QbD for Tangential Flow Filtration

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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)

<table>
<thead>
<tr>
<th>Category</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy/Strength</td>
<td>Does the production process result in product/residues that interfere with final product strength or efficacy?</td>
</tr>
<tr>
<td>Identity &amp; Purity</td>
<td>Does the production process result in product/residues that interfere with final product purity?</td>
</tr>
<tr>
<td>Safety</td>
<td>Does the production process result in product/residues that are toxic to the patient?</td>
</tr>
</tbody>
</table>
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

Current manufacturing

Restaurant bills

Airline baggage arrival

Aviation industry

Nuclear industry

Quality to patient

2σ  4σ  6σ
QbD .... Overall approach

TARGET PRODUCT PROFILE

CQA 1
CQA 2
CQA 3
CQA 4

PROCESS PARAMETERS
- Control space
- Design space
- Knowledge space

Prior Knowledge
Animal studies
In vitro studies

CLINICAL DESIGN SPACE
PRODUCT DESIGN SPACE
PROCESS DESIGN SPACE

CONCEPT > DESIGN > PRE-CLINICAL > CLINICAL > MASS PRODUCTION
QbD: From process ..... To step ......
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

![Diagram of TFF UF process]

**Graph:**
- Optimum Point: TMP = 30 psid, J = 150 LMH
- Feed Flux = 5 L/min/m², Feed DP = 20 psi
- Optimum Point: TMP = 25 psid, J = 86 LMH
- Feed Flux = 3 L/min/m², Feed DP = 10 psi
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

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Biomax 1000kD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feed flow (l/min/m²)</td>
<td>6</td>
</tr>
<tr>
<td>TMP (bar)</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>Initial flux (LMH)</td>
<td>30</td>
</tr>
<tr>
<td>Final flux (LMH)</td>
<td>30</td>
</tr>
<tr>
<td>Average flux (LMH)</td>
<td>30</td>
</tr>
<tr>
<td>Volumetric Concentration Factor</td>
<td>10</td>
</tr>
<tr>
<td>Diafiltration volume</td>
<td>2</td>
</tr>
</tbody>
</table>
With or Without Permeate Control

Contaminant removal and Antigen retention Vs. VCF under different set of operating conditions

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

- Principles of boundary layer flow, Fickian diffusion, Darcy pore flow, Film theory
- Eddy diffusivity model, turbulent/laminar flow, Reynolds/Schmidt/Sh erwood numbers

Mechanistic understanding of hydrodynamic principles governing separation process

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

QbD
Principles of boundary layer flow, Fickian diffusion, Darcy pore flow, Film theory
Eddy diffusivity model, turbulent/laminar flow, Reynolds/Schmidt/Sh erwood numbers
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

<table>
<thead>
<tr>
<th>Function</th>
<th>Performance Specs</th>
<th>Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Product (CQA)</strong></td>
<td><strong>Performance (KPA)</strong></td>
</tr>
<tr>
<td>Harvest</td>
<td>Concentration (dewatering), Purification LRV (HCP, NA), Clarification LRV (Turbidity), Yield, Cost, Time</td>
<td>Purification LRV (HCP, NA)</td>
</tr>
<tr>
<td>Purification / Fractionation</td>
<td>Purification LRV (HCP, NA, Benzonase®, Conjugation reagents, ADH), Yield, Cost, Time</td>
<td>Purification LRV (HCP, NA, Benzonase®, Conjugation reagents, ADH)</td>
</tr>
<tr>
<td>Formulation</td>
<td>UFDF final concentration, buffer composition, LRV process extractable, Yield, Cost, Time</td>
<td>UFDF final concentration, buffer composition, LRV process extractable</td>
</tr>
</tbody>
</table>
### Examples of UF product CQAs in a Vaccine process

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Product CQA</th>
<th>Process template</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Influenza</strong></td>
<td>Contaminant removal (Ovalbumin, Ovotransferrin, Ovoglobulins, Lysozyme and others)</td>
<td>![Process Diagram]</td>
</tr>
<tr>
<td></td>
<td>Product conc./ quality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>KPA – Yield, COGs, Time</td>
<td></td>
</tr>
<tr>
<td><strong>Vectored Vaccine</strong></td>
<td>Benzonase® / NA removal</td>
<td>![Process Diagram]</td>
</tr>
<tr>
<td>(Malaria, Dengue)</td>
<td>Product conc./ quality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Buffer change</td>
<td></td>
</tr>
<tr>
<td></td>
<td>KPA – Yield, COGs, Time</td>
<td></td>
</tr>
</tbody>
</table>
## Examples of UF product CQAs in a Vaccine process

