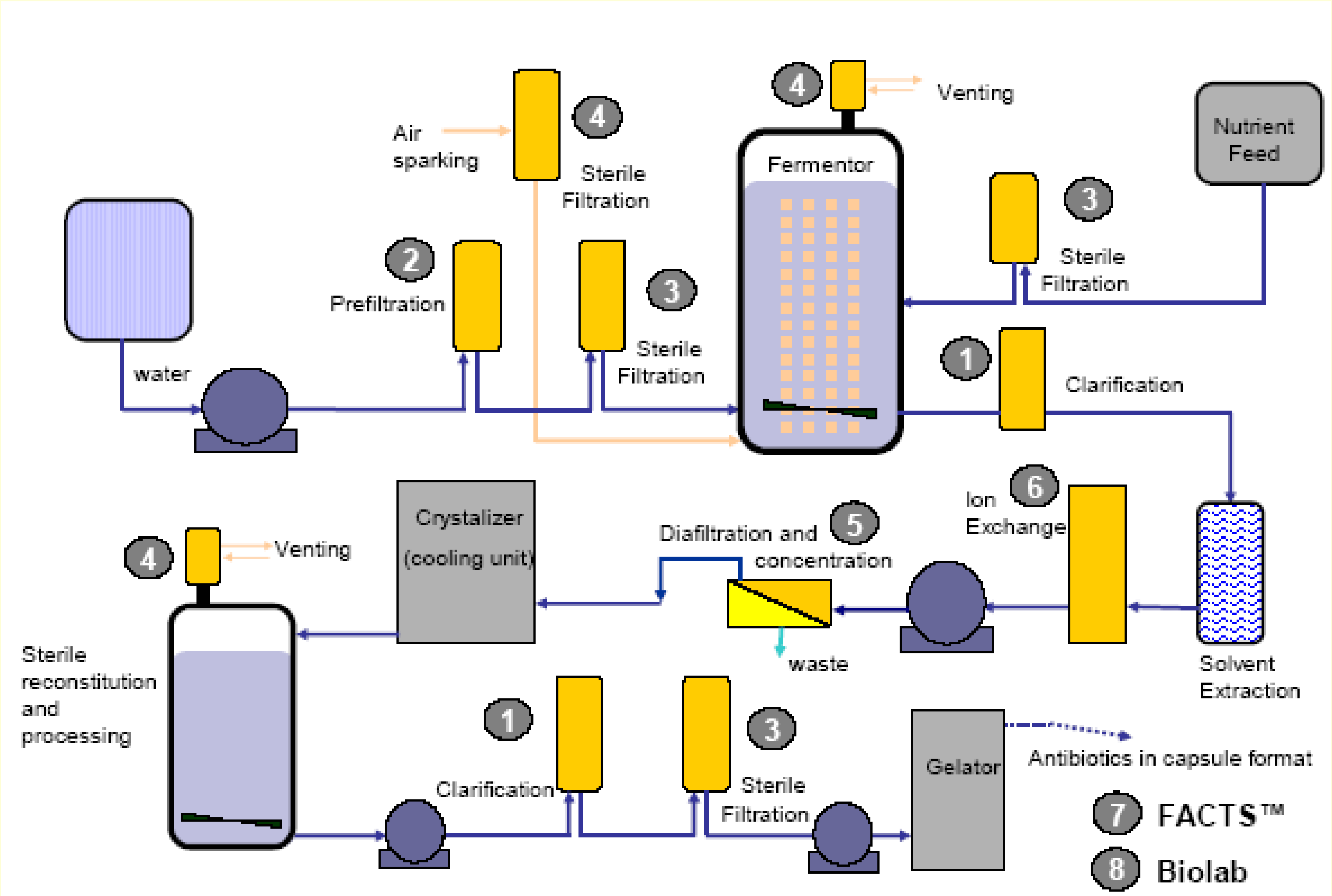
Practical Applications

- Vaccine: Large Scale Processing
  - Cell Debris Separation / Removal
  - Diafiltration & Concentration
- Plasma Process: IgG Concentration
- Cell Culture Process: cell sep / removal
- Protein Purification

