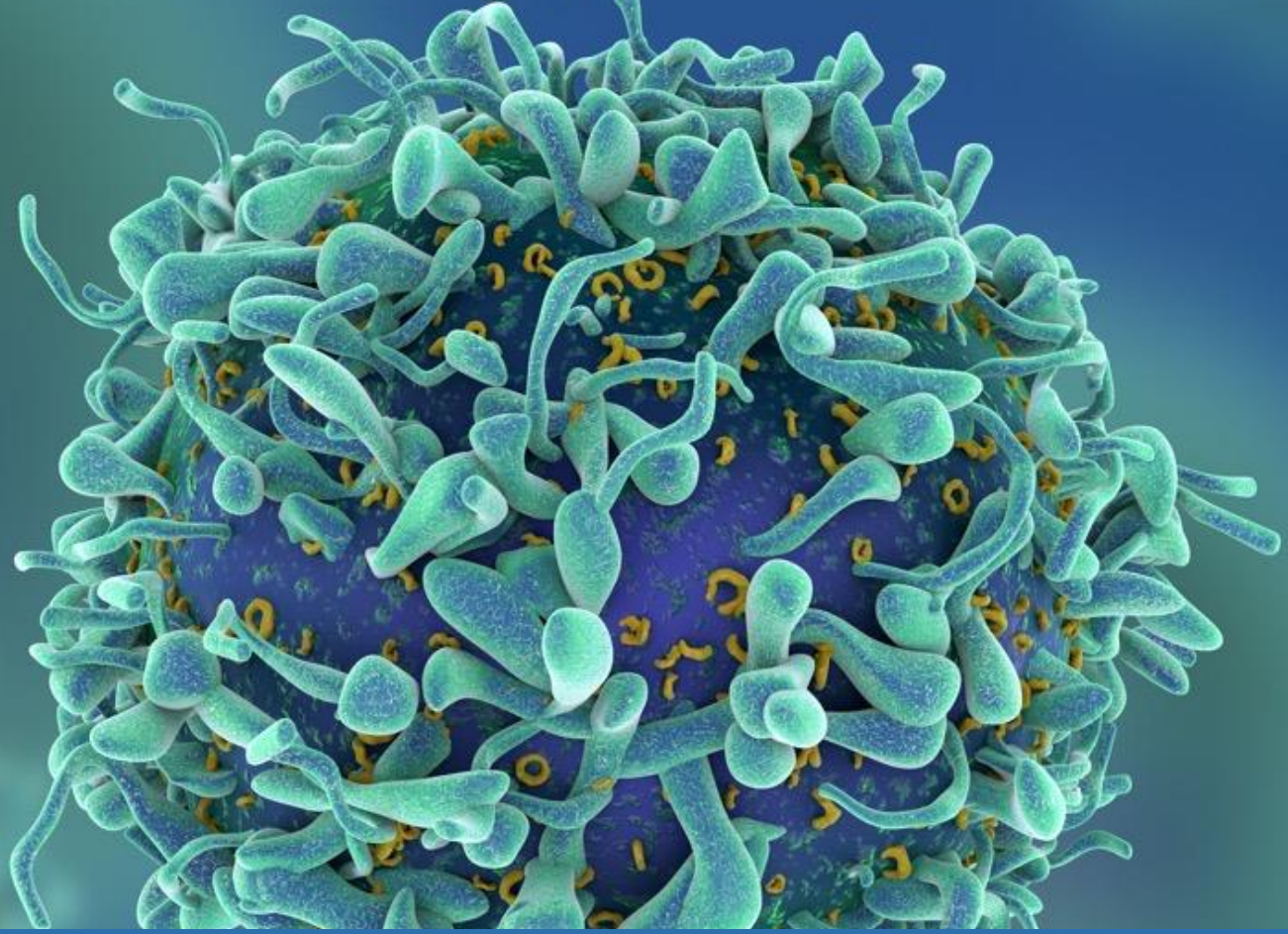
3D illustration of T cells or cancer cells