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Product CQA</th>
<th>Process template</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysaccharide Conjugate Vaccines (Pneumonia, Meningitis, Influenza)</td>
<td>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</td>
<td><img src="image" alt="Process diagram" /></td>
</tr>
</tbody>
</table>
### Examples of UF product CQAs in a Vaccine process

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Product CQA</th>
<th>Process template</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live Attenuated Viral Vaccines</td>
<td>Product conc. Purity</td>
<td></td>
</tr>
<tr>
<td>(MMR, Dengue, JE, Oral polio)</td>
<td>Buffer exchange</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benzonase® / NA removal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>KPA – Yield, COGs, Time, Operator safety (Clarification)</td>
<td></td>
</tr>
</tbody>
</table>
Link Material attributes and Process parameters to CQA & KPA

Raw Material*  →  Process (TFF)  →  Retentate (Attributes)

Process Parameters

- 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

Overview of process and material attributes

- 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

\[ X \text{ (adsorptive loss)} = \frac{(C_f V_f - C_r V_r - C_p V_p)}{A} \]

\[ Y \text{ (% product loss)} = 100 \times \left[ 1 - \left( e^{\frac{V_p}{V_f} X (1-R)} \right)^{-1} \right] \]

\[ J_{\text{filtrate}} = k \times \text{TMP} = \left[ \frac{1}{R_g + R_m} \right] \times \text{TMP} \]
### Link Material attributes and Process parameters to CQA & KPA

#### CQA
- Product concentration,
- Product quality,
- Osmolality, pH
- Contaminant removal
- Fractionation profile

#### KPA
- Yield/retention
- COG’s, (Membrane reuse)
- Time

#### Membrane characteristics (MOC / R value)
- Device characteristics (screen / Channel)
- Feed characteristics
- Shear – Quality
- Diaphragation (contaminant removal / purity / exchange)
- TMP
- Feed flow / Cross flow
- Cleaning
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 (or Process) Attributes

<table>
<thead>
<tr>
<th>Process Parameters</th>
<th>Quality (or Process) Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact Score</td>
<td>Weight Score</td>
</tr>
<tr>
<td>Strong relationship known based on available data and experience</td>
<td>10</td>
</tr>
<tr>
<td>Strong relationship is expected</td>
<td>7</td>
</tr>
<tr>
<td>Not-so-strong relationship expected or known</td>
<td>5</td>
</tr>
<tr>
<td>Known to not have a relationship</td>
<td>1</td>
</tr>
</tbody>
</table>

*Cumulative score = \( \sum (\text{Impact of parameter} \times \text{Weight of quality attribute}) \)*
### TFF Risk Analysis – Example of a UF-DF in typical formulation application

<table>
<thead>
<tr>
<th>Phase</th>
<th>Parameter</th>
<th>Attribute Weight</th>
<th>Process Attribute</th>
<th>Product Attribute</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Step Yield</td>
<td>Membrane Reuse</td>
<td>Process Time</td>
</tr>
<tr>
<td>Conc/Diaf</td>
<td>Feed Flow Rate (LPM/m²)</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Transmembrane Pressure (psi)</td>
<td>1</td>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Process Loading, L/m²</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>No of DiaVolumes</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Feed characteristics (Titre)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Recovery, L/m²</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Membrane characteristics</td>
<td>5</td>
<td>1</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Temperature</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>
# TFF Risk Analysis – Example of a UF-DF in typical purification application

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Weight</th>
<th>Feed Flow Rate (LPM/m²)</th>
<th>Transmembrane Pressure (psi)</th>
<th>Process Loading, L/m²</th>
<th>No of DiaVolumes</th>
<th>Feed characteristics (Titre)</th>
<th>Recovery, L/m²</th>
<th>Membrane characteristics</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process Attribute</td>
<td>7</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>127</td>
<td>142</td>
</tr>
</tbody>
</table>
# TFF Risk Analysis – Example of a UF-DF in typical fractionation application

