QbD for Tangential Flow Filtration

Tathagata Ray
Manager
Biomanufacturing Sciences Network

Agenda

1. QbD Concept
2. Review of TFF
3. Key Application of TFF in common vaccines
4. QbD workflow

Quality is a key regulatory concern

Suitability of either a drug substance or product for its intended use (ICH Q6A)

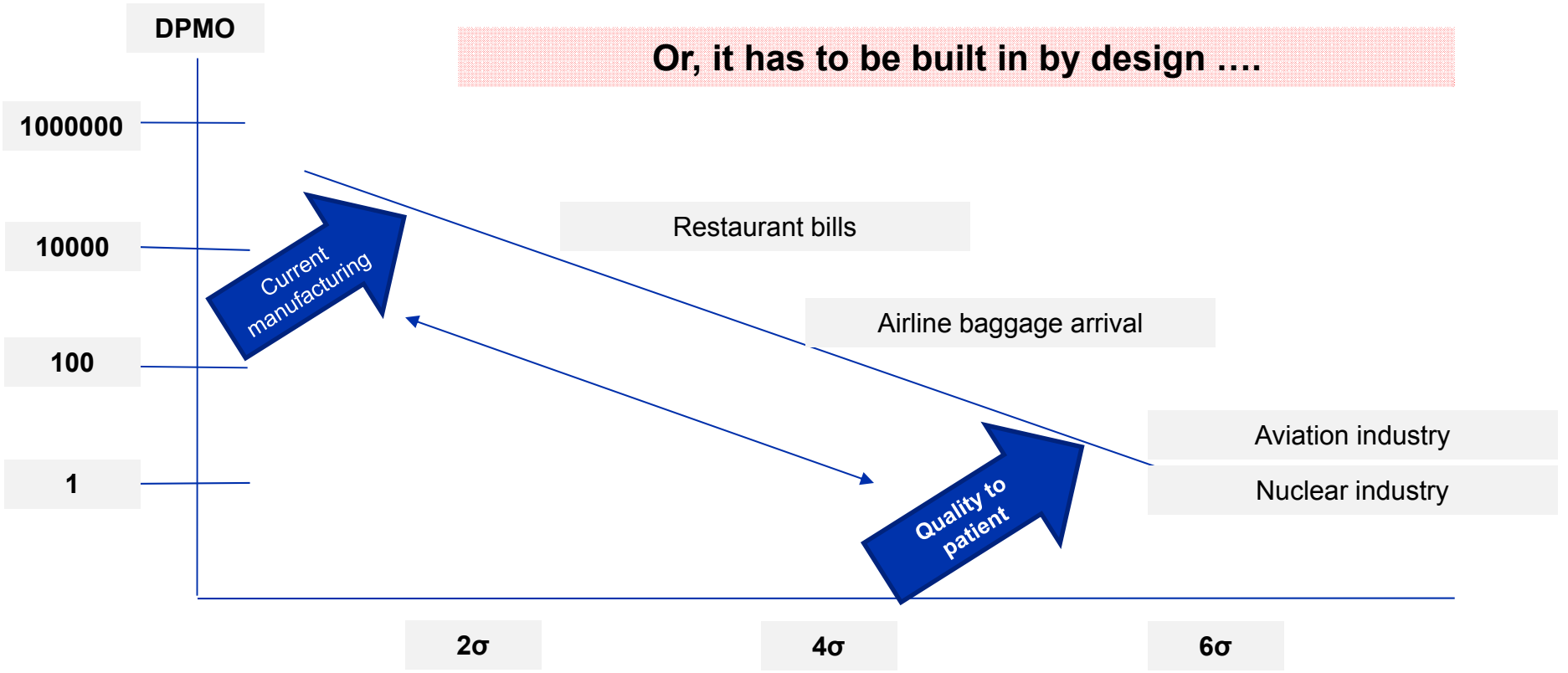
Efficacy/Strength	Does the production process result in product/residues that interfere with final product strength or efficacy?
Identity & Purity	Does the production process result in product/residues that interfere with final product purity?
Safety	Does the production process result in product/residues that are toxic to the patient?

Quality in Biopharmaceuticals:

Where we stand …….. Where we intend to …….

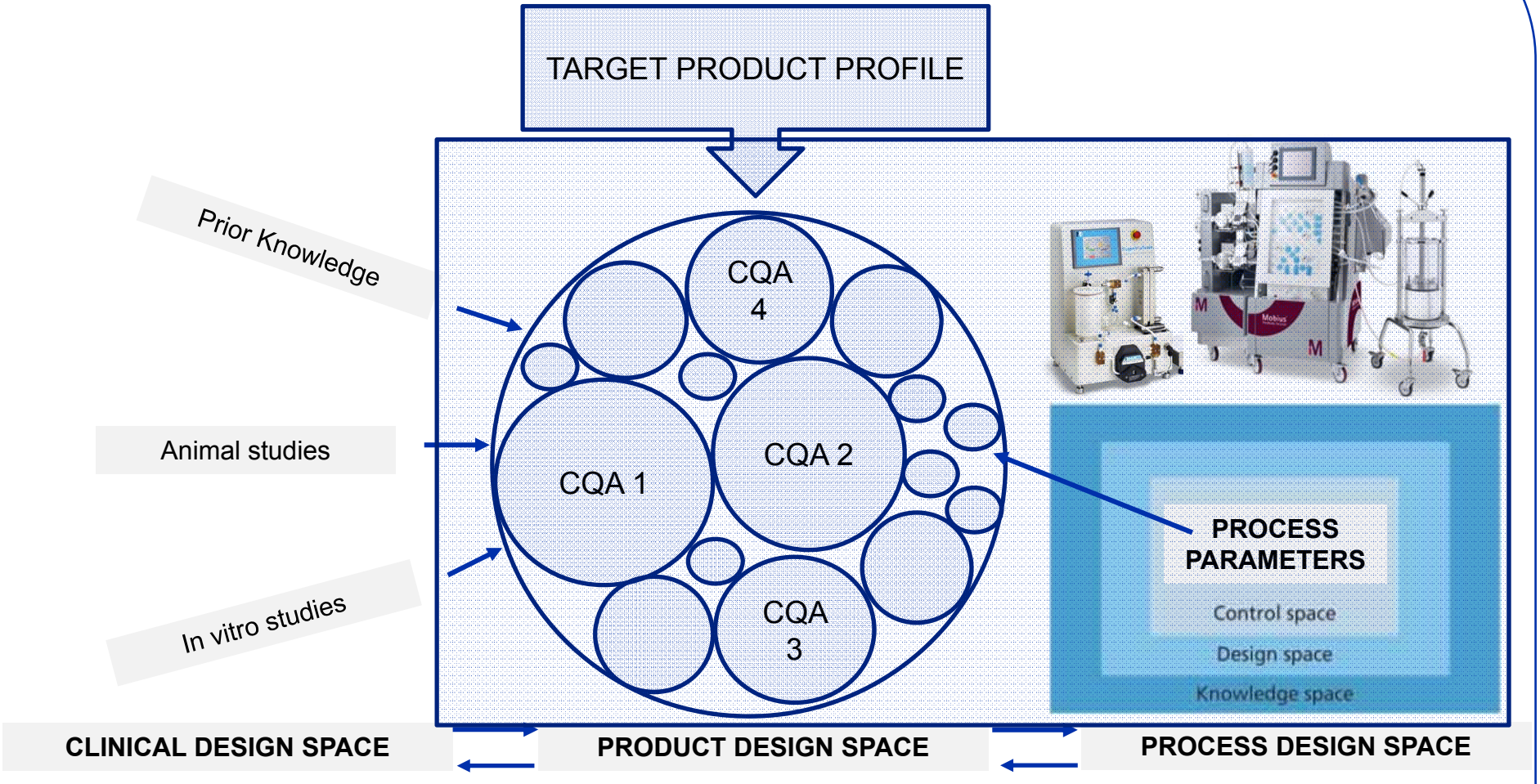
How do we bridge this quality gap ? ……. By testing !!!

Or, it has to be built in by design ….



DPMO – Defects per million opportunities

QbD …. Overall approach



CONCEPT > DESIGN > PRE-CLINICAL > CLINICAL > MASS PRODUCTION

QbD: From process ….. To step ……

Design formulation

Design Process

Quality target product profile

Identify CQAs

CQA$_{int1}$

CQA$_{int2}$

Material attributes and Process parameters

Identify and control sources of variability

Monitor and update

Process Step Characterization based on risk assessment / control

ie – TFF

Basic UF Applications & Schematic

Clarification

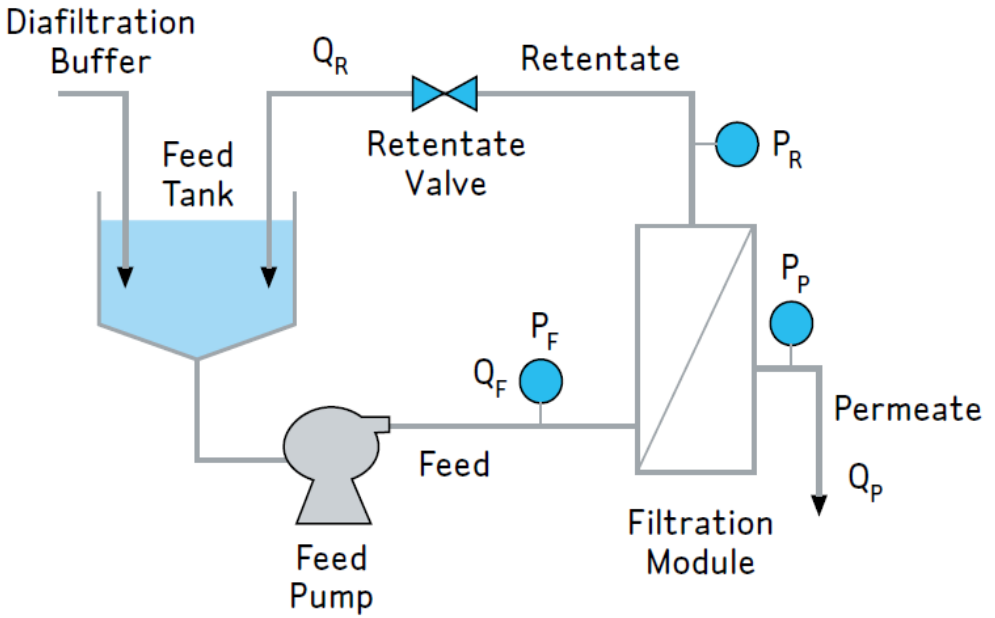
- Product passes through the membrane
- Larger particles / molecules retained by membrane

Concentration

- Product retained by the membrane
- Solvent (buffer) passes through the membrane

Diafiltration (Buffer Exchange or contaminant removal)

- Product retained by the membrane
- Solvent (buffer) passes through the membrane, new solvent added to product
- Contaminant removal



Pressures and Flows in UF Membranes

P_F = feed pressure [bar or psi]

P_R = retentate pressure [bar or psi]

P_f = filtrate pressure [bar or psi]

