APPLICATION OF QUALITY BY DESIGN PRINCIPLES TO ULTRAFILTRATION OPERATIONS IN BIOPROCESSING

Asia Seminar Series
Dec, 2015

Gregory S Blank, Ph.D.
Bala Raghunath, Ph.D.
Overview

- Quality by Design (QbD)
- Adopting QbD Principles for Ultrafiltration Operations (TFF) in Biologics Processing
ICH Q8: Design Space

Quality by Design

Product Understanding

Product Specifications

Product Knowledge

Desired Product Performance

Product Design

Dosage form, stability, formulation, etc.

Product Quality Attributes

Process Design

Unit operations, control strategy, etc.

Process Parameters

Continuous Improvement

Process Understanding

Process Performance

Cpk, robustness, etc.
Quality by Design (QbD)

Official Definition

- A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (ICH Q8R1).

FDA Guidance for Industry – Biosimilars Feb 2012

- The use of Quality-by-Design approaches to pharmaceutical development, along with quality risk management and effective quality systems, will facilitate the consistent manufacturing of a high-quality product.
What is QbD

QbD is a FDA initiative that in exchange for more process knowledge, understanding and definition at time of approval will allow companies to make post approval changes within the approved “Design Space” without FDA approval.

QBD is not mandatory
- Although features as part of QBD (PC design, etc.) are an expectation
QbD Elements

Target Product Profile
■ Product characteristics that deliver a desired clinical performance.

Risk Assessments at multiple points in development
■ FMEA, PHA, etc.
■ Determine CQAs, CPPs, PC study design, worst case studies, linkage studies, Design Space
Critical Quality Attributes

Definition
- A critical quality attribute (CQA) is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. ICH Q8.

General
- Aggregate, endotoxin, HCP, HC-DNA

Product Specific
- Related to mechanism of action (MOA)
- Deamidation, type of glycosylation
Critical Quality Attribute (CQA): A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality [Q8R1]
Quality by Design (QbD)

Practical Application
- If a BLA is filed as a QbD submission a Design Space will be proposed.
- When the BLA and Design Space are approved the manufacturer can move process parameter ranges within the Design Space without prior approval.
- The amount of data to support a QbD submission is much greater than a non QbD submission
  ▶ One company estimated an extra $14M
Design Space

DESIGN SPACE

- The FDA approved range of all process parameters within which the process meets the CQAs.
- The manufacturer may move the process within these ranges without FDA approval.

design space

- A frequently used term which can denote the range(s) within the process “works”.
Design Space – Control Space

Design Space – The overall approved process space
Control Space – Routine manufacturing space
QbD Points

FDA is requiring significantly more process understanding at approval time.

- Test edges of processes from cell culture through formulation.
- How is process performance and critical quality attributes impacted by process variability?
- The impact of raw material variability to process performance is becoming an element the regulatory agencies are expecting in submissions.
ADOPTING QBD PRINCIPLES FOR ULTRAFILTRATION OPERATIONS (TFF) IN BIOLOGICS PROCESSING
Key Concepts – Attributes, Parameters

**Parameters**
- **Feed**
  - Upstream
- **Consumable**
  - Filter, Resin, Chemicals
  - Flexware
- **Operation**
  - Setup
  - Processing & recovery

**Attributes**
- **Product Quality**
  - Efficacy
  - Purity
  - Safety
- **Process Performance**
  - Yield
  - Cost
  - Ease of manufacturing

**QbD Workflow**
1. Identify & rank attributes
2. Identify parameters
Begin with the risk assessment

- Link raw material attributes and process parameters to the CQAs

*Raw Material attributes: from Feed solution, buffers, From Filters
Identify parameters: Raw Matl. attributes in mAb TFF process

Example

From Feed solution
► Starting concentration
► pH, conductivity,
► Feed buffer composition
► DF buffer

From Filter
► Lot number
► UF Membrane type
► MWCO
Identify parameters: Process Parameters in mAb TFF Process