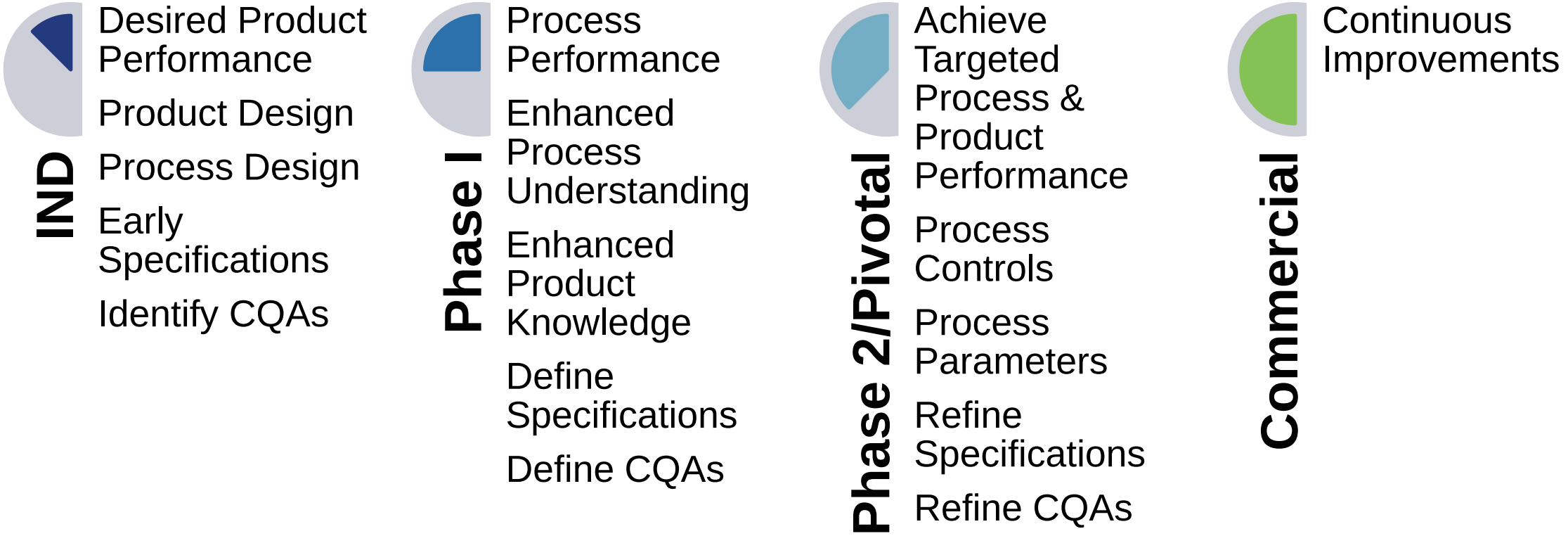


Implementation of AQbD Principles in Potency Assay Development & Overcoming Challenges on the Road to Commercialization

