Being Clinically Relevant While Setting Specifications

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Outline

- Definitions and Background
- Setting Clinically Relevant Acceptance Criteria and Decision Tree
- ADC Case Studies
  - Background
  - Decision Tree Examples
    - Compendial Tests
    - Unconjugated Calicheamicin
    - Unconjugated mAb
    - Moisture
Specifications are ONE element of Control Strategy.
Specifications ICH Q6B

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria. It establishes the set of criteria to which a drug substance, drug product, or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. “Conformance to specification” means that the drug substance and drug product, when tested and analyzed, meet the established requirements that will ensure the quality of the finished product. Specifications are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

Specifications are ONE part of a total control strategy designed to ensure product quality and confidence in the drug substance and drug product during development, upon which many of the specifications are based. Adherence to Good Manufacturing Practices, a validated manufacturing process, raw materials testing, in-process testing, stability testing, etc.

Specifications are chosen to confirm the quality of the drug substance and drug product, thereby ensuring the safety and efficacy of the product.
ICH Q6B

SPECIFICATIONS
Acceptance criteria should be established and justified based on:

• data obtained from lots used in preclinical and/or clinical studies,
• data from lots used for demonstration of manufacturing consistency,
• data from stability studies, and
• relevant development data.

Statistical Concepts
Appropriate statistical analysis should be applied, when necessary, to quantitative data reported. The methods of analysis, including justification and rationale, should be described fully. These descriptions should be sufficiently clear to permit independent calculation of the results presented.

ICH Q6B speaks to what data should be used to define acceptance criteria and also speaks to appropriate statistical analysis, but does not explicitly state that the statistical analysis is inherently part of defining acceptance criteria or address the relative weight of data in justifying acceptance criteria.
Clinically Relevant Specifications are tests and acceptance criteria with ranges to which the product should conform to, in order for the product to be safe and efficacious when used as labeled.

- **Clinical Justification:** Use of prior knowledge, structure function studies, in vivo surrogates, etc.

- **Clinical Experience:** Range of materials that have been part of clinical trials.

What about Process Capability?
The Challenge

Manufacturing
- Process Capability (ppk)
- Failed lots → Supply
- Lower costs
- Lose Flexibility

Patient
- Clinical Outcome
- Patient Safety
- Patient Risk
- Ensure appropriate control
The Value Proposition of Clinically Relevant Specifications

Safety & Efficacy that Meets Patient Needs

PATIENT VALUE

Manufacturability, Supply Continuity & Cost Control

Leveraging Prior Knowledge & Enhancing Product Understanding
### Setting Clinically Relevant Acceptance Criteria

<table>
<thead>
<tr>
<th>APPROACH</th>
<th>REGULATORY IMPLICATIONS</th>
<th>MANUFACTURING RAMIFICATIONS</th>
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<tbody>
<tr>
<td>Min-Max of Clinical Exposure</td>
<td>No or Limited Regulatory Risk to Tighten</td>
<td>No or Limited Accommodation for Mfg. Supply Issues. Limits for</td>
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<td></td>
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<td>Patient Delivery</td>
</tr>
<tr>
<td>Clinical Experience With Justified</td>
<td>Moderate Regulatory Risk to Tighten</td>
<td>Some Accommodation for Mfg. Process Variability</td>
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<tr>
<td>Statistical Interval</td>
<td></td>
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<tr>
<td>Beyond Clinical Exposure w/ Justification</td>
<td>High Regulatory Risk to Tighten</td>
<td>Accommodates Justifiable Mfg. Process Variability</td>
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<tr>
<td>by Relevant Surrogate Criteria</td>
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Leverage Risk Assessments Relative to Potential Impact to Safety, Efficacy & *Residual Uncertainty*

Increased probability of rejected batches (30%-40% for n<10) & likely result in drug shortages
Clinically Relevant Specification Setting Decision Tree

- **Align to USP, Ph Eur, JP, etc.**
  - YES
  - NO
  - *Based on compendial & regulatory requirements*

- **Follow ICH Impurity Guidelines**
  - YES
  - NO
  - YES

- **Pharmacopeial?**
  - YES
  - NO

- **Established Impurity Criteria?**
  - YES
  - NO

- **Justification Beyond Clinical Exposure?**
  - YES
  - NO

- **Known Safety Impact?**
  - YES
  - NO
  - YES
  - NO

- **Acceptance Criteria Defined by Justified Statistical Interval**
  - YES
  - NO
  - YES
  - NO

- **Process Concern?**
  - YES
  - NO

- **Acceptance Criteria Defined by Justified Statistical Interval**
  - YES
  - NO

