An Introduction to Quality by Design with Case Study

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Outline

- What is Quality by Design (QbD) ?
- Implementation of QbD - Case Study for a monoclonal antibody
- Summary
What is Quality by Design (QbD) ?
What is Quality by Design (QbD) ?

ICH Q8: 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.

- Leverages knowledge of structure-function relationship to define product attributes that are important.

- Uses science-based and risk-based approaches to define the commercial manufacturing process and the management of the post-approval lifecycle.

- Aims at developing deeper product & process understanding throughout the lifecycle of a product:
  - Control system tailored to product requirements
  - Process robustness enhanced
  - Deviation and change assessments facilitated
QbD Approach – Beginning With the End in Mind

- **TPP** – The targeted commercial labeling claims

- **QTPP** - A prospective summary of the quality characteristics of a Drug Product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the Drug Product.

- **QRM** – A systematic process of organizing information to support decision making based on identification of hazards and evaluation of risks management associated with those hazards.

- **(p)CQA** – A physical, chemical or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality \((p) = \text{potential}\). **Considers the relevant Mechanisms of Action.**

- **(p)CPP, (p)CMA** – A process parameter or material whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality \((p) = \text{potential}\).

- **DSp** – The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

- **CS** – A planned set of controls, derived from current product and process understanding that ensures process performance and product quality.
Regulatory Considerations for Design Space

• **Movement within the design space is not considered as a change** (from a regulatory reporting point of view)

• **Movement out of the design space is considered to be a change** (requires regulatory reporting according to regional requirements)

• Control of all parameters including changes are managed in the Manufacturer’s Quality System, regardless of whether they are reportable or require pre-approval

Roche’s Design Space definition is currently the combination of all of the unit operations, their associated CPPs and non-CPPs described in the Module 3 Process Description
Implementation of QbD

Case Study: Monoclonal Antibody
## General Introduction – Monoclonal Antibody

<table>
<thead>
<tr>
<th></th>
<th>Monoclonal Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecule</strong></td>
<td>Recombinant, humanized, monoclonal antibody (IgG1)</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>Oncology</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Intravenous (IV) infusion</td>
</tr>
<tr>
<td><strong>Dosage form</strong></td>
<td>Concentrate for solution for infusion&lt;br&gt;Single 1,000 mg dose in a 50 mL glass vial containing 40 mL of liquid concentrate</td>
</tr>
<tr>
<td><strong>Composition</strong></td>
<td>25 mg/mL of antibody in&lt;br&gt;20 mM L-histidine/L-histidine hydrochloride,&lt;br&gt;240 mM trehalose, 0.02% poloxamer 188, pH 6.0</td>
</tr>
<tr>
<td><strong>Storage conditions</strong></td>
<td>2°C - 8°C, protected from light; shelf life 36 months</td>
</tr>
</tbody>
</table>
Quality by Design Tools and their Purpose
Systematic approach to Control System and Design Space

CQA Identification (RRF Tool)

Which attributes are critical?

CQA Acceptance Criteria Determination

Which levels are critical?

Attribute Testing Strategy (RRF Tool)

What should be tested?

Attribute Testing Strategy Robustness

Do we have the right tests?

Risk Assessments for Process Parameters

Which parameters should be studied?

Multivariate & Univariate PC/PV Studies

How does the process impact the CQAs?

Linkage Studies of Worst-Case Conditions

How robust is the overall process?

CPP Identification and Design Space Definition

Which parameters need to be controlled?

QbD provides a systematic approach to answer these questions
The Roche QbD Workflow

Critical Quality Attribute (CQA) Identification (RRF Tool)

What should be measured?

CQA Acceptance Criteria Determination

What levels?

Attribute Testing Strategy (RRF Tool)

What should be tested?

Attribute Testing Strategy Robustness

Do we have the right tests?

Process Characterization (PC/PV Study Design RRF)

What parameters should be studied?

Design of Experiments & Univariate Studies

How does the process impact the CQAs?

Linkage Studies for Worst-Case Conditions

How robust is the overall process?

CPPs Identification & Design Space Definition

What is critical?

Control System

Design Space
What are Potential Critical Quality Attributes for a Monoclonal Antibody?