Kim Nguyen
Kite, A Gilead Company

Kite
A GILEAD Company

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

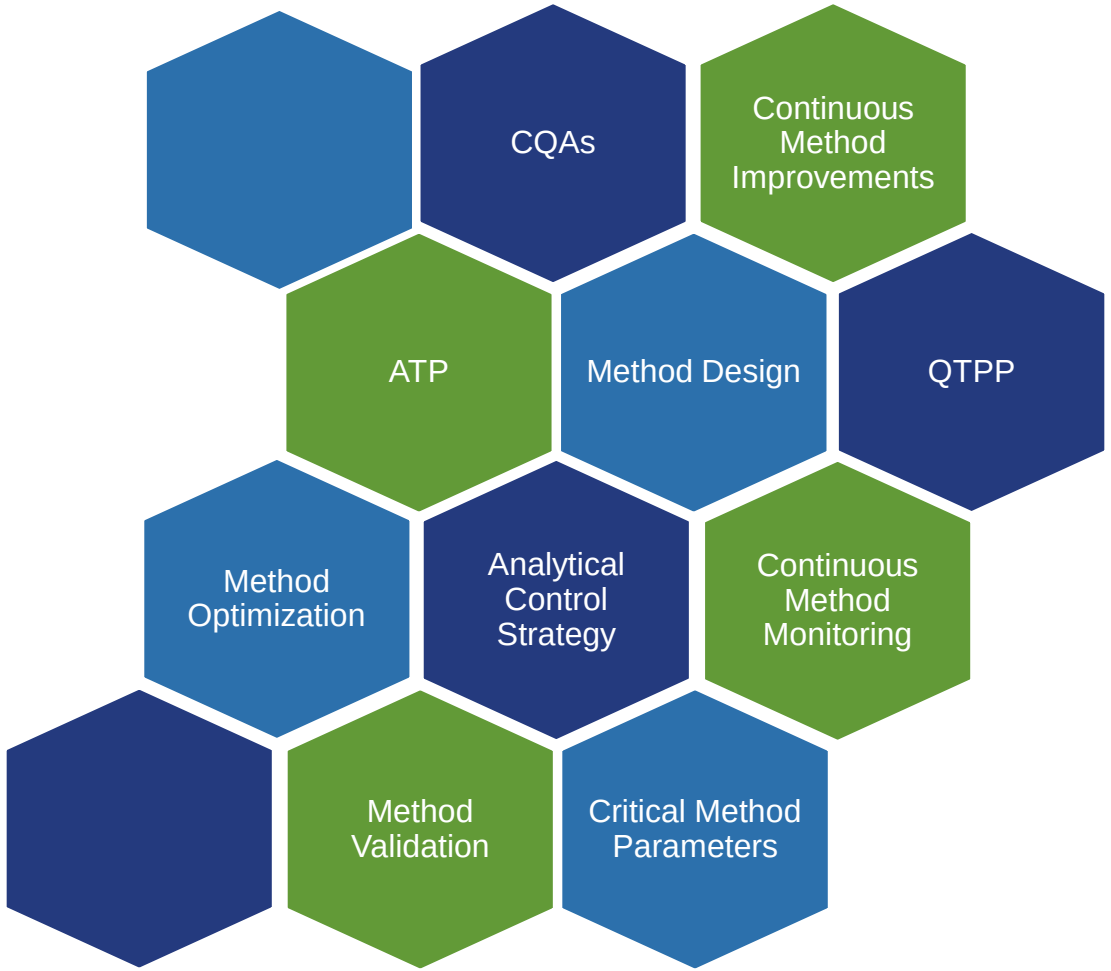


QbD designs quality into the process and/or drug product to ensure product efficacy and patient safety

