Identification of Critical Product Quality Attributes: Impact of Product Variants on Safety and Efficacy

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Why do we need to identify critical quality attributes (CQAs)?

How to identify CQAs?

When to identify CQAs?

MedImmune case studies
- Fc vs. CDR deamidation
- Fc vs. CDR glycosylation
Why Do We Need to Identify Critical Product Quality Attributes?

- “Drug product CQAs are used to guide the product and process development” (ICH Q8 R1)

- Provide scientific understanding of the product

- Define control strategy
  - Provide rationale for the testing plan
  - Implement process controls

- Utilize quality attribute listing to link quality attribute, tests, and control strategy
Risk Assessment and Control Strategy

Identify All Product Quality Attributes

Risk Assessment

Severity (Define CQA)

Probability

- Relationship of product knowledge to process capability

Impact on safety or efficacy

- Capability of analytical methods

Detectability

Develop Control Strategy

- Raw material control
- Operational parameters
- Procedural controls
- In-process testing

- Process validation (commercial)
- Lot release testing
- Stability testing
- Characterization testing

Re-assess as product knowledge and process understanding increase
Severity Analysis - Criticality Continuum

- Relative ranking of severity from most critical to least critical.
- Reflects the relative range of impact that quality attributes might have on the patient.
- Most critical attributes become preliminary CQAs.
- Less critical attributes may be evaluated less frequently.

A-Mab Case Study
Identification of CQAs for Product Variants

- **Severity determined by combined risk score of impact and uncertainty**
  - No consideration of the level of attributes or process control
  - Need to understand the nature of attributes and establish target product profile (TPP)

- **Impact on safety and efficacy**
  - Four ranks based on the effect
  - Impact scores have more weight than uncertainty scores
  - When impact score is moderate or high, the attribute is CQA regardless of uncertainty score

- **Uncertainty of impact on safety and efficacy**
  - Four scores based on the source of information
## Identification of CQAs - Impact Score

<table>
<thead>
<tr>
<th>Impact (Score)</th>
<th>Biological Activity or Efficacy</th>
<th>PK/PD</th>
<th>Safety</th>
<th>Immunogenicity</th>
<th>Interaction with Other QAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (10)</td>
<td>Marked change</td>
<td>Marked change in PK/PD</td>
<td>Irreversible or life-threatening AE</td>
<td>ADA detected &amp; confers limits on safety or efficacy</td>
<td>High impact</td>
</tr>
<tr>
<td>Moderate (8)</td>
<td>Moderate change</td>
<td>Moderate change in PK/PD</td>
<td>Reversible or manageable AE</td>
<td>ADA detected with moderate effect on safety or efficacy</td>
<td>Moderate impact</td>
</tr>
<tr>
<td>Low (4)</td>
<td>Minimal change</td>
<td>Minimal change in PK/PD</td>
<td>Minor, transient AE</td>
<td>ADA detected with minimal in vivo effect</td>
<td>Low impact</td>
</tr>
<tr>
<td>None (2)</td>
<td>No change</td>
<td>No change in PK/PD</td>
<td>No AE</td>
<td>ADA not detected or ADA detected with no relevant in vivo effect</td>
<td>No impact</td>
</tr>
</tbody>
</table>

ADA = anti-drug antibody; AE = adverse event; QA = quality attribute

Adapted from A-Mab case study; R. J. Harris. Critical Quality attributes for monoclonal antibodies. WCBP 2009
# Identification of CQAs - Uncertainty and Severity Scores

<table>
<thead>
<tr>
<th>Uncertainty</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No available information</td>
<td>5</td>
</tr>
<tr>
<td>Information from literature or from related molecules available</td>
<td>4</td>
</tr>
<tr>
<td>Data from laboratory or nonclinical studies with this molecule, or data from laboratory, nonclinical or clinical studies with related in-house molecules</td>
<td>3</td>
</tr>
<tr>
<td>Data from clinical studies with this molecule</td>
<td>2</td>
</tr>
</tbody>
</table>

**Uncertainty**

<table>
<thead>
<tr>
<th>Impact</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>12</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>24</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
</tr>
</tbody>
</table>

**Severity = Impact x Uncertainty**

- CQA (red, ≥16): 16, 20, 24, 30, 32, 40 and 50
- Less critical (blue, < 16): 4, 6, 8, 10, 12
Severity Assessment:
Points-to-consider

- **Patient population**
  - Premature infants/pediatric patients; adults

- **Indication**
  - Life-threatening diseases; diseases prone to immune reactions

- **Route of administration**
  - SC or inhalation may increase risk of immunogenicity compared to IV

- **Product platform**
  - IgG isotypes; mechanism of action (MOA)
Key Challenges for the Identification of CQAs

- Difficult to establish the linkage between each specific attribute to clinical performance
  - Drug product tested in clinical trials may contain multiple quality attributes (QAs) at varying levels

- Difficult to predict immunogenicity and its impact on safety and efficacy

- Bioassays or efficacy in animal models may not predict clinical outcome

- Product may not show pharmacological activity in rodent species

- Need to evaluate interaction of QAs
Strategies to Address Key Challenges for the Identification of CQAs

- Establish the linkage of specific attribute to clinical performance
  - Test for a specific attribute in clinical or enriched samples
  - Design nonclinical or clinical studies

- Predict immunogenicity and its impact
  - Evaluate theoretical tools to predict immunogenicity in humans
  - Identify variants naturally existing in plasma-derived IgGs

- Efficacy
  - Develop bioassay and orthogonal assays that reflects MOA
  - Evaluate transgenic animal models

- Lack of pharmacological activity in rodent species
  - Use surrogate antibody platform in rodent species

- Establish potential correlations between QAs during product characterization
When to Identify CQAs?