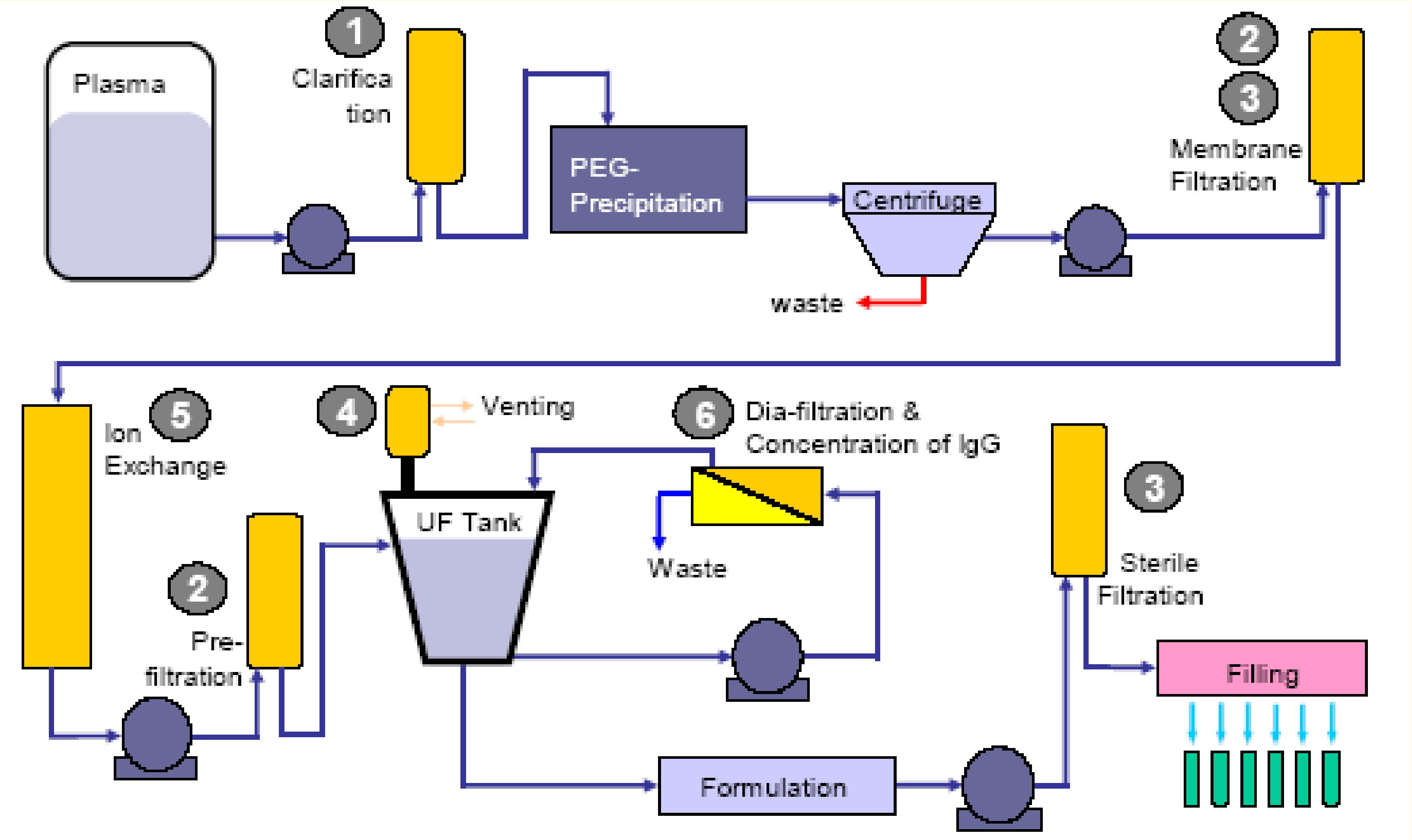
Vaccine Processing



Antibiotics

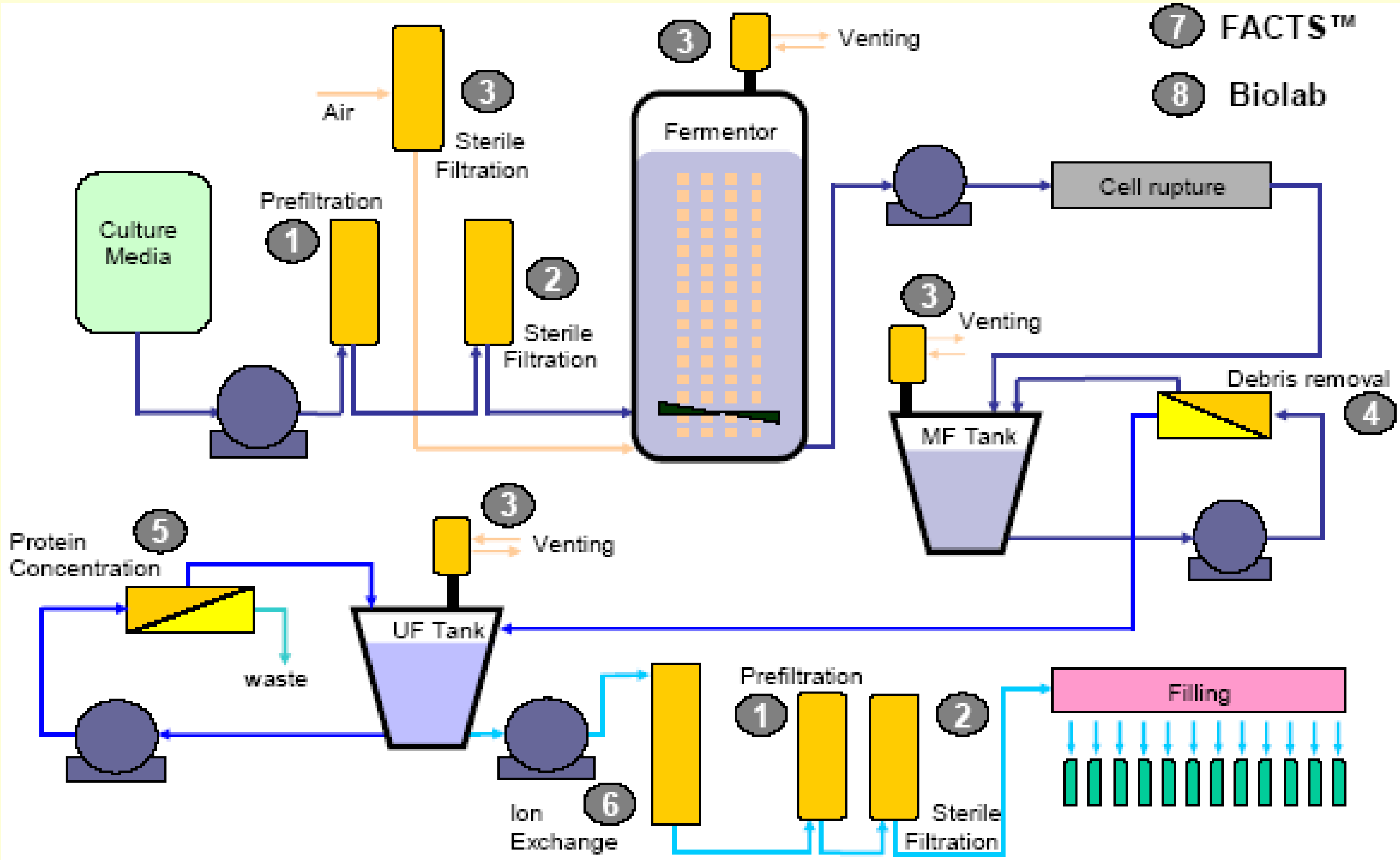


Plasma 1

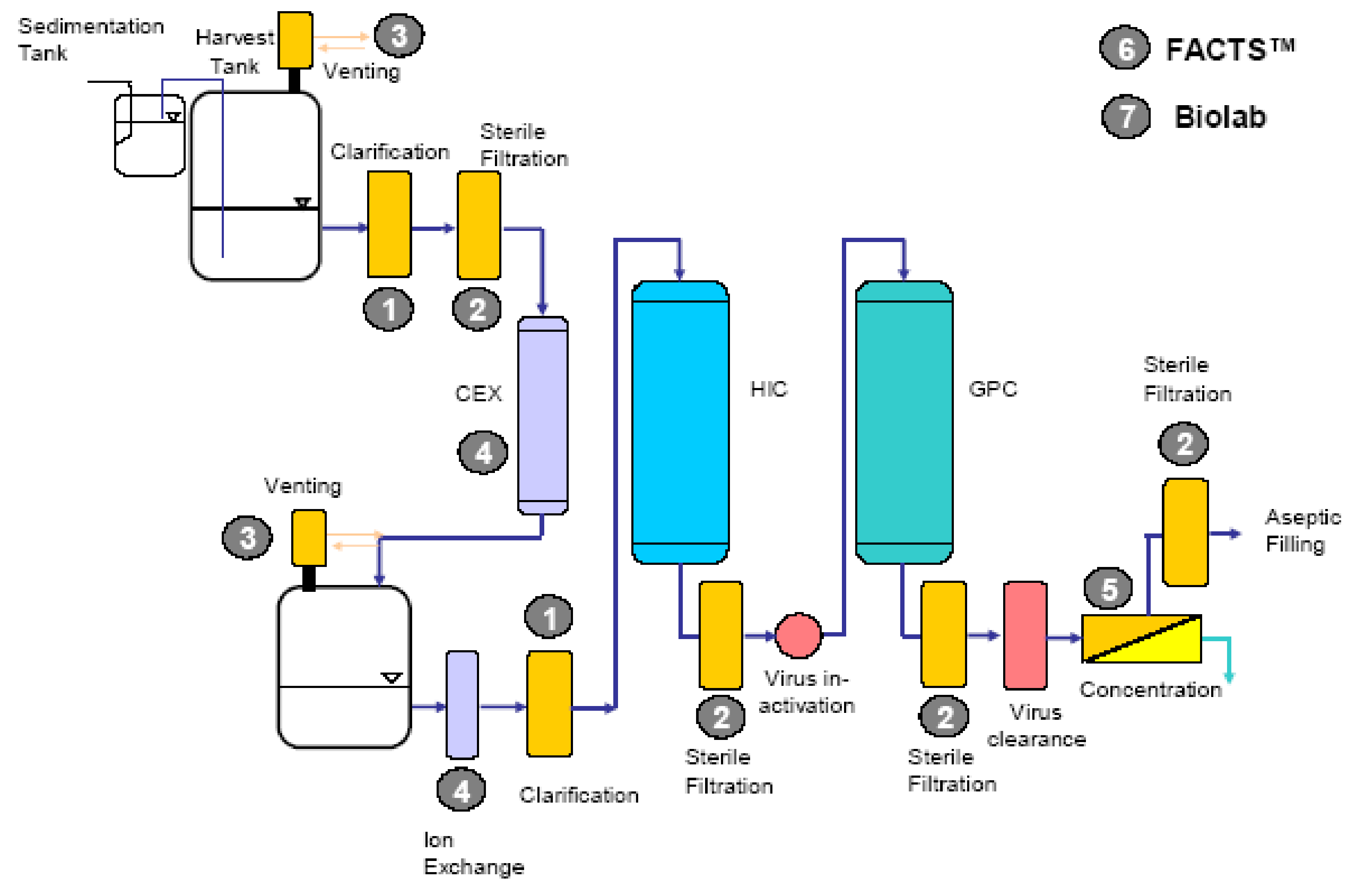


Plasma
1
Clarifica
tion
PEG-
Precipitation
Centrifuge
waste
2
3
Membrane
Filtration
5
Ion
Exchange
4
Venting
6
Dia-filtration &
Concentration of IgG
UF Tank
Waste
2
Pre-
filtration
3
Sterile
Filtration
Filling
Formulation