Limited Guidance for Applying AQbD Principles to Analytical Methods Development

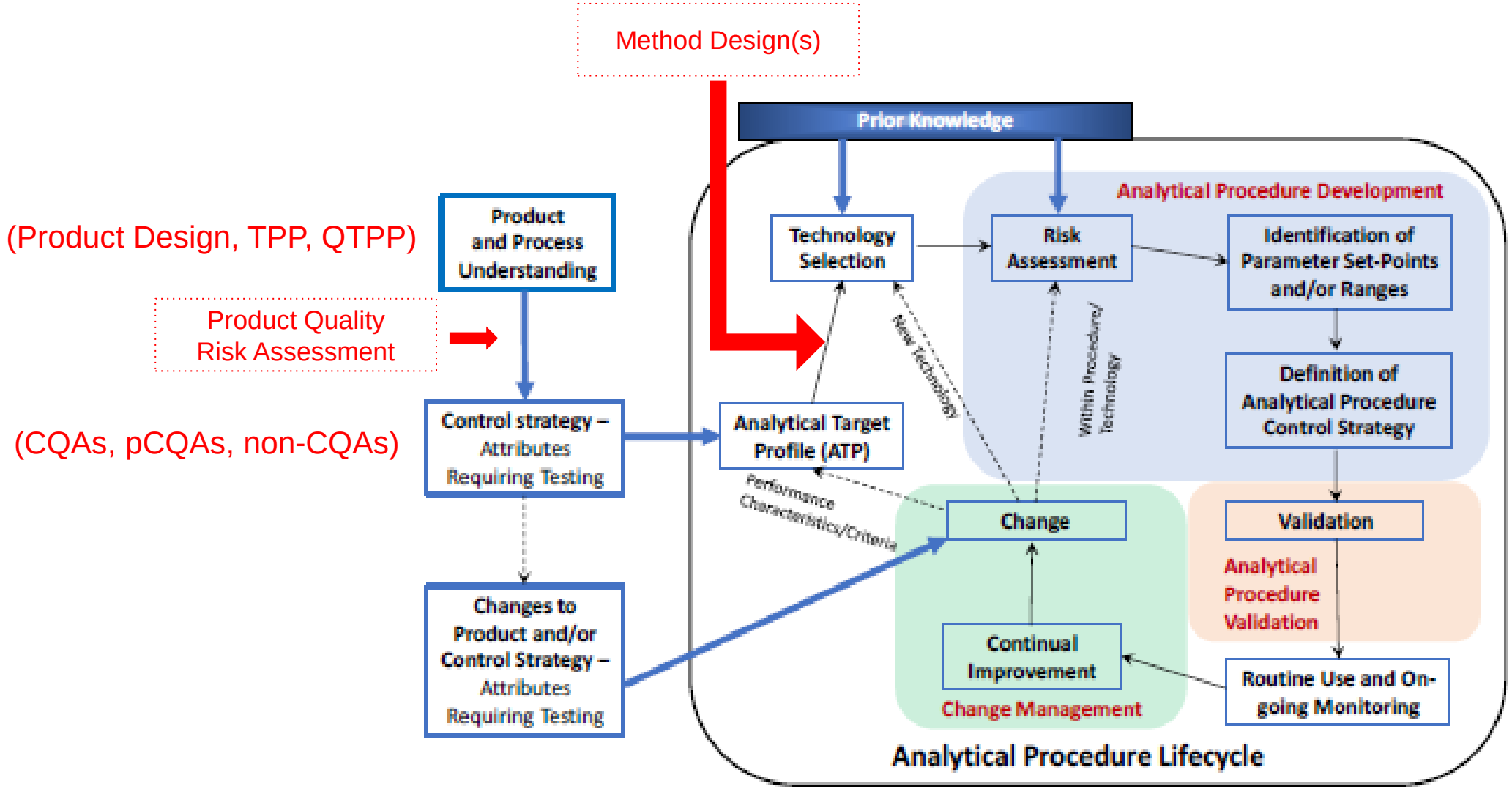
Limited guidance on Analytical QbD (AQbD)

- 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

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

A-Cell, 2021

Potency:

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

<u>Various definitions:</u>

- Cytokine Production
- Degranulation
- Killing
- Proliferation

Risk Categorization for Potency Attributes Based on Impact to Product Efficacy & Patient Safety

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

		Uncertainty		
		1 (Low)	2 (Medium)	3 (High)
Severity	1 (Low)	1 (non CQA)	2 (non CQA)	3 (pCQA)
	3 (Medium)	3 (pCQA)	6 (pCQA)	9 (pCQA)
	10 (High)	10 (CQA)	20 (CQA)	30 (CQA)

Table adapted from PDA Technical Report No. 81; Cell-Based Therapy Control Strategy, with permission of PDA, Inc.