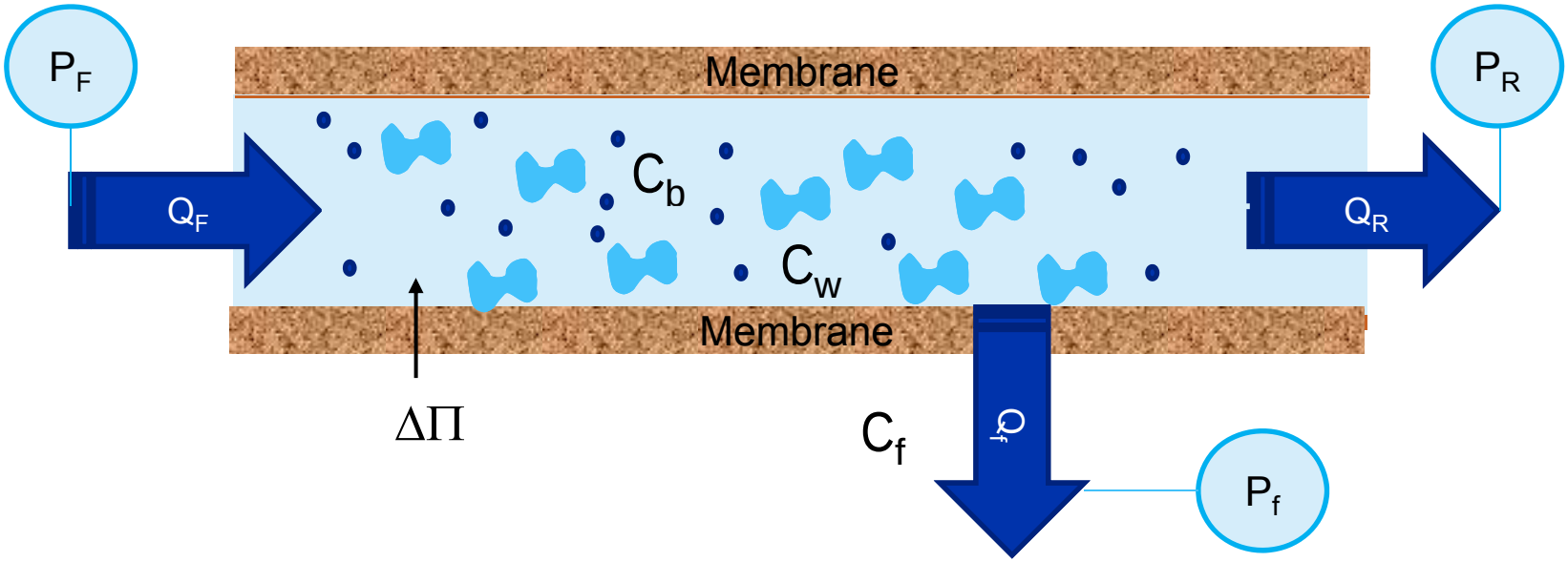
$\Delta\Pi$ = osmotic pressure [bar or psi]

Q_F = feed flow rate [L h^{-1}]

Q_R = retentate flow rate [L h^{-1}]

Q_f = filtrate flow rate [L h^{-1}]

k = mass transfer coefficient [L/m^2*h]

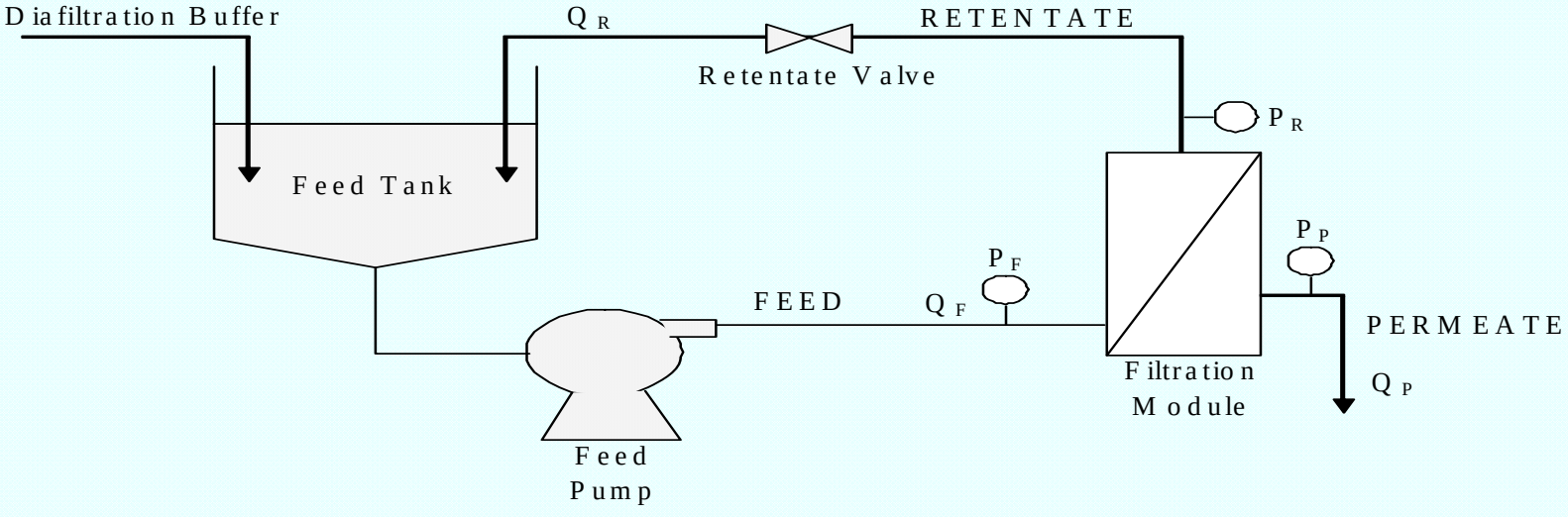


C_b = protein concentration in bulk solution [g L^{-1}]

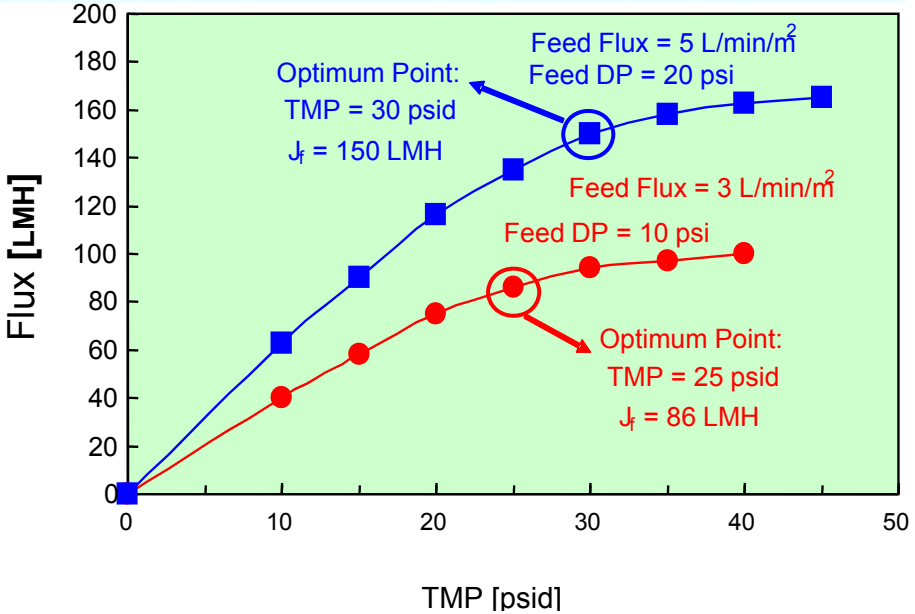
C_w = protein concentration at membrane [g L^{-1}]

C_f = protein concentration in filtrate [g L^{-1}]

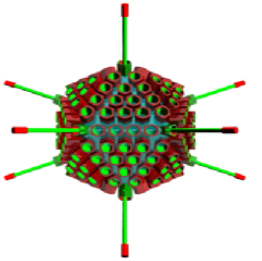
Typical TFF UF applications



- Single pump / Retentate control
- Low permeability / High TMP
- TMP / delta P controlled
- Optimization of Feed flow / TMP / Diafiltration strategy

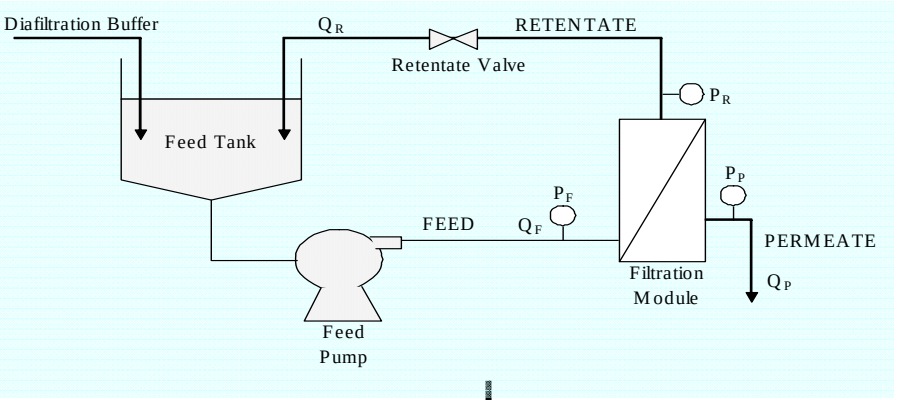


Adenovirus vaccine: Typical UF TFF process parameters



Purification: last UF/DF Step

- Success Criteria
  - Good Yield & Retention
  - Contaminant removal
    - RNA
- Solution
  - No permeate control
  - Pellicon® 2 Biomax® or Ultracel® 100 or 300kD, C screen