ICH Q8 R1: Critical Quality Attributes - Link Directly to Patient Safety & Efficacy

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.

- High Molecular Weight Species
- N-terminal Variants
- Host Cell Protein
- Fragmentation
- Composition and Strength
- Glycation
- Deamidation
- Sequence Variants
- Proline Amidation
- C-terminal Lysine
- Cysteine Forms
- Leachables
- Leached Protein A
- Host Cell DNA
- Adventitious Agents
- Oxidation Variants
- Glycosylation Variants
- Aspartic Acid Isomerization
- Host Cell Protein
- Raw Materials
- Drug Product Specific
## Critical Quality Attributes (CQAs) Categorization

<table>
<thead>
<tr>
<th>Category of Attribute</th>
<th>Assessment</th>
<th>Rationale for Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Variants</td>
<td><strong>Risk Ranking and Filtering</strong></td>
<td>Impact to patient safety and product efficacy is specific to variant in question, mechanisms of action, route of administration, etc.</td>
</tr>
<tr>
<td>Process-related impurities</td>
<td><strong>Risk Ranking and Filtering</strong></td>
<td>Clinical data from similar products can be used to assess safety</td>
</tr>
<tr>
<td>Composition and Strength</td>
<td>Obligate CQA</td>
<td>Potentially high impact to safety and efficacy</td>
</tr>
<tr>
<td>Adventitious Agents</td>
<td>Obligate CQA</td>
<td>Potentially high impact to safety</td>
</tr>
<tr>
<td>Raw Materials</td>
<td><strong>Compare Estimated Daily Intake and Acceptable Daily Exposure</strong></td>
<td>Extensive data available from safety and toxicity studies</td>
</tr>
</tbody>
</table>
Critical Quality Attributes (CQAs)

Identification: Risk Ranking & Filtering Tool

Risk = Impact Score x Uncertainty Score
(2, 4, 12, 16, 20)                   (1, 2, 3, 5, 7)

Risk that an attribute impacts safety or efficacy.

Impact attribute has on safety and efficacy.
Determined by the available knowledge.
More severe impact $\Rightarrow$ higher value.

Uncertainty in assigning impact.
Determined by relevance of knowledge.
Reflects the degree of confidence.
Higher uncertainty $\Rightarrow$ higher value.

Risk = Impact Score x Uncertainty Score

Safety
PK
Bioactivity
Immunogenicity

Impact and Uncertainty rankings have different scales to reflect the relative importance
# Example – CQAs for Monoclonal Antibody

## Product Variant CQAs
- High-molecular-weight species
- Low-molecular-weight species
- Deamidation
- Unknown acidic charge variants
- Glycation
- Aspartic acid isomerization
- Oxidation
- Afucosylation
- Hybrid glycans
- Mannose5
- Sialylation (NANA)
- Non-glycosylated Heavy Chain (NGHC)
- Sequence variants
- Protein structure
- Cysteine forms

## Product Variant Non-CQAs
- C-terminal lysine
- N-terminal pyroglutamic acid
- C-terminal proline amidation
- Galactosylation

## Process-Related Impurity CQAs
- Host cell proteins (HCP)
- Host cell DNA
- Leached protein A
- Some raw materials

## Obligatory CQAs

### Composition and Strength
- Protein Content, Osmolality, pH
- Appearance (color, opalescence, clarity)
- Content of: L-histidine, trehalose and poloxamer 188

### Drug Product Specific
- Subvisible Particles
- Visible Particles
- Extractable Volume
- Sterility

Most of the quality attributes are critical quality attributes or obligatory critical quality attributes.
CQA Acceptance Criteria (CQA-AC)

- The CQA-AC represents a numerical limit a CQA must meet end of shelf life in order to ensure the desired quality of the product.
  - Based on patient impact, not on product-specific (clinical) manufacturing
  - Collective effect of QAs considered to ensure PK and biological activity
  - Drive CPP identification, definition of the Control Strategy and process Design Space

- CQA-AC are established based on:
  - Product-specific non-clinical and clinical experience
  - Platform knowledge and published literature
  - Process capability and testing strategy considerations
  - For CQAs that are not formed, no CQA-ACs are set

- May extend beyond product-specific clinical and non-clinical historical ranges with justification

- Not necessarily specification acceptance criteria
The Roche QbD Workflow

**Critical Quality Attribute (CQA) Identification (RRF Tool)**
- What should be measured?

**CQA Acceptance Criteria Determination**
- What levels?

**Attribute Testing Strategy (RRF Tool)**
- What should be tested?
- Do we have the right tests?

**Process Characterization (PC/PV Study Design RRF)**
- Does the process control this? Is it stable?
- What parameters should be studied?