<table>
<thead>
<tr>
<th>Phase</th>
<th>Parameter</th>
<th>Attribute Weight</th>
<th>Process Attribute</th>
<th>Product Attribute</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Step Yield</td>
<td>Membrane Reuse</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Process Time</td>
<td>Product aggregation (quality)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Product titre (Retentate conc)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% product</td>
<td></td>
</tr>
<tr>
<td>Conc/Diaf</td>
<td>Feed Flow Rate (LPM/m²)</td>
<td>7</td>
<td>5</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Transmembbrane Pressure (psi)</td>
<td>1</td>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Process Loading, L/m²</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>No of DiaVolumes</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Feed characteristics (Titre)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Recovery, L/m²</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Membrane characteristics</td>
<td>7</td>
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<td>7</td>
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<tr>
<td></td>
<td>Temperature</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>
### TFF Risk Analysis – Example of a UF-DF in a Influenza formulation - Sample experimental design for DOE characterization

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low</th>
<th>Middle</th>
<th>High</th>
<th>Score</th>
<th>Scientific Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feed Flow Rate (LPM/m²)</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>175</td>
<td>Impacts polarization, fouling &amp; potentially quality</td>
</tr>
<tr>
<td>Transmembrane Pressure (psi)</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>180</td>
<td>Impacts flux (time), polarization and fouling</td>
</tr>
<tr>
<td>No of Diavolumes</td>
<td>6</td>
<td>10</td>
<td>14</td>
<td>207</td>
<td>Impacts time and buffer exchange efficiency</td>
</tr>
<tr>
<td>Loading, L/m²</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>177</td>
<td>Potential impact on process time, COGs</td>
</tr>
<tr>
<td>Feed Stock</td>
<td>2-3 lots representing variability in Feed</td>
<td>Linking Variable</td>
<td>Potential for variability in feed titre, or impurity levels to impact UF-DF performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filter</td>
<td>2-3 lots representing variability in Membrane characteristics</td>
<td>Linking Variable</td>
<td>Variability in membrane retention can potentially influence yield, contaminant removal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Process Parameter</th>
<th>Acceptable Range</th>
<th>Parameter Classification</th>
<th>Rationale (Justification)</th>
<th>Control Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feed Flow Rate (LPM/m²)</td>
<td>3.5-6.5</td>
<td>KPP</td>
<td>DOE</td>
<td>Skid Control</td>
</tr>
<tr>
<td>Transmembrane Pressure (psi)</td>
<td>16-45</td>
<td>KPP</td>
<td>DOE</td>
<td>Skid Control</td>
</tr>
<tr>
<td>Process Loading, L/m²</td>
<td>18-42</td>
<td>GPP</td>
<td>DOE</td>
<td>Batch Procedure</td>
</tr>
<tr>
<td>No of DiaVolumes</td>
<td>6-12</td>
<td>KPP</td>
<td>DOE</td>
<td>Skid Control</td>
</tr>
<tr>
<td>Feed Concentration, g/L</td>
<td>6-14</td>
<td>GPP</td>
<td>Modular (Prior knowledge)</td>
<td>Titre Analysis</td>
</tr>
<tr>
<td>Recovery, L/m²</td>
<td>70-90%</td>
<td>GPP</td>
<td>Modular (Prior knowledge)</td>
<td>Skid Control</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>15-30</td>
<td>GPP</td>
<td>Modular (Prior knowledge)</td>
<td>Environmental Control</td>
</tr>
<tr>
<td>CIP Feed Flow Rate (LPM/m²)</td>
<td>3.5-6.5</td>
<td>GPP</td>
<td>Modular, Vendor</td>
<td>Skid Control</td>
</tr>
<tr>
<td>CIP Transmembrane Pressure (psi)</td>
<td>8-25</td>
<td>GPP</td>
<td>Modular, Vendor</td>
<td>Skid Control</td>
</tr>
<tr>
<td>CIP time, min</td>
<td>30-90</td>
<td>GPP</td>
<td>Modular, Vendor</td>
<td>Skid Control</td>
</tr>
<tr>
<td>CIP solution concentration, M</td>
<td>0.05-0.5</td>
<td>GPP</td>
<td>Modular, Vendor</td>
<td>Batch Procedure</td>
</tr>
<tr>
<td>CIP Temperature, °C</td>
<td>15-30</td>
<td>GPP</td>
<td>Modular, Vendor</td>
<td>Environmental Control</td>
</tr>
<tr>
<td>Normal Water Permeability</td>
<td>within 25% of New</td>
<td>KPP</td>
<td>Modular, Vendor</td>
<td>Batch Procedure</td>
</tr>
<tr>
<td>Integrity Test</td>
<td>&lt; Specification</td>
<td>KPP</td>
<td>Vendor</td>
<td>Batch Procedure</td>
</tr>
</tbody>
</table>