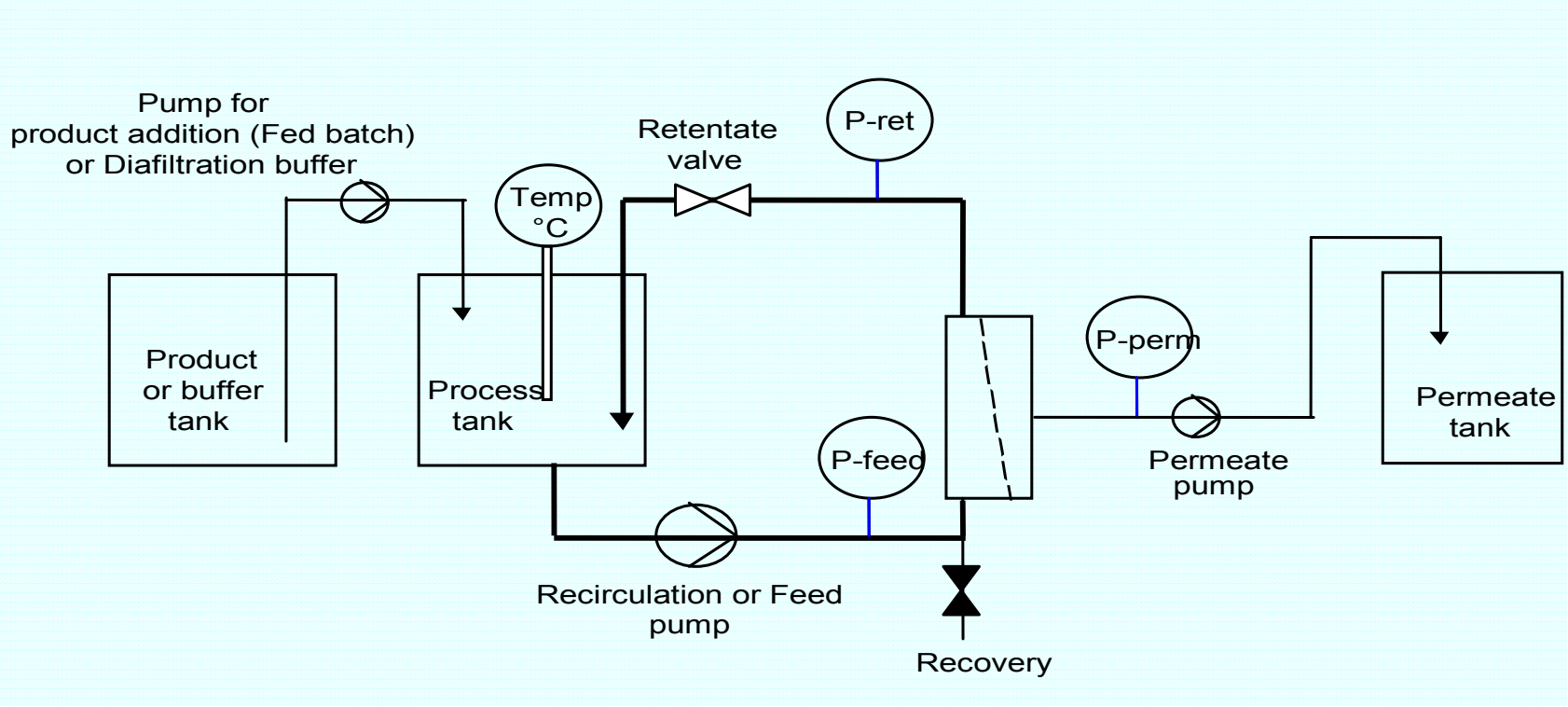


Parameters	Biomax/Ultracel 100-300 KD
Feed flow (l/min/m²)	4-8
TMP (bar)	0.3-1
Average flux (LMH)	25-50
Volumetric Concentration Factor	4-10
Diafiltration volume	5-12

Typical TFF MF / Open UF applications

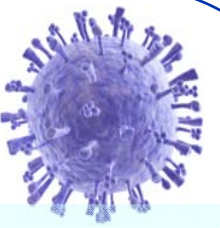
Set up of an equipment with permeate control

- 2 Pump System / Flux controlled
- Permeate Valve & Flow Meter



Viral Antigen: Egg-based Influenza Vaccine

Typical MF / Open UF TFF process parameters



Purification:

Success Criteria

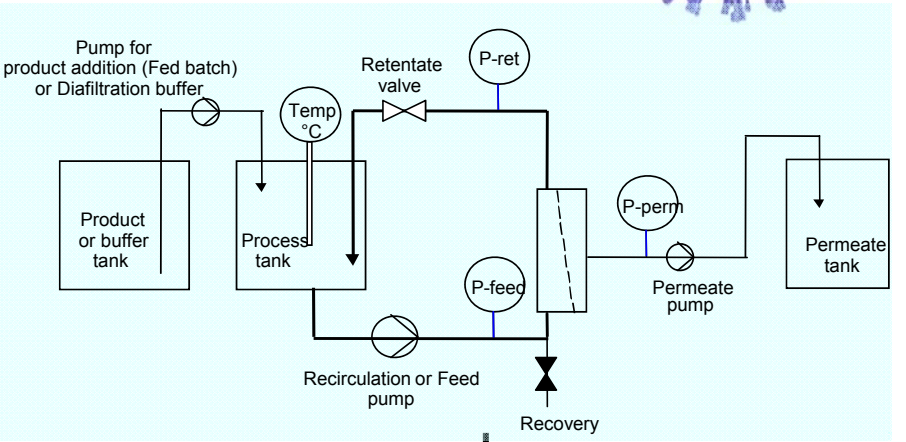
- Good yield & Retention
- Higher purity and Contaminant Removal
  - Ovalbumine

Solution

- Permeate control
- Pellicon® 2 Biomax® 1000, V Screen

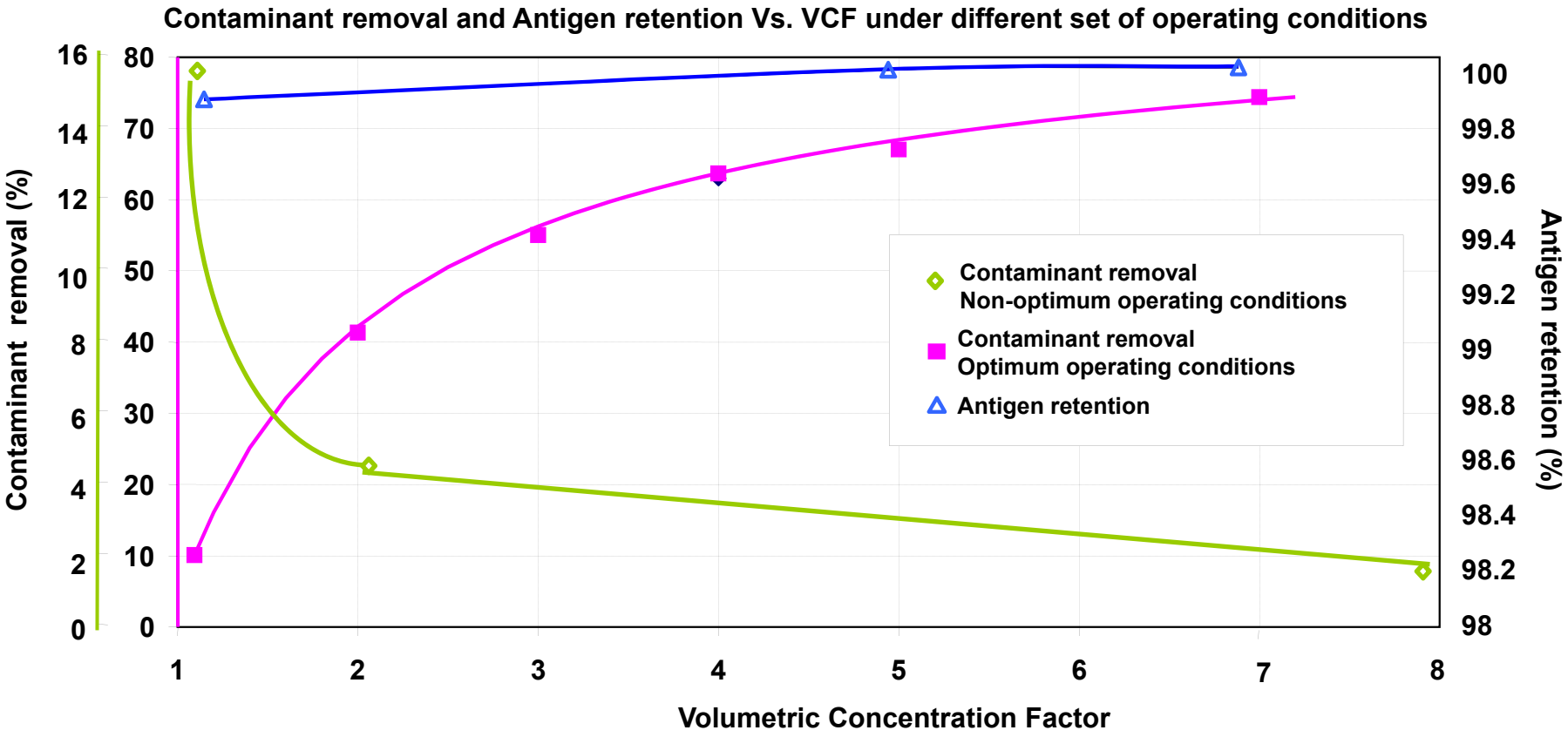
Result

- Retention > 99.99%
- Contaminant removal > 75%



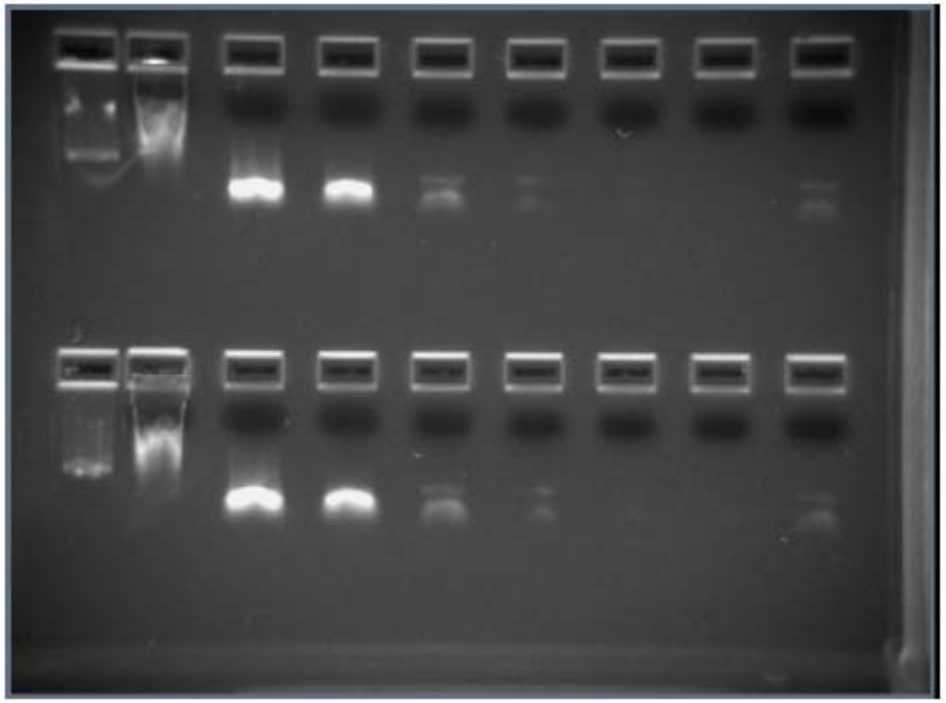
Parameters	Biomax 1000kD
Feed flow (l/min/m²)	6
TMP (bar)	<0.3
Initial flux (LMH)	30
Final flux (LMH)	30
Average flux (LMH)	30
Volumetric Concentration Factor	10
Diafiltration volume	2

With or Without Permeate Control



Optimum operating conditions: feed flow = 6 lpm/m², TMP< 0.4 bar, permeate controlled at 30 LMH
Non-optimum operating conditions: feed flow = 6 lpm/m², TMP> 1 bar, no permeate control

Case study results: Clearance of Benzonase® digested DNA across diafiltration with Pellicon® 2 Biomax® 300 kDa



- Lane 1 – Marker (100 BP)
- Lane 2 – Undigested DNA in Feed
- Lane 3 – After Benzonase® digestion
- Lane 4 – Post Recirc retentate
- Lanes 5, 6, 7, 8 – Retentate samples after 1, 3, 5, 8 DV
- Lane 9 – Permeate at 5DV