- **Potency, Immunogenicity &/or PK Impact?**
  - YES
  - NO

- **Leverage S/F, PK data &/or Relevant Surrogate Criteria**
  - YES
  - NO

- **May Warrant Internal Monitor Criteria**
  - YES
  - NO

- **Alternative Options to Justify Specification Criteria**
  - YES

- **SD = Standard Deviation**

- **QUALITY ATTRIBUTES**
  - YES
  - NO
Case Studies:
Setting Clinically Relevant Specifications for Pfizer ADCS
Pfizer ADCs

**BESPONSA**

- US approval on August 17, 2017, for treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).
- Anti-CD22 mAb (IgG4)
- Calicheamicin derivative
- Conjugated via lysine chemistry

**MYLOTARG**

- US approval on September 1, 2017, for the treatment of adults with newly diagnosed acute myeloid leukemia whose tumors express the CD33 antigen (CD33-positive AML)
- Anti-CD33 mAb (IgG4)
- Calicheamicin derivative
- Conjugated via lysine chemistry
14 lots of DP were used to justify the specification acceptance criteria
- 8 lots used in clinical study
- 6 additional lots representative of manufacturing process

Tolerance Interval (TI) of release data

Additional factors: Product knowledge, stability studies, relevant development data, experience with the analytical procedure, and alignment of DSI, DS and DP specifications

~80 lots of DP were used to justify the specification acceptance criteria
- 33 lots used in clinical study
- 75 lots are commercial and/or clinical lots (potential human exposure)*

3 Standard Deviations (SD) of release data

Additional factors: stability studies, relevant development data, experience with the analytical procedure, and alignment of DSI, DS and DP specifications

* Note: US Approval 2000 and withdrawn in 2010 (PMC clinical study)
Japan Approval 2005 and remains on the Japanese market
Applying Appropriately Justified Statistics

- Reference line reflects 3SD acceptance range based on 80 lots of data for Mylotarg. Assume this is “true”.
- Computer generated 1000 random sample sets (blue dots) of either N=12 or N=50
- Associated 3SD Limit for each of these data sets is shown by the red line plotted in order of mean + 3SD
- Use of appropriately justified statistical interval ensures needed when N is limiting
Decision Tree- Compendial Tests

Align to USP, Ph Eur, JP, etc. → YES

Pharmacopeial? → QUALITY ATTRIBUTE

Established Impurity Criteria? → NO

Follow ICH Impurity Guidelines → YES

Acceptance Criteria Defined by Justified Statistical Interval → YES

Known Safety Impact? → NO

Potency, Immunogenicity &/or PK Impact? → NO

May Warrant Internal Monitor Criteria

Acceptance Criteria Defined by Justified Statistical Interval → NO

Justification Beyond Clinical Exposure? → NO

Leverage S/F, PK data &/or Relevant Surrogate Criteria → NO

Alternative Options to Justify Specification Criteria → YES

* Based on compendial & regulatory requirements

SD = Standard Deviation
The pharmacopoeias are committed to developing identical or methodologically equivalent test procedures and acceptance criteria.

- ICHQ6B

<table>
<thead>
<tr>
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<th>Meets compendial criteria</th>
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<tbody>
<tr>
<td>Appearance – Subvisible Particles</td>
<td></td>
</tr>
<tr>
<td>Content Uniformity</td>
<td></td>
</tr>
<tr>
<td>Sterility</td>
<td></td>
</tr>
<tr>
<td>Endotoxin (LAL)</td>
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Have recently received some pushback from regulators to align some acceptance criteria with process capability.
**Decision Tree - Attributes Linked to Safety**

1. **Alignment to USP, Ph Eur, JP, etc.**
   - **YES**

2. **Pharmacopeial?**
   - **YES**
   - **NO**

3. **Justified Statistical Interval**
   - **YES**
   - **NO**

4. **Known Safety Impact?**
   - **YES**
   - **NO**

5. **Impurity Criteria?**
   - **YES**
   - **NO**

6. **Potency, Immunogenicity &/or PK Impact?**
   - **YES**
   - **NO**

7. **Process Consistency Concern?**
   - **YES**
   - **NO**

8. **Acceptance Criteria Defined by Justified Statistical Interval**
   - **YES**
   - **NO**

9. **Callout:**
   - **YES**
   - **NO**

**Callout:**
- *Based on compendial & regulatory requirements

**Additional Notes:**
- Align to USP, Ph Eur, JP, etc.
- Follow ICH Impurity Guidelines
- Acceptance Criteria Defined by Justified Statistical Interval
- Leverage S/F, PK data &/or Relevant Surrogate Criteria
- May Warrant Internal Monitor Criteria
- SD = Standard Deviation
Unconjugated Calicheamicin