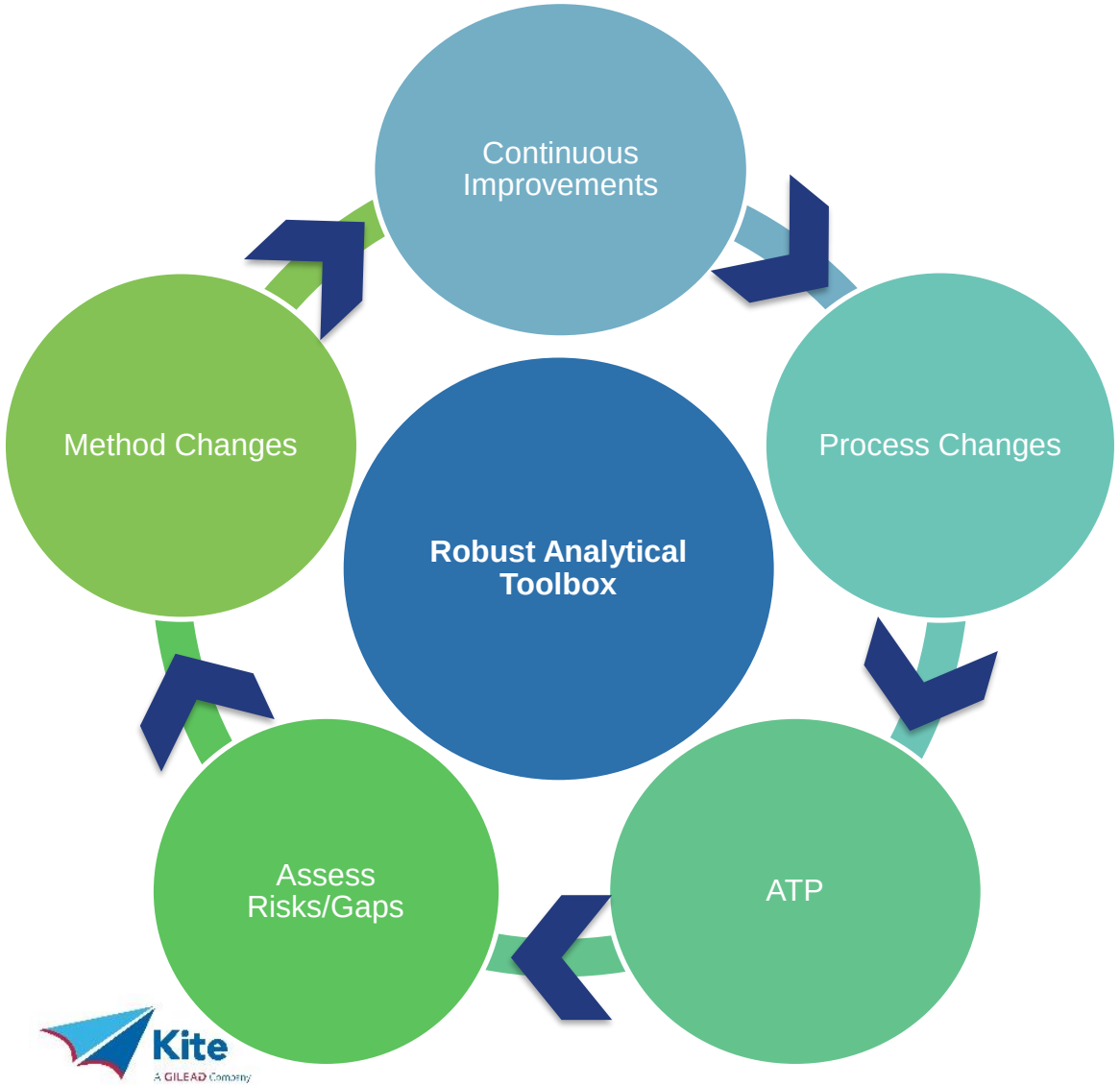
Exercise to determine risk category for potency:

Attribute	Severity	Uncertainty	Total
Potency	10	2	20 (CQA)
Cytokine	1	1	1 (non CQA)
Degranulation	3	2	6 (pCQA)
Killing	10	2	20 (CQA)
Proliferation	3	2	6 (CQA)

Category	Severity	Uncertainty
Low	Minor or negligible potential for decreased safety/efficacy. Marginal patient impact or minor transient adverse events are expected based on historical experience.	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.
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.	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.
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.	Limited scientific understanding, no published external scientific literature and no internal data from this or similar class products.