**Design of Experiments & Univariate Studies**
- How does the process impact the CQAs?

**Linkage Studies of Worst-Case Conditions**
- How robust is the overall process?

**CPPs Identification & Design Space Definition**
- What is critical?
Knowledge of pCQAs is used to Design & Characterize Each Unit Operation – identifying CPPs & CMAs

- **CQAs**
  - Identify CQAs for the product
  - Determine relevant levels for each CQA at each step

- **Characterize the process**
  - Perform scale-down uni- and multivariate or worst-case experiments for each unit operation
  - Monitor all relevant CQAs
  - Defines site- and scale-independent PP impacts

- **Confirm a Design Space (optional)**
  - Linkage studies for all CPPs across the whole process
  - Monitor process-wide performance for relevant CQAs

- **Traditional at-scale Process Validation**
  - Confirms consistency of the process at scale in the commercial manufacturing site
  - Confirms site- and scale-dependent validation
All traditional process validation is performed for along with new approaches that enhance the assurance of product quality

<table>
<thead>
<tr>
<th>Validation Information</th>
<th>Traditional Information</th>
<th>Enhanced Approach</th>
</tr>
</thead>
</table>
| At-Scale Process Qualification Runs | – 3 consecutive runs at manufacturing scale in the commercial facility
  – KPIs and process-related impurity clearance
  – All lots meet specifications |                                                                                  |
| Scale-Down Process Parameter Studies | – Characterization of proven acceptable ranges for manufacturing parameters
  – Generally univariate studies. Not all CQAs studied, but specified attributes assured
  – Description of scale-down models | – Greater transparency of experimental design & data analysis
  – Impact of parameter ranges on all relevant CQAs studied in multivariate studies
  – Performance of “Linkage Studies” ensures product quality within the claimed ranges
  – Statistical evaluation of scale-down models |
| Scale-Down Process Performance Studies |                                                                                  | – Process-related impurity clearance
  – Virus removal and refiltration
    – Pool hold times
    – Resin lifetime
  – Limit of in vitro cell age
  – Membrane carry-over
  – Filter leachables and extractable |
The Approach to a Process Model

- Use qualified small scale models
- Perform multivariate studies whenever possible
- Perform multiple rounds of experiments if required (e.g. screening and response surface)
Identification of CPPs

Definition

ICH Definition: “A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality”

CPPs are all PPs that have a meaningful impact on CQAs (i.e. lead to a >10% CQA change relative to the allowed range).

All CPPs are controlled and maintained within ranges to guarantee CQAs remain within their acceptance criteria.

- CQA remains within its acceptance criteria when CPP is at the limit of its range
- CQA remains within its acceptance criteria considering CPP interaction at the limits of their ranges (interaction)
- Impact on CQA (e.g. impurity level) on a given unit operation can be managed adequately by the following unit operations (e.g. impurity removal downstream) (linkage)
Process Parameter Criticality is Systematically Assessed

- **Specified range (design space)**
- **Normal operating range**
- **Process Parameters**
  - **Low Limit**
  - **High Limit**
  - **Setpoint**

**High-Impact CPP:** Impact Ratio > 0.33
**Low-Impact CPP:** 0.10 ≤ Impact Ratio ≤ 0.33
**Non-CPP:** Impact Ratio < 0.10

- **40% (IR = 0.4)**
- **High-impact CPP**

Model prediction
CI₉₅% of process model prediction

CQA vs. PP

CQA-AC

Non-CPP
The Roche QbD Workflow

1. Critical Quality Attribute (CQA) Identification (RRF Tool)
   - What should be measured?
   - What levels?
   - Does the process control this? Is it stable?