- Unconjugated payload in an antibody drug conjugate for an oncology indication
- Critical Quality Attribute linked to safety
- ICH Q3A Q3B and M7 Exempt
- ICH Q6B, “the acceptance criteria for impurities should be based on data obtained from lots used in preclinical and clinical studies and manufacturing consistency lots”
- MAPP 5017.2 “Establishing Impurity Acceptance Criteria As a Part of Specifications for NDAs, ANDAs and BLAs Based on Clinical Relevance”. Issued after BLA was filed. Small molecules link to qualification threshold. ‘Complex’ products link to process capability and risk assessments for establishing acceptance criteria

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<tr>
<th></th>
<th>Initial Proposal</th>
<th>Revised Proposal</th>
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<tbody>
<tr>
<td>Acceptance criteria</td>
<td>≤ 4.0%</td>
<td>≤ 3.1%</td>
</tr>
<tr>
<td>Justification</td>
<td>1/25 NOAEL</td>
<td>Tolerance Interval of all lots</td>
</tr>
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Decision Tree – Attributes Assessments on Impact to Potency, Immunogenicity or PK

Align to USP, Ph Eur, JP, etc.

Pharmacopeial?

NO

Established Impurity Criteria?

NO

Acceptance Criteria Defined by Justified Statistical Interval

YES

Follow ICH Impurity Guidelines

YES

Impurity Criteria?

YES

Beyond Clinical Exposure?

NO

Potency, Immunogenicity &/or PK Impact?

YES

Process Consistency Concern?

YES

Justification Beyond Clinical Exposure?

YES

May Warrant Internal Monitor Criteria

SD = Standard Deviation

Acceptance Criteria Defined by Justified Statistical Interval

* Based on compendial & regulatory requirements

* Based on compendial & regulatory requirements

* Based on compendial & regulatory requirements

Alternative Options to Justify Specification Criteria

Leverage S/F, PK data &/or Relevant Surrogate Criteria
## Unconjugated mAb

<table>
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<tr>
<th>Besponsa</th>
<th>Mylotarg</th>
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</table>
| • Chromatographic purification process effectively removes unconjugated mAb after the conjugation reaction  
• Batch to batch consistency of very low unconjugated mAb level  
• Level of unconjugated mAb does not change from DS to DP and on storage  
• Besponsa samples spiked with unconjugated mAb up to 50% retained bioactivity | • Historic chromatographic purification process yields levels of low conjugated fractions (including unconjugated mAb) consistently  
• Historically tested on release as part of low conjugated fractions  
• Process control needed to ensure consistency of drug substance manufacture.  
• Lack of additional structure function data |

### NON-CQA

Tested for process validation, comparability and RS characterization, no routine tests for DS and DP

### CQA

Tested at release for low conjugated fraction. Specification based on 3SD of DP, but aligned with DS data.
**Decision Tree: Justifications Beyond Clinical Exposure**

- **Align to USP, Ph Eur, JP, etc.**
  - YES → **Pharmacopeial?**
  - NO → **Justification Beyond Clinical Exposure?**

- **Follow ICH Impurity Guidelines**
  - YES → **Established Impurity Criteria?**
  - NO → **Known Safety Impact?**

- **Acceptance Criteria Defined by Justified Statistical Interval**
  - YES → **Potency, Immunogenicity &/or PK Impact?**
  - NO → **Process Consistency Concern?**

- **Acceptance Criteria Defined by Justified Statistical Interval**
  - YES → **Leverage S/F, PK data &/or Relevant Surrogate Criteria**
  - NO → **May Warrant Internal Monitor Criteria**

- **Justification Beyond Clinical Exposure?**
  - YES → **Potency, Immunogenicity &/or PK Impact?**
  - NO → Alternative Options to Justify Specification Criteria
Moisture

- Moisture is not directly linked to safety, potency, PK or immunogenicity.
- However, the level of moisture affects the rate of degradation of the drug product over time → CQA.
- Process capable of achieving low levels of moisture consistently.
- Development studies have confirmed levels of moisture content that have no negative impact on the quality of the drug product.
- Development, validation studies, stability and moisture data from early clinical batches also evaluated.

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<tr>
<th></th>
<th>Besponsa</th>
<th>Mylotarg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Release and Stability Data</td>
<td>Range up to 2.0%</td>
<td>2.7% (3SD)</td>
</tr>
<tr>
<td>Development Data and Final Acceptance Criteria</td>
<td>2.5%</td>
<td>4%</td>
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Conclusions

Patient-Centric

Clinically Relevant Specifications are a key aspect of a product control strategy to ensure safety and efficacy for the patient.

A decision tree for each attribute allows for a systematic, science-driven approach to establish specifications and set acceptance criteria →

One size will not fit all!

Acceptance criteria established and justified based on:
PRODUCT KNOWLEDGE, lots used in preclinical and/or clinical studies, lots used for demonstration of manufacturing consistency, and stability studies, and relevant development studies with appropriate statistical analysis applied.
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