Table adapted from PDA Technical Report No. 81; A-Cell, 2021

A Robust Analytical Toolbox Addresses the 'CQA' Challenge for Potency Methods



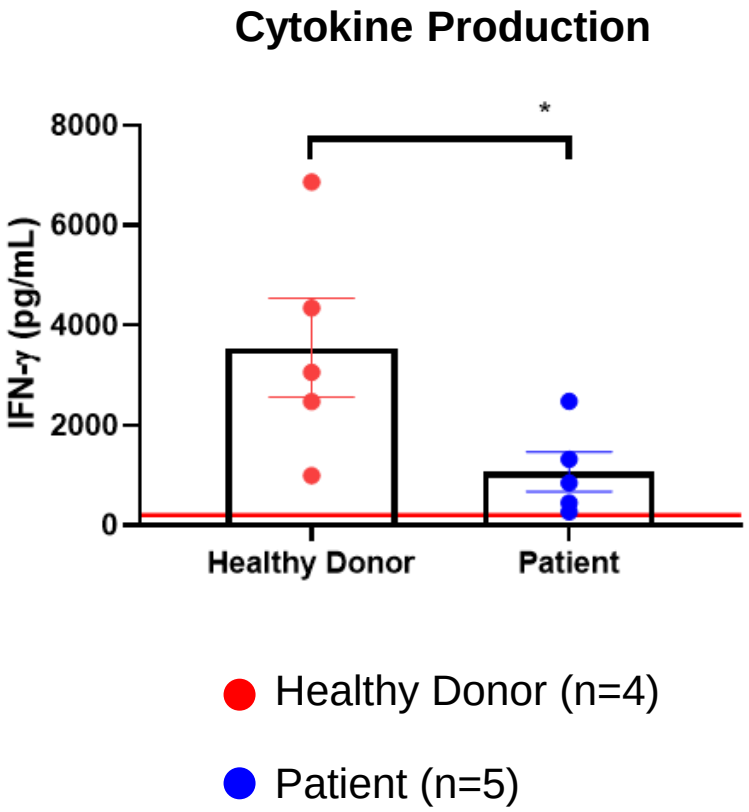
- Use of healthy donor material in early development may not be representative of product manufactured from patient material
- ATP for potency may be difficult to define and potency methods may not be MoA reflective in early development
- Process changes to address manufacturing performance in late development 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

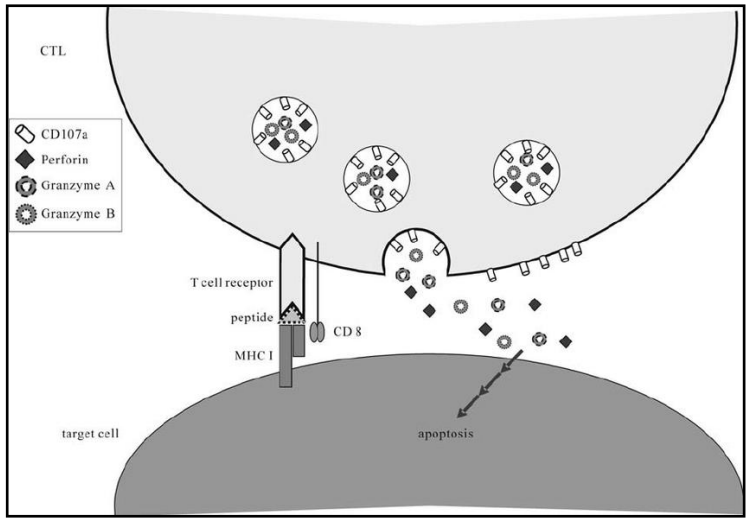
- However, representative material used to assess system suitability



Product manufactured from patient material exhibits reduced “potency” relative to healthy donor

