Roundtable Session 2 – Table 6 – Development of Phase Appropriate Specifications

Facilitator: Li Zang, *AbbVie Inc.*

Scribe: Sandy Tang, *Orca Bio*

Abstract:

The development of phase-appropriate specifications for cell and gene therapies presents unique challenges due to product complexity, inherent variability, and evolving process understanding. Unlike traditional therapeutics, these products may be derived from living systems, involve patient-specific manufacturing, and show heterogeneity across lots and donors. Specification-setting must therefore balance limited early data, product quality, and clinical feasibility.

In early development, specifications are typically based on available knowledge of safety, critical quality attributes, and key indicators of identity, purity, potency, viability, or transduction performance. As the product and process mature, specifications should evolve with improved analytical capability, greater process control, and stronger clinical and mechanistic understanding.

This roundtable will explore how to establish, justify, and refine phase-appropriate specifications across development stages for cell and gene therapies. Topics will include the use of platform knowledge, management of assay variability and limited sample sizes, alignment with control strategy, and the transition toward commercial readiness. The discussion aims to share practical and regulatory perspectives that support scientifically justified and clinically relevant specification-setting.

Discussion Questions:

1. What are the key differences in setting phase appropriate specifications for cell and gene therapies versus conventional biologics?
2. Which critical quality attributes are most important to include in early-phase specifications for various types of cell and gene therapy products?
3. How can limited batch numbers and small patient cohorts inform meaningful specification setting?
4. What role should platform knowledge, prior product experience, or class-based understanding play in defining specifications?
5. How do current regulatory expectations influence the development of phase appropriate specifications for cell and gene therapies?

Notes:

- Biologics vs cell and gene therapies
    - Biologics
        - Better understanding of characteristics of the product
        - Easy to characterize
    - CGT
        - Harder to understand where purity, potency, etc. should fall
        - Different CQAs and diversified technologies
- Define drug substance vs critical material early on
    - Invest in characterizing the drug substance
    - Safety risks are important in early stages
- LNP and targeted LNP – DS or excipient?
    - Answer: excipient, not drug substance
        - Not expected to have potency or specifications BUT needs to be GMP-level quality (can have flexibilities)
    - New modality, so still a work in progress
    - Consider where does activity from the drug come from; is it related to mechanism of action?
        - Could be only aiding delivery, analogous to excipients in pharmaceuticals aiding delivery
- mRNA modalities – when to look at expression and potency?
    - Early stage – measure expression, looking at protein levels
        - Potency assay: transfect cells and see translation and protein expression
        - Baseline: need to know sequence for product identity
- Complex products
    - Needs potency assurance with matrix of assay
- How to set potency specification with early understanding?
    - LNP based:
        - Animal studies and tox studies using research grade potency assay
        - Relevant to evaluating potency asays
        - Engage with agency early to discuss
    - Recommend having a relative potency assay
        - Set acceptance criteria based on initial lots and have later lots relative to that lot
            - May be better for late stage
        - In early stage, is there a representative lot you can use?
            - Invest in developing reference standards
            - Precision analytics will be helpful for comparability and tech transfers
        - Reference standard in early stage
            - Use relative potency to compare batch to batch consistency

                - Have something to bridge as you work from working reference standard to primary reference standard
        - For initial batches, use non-clinical studies and tox studies to set some specifications
            - Should have enough information to set impurity specifications
            - N = 5 or 6 for justification of specs (including tox batch, development batch, engineering runs, GMP batch)
                - Assuming tx batch is representative
        - For late stage batches, use relative potency to create stringent specifications in pivotal
            - Use validated methods and PPQ to understand process and analytical variability
            - For products with small number of batches to set specifications (rare and ultra rare diseases for small populations)
                - Use umbrella IND with similar modalities and slight variations
                    - Leverage platform knowledge
                - Discuss with agency
                    - Will need to make at least 1PPQ batch, so that's one more batch
- Post approval potency specification expansion
    - Easier to do pre-approval specification expansion during clinical trial
    - Consider why specification needs to be expanded
        - If there's high variability, then maybe manufacturing process isn't mature enough
    - 10 batches in cell and gene therapy is acutally quite a bit
    - Can propose scientifically justified wide specifications with commitment to evaluated after XX batches
- Data driven approach to apply expectation across all trials
    - Science-based rationale to set acceptance criteria for release
- For cell therapies:
    - Viability is likely a critical CQA with an expected specification
    - Expected to continue characterizing leading up to pivotal
        - Expected all assays qualified for its intended use
        - Methods need to be validated for BLA
    - ISO standard for mammalian cell viability (May 2026)