Critical Quality Attributes for Monoclonal Antibodies

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Acknowledgements

Gail Burnett
Stephen Gomez
Amita Joshi
Yung-Hsiang Kao
Lynne Krummen
Paul Motchnik
Wassim Nashabeh
Valerie Quarmby
Ron Tatischek
and many others!
Definition

• Critical Quality Attribute:
  “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 R1]
Quality by Design concepts

- Historical ranges
- Regulatory precedents
- Control space
- Target product profile
- Patient impact
- Scientific knowledge
- Process capabilities
- Specifications
- Critical process parameters
- Clinical experience
- Design space
Defining Critical Quality Attributes

- Historical ranges
- Regulatory precedents
- Control space
- Target product profile
- Patient impact
- Scientific knowledge
- Process capabilities
- Specifications
- Critical process parameters
- Clinical experience
- Design space
CQA Assessments

1. What is the potential impact to patients when high or low levels of a variant or impurity are present?
   - Impact: 2 – 20 points
   - Four impact aspects to consider:
     * Biological activity  * Immunogenicity
     * Pharmacokinetics  * Safety

2. How certain are we about question #1?
   - Uncertainty: 1 – 7 points

   • Combine as a “risk ranking & filtering” assessment

   • Assessment will need to reflect route of administration, patient class, therapeutic window etc.

   • Assigning CQAs is independent of:
     - historical ranges
     - our ability to control their levels
## Impact Definitions: Biological Activity

<table>
<thead>
<tr>
<th>Impact &amp; Rating</th>
<th>Biological Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very High</strong></td>
<td>&gt;100% change</td>
</tr>
<tr>
<td>(20)</td>
<td></td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>40-100% change</td>
</tr>
<tr>
<td>(16)</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>20-40% change</td>
</tr>
<tr>
<td>(12)</td>
<td></td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>&lt;20% change</td>
</tr>
<tr>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td><strong>None</strong></td>
<td>No change</td>
</tr>
<tr>
<td>(2)</td>
<td></td>
</tr>
</tbody>
</table>

**Consider:**
- Loss of potency for isolated forms
- Certain forms may be super-potent
  - afucosylated anti-CD20s
  - aggregates
## Impact Definitions: Pharmacokinetics

<table>
<thead>
<tr>
<th>Impact &amp; Rating</th>
<th>Pharmacokinetic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High (20)</td>
<td>&gt;40% change on PK</td>
</tr>
<tr>
<td>High (16)</td>
<td>20-40% change with impact on PD</td>
</tr>
<tr>
<td>Moderate (12)</td>
<td>20-40% change with no impact on PD</td>
</tr>
<tr>
<td>Low (4)</td>
<td>&lt;20% change with no impact on PD</td>
</tr>
<tr>
<td>None (2)</td>
<td>No impact on PK or PD</td>
</tr>
</tbody>
</table>

### Consider:
- PK: Area Under Curve (AUC)
- PD: if available

#### Example: Fc glycans
- Unlike many glycoprotein types, common IgG1 Fc glycans do not affect clearance
- Example: charge variants
  - Impact of charge variation on clearance is well-documented
  - Do small pi differences matter?
  - AUC of acidic variants matched the main form for one IgG1
## Impact Definitions: Immunogenicity

<table>
<thead>
<tr>
<th>Impact &amp; Rating</th>
<th>Immunogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very High</strong> (20)</td>
<td>ATA detected &amp; confers limits on safety</td>
</tr>
<tr>
<td><strong>High</strong> (16)</td>
<td>ATA detected &amp; confers limits on efficacy</td>
</tr>
<tr>
<td><strong>Moderate</strong> (12)</td>
<td>ATA detected with <em>in vivo</em> manageable effect</td>
</tr>
<tr>
<td><strong>Low</strong> (4)</td>
<td>ATA detected with minimal <em>in vivo</em> effect</td>
</tr>
<tr>
<td><strong>None</strong> (2)</td>
<td>ATA not detected or ATA detected with no relevant <em>in vivo</em> effect</td>
</tr>
</tbody>
</table>

**Consider:**
- prior to clinical studies, variants also present on plasma-derived IgG may be presumed low risk
  - deamidated Fc
  - glycated
  - loss of C-terminal Lys
- clinical experience is needed to make the final assessment

