Justification of specification & life-cycle management of relevant analytical methods

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Specifications of Biopharmaceuticals throughout Development (focus on mAB)

- Critical Quality Attributes (CQA) and Control Strategy
- Specifications during Early and Late Stage Development
- Case Studies / Examples
- Method Life Cycle
Definition - Specifications

**Definition**
- **List of tests, references to analytical procedures**
- **Appropriate acceptance criteria** (numerical limits, ranges, or other criteria for the tests described)
- **Confirm** quality rather than full characterization

**Control**
- **Confirm Quality & Ensure Safety and Efficacy**
- **Set of criteria to consider DS/DP to be acceptable for intended use**
- **Conformance to specification means DS/DP meet the acceptance criteria, if tested**

**Regulation**
- ICH Q6B, Specifications, ICH Topic Q1A, Stability testing of new drugs and products, ICH Topic Q1E, Evaluation of stability data, ICH Q2(R1) Validation of analytical procedures

**Life Cycle linked to**
- **Manufacturing process**
- **Preclinical and clinical studies**
- **Analytical procedures**
- **Stability of substance and product**

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Risk assessment model as applied to design of control strategy

Risk Assessment

Severity
Define CQAs

Impact on safety and Efficacy

Detectability

Capability of Analytical methods

Probability

Relationship of product knowledge and process capability

Develop Control Strategy

Control Strategy

Control of Material Attributes

In process testing

Control of Process Parameters

Testing of intermediates

Procedural controls (e.g. SOPs)

End-product controls by release testing

Life Cycle Management

Stability testing

Specifications confirm the quality rather than to fully characterize.

Only a small part of CQAs needs to be specified if comprehensive process knowledge and molecule specific data is available.
### Specification evolve during development

<table>
<thead>
<tr>
<th>Early</th>
<th>Late</th>
<th>MAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CQA</td>
<td>Does not change as a result of risk management</td>
<td>CQAs controlled via stable process instead of release specification</td>
</tr>
<tr>
<td>Process knowledge</td>
<td></td>
<td></td>
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<tr>
<td>Clinical data</td>
<td>Incorporate knowledge from clinic to set acceptance criteria</td>
<td></td>
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<tr>
<td>Characterization</td>
<td>Improved understanding of probability/detectability</td>
<td></td>
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<tr>
<td>Stability data</td>
<td>Definition of end of shelf-life acceptance criteria and degradation trends</td>
<td></td>
</tr>
<tr>
<td># Analytical tests</td>
<td>Start with platform methods and develop to molecule specific methods</td>
<td></td>
</tr>
<tr>
<td># Specifications release</td>
<td>Increase with clinical phases/may decrease with gained process knowledge</td>
<td></td>
</tr>
<tr>
<td>Tightness acceptance criteria</td>
<td>Starts with report result/platform specifications, tightened during development</td>
<td></td>
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</tbody>
</table>
Is rather a combination of described approaches than a yes/no decision

Typically, more than one information is used to finally justify the specification.
Statistical approach for release and end of shelf-life criteria

Statistical calculation (tolerance intervals or mean ± 3/5 SD) considering batch data and to assess the ranges a process can deliver

Weaknesses:

If batch data is limited / no sources of potential random process variation
→ estimate of variation not representative of true process variability

Even large data set may be derived from very few raw materials or process intermediate lots, and therefore underestimate expected sources of random process variability.
Case Study – Statistical approach for high molecular weight species (HMWs)

**DS Release**  
0.657 %  
No significant degradation (± Δ 24m DS) for DS @ -40°C  
DS release = DS stability specification (usual case)

**DS Stability**  
0.657 %  
DS stability limit + Δ DS/DP release  
Δ DS/DP = Potential degradation DP manufacture

**DP Release**  
0.752 %  
DS stability limit + Δ DS/DP release + Δ 36m DP  
Δ Ci + (Δ 0.5m 25°C)  
DP release ≠ DP stability specification (usual case)

**DP Stability**  
1.236 %
Patient centric specifications

Specifications based on risk to clinical performance, not what can be achieved by the process

Advantage: Patient-centric specifications enable appropriate control over higher risk CQAs to ensure product quality for the patient, and flexibility for lower risk PQAs for a sustainable supply chain.

Established clinical range and/or justified by in-vitro studies

Acceptance criteria wider than the limits calculated statistically is justified when there is a low risk of impact to patient safety and efficacy
Case Study - Patient centric: high molecular weight species exposure

**Request from Health Authority:** ...the specification for aggregates should be tightened in line with batch data only or it should be justified that the proposed specification is clinically qualified.