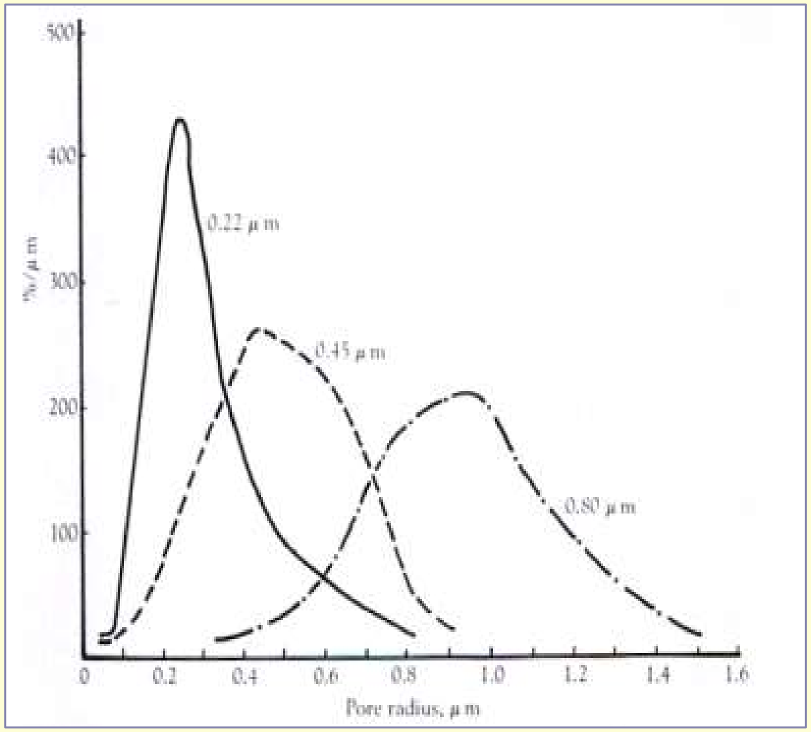
Cell Culture



Purification



Membrane Characterization



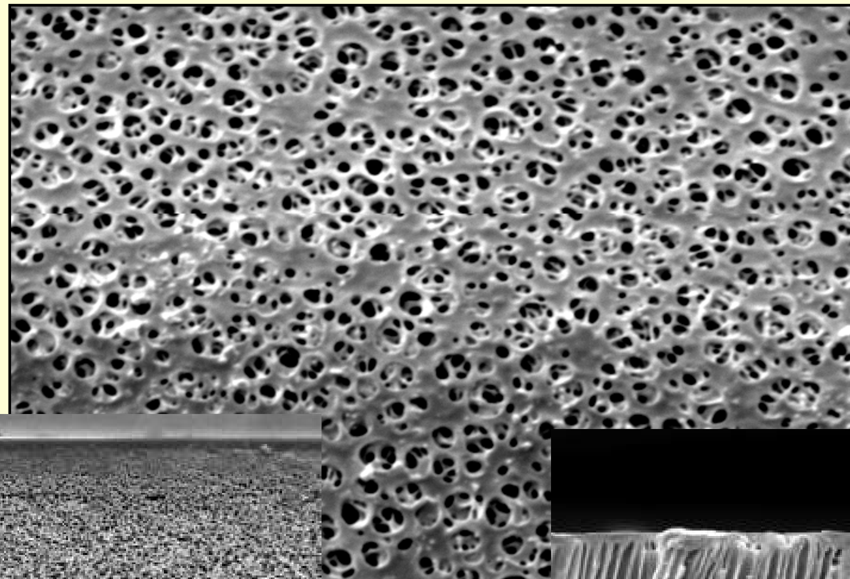
- Sterilizing-Grade Microfilters are characterized by bacterial retention and regulated by FDA:
  - 0.1 µm A. laidlawii
  - 0.2 µm B. diminuta
  - 0.45 µm S. marscesens

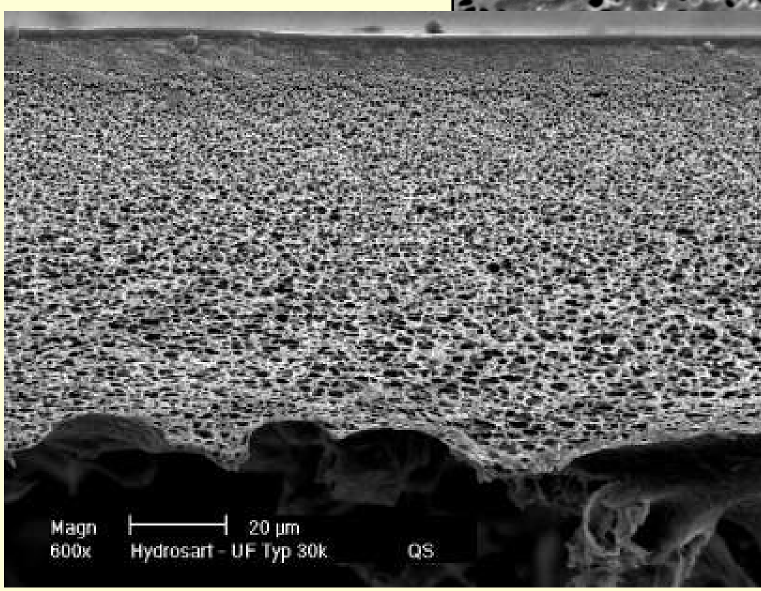
➢**Pore-Size Distribution**
The range of pore sizes in a filter that are used to determine the filter's average pore size.