Benzonase® can also be effectively removed with diafiltration

Or

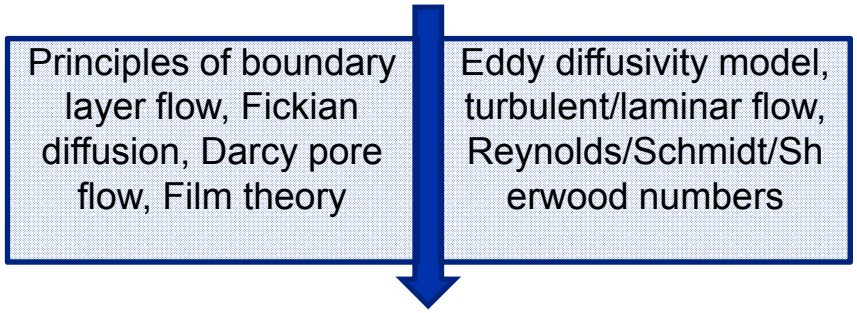
Can also be removed in subsequent chrom operations

TFF and QbD

TFF

Well known mass transfer fundamentals

Proven engineering principles and design equations



Mechanistic understanding of hydrodynamic principles governing separation process

Identifies “Optimal operating conditions” and define “Design space”

QbD

Navigator 1

Define and agree on the **Quality Target Product Profile** (QTPP)

Determine the **Critical Quality Attributes** (CQAs)

Link raw material and process parameters to the CQAs

Risk assessment to identify **Critical Process Parameters** (CPP)

Define the **Design Space** (DOE study)

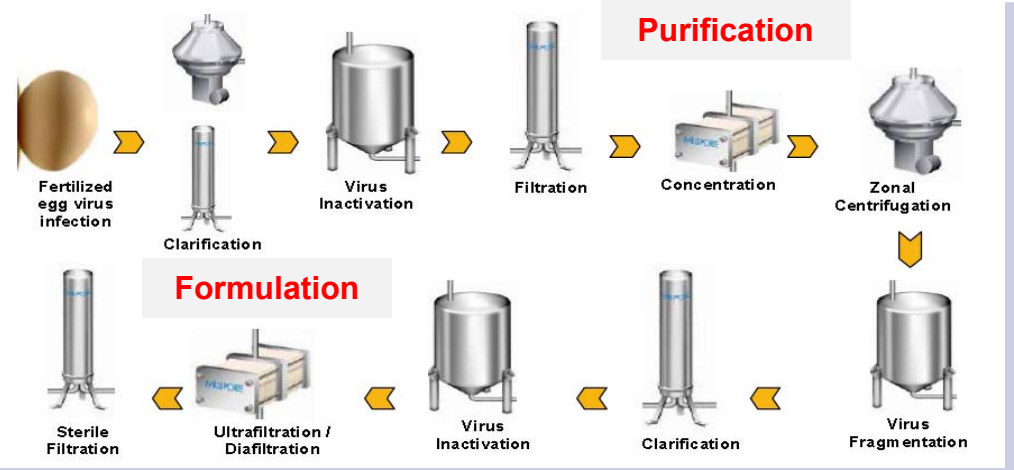
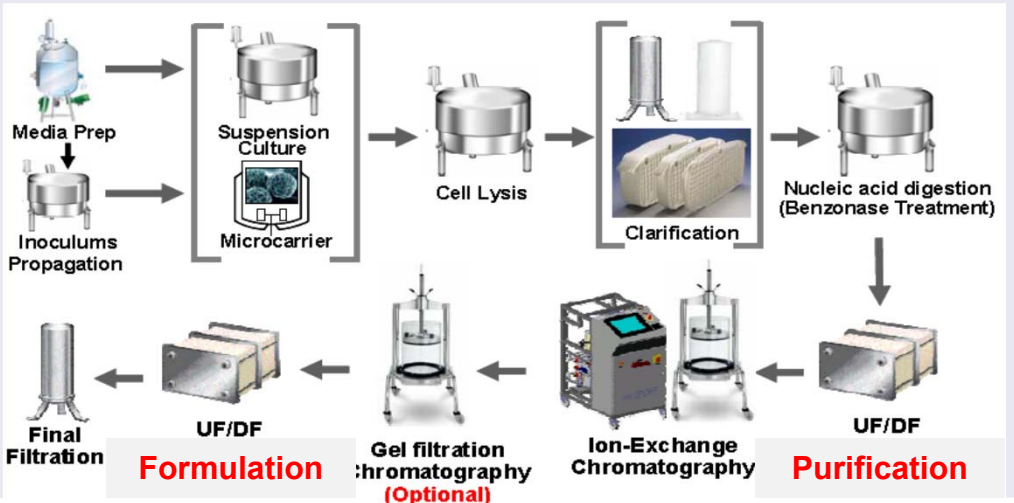
Define the **Control Strategy** to keep process within design space.

Product lifecycle management and continual improvement

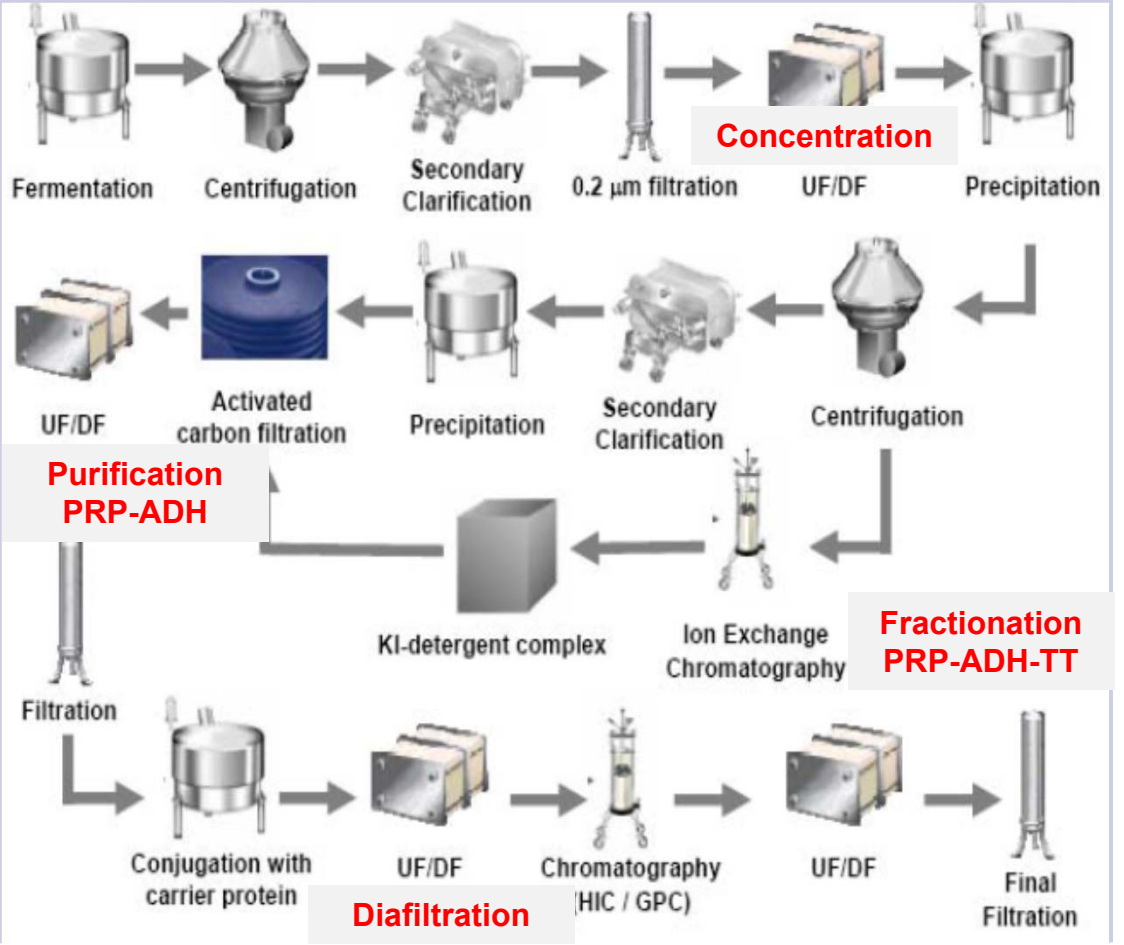
TFF step attributes - Vaccines

Function	Performance Specs	Attributes	
		Product (CQA)	Performance (KPA)
Harvest	Concentration (dewatering), Purification LRV (HCP, NA), Clarification LRV (Turbidity), Yield, Cost, Time	Purification LRV (HCP, NA)	Concentration (dewatering), Clarification LRV (Turbidity), Yield, COGs, Time
Purification / Fractionation	Purification LRV (HCP, NA, Benzonase®, Conjugation reagents, ADH), Yield, Cost, Time	Purification LRV (HCP, NA, Benzonase®, Conjugation reagents, ADH)	Yield, COGs, Time
Formulation	UFDF final concentration, buffer composition, LRV process extractable, Yield, Cost, Time	UFDF final concentration, buffer composition, LRV process extractable	Yield, COGs, Time

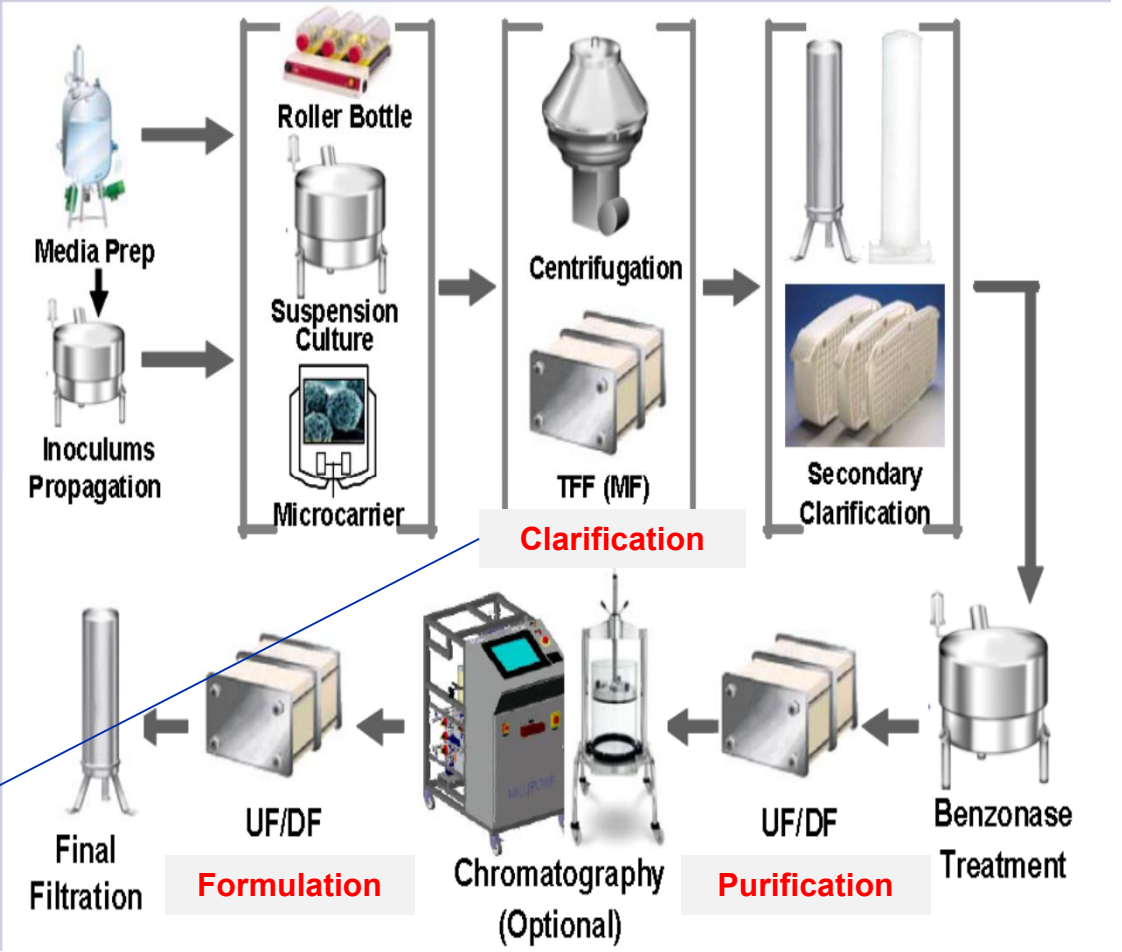
Examples of UF product CQAs in a Vaccine process