In a “Purification” application “Diafiltration” can be “CPP” based on risk assessment wrt CQA.
Navigator 3

1. Define and agree on the **Quality Target Product Profile** (QTPP)
2. Determine the **Critical Quality Attributes** (CQAs)
3. Link raw material and process parameters to the CQAs
4. Risk assessment to identify **Critical Process Parameters** (CPP)
5. **Define the Design Space** (DOE study)
6. Define the **Control Strategy** to keep process within design space.
7. Product lifecycle management and continual improvement

**Define**  | **Measure**  | **Analyze**  | **Design**  | **Verify**
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](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

CQA and Process design space

Y = f (X)

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

If too wide  Everything becomes critical
If too narrow  Nothing is critical
“Right “ Range  Meaningful determination of critical

Prior knowledge & platform parameter information serve as good guidance
Alert and Action Limits

- Action Limit
  - Discrepancy
  - Observation
  - Target
  - Alert Limit
  - Observation
  - Action Limit
  - Discrepancy

- Target Range
- Acceptable Range (License Range)
## Parameter range - UF Example

<table>
<thead>
<tr>
<th>Process Parameter</th>
<th>Target</th>
<th>Target Range</th>
<th>Acceptable Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feed Flow Rate (LPM/m²)</td>
<td>5</td>
<td>4.5-5.5</td>
<td>3.5-6.5</td>
</tr>
<tr>
<td>Transmembrane Pressure (psi)</td>
<td>30</td>
<td>25-35</td>
<td>16-45</td>
</tr>
<tr>
<td>Process Loading, L/m²</td>
<td>30</td>
<td>28-32</td>
<td>18-42</td>
</tr>
<tr>
<td>No of DiaVolumes</td>
<td>8</td>
<td>7.5-8.5</td>
<td>6-12</td>
</tr>
<tr>
<td>Feed Concentration, g/L</td>
<td>10</td>
<td>9-11</td>
<td>6-14</td>
</tr>
<tr>
<td>Recovery, L/m²</td>
<td>80%</td>
<td>75-85%</td>
<td>70-90%</td>
</tr>
<tr>
<td>Temperature, C</td>
<td>20</td>
<td>18-22</td>
<td>15-30</td>
</tr>
<tr>
<td>CIP Feed Flow Rate (LPM/m²)</td>
<td>5</td>
<td>4.5-5.5</td>
<td>3.5-6.5</td>
</tr>
<tr>
<td>CIP Transmembrane Pressure (psi)</td>
<td>16</td>
<td>12-20</td>
<td>8-25</td>
</tr>
<tr>
<td>CIP time, min</td>
<td>45</td>
<td>40-50</td>
<td>30-90</td>
</tr>
<tr>
<td>CIP solution concentration, M</td>
<td>0.2</td>
<td>0.1-0.3</td>
<td>0.05-0.5</td>
</tr>
<tr>
<td>CIP Temperature, C</td>
<td>20</td>
<td>18-22</td>
<td>15-30</td>
</tr>
</tbody>
</table>
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

- Define
- Measure
- Analyze
- Design
- Verify
Design Space and Control Strategy

- Design Space
  - Raw Material
  - Process Parameters
- Process (TFF)
- Retentate (Attributes)
- Monitoring Process Parameters
- Control
## Parameter Monitoring & Control: UF / MF Examples

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feed</td>
<td>Feed concentrations of product, impurities and buffer components can be measured directly and/or controlled through the previous step.</td>
</tr>
<tr>
<td>Filter</td>
<td>Filter properties such as retention, permeability – monitor through vendor quality audit.</td>
</tr>
<tr>
<td>Feed Flow, TMP</td>
<td>Control the feed pump flow using a mass flow meter &amp; PID control. Use retentate / permeate flow control valve &amp; pressure transmitters (feed, retentate, permeate) to control TMP (PID).</td>
</tr>
<tr>
<td>Concentration End-Point</td>
<td>Retentate tank volume (Wt) or level specification.</td>
</tr>
<tr>
<td>Diafiltration End-Point</td>
<td>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</td>
</tr>
</tbody>
</table>
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.

![Process Diagram](image-url)
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
merckmillipore.com/vaccines

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