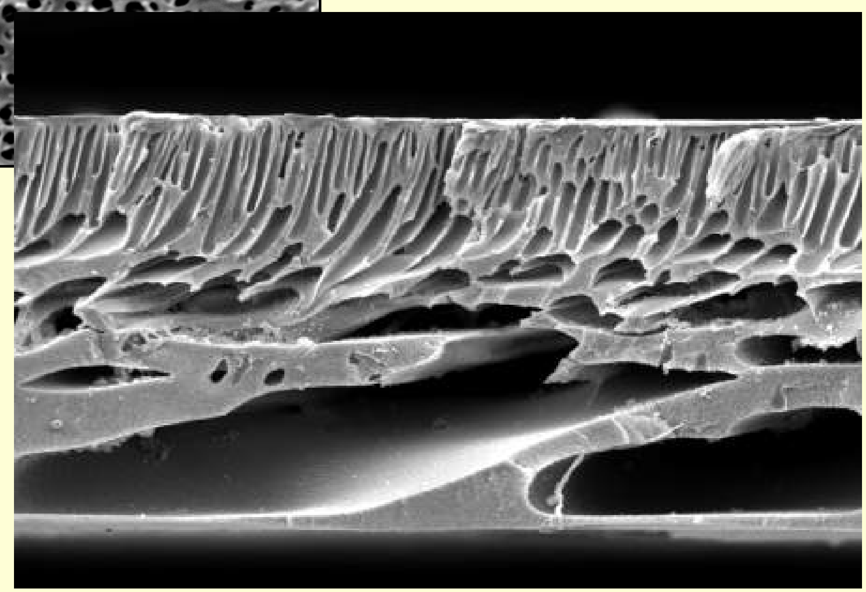
Ultrafilters

- rated by their nominal rejection of molecular weight markers.
  - Range from 1kd to 300 kd
- monitored by recovery of clean water flux

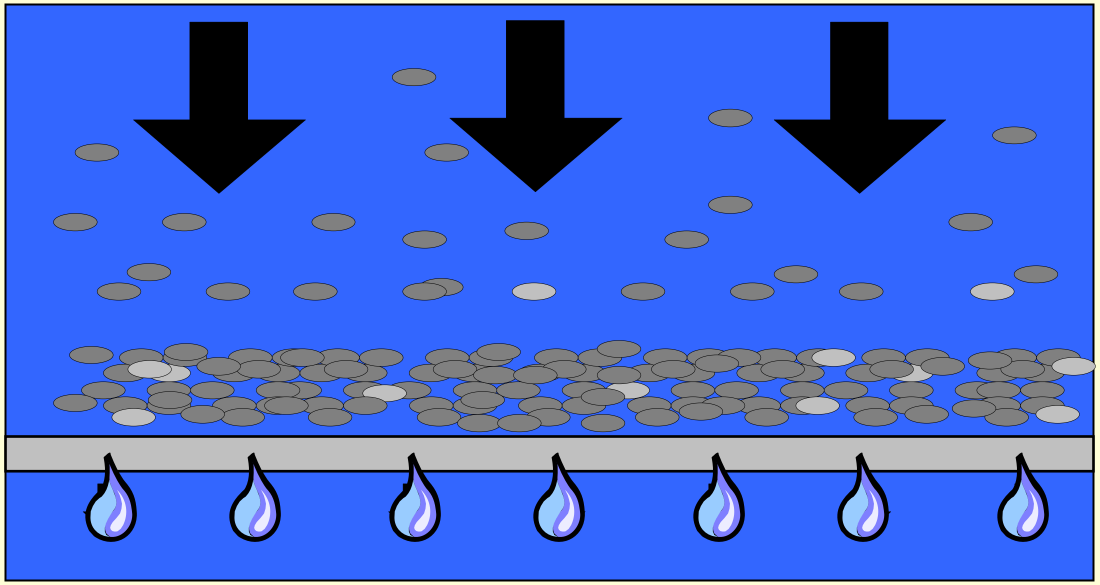
MF & UF Membranes







What are the driving forces



- **Feed**
  The starting solution prior to the filtration process.

- **Filtrate**
  Fluid that passes through a filter or membrane. [Synonym: permeate]

- **Cake**
  Solids deposited on the upstream side of filter media.

Terms

- **Foulant**

  Solute or suspended solid that interacts with the membrane causing a decrease in performance.

- **Fouling**

  Adsorption or interaction with solutes in the feed stream resulting in a decrease in membrane performance. Generally, fouling can be reversed by cleaning the membrane.

Determination of (normalized) Clean Water Flux (CWF)

$$CWF_{25} = \frac{CWF_T \cdot K_T}{A \cdot TMP}$$

CWF_{25}	CFW at 25°C [l/h m² bar]
CWF_T	CFW at X°C [l/h]
K_T	correction factor (see next slide)
A	membrane area [m²]
TMP	transmembrane pressure [bar]
T	temperature [°C]

Temperature Correction of Water Flux

Temperature	Correction coefficient		Temperature	Correction coefficient
[°C]	K_T		[°C]	K_T
6	1.647		30	0.896
8	1.551		32	0.859
10	1.463		34	0.825
12	1.383		36	0.793
14	1.310		38	0.762
16	1.243		40	0.734
18	1.181		42	0.707
20	1.126		44	0.682
22	1.072		46	0.658
24	1.023		48	0.636
25	1.000		50	0.615
26	0.978		52	0.594
28	0.935		54	0.575

Membrane Fouling

- Decreased flux (mL/min/cm^2)
- Altered MWCO (less distinct)
- Varied performance:Potential regulatory issues
- Decreased yield – increased costs
- Larger system required: capital expense
- Reduced performance with successive cleanings: loss of through-put and time

What causes membranes to foul? How does fouling impact membrane Performance?

- Protein-Membrane interactions
- Chemical-Membrane interactions
- High TMP / Temperatures

Proteins in their native state are drawn to the membrane surface by convective flow.