Example

<table>
<thead>
<tr>
<th>Step</th>
<th>Process Parameter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Installation</td>
<td>Module type, area, torque, Hydraulic compression</td>
</tr>
<tr>
<td>Flush</td>
<td>L/m² retentate &amp; permeate water</td>
</tr>
<tr>
<td>Integrity test</td>
<td>Test pressure &amp; air flow spec</td>
</tr>
<tr>
<td>Equilibration</td>
<td>L/m² retentate &amp; permeate buffer</td>
</tr>
<tr>
<td>Concentration/Diafiltration</td>
<td>Feed flow &amp; TMP, Loading, concentration end-points &amp; diavolumes, Temperature</td>
</tr>
<tr>
<td>Recovery</td>
<td>L/m² retentate DF buffer</td>
</tr>
<tr>
<td>Cleaning</td>
<td>Water flush as above, cleaner type, temperature concentration, contact time, feed flow, L/m² loading, NWP measurement conditions and specs</td>
</tr>
<tr>
<td>Sanitization</td>
<td>Chemical type/temp/concentration/time/feed flow, L/m² loading, environment</td>
</tr>
</tbody>
</table>
**Process Parameters in TFF Concentration and Diafiltration step**

**Example**

<table>
<thead>
<tr>
<th>Process Parameter</th>
<th>Typical Mfg range</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feed flow (LMM)</td>
<td>3 - 7</td>
<td>Fouling, polarization, <strong>purification</strong>, <strong>product shear stress</strong>, Flux, <strong>Process time</strong>, reuse</td>
</tr>
<tr>
<td>TMP (psi)</td>
<td>15 - 45</td>
<td>Flux, <strong>polarization</strong>, fouling, <strong>Process time</strong>, <strong>max achievable concentration</strong></td>
</tr>
<tr>
<td>Diavolumes (N)</td>
<td>6 - 10</td>
<td>Purification level, residuals, <strong>Process time</strong></td>
</tr>
<tr>
<td>Loading (L/m²)</td>
<td>20 - 40</td>
<td><strong>Process time</strong></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>10 - 25</td>
<td><strong>Product degradation</strong>, <strong>Process time</strong>, <strong>Integrity Test results</strong></td>
</tr>
<tr>
<td>Recovery volume (L/m²)</td>
<td>5 - 15</td>
<td><strong>Yields</strong>, <strong>final product concentration</strong></td>
</tr>
<tr>
<td>Mixing</td>
<td>NA</td>
<td><strong>Product oxidation</strong>, <strong>product purification</strong>, <strong>Process time</strong></td>
</tr>
</tbody>
</table>
Key Concepts – Attribute limit, Parameter limit, Set Point

- Knowledge Base
- Acceptable Parameter Limit
- Characterization Study
- Manufacturing Process/ Unit Operations
- Acceptable Attribute Limit

QbD Workflow

3. Identify attribute limits
4. Identify parameters limits: knowledge base/characterization studies
5. Set parameter limits- design space
Risk Assessment to classify PP

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

- Critical Process Parameter (CPP)
- Key Process Parameter (KPP)
- General Process Parameter (GPP)

The risk analyses help identify and categorize operating parameters by classifying them into those:

- that could employ ranges based on prior knowledge, modular claims (from previous products or literature studies)
  - GPP
- That require further evaluation (DOE studies: multivariate, univariate),
  - CPP, WC-CPP, KPP
TFF Risk Analysis – Example of a Formulation UF-DF (TFF) in a mAb process

Scoring of Process Parameters and Quality (& Process) Attributes

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

Cumulative score = \[ \sum (\text{Impact of parameter} \times \text{Weight of quality attribute}) \]

Cause and Effect Matrix risk assessment

...A mAb Case Study
## TFF Risk Analysis – Example of a Formulation UF-DF (TFF) in a mAb process