Vaccine	Product CQA	Process template
Influenza	Contaminant removal (Ovalbumin, Ovotransferrin, Ovoglobulins, Lysozyme and others) Product conc./ quality KPA – Yield, COGs, Time	
Vectored Vaccine (Malaria, Dengue)	Benzonase® / NA removal Product conc./ quality Buffer change KPA – Yield, COGs, Time	

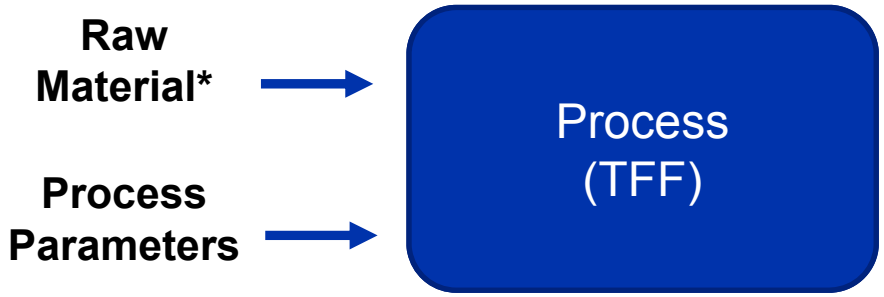
Examples of UF product CQAs in a Vaccine process

Vaccine	Product CQA	Process template
Polysaccharide Conjugate Vaccines (Pneumonia ,Meningitis, Influenza)	Product conc. Purity Buffer exchange ADH removal from PRP - ADH mass Fractionation of PRP-ADH-TT complex from unreacted mass Removal of reaction chemicals KPA – Yield, COGs, Time	

Examples of UF product CQAs in a Vaccine process

Vaccine	Product CQA	Process template
Live Attenuated Viral Vaccines (MMR, Dengue, JE, Oral polio)	Product conc. Purity Buffer exchange Benzonase® / NA removal KPA – Yield, COGs, Time, Operator safety (Clarification)	

Link Material attributes and Process parameters to CQA & KPA



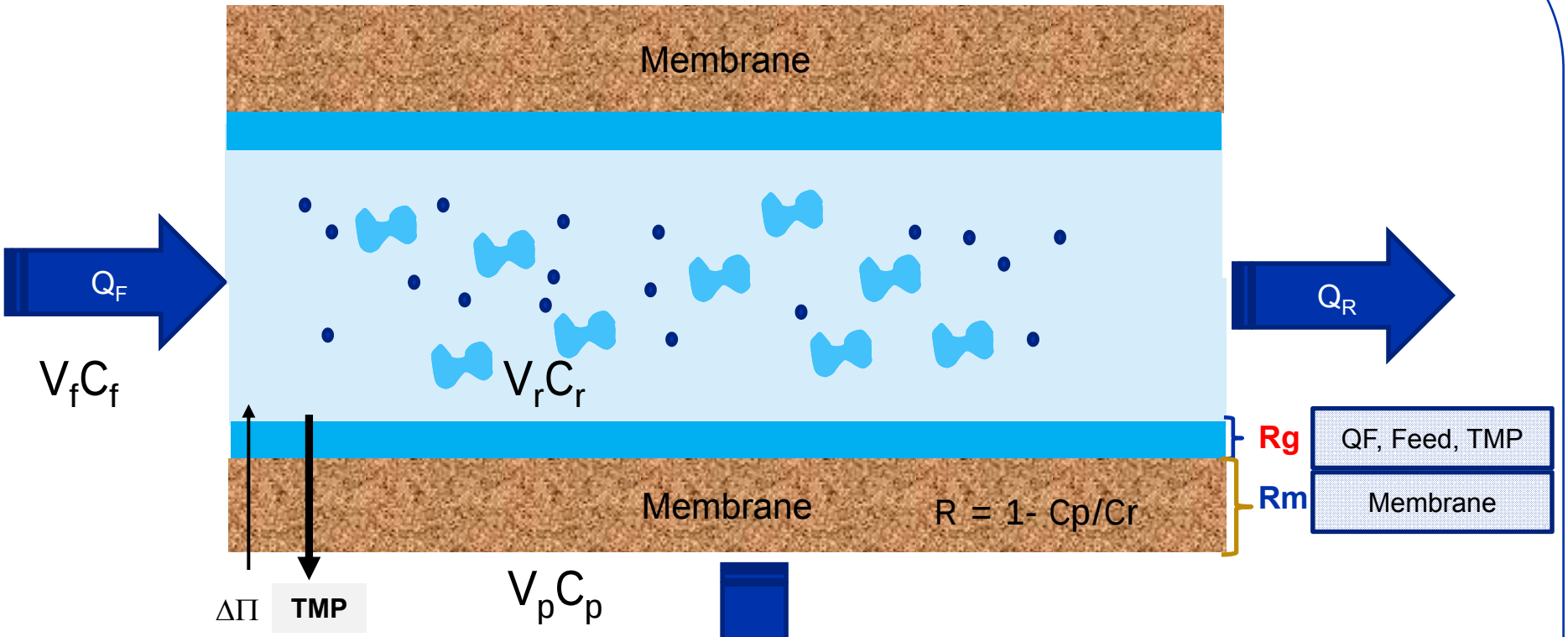
Retentate (Attributes)

- Product concentration,
- Product purity,
- Osmolality, pH
- Contaminant removal
- Fractionation profile

- Yield/retention
- COG's, (Membrane reuse)
- Time

*Raw Material attributes: Feed solution, buffers, filters

Overview of process and material attributes



X (adsorptive loss) = (CfVf – CrVr – CpVp) / A

Y (% product loss) = 100 X [1- { e $^{(Vp/Vf)X(1-R)}$ }$^{-1}$]

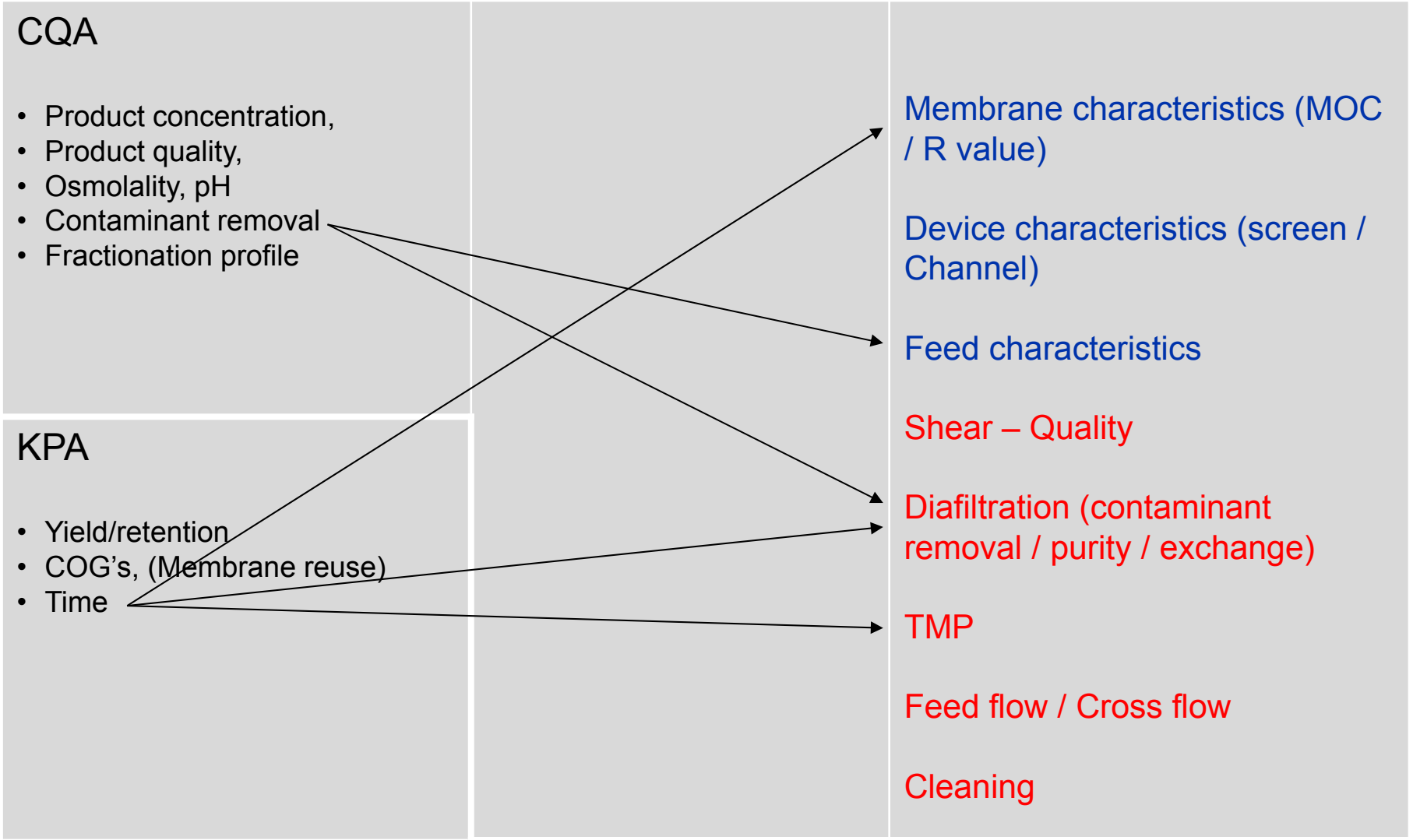
$J_{filtrate}$ = k X TMP = [1/Rg+Rm] X TMP

Mass Transfer coefficient (k) = 1 / Rg+Rm

Overall R(retention) depends on membrane retention (R90) / gel layer

Rproduct High / Rcontaminant Low – when Product in Retentate

Link Material attributes and Process parameters to CQA & KPA



Navigator 2

Define and agree on the **Quality Target Product Profile** (QTPP)

Determine the **Critical Quality Attributes** (CQAs)

Link raw material and process parameters to the CQAs

Risk assessment to identify **Critical Process Parameters** (CPP)

Define the **Design Space** (DOE study)

Define the **Control Strategy** to keep process within design space.