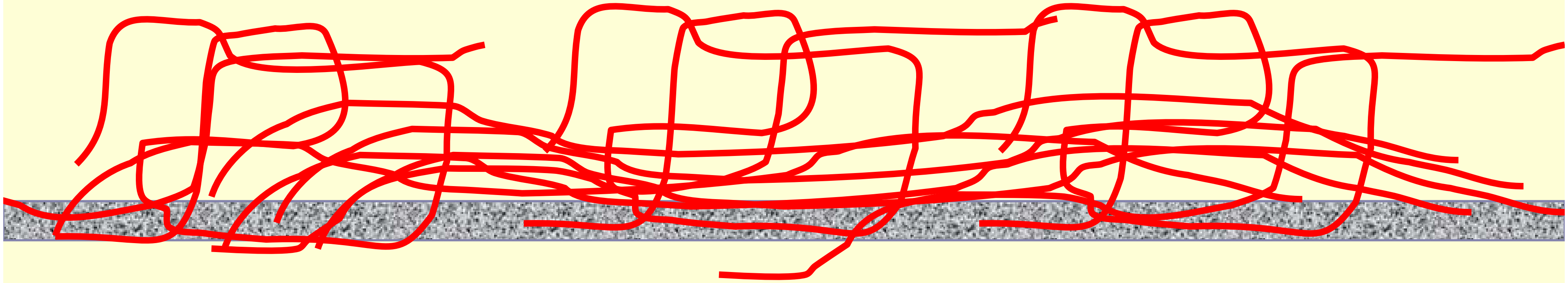
Reassociation (junction zone formation) followed by formation of a Secondary layer

