Analytical Control Strategy for Biologics

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Outline

◆ In-Process Testing
◆ Process (Analytical) Control Strategy
◆ Defining Product Critical Quality Attributes (CQA)
◆ Process Mapping - Aligning CQA Assessment with:
  – CMC & Technology Transfer Process
  – Specification Life Cycle Management
◆ Specification Setting & Review process
◆ Summary & Discussion points
Process Testing

- Cell Bank: Cell-line stability, Productivity
- Manufacture: In-Process Testing
- Purification: Removal of Impurities (multiple steps)

Proprietary to MedImmune
Analytical Requirements

◆ Testing throughout the process
  – Required for process development, capability understanding and monitoring
  – Support product quality and consistency

◆ Defined controlled process = Defined controlled product
  – Understanding effect of process change (setting CPPs)

◆ Dependent on appropriate analytical tools
  – ICH Q6B: Specifications…..for drug substance and drug products should be considered as the result of a **total quality control strategy which includes cloning strategy, expression and genetic stability, thorough product characterisation, validation and consistency of the manufacturing process**, **stability data** as well as quality of the batches … in some cases additional studies on protein structure, impurity profile and/or biological activity may be needed
  
  – ICH Q5E: To ensure the quality, safety and efficacy of the drug product produced by a changed manufacturing process
  – ICH Q8 (R2): Understanding product critical quality attributes (CQAs) used to define testing requirements for process control
Process Control Strategy
(From A-Mab case study)

1. Quality attributes to be considered and/or controlled by manufacturing process
   2. Acceptable ranges for quality attributes to ensure drug safety and efficacy

Attributes that do not need to be considered or controlled by manufacturing process

Product Quality Attributes

Criticality Assessment

Safety and Efficacy Data

Prior Knowledge
Clinical Studies
Animal Studies
In-Vitro Studies

High Criticality Attributes

Low Criticality Attributes

Process Targets for Quality Attributes

Process Development and Characterization

Design Space

Control Strategy Elements

Input Material Controls
Process Controls
Procedural Controls
Process Parameter Controls

Testing
In-Process Testing
Specifications
Characterization & Comparability Testing
Stability
Process Monitoring

Continuous Process Verification

Product Understanding

Process Understanding

Link to document: http://www.casss.org/displaycommon.cfm?an=1&subartlenbr=286
Process Control Strategy

◆ **Key Elements:**
  – Raw Material Controls
  – Procedural Controls
  – Operational Parameters
  – Process Validation
  – Adherence to GMP

◆ **Analytical Control Strategy**
  – Identification of CQAs
  – Lot release & Stability testing (specification setting)
  – Characterisation and comparability testing
  – In-process testing & monitoring
Defining Product ‘Critical Quality Attributes’

◆ Platform and Product-specific Critical Quality Attributes
  – Physical, chemical, biological or microbiological property/characteristic that should be within appropriate limit, range, or distribution to ensure the desired product quality

◆ Early assessment of potential CQAs
  – Physicochemical attributes that may impact on product development e.g. during manufacturing, storage, administration
  – Minimize high risk attributes, understanding process capability (testing plan) & development
  – Define quality control strategy

◆ Patient impact: Severity assessment of the process (product)
  – Potential impact of molecular attributes and formulation components
  – Process-related impurities and contaminants
  – Product-related impurities; degradation (fragments), aggregation, PTMs (deamidation)
  – Severity Risk Assessment (scoring):
    • Impact of the attribute on safety and efficacy
    • Uncertainty in the knowledge regarding the Impact
    • **Severity (risk score) = Impact × Uncertainty**
Risk Assessment and Control Strategy

Identify All Product Quality Attributes

Risk Assessment
(Risk Priority Number: Severity x Probability x Detectability)

Severity (Define CQA)

Probability
Relationship of product knowledge to process capability

Impact on safety or efficacy

Detectability
Analytical capability & control

Develop Control Strategy

Raw material control
Operational parameters
Procedural controls
In-process testing

Process validation
Lot release testing
Stability testing
Characterization testing

Re-assess as product knowledge and process understanding increase
CQA Development, CMC Changes, and Specifications

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<thead>
<tr>
<th>QTPP</th>
<th>FTIH</th>
<th>POC</th>
<th>BLA</th>
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<tr>
<td>Product &amp; Process Design</td>
<td>Potential CQAs</td>
<td>Final CQAs &amp; Control Strategy</td>
<td>Life-Cycle Management</td>
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<tr>
<td>Pre-IND</td>
<td>PHASE 1/2</td>
<td>PHASE 3</td>
<td>POST-APPROVAL CHANGES</td>
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<tr>
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<th>Method transfer</th>
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<td>Delivery Device</td>
<td>Global Supply</td>
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CQA Development, CMC Changes, and Specifications
CMC/Tech Transfer Process