Product lifecycle management and continual improvement

Risk assessment

Scoring of Process Parameters and Quality (& Process) Attributes

Process Parameters		Quality (or Process) Attributes	
Impact Score	Ranking Criteria	Weight Score	Ranking Criteria
10	Strong relationship known based on available data and experience	10	Established or expected direct relationship to product quality or safety (incl. mfg safety)
7	Strong relationship is expected	7	Unsure. Impact to product quality or safety or key business drivers expected
5	Not-so-strong relationship expected or known	5	Unlikely to impact product quality or safety
1	Known to not have a relationship	1	No product or safety impact expected

Cumulative score = ∑ (Impact of parameter x Weight of quality attribute)

TFF Risk Analysis – Example of a UF-DF in typical formulation application

	Attribute Weight	10	5	5	10	7	10	
		Process Attribute			Product Attribute			
Phase	Parameter	Step Yield	Membrane Reuse	Process Time	Product aggregation (quality)	Product titre (Retentate conc)	Transfer to formulation buffer	**Score**
Conc/Diaf	Feed Flow Rate (LPM/m^2)	**1**	**5**	**5**	**7**	**5**	**1**	175
	Transmembrane Pressure (psi)	**1**	**5**	**10**	**5**	**5**	**1**	180
	Process Loading, L/m^2	**5**	**5**	**7**	**5**	**1**	**1**	177
	No of DiaVolumes	**1**	**1**	**7**	**5**	**1**	**10**	207
	Feed characteristics (Titre)	**1**	**1**	**1**	**5**	**5**	**1**	115
	Recovery, L/m^2	**10**	**1**	**1**	**1**	**1**	**1**	137
	Membrane characteristics	**5**	**1**	**7**	**1**	**1**	**1**	117
	Temperature	**1**	**1**	**7**	**5**	**1**	**1**	117

TFF Risk Analysis – Example of a UF-DF in typical purification application

	Attribute Weight	7	5	5	5	5	10	
Phase	Parameter	Process Attribute			Product Attribute			Score
		Step Yield	Membrane Reuse	Process Time	Product quality	Product titre (Retentate conc)	Removal of contaminants (eg - Albumin / Benzonase /	
Conc/Diaf	Feed Flow Rate (LPM/m^2)	1	5	5	7	5	1	127
	Transmembrane Pressure (psi)	1	5	10	5	5	1	142
	Process Loading, L/m^2	5	5	7	5	1	1	135
	No of DiaVolumes	1	1	7	5	1	10	177
	Feed characteristics (Titre)	1	1	1	1	7	5	107
	Recovery, L/m^2	10	1	1	1	1	1	100
	Membrane characteristics	7	1	7	1	1	5	149
	Temperature	1	1	7	5	1	1	87

TFF Risk Analysis – Example of a UF-DF in typical fractionation application

	Attribute Weight	7	5	5	5	7	10	
Phase	Parameter	Process Attribute			Product Attribute			Score
		Step Yield	Membrane Reuse	Process Time	Product aggregation (quality)	Product titre (Retentate conc)	% product	
Conc/Diaf	Feed Flow Rate (LPM/m^2)	**1**	**5**	**5**	**7**	**5**	**1**	137
	Transmembrane Pressure (psi)	**1**	**5**	**10**	**5**	**5**	**1**	152
	Process Loading, L/m^2	**5**	**5**	**7**	**5**	**1**	**1**	137
	No of DiaVolumes	**1**	**1**	**7**	**5**	**1**	**10**	179
	Feed characteristics (Titre)	**1**	**1**	**1**	**1**	**7**	**5**	121
	Recovery, L/m^2	**10**	**1**	**1**	**1**	**1**	**1**	102
	Membrane characteristics	**7**	**1**	**7**	**1**	**1**	**7**	171
	Temperature	**1**	**1**	**7**	**5**	**1**	**1**	89

TFF Risk Analysis – Example of a UF-DF in a Influenza formulation - Sample experimental design for DOE characterization

Parameter	Low	Middle	High	Score	Scientific Rationale
Feed Flow Rate (LPM/m^2)	3	5	7	175	Impacts polarization, fouling & potentially quality
Transmembrane Pressure (psi)	2	4	6	180	Impacts flux (time), polarization and fouling
No of Diavolumes	6	10	14	207	Impacts time and buffer exchange efficiency
Loading, L/m^2	20	30	40	177	Potential impact on process time, COGs
Feed Stock	2-3 lots representing variability in Feed			Linking Variable	Potential for variability in feed titre, or impurity levels to impact UF-DF performance
Filter	2-3 lots representing variability in Membrane characteristics			Linking Variable	Variability in membrane retention can potentially influence yield, contaminant removal

QbD Concept - Process Parameters

Process parameters, whose variability has an impact on a CQA, need to be monitored and controlled

1

Critical Process Parameter (CPP)

- Variability in CPP has an impact on critical quality attribute and therefore should be monitored or controlled to ensure process produces the desired quality.
- A CPP has a high risk of falling outside the design space.

2

Well Controlled Critical Process Parameter (WC-CPP)

- Variability in CPP has an impact on critical quality attribute and therefore should be monitored or controlled to ensure process produces the desired quality.
- A CPP has a low risk of falling outside the design space.

3

Key Process Parameter (KPP)

- An adjustable parameter (variable) of the process that, when maintained within a narrow range, ensures operational reliability.
- A key process parameter does not affect critical quality attributes.

4

General Process Parameter

- All “other” parameters

A Hypothetical Summary of Process Parameter Classification and Ranges - Formulation

Process Parameter	Acceptable Range	Parameter Classification	Rationale (Justification)	Control Strategy
Feed Flow Rate (LPM/m^2)	3.5-6.5	KPP	DOE	Skid Control
Transmembrane Pressure (psi)	16-45	KPP	DOE	Skid Control
Process Loading, L/m^2	18-42	GPP	DOE	Batch Procedure
No of DiaVolumes	6-12	KPP	DOE	Skid Control
Feed Concentration, g/L	6-14	GPP	Modular (Prior knowledge)	Titre Analysis
Recovery, L/m^2	70-90%	GPP	Modular (Prior knowledge)	Skid Control
Temperature, C	15-30	GPP	Modular (Prior knowledge)	Environmental Control
CIP Feed Flow Rate (LPM/m^2)	3.5-6.5	GPP	Modular, Vendor	Skid Control
CIP Transmembrane Pressure (psi)	8-25	GPP	Modular, Vendor	Skid Control
CIP time, min	30-90	GPP	Modular, Vendor	Skid Control
CIP solution concentration, M	0.05-0.5	GPP	Modular, Vendor	Batch Procedure
CIP Temperature, C	15-30	GPP	Modular, Vendor	Environmental Control
Normal Water Permeability	within 25% of New	KPP	Modular, Vendor	Batch Procedure
Integrity Test	< Specification	KPP	Vendor	Batch Procedure

In a "Purification" application "Diafiltration" can be "CPP" based on risk assessment wrt CQA

Navigator 3

Define and agree on the **Quality Target Product Profile** (QTPP)

Determine the **Critical Quality Attributes** (CQAs)

Link raw material and process parameters to the CQAs

Risk assessment to identify **Critical Process Parameters** (CPP)

Define the **Design Space** (DOE study)

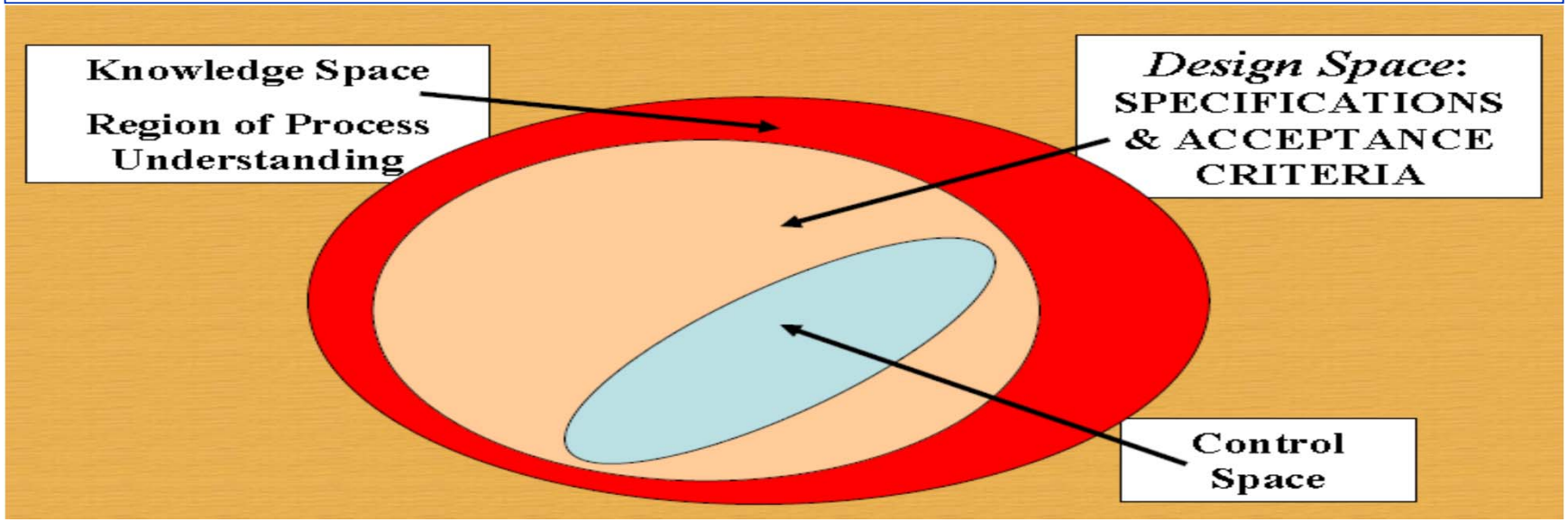
Define the **Control Strategy** to keep process within design space.