Denaturation complete

begins

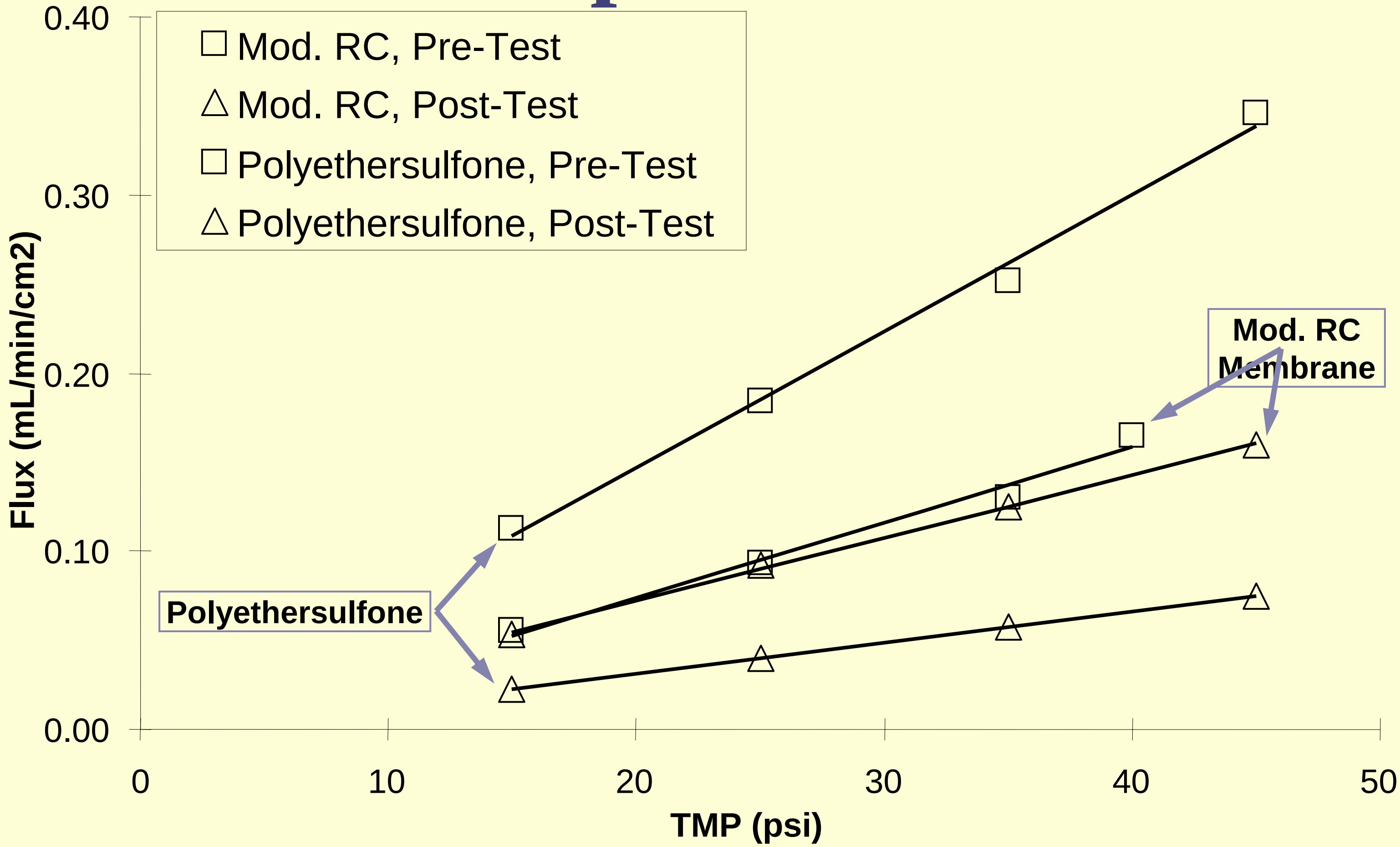
Denaturation begins

Due to possible hydrophobic interactions between the membrane and proteins

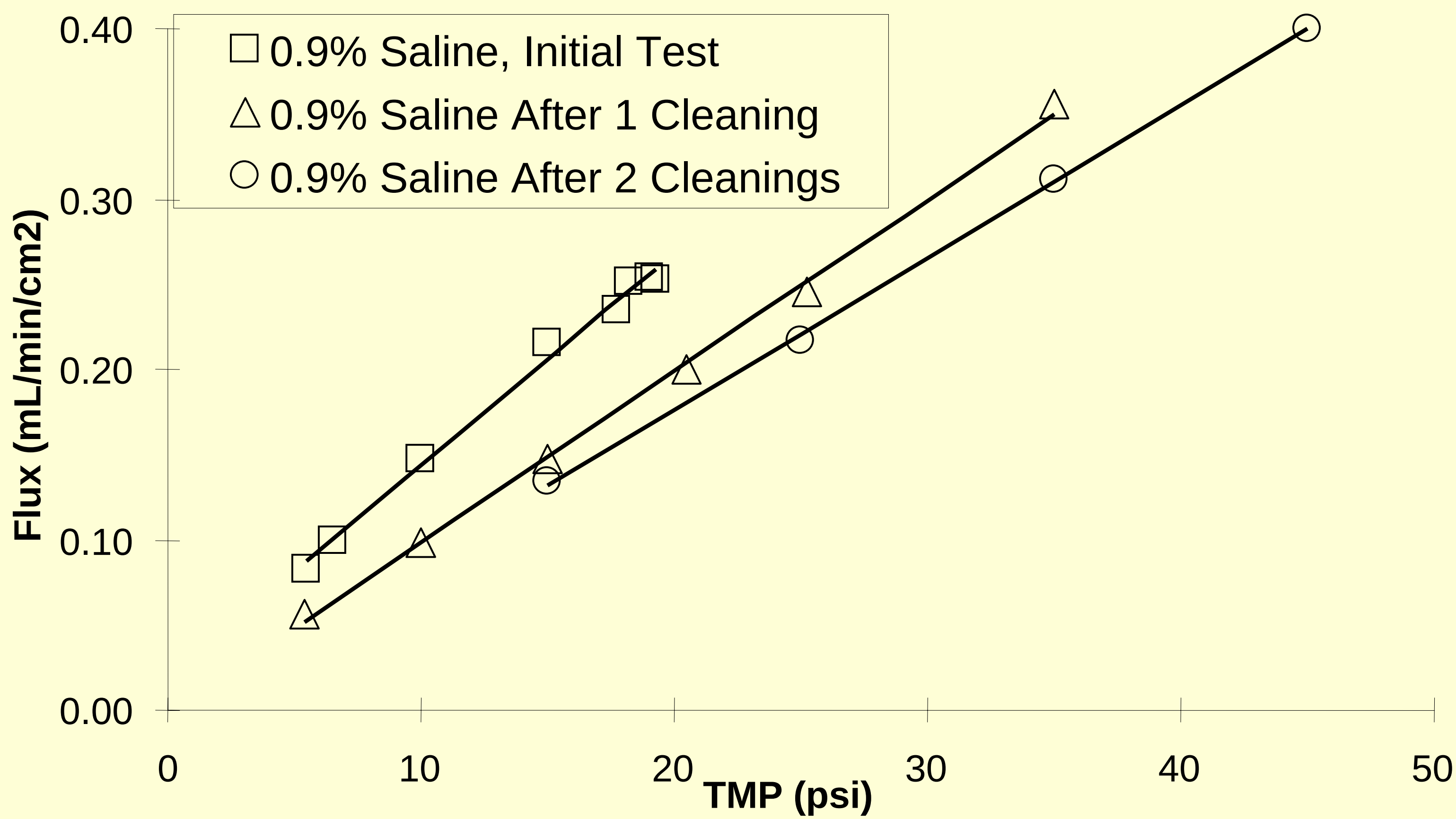


Denaturation continues

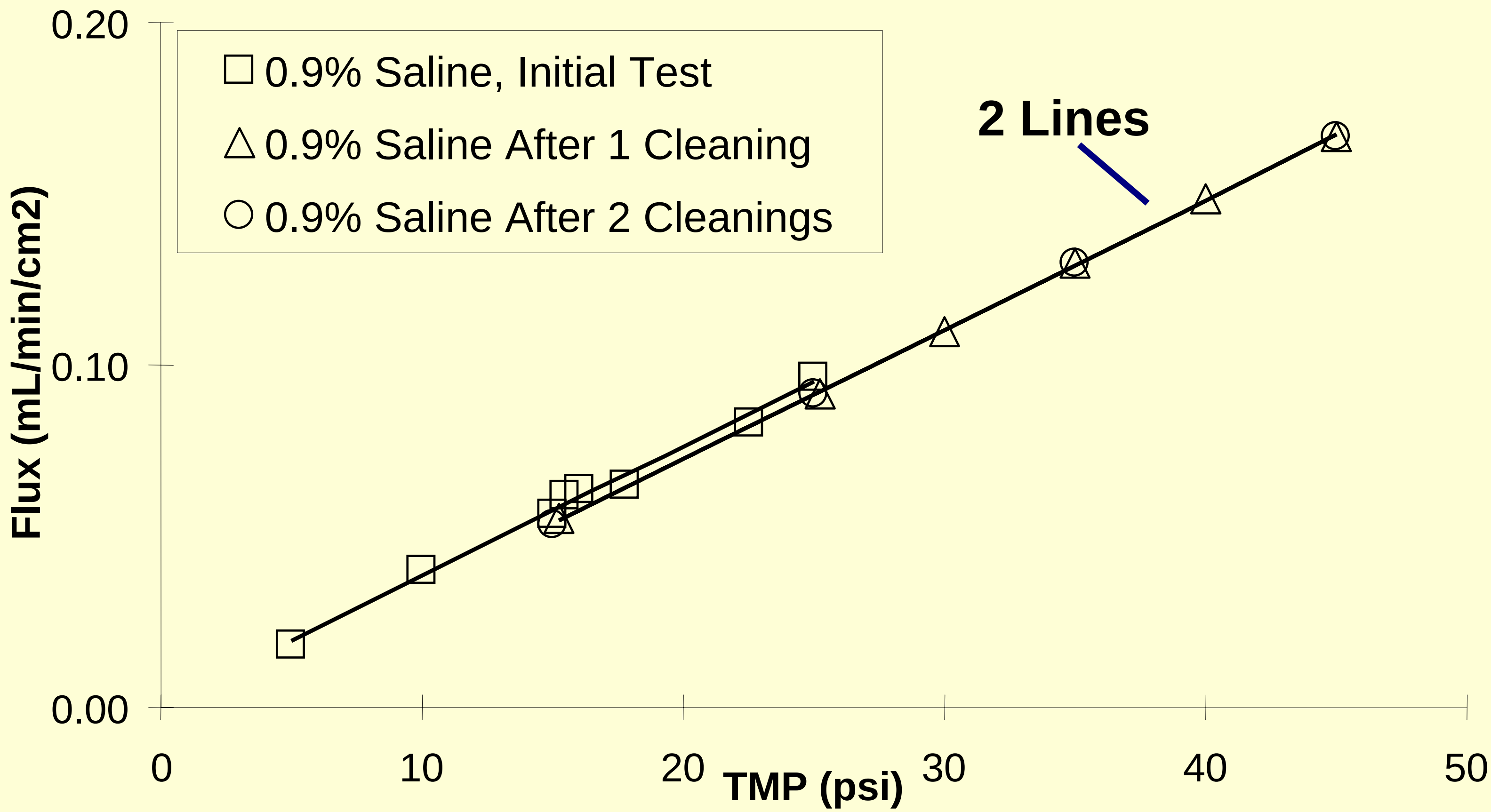
Performance after Protein Exposure



Cleanability of PES



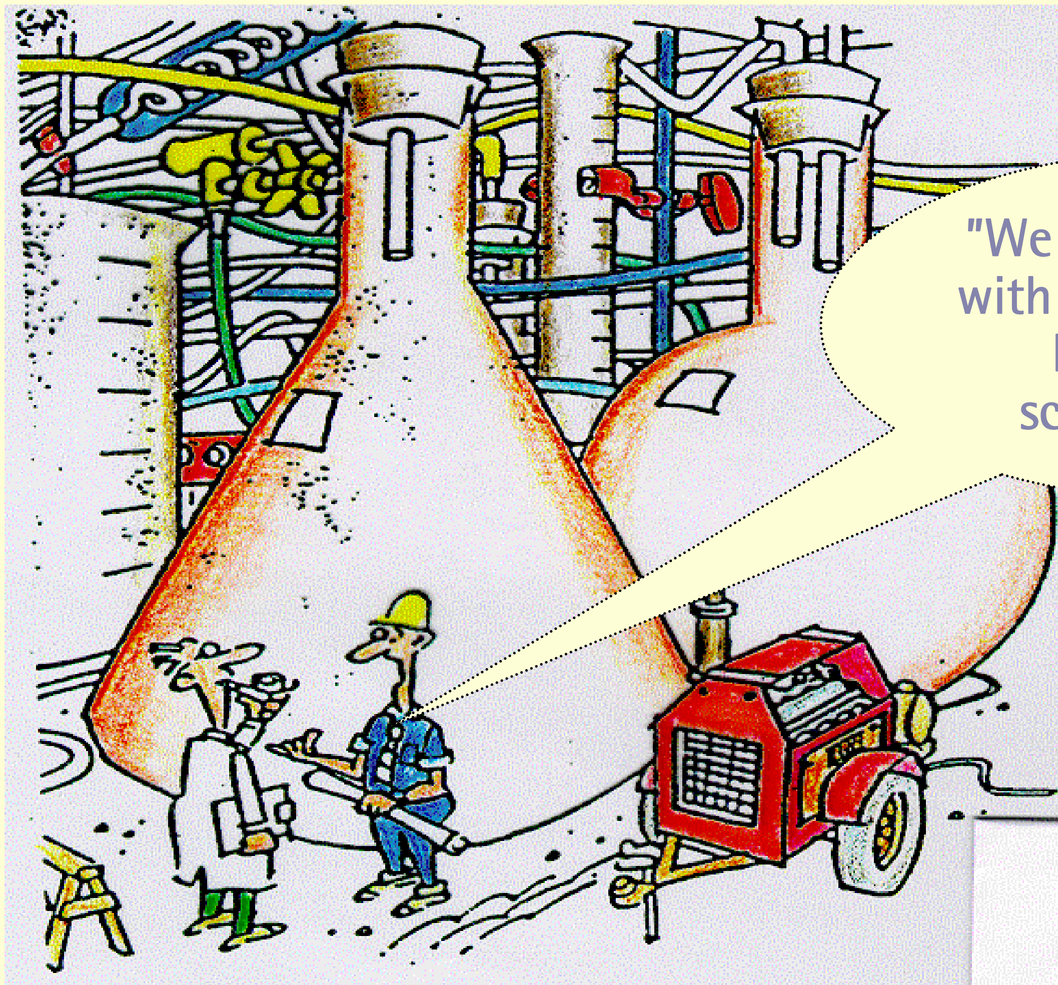
Cleanability of Mod. RC



Modern Application History and the requirement for new polymers

- 1970-80's Vaccines / Polysulfone membranes.
  - Poorly defined solutions
  - Loss of flux
- 1980-90 IgG's and other Biotech products / PES and CTA, RC.
  - Higher value products
  - Better defined process streams
- 1990's to now Oligio's and protein products / mod PES, RC, modified RC
  - High value products – higher yields
  - Well-defined process streams
  - Improved Norm. Water Flux performance

Scale - Up



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