Rethinking Specification Setting in Autologous Cell and Gene Therapies:

From Variability to Global Alignment

Shilpa Suravajhala
Associate Director / Analytical CMC Strategy
Vertex Pharmaceuticals Incorporated

June 2026

Traditional Paradigm for Specification Setting

Typical Assumptions

- Extensive manufacturing history
- Relatively controlled and consistent inputs
- Large datasets supporting statistical assessment
- Stable analytical methods over development lifecycle

Guiding Principles

- Statistical approaches used to define acceptance criteria
- Specifications expected to reflect process capability and product quality
- ICH Q6B is still largely applicable

References: ICH Q6B; ICH Q2(R2)

The Core Challenge

Every batch starts with a **different patient,** yet Justification of Specifications is expected to follow the **traditional frameworks**

What are we actually setting specifications against?

Key Challenges in Specification Setting

Specifications must be defined and maintained across shifting data, methods, and regulatory expectations.

Accelerated development timelines intensify each of these challenges

01 Method Lifecycle Transitions

Method changes during development create data continuity challenges and require bridging strategies that span pre- and post-change datasets

02 Evolving Method Purpose

Methods initially developed for characterization may later need to serve as routine release or stability tests, requiring reassessment of fitness for purpose

03 Analytical Complexity

Orthogonal assays measure different biological attributes and may not correlate, making integrated interpretation and specification setting inherently complex

04 Lifecycle & Global Harmonization

Specification changes must be coordinated across manufacturing sites, regions, and regulatory bodies with differing expectations and timelines

Managing Method Transitions in Accelerated Programs

Typical Scenario

- Clinical-phase data generated with qualified methods
- Commercial-phase data generated with validated methods
- Bridging assessments reveal measurable offsets between methods

Lifecycle Considerations

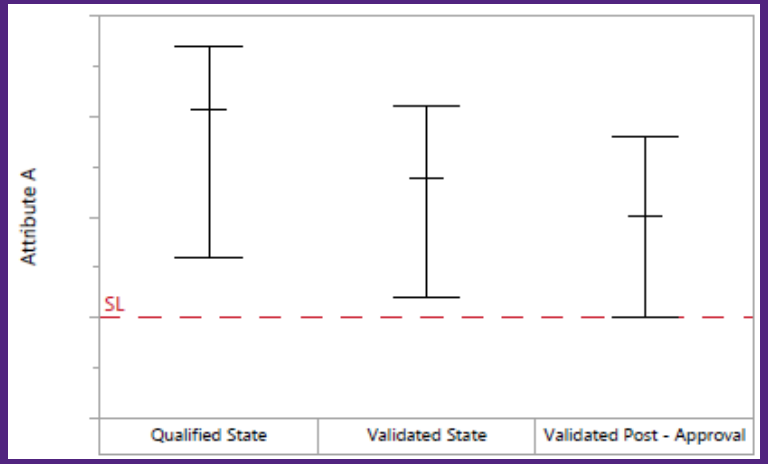
- Specifications should evolve with growing datasets and product understanding
- Post-market commitments enable iterative refinement
- Transparent documentation of changes supports regulatory alignment

Method transitions require integration of statistical, clinical, and analytical considerations

Ref: ICH Q6B, ICH Q2(R2)

Common Challenges

- Systematic offsets between qualified and validated methods
- Small sample sizes limit statistical power for bridging
- Clinical and commercial datasets may not be directly comparable due to the method offsets
- Donor variability compounds method-related differences



Recommended Approaches

- Conduct method bridging studies early to quantify offsets
- Anchor initial specifications to clinical experience
- Commit to post-approval re-evaluation with expanded data
- Document method changes and their impact transparently

From Characterization to Release: How Method Purpose Evolves

Development & Submission

Methods serve as fit-for-purpose characterization tools for product and process understanding — distinct from routine release testing

Regulatory Dialogue

Agency feedback may require justifying method purpose or incorporating assays into the release and stability strategy with formal specifications

Data Limitations

Data is often limited at implementation, methods are still evolving, and long-term stability data may not yet be available

Navigating Forward

Establish initial specifications using available data and a risk-based approach, then refine through lifecycle-driven strategies as understanding matures

Staged, lifecycle-driven specifications enable initial control while allowing refinement as data and method understanding mature

Orthogonal Potency Strategies – Specification Setting Challenges

Early Development Potency Framework

Multiple orthogonal assays implemented to support broad product understanding

Assays Evaluated:

- Upstream mechanistic activity
- Downstream biological response
- Cellular differentiation/ morphology behavior

Broad potency characterization supported early clinical and analytical understanding

Emerging Lifecycle Challenge

Evolving regulatory and lifecycle expectations

- Regional expectations for long-term assay retention evolved differently across regions
- Some assays transitioned between:
  - Release
  - Characterization
  - Extended Supportive understanding
- Historical datasets generated complicated
  - Specification alignment
  - Harmonization of control strategies

Strategic Implementation Approach

Recommended Lifecycle Strategy

- Risk-based assay refinement as product understanding matures
- Specification relevance evaluated based on
  - Biological meaning
  - Mechanism-of- Action linkage
  - Analytical robustness
  - Lifecycle utility
- Phased implementation and bridging strategies, and dual testing during transitional lifecycle stages with a Long-term focus on globally harmonization

Orthogonal potency strategies may require phased lifecycle driven refinement of specification frameworks to support evolving product understanding, and global regulatory expectations

FDA Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products; ICH Q6B

Lifecycle Management and Global Implementation

01 **Lifecycle Reality**

Specifications and methods evolve as product knowledge deepens
- Driven by accumulating data and process understanding
- Enhanced analytical capability and control strategy improvement

02 **Implementation Challenges**

Method updates across multiple sites introduce complexity and risk
- Maintaining consistent method performance and comparability across testing sites
- Complex implementation with cascading impact on release testing, stability programs, and specifications

03 **Global Complexity**

Differing regional expectations lead to divergent specification requirements
- Misaligned submission and approval timelines
- Coordinated implementation across regions

Lifecycle changes must be implemented in a controlled and coordinated manner to maintain consistency across sites and regions

What Does This Mean for Specification Setting?

- **Specifications are not static**
  They evolve as data, methods, and product understanding mature
- **Multiple lines of evidence are essential**
  Clinical, analytical, and process insights are complementary — no single dataset is sufficient
- **Data is non-uniform and evolving**
  Method transitions and new assays complicate interpretation; context is critical
- **Lifecycle and global context matter**
  Changes must be implemented consistently across sites and regions

Specification setting is an evolving, lifecycle-driven process, not a one-time statistical exercise

The goal is not to eliminate variability…

…but to ensure that what we control truly reflects

product function and patient impact

THANK YOU