2. CQA Acceptance Criteria Determination
   - What should be tested?

3. Attribute Testing Strategy (RRF Tool)
   - Do we have the right tests?

4. Robustness

5. Process Characterization (PC/PV Study Design RRF)
   - What parameters should be studied?
   - How does the process impact the CQAs?

6. Design of Experiments & Univariate Studies
   - How robust is the overall process?

7. Linkage Studies of Worst-Case Conditions

8. CPPs Identification & Design Space Definition
   - What is critical?

The Roche QbD Workflow provides a systematic approach to identifying critical quality attributes, determining acceptance criteria, and developing robust testing strategies.
Roche’s Design Space Definition

The Drug Substance and Drug Product design space includes

- All unit operations and their sequence
- All process parameters describing the operation of each of the unit operations (described in Section S.2.2 and P.3.3)
- All raw materials

The design space is limited by the multivariate acceptable ranges for all relevant process parameters

- CPPs
- Non-CPPs
The Roche QbD Workflow

Critical Quality Attribute (CQA) Identification (RRF Tool)

- What should be measured?

CQA Acceptance Criteria Determination

- What levels?

Attribute Testing Strategy (RRF Tool)

- What should be tested?

Attribute Testing Strategy Robustness

- Do we have the right tests?

Process Characterization (PC/PV Study Design RRF)

- Does the process control this? Is it stable?

Design of Experiments & Univariate Studies

- How does the process impact the CQAs?

Linkage Studies of Worst-Case Conditions

- How robust is the overall process?

CPPs Identification & Design Space Definition

- What is critical?
Attribute Testing Strategy (ATS) – A Major Component of the Overall Control Strategy

1. **CQA RRF**
   - CQA-AC definition

2. **CQA**
   - Residual risk to be outside CQA-AC
   - Low risk to be outside CQA-AC
   - Lowest risk to be outside CQA-AC

3. **Process impact/stability impact**
   - ATS RRF

4. **Control System**
   - Monitoring
   - No Testing

5. **Robustness assessment**
   - Attribute Testing Strategy confirmed

6. **QAs**
   - Non-CQA
   - Evaluation of residual risk of process and stability to stay in AC defines testing strategy

7. **Acceptable levels determined**
   - CQAs are defined

8. **CQAs are defined**
   - Attribute Testing Strategy confirmed

9. **ATS RRF**
   - CQA RRF
Attribute Testing Strategy Score Defines Testing Strategy

CQA Impact Score \( (2,4,12,16,20) \)  \( \times \)  Process/ Stability Impact Score \( (1, 2,4,10) \) = Attribute Testing Strategy Score

**Process Impact Tree**

**Stability Impact Tree**

Attribute Testing Strategy (ATS) Score

\(< 21 \) No testing required

\(21 - 50\) Monitoring required

\(> 50\) Control System testing required
ATS Robustness Assessment

• Performed by Subject Matter Experts for every Quality Attribute (QA)

• It takes the following aspects under consideration:

  • **Criticality/Risk**
    The criticality is assessed as the impact of the QAs on safety, immunogenicity, and efficacy.

  • **Likelihood of formation**
    Likelihood of formation of the variant during the manufacturing process and/or storage.

  • **Capability of the Process**
    Ability of the process to control the attribute.

  • **Capability of the analytical procedure**

  • **Additional Control**
    Coverage of attribute by other analytical procedures in the ATS

  • **Conclusion** Considering regulatory requirements

Assessment guides if any adaptations to the proposed testing strategy may be needed and can lead to elevating or downgrading attributes in the testing strategy categories or to redefining limits and methods. Attributes with ATS scores > 50 are not removed from the control system testing by this assessment.
### Attribute Testing Strategy (ATS) Score

<table>
<thead>
<tr>
<th>CQA Category</th>
<th>CQA Impact Score</th>
<th>Drug Substance</th>
<th>Drug Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size-Related Variants</td>
<td>20</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>HMWS</td>
<td>16</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>LMWS</td>
<td>16</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Charge-Related Variants:</td>
<td>12</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Deamidation in CDR</td>
<td>16</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Deamidation in non-CDR</td>
<td>16</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Unknown Acidic Charge Variants</td>
<td>16</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Glycation in CDR</td>
<td>16</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

### Example: Attribute Testing Strategy

- **Attribute Testing Strategy (ATS) Score**
  - **<21**: No testing required
  - **21-50**: Monitoring required
  - **>50**: Control System testing required
The Roche QbD Workflow

1. **Critical Quality Attribute (CQA) Identification (RRF Tool)**
   - What should be measured?