**Analytical**
- Qualification
- Validation

**Manufacturing**
- Mfg Process Change
- Mfg Transfer
- PQ lots
- Process Verification

**Strategic or Tactical Changes**
- Dose change
- Delivery Device
- Global Supply

**Development of Control Strategy**

**Specification Life Cycle Management**
Specification Setting Process

Acceptance Criteria

- Existing Knowledge of Mfg/Analytical Capability
- Historical Data from this specific Product and Process
- "Platform" Knowledge from Similar Product and Process
- Clinical Consideration and/or Experience

*Safe & Efficacious product
Justification of Specifications

Justification of Specifications (overall risk assessment) 3.2.S.4.5

- Impurities (3.2.S.3.2)
- Elucidation of Structure (3.2.S.3.1)
- Validation of Analytical Procedures (3.2.S.4.3)
- Process Evaluation (3.2.S.2.5)
- Stability (3.2.S.7.1)
- Description of Manufacturing Process and In-process Controls (3.2.S.2.2)
- Specifications (3.2.S.4.1)
- Regulatory Requirements
- Batch Analysis (3.2.S.4.4)
Review of Specifications & Revision Process
(e.g. Purity by HPSEC)

Total of 3 Peak Areas = 100.0%

% Monomer (Intact Molecule)

% Aggregates

% Fragments

NLT 95.0%
Example for Specification Revision Process
(Purity by HPSEC)

Process Change(s):
Comparability Demonstrated

- N=1, T=2M
- N=2, T=3M
- N=3, T=12M
- N=4
- N=6
- N=10
- N=15

Historical DP Release Results (T=0M)
DP Stability Results – Recommended Temperature
NLT 95.0%

Tox => Phase 1 (FTIH)
Phase 1 => Phase 2
Phase 2 => Phase 3
Phase 3 => (Pre-) Commercial

Proprietary to MedImmune
Drug Product Release & Stability Specifications

N=12 DP batches (clinical phase 2 and 3)

Analytical Capability
Mean Purity Level
Statistical Tolerance Limit

Representative Degradation for 3-years

Estimated Degradation Uncertainty

NLT 98.3%
NLT 98.0%
NLT 97.0%
NLT 95.0%

Historical DP Release Results (T=0M)
DP Stability Results – Recommended Temperature
Analytical Method Variation (long-term)

Tighten DP Shelf-Life Limit
Tighten DP Release Limit

Analytical Capability

Proprietary to MedImmune
Drug Substance Manufacturing Target

- NLT 98.3% (DP Release)
- NLT 98.7% (DS Mfg Target)
- Estimated Degradation Uncertainty
- Representative Degradation for Desired 1-Year DS Hold and Post-Thaw Handling

Tighten DP Release Limit

NLT 95.0%
Specification review process

- **Drug substance manufacturing target** (NLT 98.7%)
  - Set to ensure meeting drug product specifications

- **Drug product release specification** (NLT 98.3%)
  - Based on the expected manufacturing capability and clinical experience (N=12 batches from Clinical Phase 2-3)

- **Drug product shelf-life specification** (NLT 97.0%, 3-year shelf-life)
  - Based on drug product release specification and predicted degradation

- Justification (over time) for different shelf-life (stability) specifications to release specifications: Clinical verification using product of varying age

- Continuous monitoring of in-process control specifications: Process parameters replacing release specification testing (lifecycle management)

- Improved use of appropriate PAT / analytical technologies & capability
Process manufacturing model

◆ Optimal control strategy
  – Scientifically justified minimum and maximum specifications
  – Release different from expiry limits
  – Robust manufacture (good ‘process’ capability)
  – Early assessment using prior knowledge of analytical methods, manufacturing variability, and stability (target performance criteria)

◆ What has to fit within the commercial specification range
  – Upper and lower release ranges
    • Drives assay development/validation (and formulation, stability study design, etc)
  – Process capability over the lifecycle of the product
    • Affected by long term factors (e.g. manufacturing/release variability)
    • Impact of process and/or method changes
Summary & Discussion points

◆ Process Analytical Testing & Control Strategy: Product quality and consistency
◆ Defining what to Control: CQAs & Specification setting
◆ Trending: Assessing variability of process (at time of BLA)
◆ Selection of suitable control strategy for a CQA
  – Early assessment (pCQA’s) & testing plan (understanding of process capability)
  – Assessed (potential) impact on patient safety and efficacy
  – Specifications only part of the complete process control strategy
    • GMP, raw materials, operational parameters, product characterisation/comparability
◆ Risks in analytical control strategy
  – Multiplicity risk due to multiple CQAs
  – Setting specifications based on manufacturing variability
  – Over-regard for individual stability points (wider release ranges to overcome stability failure risk)
◆ Lifecycle monitoring of process performance
  – Defining criticality (setting specifications); use of clinical data/qualification (ICH Q6B)
  – Real-time testing (continuous process monitoring, rather than release specifications)
  – Post-approval changes: Internal process control (safety) over need for revised specifications
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