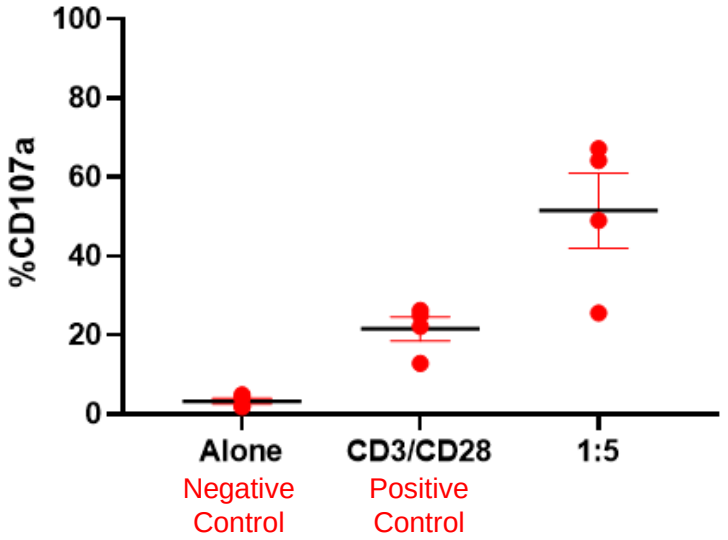
Case Study: Addressing ‘CQA’ Challenge and Defining Potency with Surrogate Markers

Elucidating MoA via Degranulation

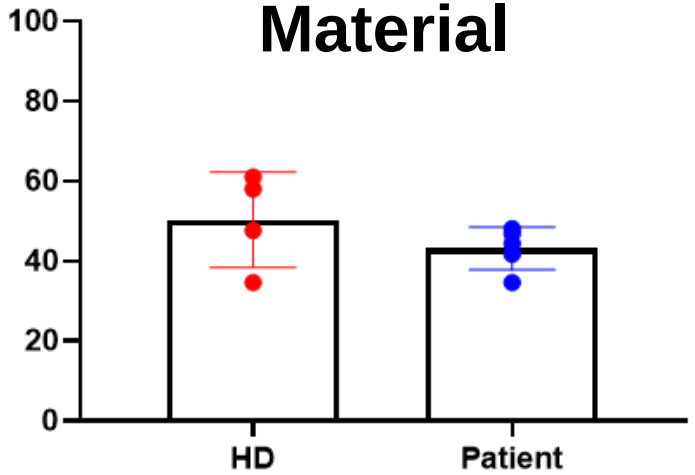


Schulte, I., et al (2008). Virologica Sinica. 23. 107-115. 10.1007/s12250-008-2941-z.

ATP Insights via Assays Controls



System Suitability Testing w/ Representative Material



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

ATP - Potency	
Intended Purpose	Analytical procedure should allow for quantification of drug product potency and determination of antigen specific response.
Link to CQA	Determine specific capacity of drug product to elicit an antigen specific response to a target and quantify biological activity relative to non-target control.
Characteristics of Reportable Results	
Method Characteristics	**Acceptance Criteria**
Accuracy	80-120% recovery of spiked drug product with “signal,” in the presence of targets.
Precision	For “signal,” intermediate precision of <25% CV demonstrated with qualified reference material (n>5).
Specificity	Analytical procedure should demonstrate “signal” to targets compared to product alone and non-target conditions.
Reportable Range	“Signal” greater than non-target condition by 10-fold; lower detection range not verified.

ATP Enables Better Implementation of Different Potency Methods Throughout the Program Lifecycle

ATP - Potency		Cytokine Production	Degranulation
Intended Purpose	Analytical procedure should allow for quantification of drug product potency and determination of antigen specific response.	✓	✓
Link to CQA	Determine specific capacity of drug product to elicit an antigen specific response to a target and quantify biological activity relative to non-target control.	✓	✓
Characteristics of Reportable Results			
Method Characteristics	**Acceptance Criteria**		
Accuracy	80-120% recovery of spiked drug product with “signal,” in the presence of targets.	✓	✓
Precision	For “signal,” intermediate precision of <25% CV demonstrated with qualified reference material (n>5).	✓	✓
Specificity	Analytical procedure should demonstrate “signal” to targets compared to product alone and non-target conditions.	✓	✓
Reportable Range	“Signal” greater than non-target condition by 10-fold; lower detection range not verified.	✓	✓