<table>
<thead>
<tr>
<th>HMW (%)</th>
<th>Release</th>
<th>Stability (24 months, 5°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.85</td>
<td>3.24</td>
</tr>
<tr>
<td></td>
<td>2.81</td>
<td>3.41</td>
</tr>
<tr>
<td></td>
<td>1.83</td>
<td>2.83</td>
</tr>
<tr>
<td></td>
<td>1.98</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.25</td>
<td></td>
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</tbody>
</table>

**Highest level used in clinic was at 3.4% HMW at 24 months**

**Drug product close to end of shelf-life had no impact on ADA incidence or ADA titers**

**Highest dose in clinic for same indication 15% higher than proposed commercial dose, i.e. up to 3.9 % HMWs could be justified**

**3.9% HMW proposed as commercial stability specification for DP**

ADA, anti-drug antibodies; DP, drug product; UP-SEC, ultra-high-performance size-exclusion chromatography
Case Study - CQA high mannose controlled via process and product knowledge I/II

I. Critical Quality Attribute (CQA) Understanding

Structure-function studies of variants
No Impact on Efficacy
Increased clearance (PK; in house data)
Literature data (e.g. 10% no impact on PK - Goetze et al 2011)
II. Development
Upstream process characterization study (PCS) increase process knowledge
Seeding cell density, temperature and feeding influence high mannose content
To control high mannose the PAR seeding, temperature and feeding was tighten

III. Process Robustness
Presence of high mannose structures robust at all scales
2-4 % across all scales an batches

before PCS
after PCS
**Method life cycle**

**Early Stage**
- Platform methods
- Loose acceptance criteria
- Validation of key parameters „fit for purpose“

**Late Stage**
- Development of molecule specific methods (optimization)
- Tightening of acceptance criteria
- Validation of additional parameters (robustness data)

**Commercial life cycle**
- Commercial methods
- Commercial acceptance criteria
- Full validation
- Periodic review of methods and acceptance criteria

**Registration**

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Summary and Conclusion

Specification setting is a complex undertaking requiring profound understanding of the molecule and its manufacturing process.

Responsible specification setting ensures safety, efficacy and quality and takes accountability to minimize the risk of „false“ rejection of batches (supply risk).

There is not a single approach for setting specifications.

Specification setting is a continuous/continued process.
Thank you for your attention!

QUESTIONS?
Additional Information
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>CMC</td>
<td>Chemistry, Manufacturing, and Control</td>
</tr>
<tr>
<td>CQA</td>
<td>Critical Quality Attribute</td>
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<tr>
<td>CPP</td>
<td>Critical process parameter</td>
</tr>
<tr>
<td>DS</td>
<td>Drug Substance</td>
</tr>
<tr>
<td>DP</td>
<td>Drug Product</td>
</tr>
<tr>
<td>EoS</td>
<td>End of shelf-life</td>
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<tr>
<td>HMW</td>
<td>High molecular weight species</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>PCS</td>
<td>Process characterization study</td>
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<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
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<tr>
<td>PQA</td>
<td>Product quality attribute</td>
</tr>
<tr>
<td>3 (5) SD</td>
<td>3 (5) Standard deviation</td>
</tr>
<tr>
<td>SEC</td>
<td>Size exclusion chromatography</td>
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</tbody>
</table>
Legend for Case Study – Statistical approach (SEC- HMWs)

- **DS (-40°C)**
  - Logarithmic scale (EMW [%])
  - Time [months]: -5, 0, 5, 10, 15, 20, 25, 30, 35, 40

- **DP (2-8°C)**
  - Logarithmic scale (EMW [%])
  - Time [months]: -5, 0, 5, 10, 15, 20, 25, 30, 35, 40

Legend:
- ○ ○ ○ Release data
- ○ ○ ○ Stability data
- solid line: Prediction from regression (stability)
- dot-dashed line: Two-sided tolerance interval from regression (stability)
- dashed line: One-sided tolerance interval from regression (stability)
- 2 2 2 Two-sided tolerance interval (release)
- 1 1 1 One-sided tolerance interval (release)
- 3 3 3 3-sigma limit (release and end of shelf-life)
- 5 5 5 5-sigma limit (release and end of shelf-life)
- solid line: Two-sided prediction interval from regression (stability)
- dash-dotted line: One-sided prediction interval from regression (stability)
- dashed line: Confidence interval from regression (stability)
High-mannose glycans on the Fc region of therapeutic IgG antibodies increase serum clearance in humans
Andrew M Goetze, Y Diana Liu, Zhongqi Zhang, Bhavana Shah, Edward Lee, Pavel V Bondarenko, Gregory C Flynn

**Strategies for Setting Patient-Centric Commercial Specifications for Biotherapeutic Products**
Margaret N. Ruescha, Luca Benettib, Eileen Berkayc, David J. Cirellia, Neha Frantzd, Martin H. Gastense, Wayne P. Kelleyf, Juliana Kretsinger, Mike Lewisc, Shawn Novickh, Barbara Rellahani, Laura Packj, Corné J. M. Stroopk, AnnSubashil, PingYinmMingZengn, JohnStults
*Journal of Pharmaceutical Sciences*, Volume 110, Issue 2, February 2021, Pages 771-784

Current and future issues in the manufacturing and development of monoclonal antibodies
Steven Kozlowskia & PatrickSwann
*Advanced Drug Delivery Reviews* Volume 58, Issues 5–6, 7 August 2006, Pages 707-722