Product lifecycle management and continual improvement

QbD Concept - Design Space

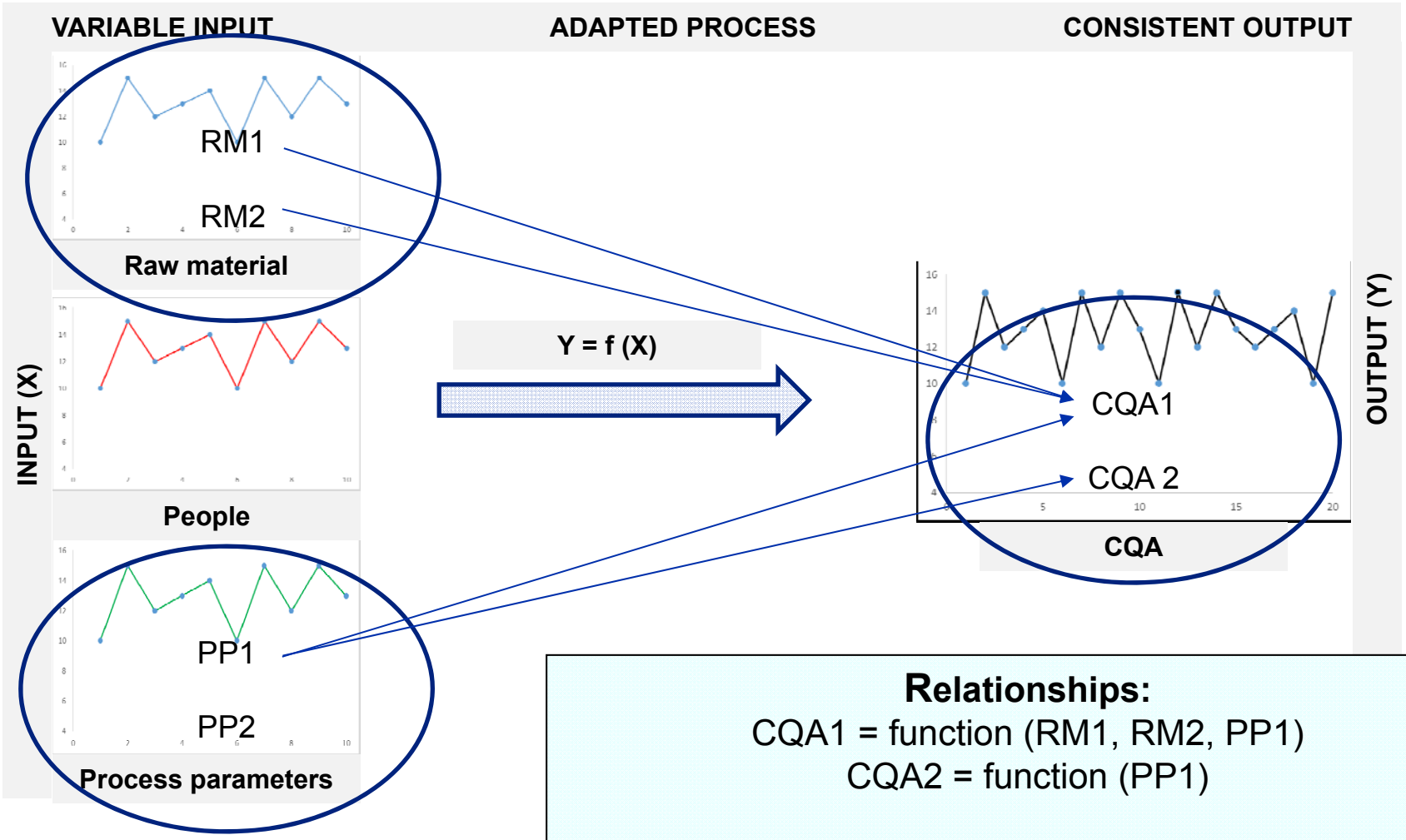
Design Space

- Defined as: “the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.” ICH Q8(R2), http://www.fda.gov/downloads/Drugs/Guidances/ucm073507.pdf
- Demonstrated range of all process parameters where process meets the CQAs
- Consists of Knowledge space, design space and control space



“Implementation of Quality by Design”. J.F. Haury, Amgen 2006 http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm118776.pdf

CQA and Process design space



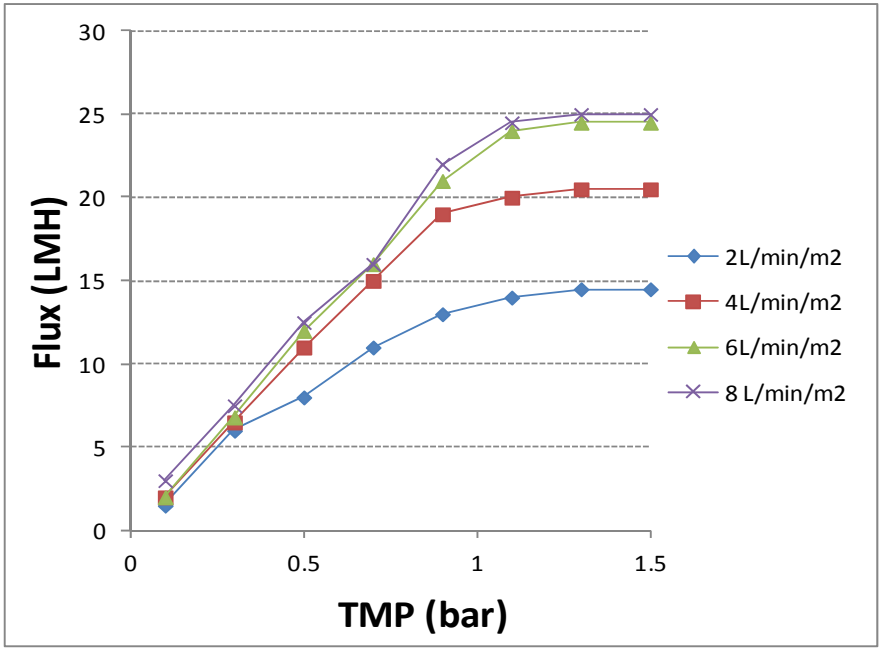
Relationships:

CQA1 = function (RM1, RM2, PP1)

CQA2 = function (PP1)

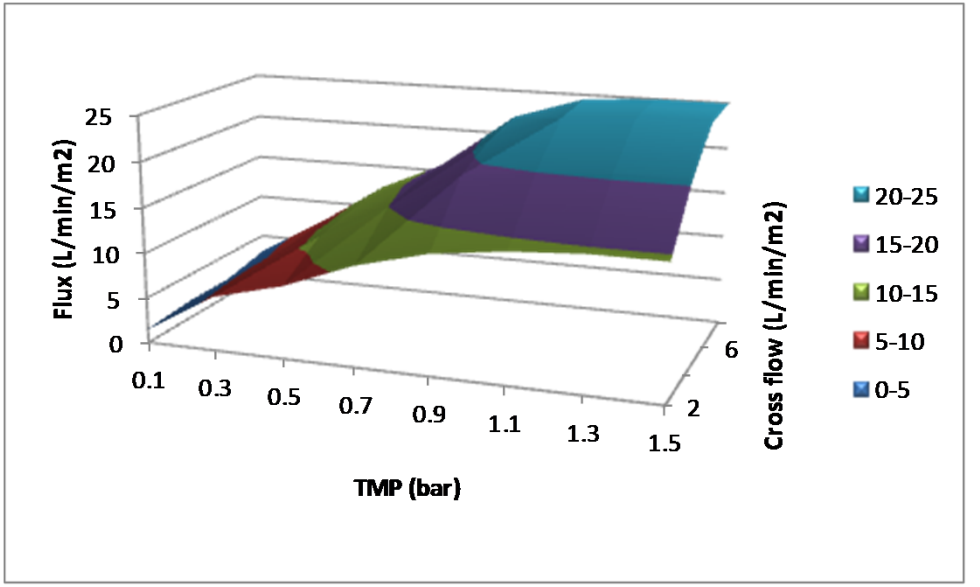
PP2 might not be needed in the establishment of design space

Example of Experiments to Determine Acceptable Range of Process parameters



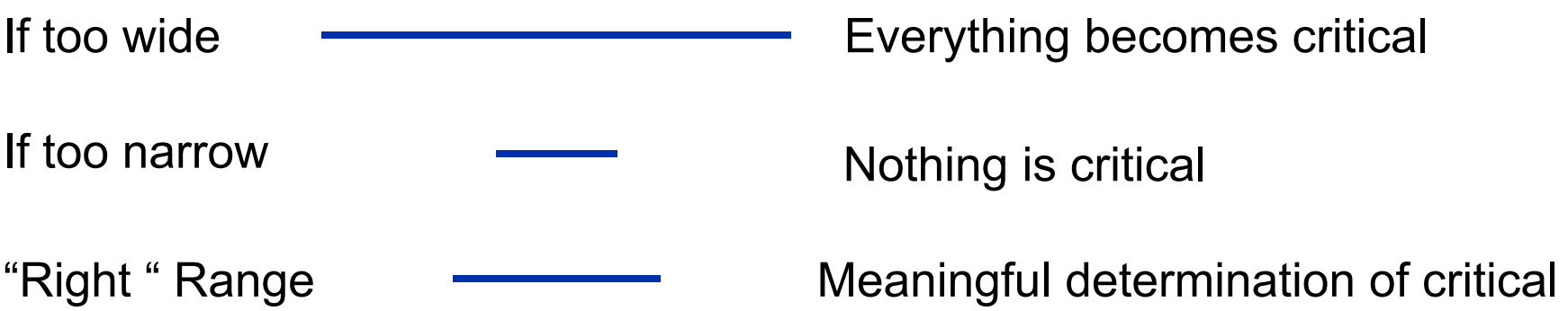
Typical flux excursion experiments have two variables and an output.

