Implementation of AQbD Principles in Potency Assay Development & Overcoming Challenges on the Road to Commercialization

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Implementation of QbD Principles to Process Development Starts with an End in Mind

QbD designs quality into the process and/or drug product to ensure product efficacy and patient safety.
Limited guidance on Analytical QbD (AQbD)

- ICH Q14: Analytical Procedure Development
- ICH Q2(R2): Validating Analytical Procedures
- USP <1220> Analytical Procedure Life Cycle
- British Pharmacopeia (BP): Application of AQbD to Pharma Methods

Desired product design and performance informs analytical control strategy including identification of CQAs and approach to method development
Lifecycle of Analytical Methods Begin with Product Design and Control System Strategy

ICH Q14: Analytical Procedure Development
QTPP Describes Desired Product Performance and Informs the Analytical Control Strategy

<table>
<thead>
<tr>
<th>Category</th>
<th>Attributes for cell therapy product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>Bacterial endotoxins, sterility, mycoplasma, adventitious viruses</td>
</tr>
<tr>
<td>Identity</td>
<td>Expression of surface markers specific to the intended cell phenotype (e.g., T-cell marker CD3+)</td>
</tr>
<tr>
<td>Purity and impurities</td>
<td>Cellular impurities, dead cells/cell viability, process-related impurities (e.g., residual media components, DMSO, anticoagulant)</td>
</tr>
<tr>
<td>Potency</td>
<td>Functional response, biological activity</td>
</tr>
<tr>
<td>General attributes</td>
<td>pH, osmolality</td>
</tr>
<tr>
<td>Appearance</td>
<td>Color, opalescence, visible foreign particles</td>
</tr>
<tr>
<td>Content (Quantity, strength)</td>
<td>Total cell number, cell concentration, viability</td>
</tr>
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</table>

Potency:
- ATP is difficult to define
- Insights into MoA not available until later development stages

Various definitions:
- Cytokine Production
- Degranulation
- Killing
- Proliferation
Risk Categorization for Potency Attributes Based on Impact to Product Efficacy & Patient Safety

### Category Severity

- **Low**: Minor or negligible potential for decreased safety/efficacy. Marginal patient impact or minor transient adverse events are expected based on historical experience.

- **Medium**: Moderate potential for decreased safety or efficacy within clinical history of product. Attribute may result in manageable adverse effect, but significant patient impact is improbable.

- **High**: Potential severe effect on patient. Potential significant change in safety/efficacy or risk/benefit profiles. May result in a serious (reversible or irreversible) adverse effect.

### Uncertainty

- **Well characterized effect based on extensive in-house data (in vitro, in vivo, or clinical). Large body of knowledge in the literature for similar class of products.**

- **External published literature available on similar class of products. Well characterized effect of known. Some available internal data (in vitro, in vivo, or clinical) from this or similar class products.**

- **Limited scientific understanding, no published external scientific literature and no internal data from this or similar class products.**

### Table 4-4: Example product attribute criticality assessment outcome

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Severity</th>
<th>Uncertainty</th>
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<tbody>
<tr>
<td>Potency</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Cytokine</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Degranulation</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Killing</td>
<td>10</td>
<td>2</td>
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<td>Proliferation</td>
<td>3</td>
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<table>
<thead>
<tr>
<th>Attribute</th>
<th>Total</th>
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<tbody>
<tr>
<td>Potency</td>
<td>20 (CQA)</td>
</tr>
<tr>
<td>Cytokine</td>
<td>1 (non CQA)</td>
</tr>
<tr>
<td>Degranulation</td>
<td>6 (pCQA)</td>
</tr>
<tr>
<td>Killing</td>
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<td>Proliferation</td>
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Table adapted from PDA Technical Report No. 81; Cell-Based Therapy Control Strategy, with permission of PDA, Inc.