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Process Attribute</th>
<th>Product Attribute</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Step Yield</td>
<td>Membrane Reuse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Process Time</td>
<td>Time Impurity and/or Contaminant</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retentate Protein Content</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aggregate</td>
<td></td>
</tr>
<tr>
<td>Feed Flow Rate (LPM/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmembrane Pressure (psi)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process Loading, L/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of DiaVolumes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feed Concentration, g/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovery, L/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feed Flow Rate (LPM/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmembrane Pressure (psi)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>time, h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIP solution concentration, M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*List of all process parameters*

*List of all Quality & Process Attributes*

*Missing?*
- pH
- Osmolality
- Acetate
- Sucrose
- Surfactant
TFF Risk Analysis – Example of a Formulation UF-DF (TFF) in a mAb process

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Attribute Weight</th>
<th>6</th>
<th>5</th>
<th>4</th>
<th>7</th>
<th>7</th>
<th>10</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Process Attribute</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step Yield</td>
<td></td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>Membrane Reuse</td>
<td></td>
<td>3</td>
<td>1</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>131</td>
</tr>
<tr>
<td>Process Time</td>
<td></td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>77</td>
</tr>
<tr>
<td>Impurity and/or Contaminant</td>
<td></td>
<td>3</td>
<td>1</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>117</td>
</tr>
<tr>
<td>Protein Content (Retentate conc)</td>
<td></td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>57</td>
</tr>
<tr>
<td>Aggregate</td>
<td></td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Product Attribute</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feed Flow Rate (LPM/m²)</td>
<td></td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>64</td>
</tr>
<tr>
<td>Transmembrane Pressure (psi)</td>
<td></td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>49</td>
</tr>
<tr>
<td>Recovery, L/m²</td>
<td></td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>64</td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>64</td>
</tr>
<tr>
<td>Feed Concentration, g/L</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>64</td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## TFF Risk Analysis – Example of a Formulation UF-DF (TFF) in a mAb process

<table>
<thead>
<tr>
<th>Attribute Weight</th>
<th>6</th>
<th>5</th>
<th>4</th>
<th>7</th>
<th>7</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process Attribute</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step Yield</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Membrane Reuse</td>
<td>3</td>
<td>1</td>
<td>7</td>
<td>3</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Process Time</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Impurity and/or Contaminant</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Protein Content (Retentate conc)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Aggregate</td>
<td>3</td>
<td>1</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Score</strong></td>
<td>95</td>
<td>131</td>
<td>77</td>
<td>57</td>
<td>74</td>
<td>60</td>
</tr>
</tbody>
</table>

For Further Evaluation

- Feed Flow Rate (LPM/m²)
- Transmembrane Pressure (psi)
- Process Loading, L/m²
- No of DiaVolumes
- Feed Concentration, g/L
- Recovery, L/m²
- Temperature
- Feed Flow Rate (LPM/m²)
- Transmembrane Pressure (psi)
- time, h
- CIP solution concentration, M
- Temperature
Design Space

The Process Characterization study helps in the establishment of the design space

A Hypothetical Summary of Process Parameter Classification and Ranges

<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>
Key Concepts – Control Strategy

QbD Workflow

3. Identify attribute limits
4. Identify parameters limits: knowledge base/characterization studies
5. Set parameter limits- design space
6. Control strategy
Control of Process Parameters

- Control Strategy
  - A method to keep or maintain the ‘process’ within the design space.

- Ensure product quality and safety (for CPPs)
  - Control within design space to ensure consistent product quality

- 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
Feed

Feed concentrations of protein product, aggregates, bioburden, 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 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 & use either time or permeate volume measurement.
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 – example of formulation UF step in a mAb process indicates
  - No CPPs
  - Feed flow, TMP (flux), Diavolumes emerge as KPPs
- Process control strategies help ensure that process parameters are maintained within the desired range to ensure product quality and reliable process operation
Thank you

Acknowledgments:
Herbert Lutz
Renato Lorenzi
Michael Payne
Gregory Blank
T. Ray