Prior Knowledge

Lead Selection
- Select the best lead. Engineer out high risk attributes. Understand attributes, TPP, and MOA.

Pre-IND
- Identify potential CQA based on literature, similar products and in vitro/nonclinical studies.

Phase I
- Gather product knowledge.

Phase II
- Revise potential CQA based on in vitro, nonclinical and clinical studies.

Phase III
- Finalize CQA based on in vitro, nonclinical and clinical studies. Studies may be designed to evaluate specific attributes.

Post-market
- Life cycle management. Continue to gather knowledge to refine CQA.

Product-specific Knowledge

CQA evaluation starts in the Research stage to ensure optimal molecular design.
IgG Product Variants

- Deamidation
- Glycation
- Hydroxyproline
- Oxidation
- Isomerization
- Deamidation
- Glycation
- Cyclization
- Thioether formation (NS0)
- Tri-sulfide bond
- Fragmentation
- Glycosylation
- Truncation

http://people.cryst.bbk.ac.uk/~ubcg07s/History.html
Case Study 1: Fc vs. CDR Deamidation

-Bioactivity/PK: Fc Deamidation of MAb A is not a CQA

- Literature and information from similar products
  - Fc region not involved in mechanism of action
  - Information from a similar MAb: no impact

- Laboratory experience
  - Fc region not involved in mechanism of action
  - IEC fractions and pH/temp stressed samples showed no impact on activity
  - Human plasma incubation study showed no impact on activity

- Non-clinical experience
  - Deamidated samples tested in animal model showed no impact on PK and activity

Bioactivity or PK: Impact x Uncertainty = 2 x 3 = 6
Case Study 1: Fc vs. CDR Deamidation

-Immunogenicity/Safety: Fc Deamidation of MAb A is not a CQA

- Literature
  - No report on immunogenicity in MAb linked to deamidation

- Laboratory experience
  - Human plasma incubation study to show deamidation is naturally occurring

- Non-clinical experience
  - No impact in an animal model

- Clinical experience:
  - Immunogenicity ELISA using normal and highly deamidated MAb did not show increase in signal when tested in pooled serum

  Immunogenicity: 2 x 2 = 4; Safety: 2 x 3 = 6

  Choose the highest score: Severity = 6 (not a CQA)
Case Study 1: Fc vs. CDR Deamidation
- Bioactivity: CDR Deamidation of MAb B is a Potential CQA

- Literature or similar products: potential impact
  - Experience with other molecules containing CDR deamidation
  - Literature on the impact of CDR deamidation in other proteins

- Laboratory experience:
  - Stressed study at pH 8.5 showed moderate impact on bioactivity
  - Evaluation of stability samples at elevated temp. showed moderate impact
  - Human plasma incubation study confirmed moderate impact

- Clinical experience:
  - Tested human PK samples confirmed moderate impact

**Bioactivity:** $8 \times 2 = 16$

**Severity = 16 (CQA)**
Major glycoforms are biantennary G0f, G1f and G2f

MAb bioactivity is dependent on the Fab binding activity and is not affected by Fc-mediated functions
  - MAb prevents binding of ligand to receptor

Potential impact on clearance
  - Variation of proportion of neutral oligosaccharides G0f, G1f and G2f has no impact on PK

A similar product did not show impact of G0f, G1f and G2f on bioactivity or PK

Jones et al., Glycobiology 2007, 17, 529-540
Case Study 2: Fc vs. CDR Glycosylation
-Bioactivity/PK: Fc Glycosylation of MAb A is not a CQA

■ Laboratory experience
  - Deglycosylated MAb and G0f or G2f enriched MAb showed no impact on activity
  - Fc not required for neutralizing activity
  - No detectable effect on ADCC and CDC activity

■ Non-clinical experience
  - Animal studies using MAb and deglycosylated MAb show no significant effects on bioactivity and PK due to oligosaccharides

■ Clinical experience
  - Human PK modeling studies show a wide range of bioequivalence for oligosaccharide proportions

Bioactivity: 2 x 3 = 6; PK: 4 x 2 = 8
Literature and information from similar products

- A humanized IgG1 minimizes safety risk
- Major glycoforms are naturally occurring in humans and are expected to present minimal immunogenicity or safety risk

Non-clinical experience

- Animal studies showed no significant effects on immunogenicity or safety

Clinical experience: no impact

Gonzales et al., Tumor Biol. 2005, 26, 31-43
Liu, TIBTECH. 1992, 10, 114-120

Immunogenicity: 2 x 2 = 4; Safety: 2 x 2 = 4
Choose the highest score: Severity = 8 (not a CQA)
Case Study 2. Fc vs. Fab Glycosylation

- CDR Glycosylation of MAb C is a Potential CQA: Bioactivity

- **Attribute:** O-linked glycan in CDR of LC

- **Literature or similar products:** potential impact
  - Literature on the impact of CDR glycosylation of other proteins

- **Laboratory experience:**
  - Isolated O-glycan containing MAb showed moderate impact on bioactivity

- **Non-clinical and clinical experience:** not collected yet

  **Bioactivity:** $8 \times 3 = 24$

  **Severity = 24 (CQA)**
Acceptable range based on prior knowledge, laboratory, nonclinical and clinical experience
Identification of CQAs is critical for product understanding and process development.

Identification of CQAs is based on impact on efficacy and safety to patient and certainty of impact.

CQA evaluation starts from the Research stage to ensure optimal molecular design; CQAs can be refined as product knowledge increases during development and life cycle management.
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