- Variables – feed flow rate/cross flow rate and TMP
- Output - Flux



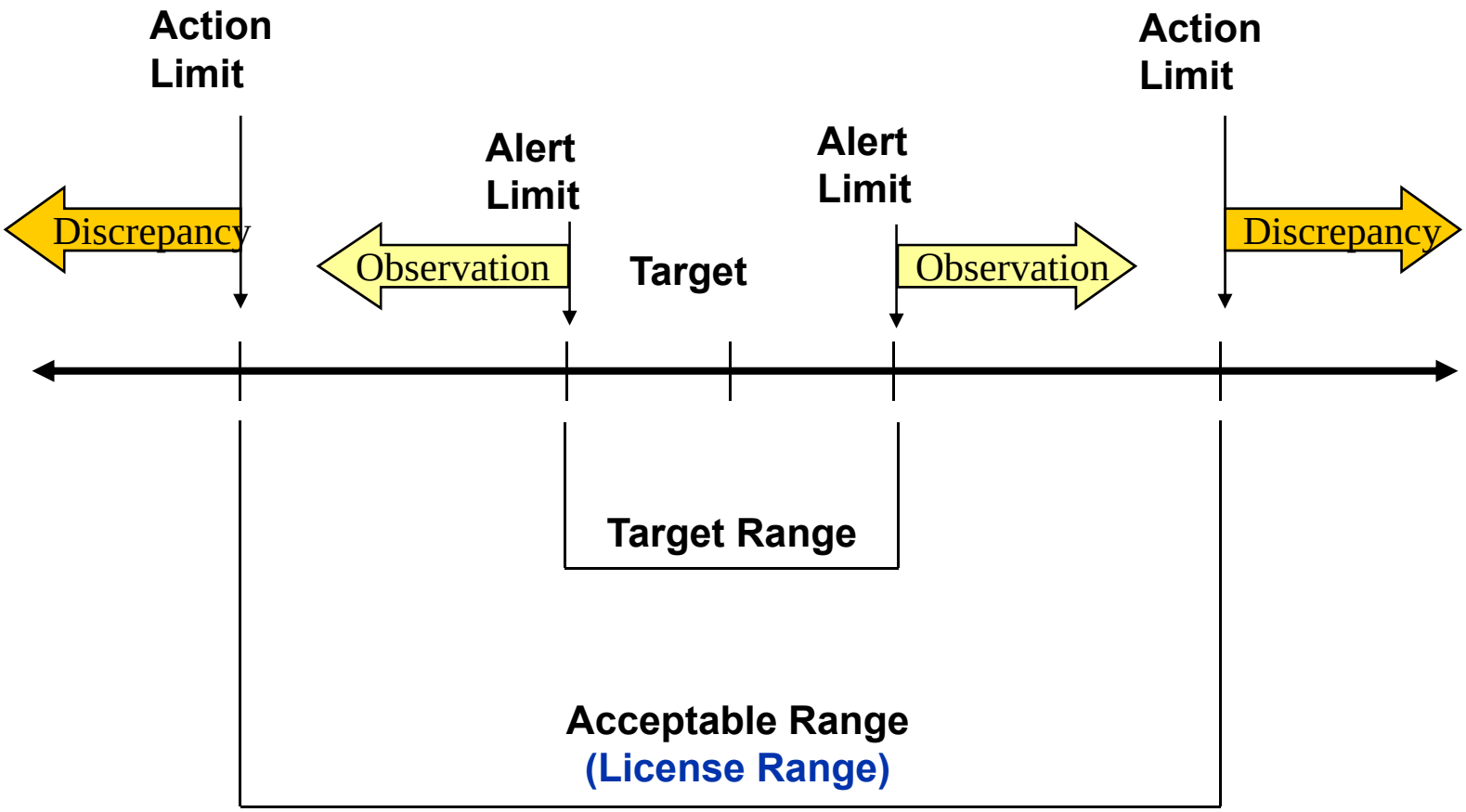
Parameter Ranges

Challenges in setting Process Parameter Ranges in DOE studies



Prior knowledge & platform parameter information serve as good guidance

Alert and Action Limits



Parameter range - UF Example

Process Parameter	Target	Target Range	Acceptable Range
Feed Flow Rate (LPM/m^2)	5	4.5-5.5	3.5-6.5
Transmembrane Pressure (psi)	30	25-35	16-45
Process Loading, L/m^2	30	28-32	18-42
No of DiaVolumes	8	7.5-8.5	6-12
Feed Concentration, g/L	10	9-11	6-14
Recovery, L/m^2	80%	75-85%	70-90%
Temperature, C	20	18-22	15-30
CIP Feed Flow Rate (LPM/m^2)	5	4.5-5.5	3.5-6.5
CIP Transmembrane Pressure (psi)	16	12-20	8-25
CIP time, min	45	40-50	30-90
CIP solution concentration, M	0.2	0.1-0.3	0.05-0.5
CIP Temperature, C	20	18-22	15-30

Navigator 4

Define and agree on the **Quality Target Product Profile** (QTPP)

Determine the **Critical Quality Attributes** (CQAs)

Link raw material and process parameters to the CQAs

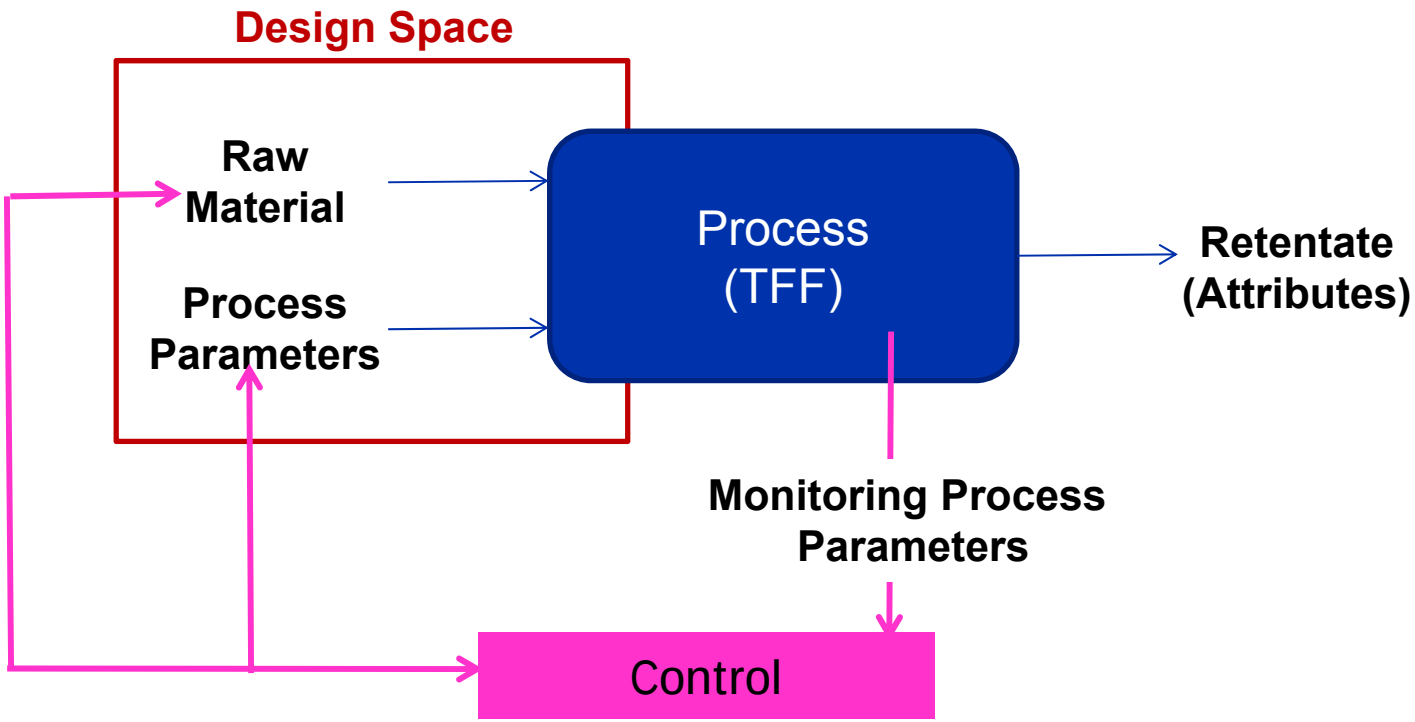
Risk assessment to identify **Critical Process Parameters** (CPP)

Define the **Design Space** (DOE study)

Define the **Control Strategy** to keep process within design space.

Product lifecycle management and continual improvement

Design Space and Control Strategy



Parameter Monitoring & Control: UF / MF Examples

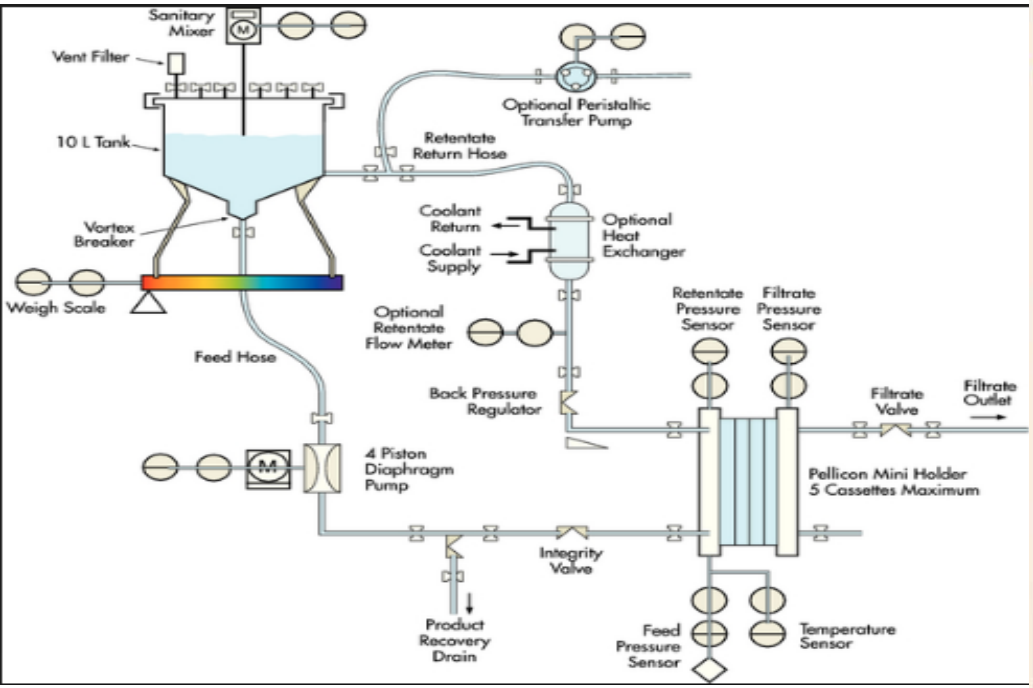
Feed	Feed concentrations of product, impurities and buffer components can be measured directly and/or controlled through the previous step.
Filter	Filter properties such as retention, permeability – monitor through vendor quality audit.
Feed Flow, TMP	Control the feed pump flow using a mass flow meter & PID control. Use retentate / permeate flow control valve & pressure transmitters (feed, retentate, permeate) to control TMP (PID).
Concentration End-Point	Retentate tank volume (Wt) or level specification.
Diafiltration End-Point	Maintain diafiltration flow rate = permeate flow rate through retentate level control. Time or permeate volume measurement. High end analytical support in case of purification /fractionation

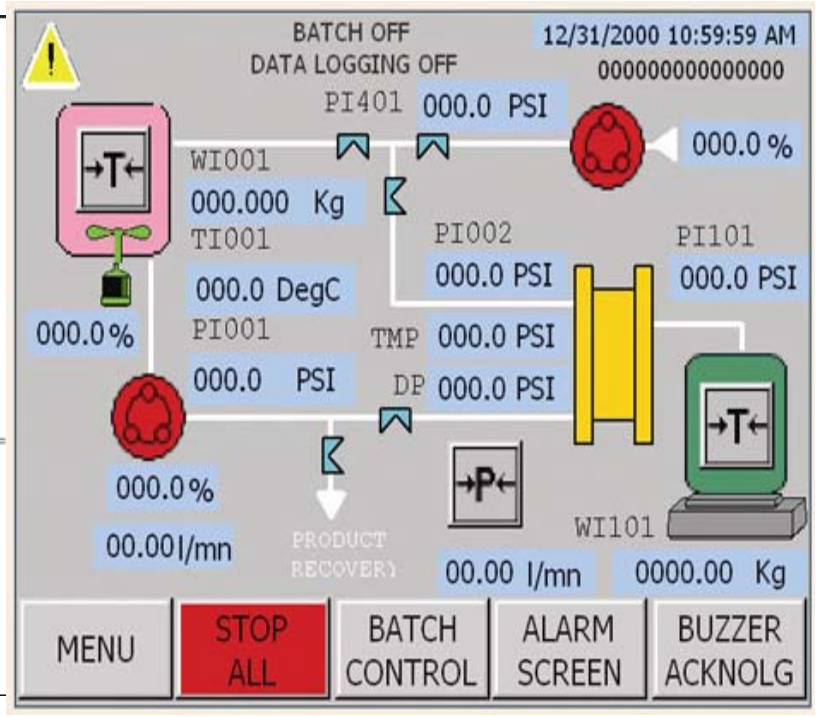
Control of Process Parameters

- Ensure product quality and safety (for CPPs)
  - Control within design space to ensure consistent product quality and process performance
- Ensure that the commercial manufacturing process is consistent and robust (KPPs)
  - Also, controlled within target range to ensure consistent process performance
    - Non CPPs need to be controlled just as much as CPPs do

Control of Process Parameters

- Control Strategy
  - A control plan derived from current product and process understanding that assures product quality and process performance
  - A method to keep or maintain the ‘process’ within the design space.





Summary

- QbD – represents a scientific approach to build-in & ensure quality in drug products
  - Emphasizes process understanding, relationship between CPPs, CQAs, QTPPs using a methodical approach (risk assessment)
- QbD principles may be applied to TFF to determine the important process parameters

- Feed flow, TMP (flux), Diavolumes can be CPPs or KPPs

- Process control strategies help ensure that process parameters are maintained within the desired range to ensure product quality and reliable process operation

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Tathagata Ray
t.ray@merckgroup.com