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

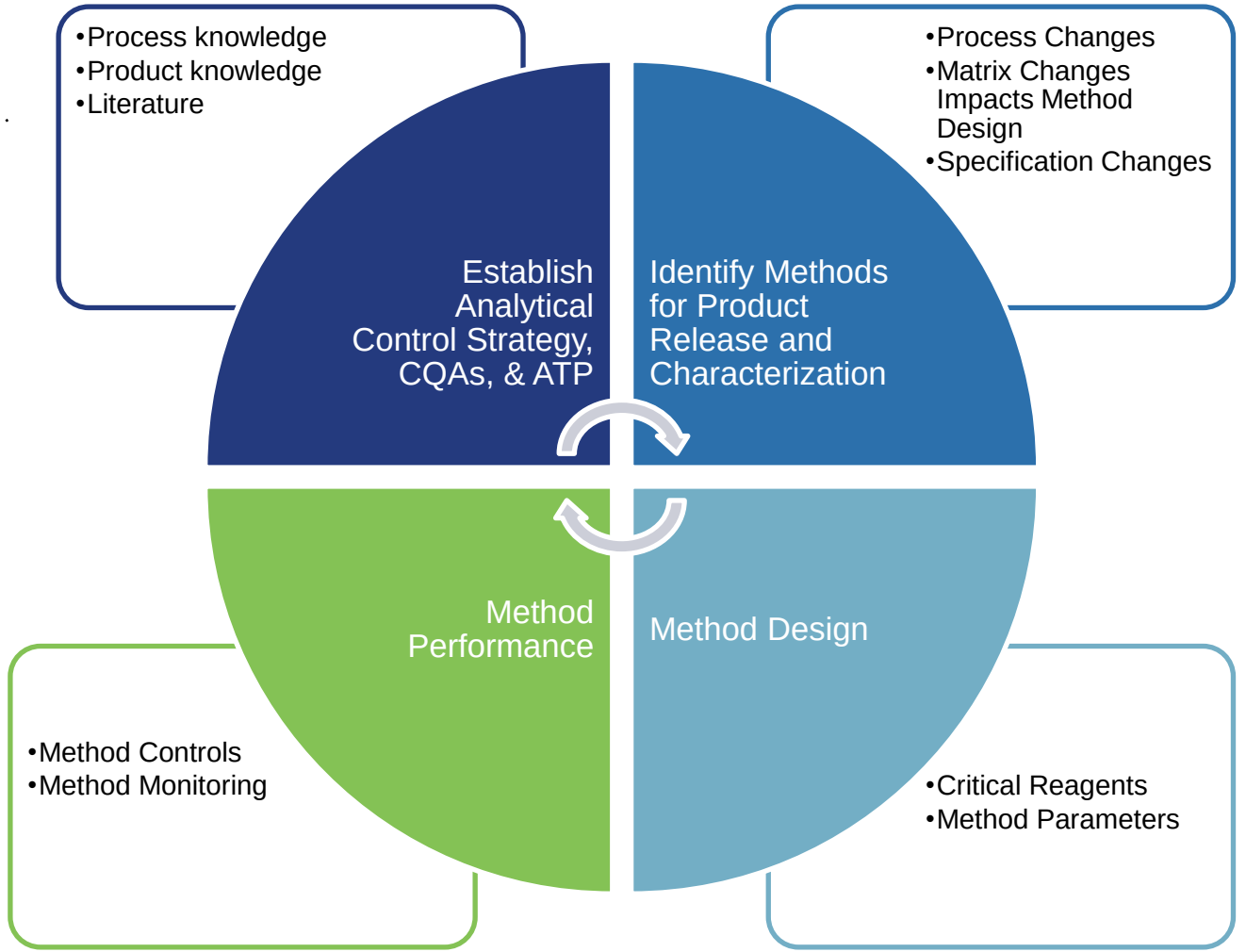
- Method Monitoring
- Continuous Improvements

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



Summary

- 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

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