2. **CQA Acceptance Criteria Determination**
   - What levels?

3. **Attribute Testing Strategy (RRF Tool)**
   - What should be tested?

4. **Attribute Testing Strategy Robustness**
   - Do we have the right tests?

5. **Process Characterization (PC/PV Study Design RRF)**
   - What parameters should be studied?

6. **Design of Experiments & Univariate Studies**
   - How does the process impact the CQAs?

7. **Linkage Studies of Worst-Case Conditions**
   - How robust is the overall process?

8. **CPPs Identification & Design Space Definition**
   - What is critical?
## Control System for Drug Substance

<table>
<thead>
<tr>
<th>Testing of</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Potency by Bioassay</td>
</tr>
<tr>
<td>Clarity/Opalescence</td>
<td>Identity</td>
</tr>
<tr>
<td>pH</td>
<td>Purity (e.g. by SE-HPLC, CE-SDS, IE-HPLC)</td>
</tr>
<tr>
<td>Osmolality</td>
<td>Glycosylation (e.g., Afucosylation)</td>
</tr>
<tr>
<td>Content of Excipients</td>
<td>Bioburden</td>
</tr>
<tr>
<td>Content of Protein</td>
<td>Bacterial Endotoxins</td>
</tr>
</tbody>
</table>

- Obligatory testing is implemented
- Testing is based on the residual risk of attributes to stay within acceptance criteria:
  - In case of residual risk: attribute is tested and specified
  - Testing may differ between release and stability
## Control System for Drug Product

<table>
<thead>
<tr>
<th>Testing of</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical State</td>
<td>Identity</td>
</tr>
<tr>
<td>Color</td>
<td>Purity (e.g. by SE-HPLC)</td>
</tr>
<tr>
<td>Clarity/Opalescence</td>
<td>Potency by Bioassay</td>
</tr>
<tr>
<td>Extractable Volume</td>
<td>Content of Protein</td>
</tr>
<tr>
<td>Particles (visible, subvisible)</td>
<td>Sterility</td>
</tr>
<tr>
<td>pH</td>
<td>Bacterial Endotoxins</td>
</tr>
<tr>
<td>Osmolality</td>
<td></td>
</tr>
</tbody>
</table>
The overall commercial control strategy covers different aspects:

• allowed ranges for CQAs and process parameters
• control of materials
• GMP controls
The PALM Plan describes how process parameters and CQAs are monitored during product lifecycle.

The PALM Plan describes how changes are managed in the Quality Management System.
The marketing application for the monoclonal antibody of this case study has currently been approved by approx. 60 countries.

Approved in EU, USA, Switzerland, Canada, Australia, New Zealand, Brazil, Russia, South Korea, Taiwan, many others.

Design Space and PALM plan have been approved in all countries.
Summary
Bottom Line: What has changed?

- Enhanced knowledge results in more robust routine process
- Effects of process parameters on quality attributes well understood
  - Deviations and changes can be assessed more precisely
  - When moving into «unknown territory» model predictions have to be verified
- Definition of a Design Space in which we can move freely without HA approval/report
- Control system systematically covers all known risks and can be adapted during lifecycle (e.g. frequency of testing monitoring attributes)
- Process monitoring systematically adds to process understanding
- No fundamental changes in manufacturing rules or Quality System (new only: «monitoring attributes» according to PALM Plan)
Benefits of QbD

• QbD can be a highly effective global driver of change in the industry providing:
  – Enhanced level of product quality and process robustness
  – The foundation for continued improvement

• The work done to enable Design Space claims has clearly enhanced overall process robustness and product quality
  – More extensive evaluation of process impacts on CQAs
  – Driven DoE approaches to become “state of the art”
  – More systematic and inclusive identification of CPPs and non-CPPs
  – More rigor in developing the overall control strategies
  – More assurance that process is robust upon approval
  – More assurance of supply
  – Facilitates change - and deviation management
Acknowledgments

Thanks to:

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Multiple Technical Development Teams

Global Health Authorities
Doing now what patients need next