Exercise to determine risk category for potency: Table adapted from PDA Technical Report No. 81; A-Cell, 2021
A Robust Analytical Toolbox Addresses the ‘CQA’ Challenge for Potency Methods

- Use of healthy donor material in early development may not be representative of product manufactured from patient material

- ATP for potency may be difficult to define and potency methods may not be MoA reflective in early development

- Process changes to address manufacturing performance in late development may have unknown impact on product potency
Case Study: Platform Potency Method & Use of Representative Material from Healthy Donor in Phase I

- Benefits gained in method understanding in using platform methods
  - Technology
  - Controls and critical materials/reagents
  - Insights into method performance

- Leveraging platform methods may decrease number of activities and shorten development time

- However, representative material used to assess system suitability

Product manufactured from patient material exhibits reduced “potency” relative to healthy donor
Case Study: Addressing ‘CQA’ Challenge and Defining Potency with Surrogate Markers

Elucidating MoA via Degranulation

A surrogate marker for T cell mediated killing, degranulation is observed to be similar between healthy donor and patient material indicating no impact to product performance.
A Well Defined ATP Enables Method Understanding and Opportunities for Continuous Improvement

**ATP:**
- Basis for analytical procedures that defines the desired method performance criteria
- Process oriented and based on specification
- Refers to method platform and not specific analytical method
- Method verification/validation viewed as interrelated and not as separate processes
- ATP remains consistent however methods can change to enable continuous improvement activities

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<td><strong>Intended Purpose</strong></td>
<td>Analytical procedure should allow for quantification of drug product potency and determination of antigen specific response.</td>
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<tr>
<td><strong>Link to CQA</strong></td>
<td>Determine specific capacity of drug product to elicit an antigen specific response to a target and quantify biological activity relative to non-target control.</td>
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**Characteristics of Reportable Results**

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<th>Method Characteristics</th>
<th>Acceptance Criteria</th>
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<td>80-120% recovery of spiked drug product with “signal,” in the presence of targets.</td>
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<td><strong>Precision</strong></td>
<td>For “signal,” intermediate precision of &lt;25% CV demonstrated with qualified reference material (n&gt;5).</td>
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<td>“Signal” greater than non-target condition by 10-fold; lower detection range not verified.</td>
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# ATP Enables Better Implementation of Different Potency Methods Throughout the Program Lifecycle

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Implementation of AQbD Principles to Analytical Method Development Begins with Product Design

**IND**
- Desired Product Performance
- Product Design
- Analytical Control Strategy
- Identify CQAs
- Early Specifications
- Define ATP
- Method Design
- Method Controls

**Phase I**
- Method Performance
- Enhanced Method Understanding
- Screen/Optimize Method Parameters
- Method Risk Assessment
- Method Operable Design Region
- Enhanced Product Knowledge
- Define Specifications
- Define CQAs

**Phase 2/Pivotal**
- Achieve ATP
- Critical Method Parameters and Robustness Testing
- Method Validation
- Refine Specifications
- Refine CQAs

**Commercial**
- Method Monitoring
- Continuous Improvements

AQbD designs quality into the analytical methods to ensure method performance meets ATP and enable continuous improvements.
Considerations for Potency Methods When Difficult to Identify MoA Reflective Methods

- MoA reflective potency methods may not be identified until clinical experience is gained through Phase 2
- Method design should consider performance and practicality to drive commercialization
- Challenges with potency methods include program specific targets, lack of representative material for development, highly variable, and long assay durations due to multiple unit operations
- To facilitate commercialization, the following should be considered for method design:
  - Simple
  - Rapid
  - Low cost
  - Automation friendly
  - Availability of critical materials and reagents
  - Controls
AQbD Integrates Product and Method Design to Ensure Method Performance and Quality

Establish Analytical Control Strategy, CQAs, & ATP

Identify Methods for Product Release and Characterization

Method Performance

Method Design

• Process knowledge
• Product knowledge
• Literature

• Process Changes
• Matrix Changes Impacts Method Design
• Specification Changes

• Critical Reagents
• Method Parameters

• Method Controls
• Method Monitoring

Quality by Design

Process Design

Process Controls

Process Parameters

Product Knowledge

Process Knowledge

Product Specifications

Product Performance

Desired Product Performance

Continuous Improvement

AQbD Integrates Product and Method Design to Ensure Method Performance and Quality
Implementation of AQbD principles to method development starts with product design and defining the control strategy

CQA challenge with various definitions and approaches to measuring attributes like potency

Along with a well defined ATP, a robust analytical toolbox enables study of surrogate potency markers to enhance method understanding and identify continuous improvement opportunities

Identifying MoA reflective potency methods may not occur until late in development with accumulating experience gained through manufacturing with patient material

Implementation of AQbD principles to potency method development should consider the desired performance as well as practically of design to drive commercialization efforts
Acknowledgments

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