ATA: anti-therapeutic antibodies
## Impact Definitions: Safety

<table>
<thead>
<tr>
<th>Impact &amp; Rating</th>
<th>Safety (Potential or Observed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High (20)</td>
<td>Irreversible AEs</td>
</tr>
<tr>
<td>High (16)</td>
<td>Reversible AEs</td>
</tr>
<tr>
<td>Moderate (12)</td>
<td>Manageable AEs</td>
</tr>
<tr>
<td>Low (4)</td>
<td>Minor, transient AEs</td>
</tr>
<tr>
<td>None (2)</td>
<td>No AEs</td>
</tr>
</tbody>
</table>

**Consider:**
- Safety effects linked to specific characteristics are going to be rare
  - Examples:
    2. Gal(α1-3Gal) on cetuximab Fab glycans (anaphylaxis)
## Uncertainty Scale

<table>
<thead>
<tr>
<th>Rating</th>
<th>Uncertainty</th>
<th>Description (Variants and Host Impurities)</th>
<th>Description (Process Raw Materials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Very High</td>
<td>No information (new variant)</td>
<td>No information (new)</td>
</tr>
<tr>
<td>5</td>
<td>High</td>
<td>Published external literature for variant in related molecule.</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Nonclinical or <em>in vitro</em> data with this molecule. Data (nonclinical, <em>in vitro</em> or clinical) from a similar molecule class.</td>
<td>Component is used in other Genentech processes</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>Variant has been present in material used in clinical trials.</td>
<td>–</td>
</tr>
<tr>
<td>1</td>
<td>Very Low</td>
<td>Impact of specific variant established in clinical studies with this molecule.</td>
<td>GRAS or studied in clinical trials</td>
</tr>
</tbody>
</table>
### CQAs assigned based on severity score

<table>
<thead>
<tr>
<th>Impact</th>
<th>Uncertainty</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>5</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>100</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>20</td>
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<td>60</td>
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<tr>
<td></td>
<td>3</td>
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<td>32</td>
<td>48</td>
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<td>12</td>
<td>24</td>
<td>36</td>
<td>60</td>
<td>84</td>
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<td>4</td>
<td>8</td>
<td>12</td>
<td>20</td>
<td>28</td>
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<td></td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>10</td>
<td>14</td>
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>13 = Critical Quality Attribute

<13 = Not a CQA
## Impact Definitions

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- no reduced uncertainty will move a high-impact attribute to a non-CQA range
- severity rating is based on highest relevant impact
Lifecycle

- **Presumptive CQAs: pre-IND period**
  - identify unusual attributes to be controlled
  - internal discussion
  - focus attention on high impact or high uncertainty attributes; target these for further study

- **Refined CQAs: end of Phase II**
  - to guide process characterization study design
  - review with health authorities at end-of-Phase II meetings

- **Final CQAs: licensing and post-approval**
  - guide control strategy decisions (testing or validation)
  - may be updated with new information
Control of CQAs

- Quality attributes
- CQA Assessment

CQAs
- Control by testing
- Specifications: IPC, release, stability

Process control
- Process characterization, validation
- Characterization, comparability assessments, other monitoring

Not CQAs
CQA decision points

under development

CQAs

Specifications: IPC, release, stability

Process control

Characterization, comparability assessments, other monitoring

Control by testing

Not CQAs

ready to apply

CQA Assessment

Quality attributes

Specifications:
IPC, release, stability

Process characterization, validation

CQAs

Control by testing

Specifications: IPC, release, stability

Characterization, comparability assessments, other monitoring

CQA decision points

under development

CQAs

Specifications: IPC, release, stability

Process control

Characterization, comparability assessments, other monitoring

Control by testing

Not CQAs

ready to apply

CQA Assessment

Quality attributes
Summary

- CQAs are based on patient impact (2–20 points) and uncertainty (1–7 points), not on process capabilities or historical ranges
  - biological activity
  - pharmacokinetics / PD
  - immunogenicity
  - safety

- Application of CQAs changes during development
  - scientific understanding
  - guide process characterization / CPPs
  - establish control strategy

- Control CQAs by testing (specs) or process control

- Strategy may need refinement based on experience
Challenge

- CQA / QBD approach may change how we control MAb products

- Can we ever eliminate certain “automatic” types of testing, if justified by our CQA assessment?
  
  *Example: charge variants may be deemed “non-CQAs” by our analysis. Would the health authorities accept a control system without a charge-based method?*

- All parties need to be committed to this approach, wherever it leads…

Thank you!