Roundtable Session 1 – Table 1 – Potency Assurance Strategies for Cell and Gene Therapies

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Abstract:

An effective potency assurance strategy is essential for the consistent clinical performance of cell and gene therapies. This strategy begins with a clear understanding of the product's mechanism of action and links it to key biologically relevant and quantitative potency assays. A tiered approach, combining primary functional assays with supportive surrogate methods, ensures robustness. Assays must be able to characterize the biological activity of a cell and gene product, be able scientifically justified, able to pick sub-potent product lots, validated, and aligned with critical quality attributes. Defined acceptance criteria, risk-based control strategies, and continuous refinement throughout the product lifecycle are key to ensuring therapeutic consistency, regulatory compliance, and long-term success.

Notes:

I. Foundational Principles: MOA & Critical Quality Attributes (CQAs)

- Mechanism of Action (MOA) is Paramount: A precise and scientifically sound definition of the product's MOA is the essential foundation for all potency assurance strategies.
- Identify MOA-Linked CQAs: Determine the specific product attributes (CQAs) that directly contribute to or are indicative of the defined MOA.
- Link CQAs to Release Testing: Explicitly connect the identified MOA-relevant CQAs to the methods used for lot release testing.

II. Potency Assay Strategy & Development

- Employ a Two-Tiered Potency Assay Approach:
    - Primary (Release) Potency Assay: A validated, quantitative, and preferably cell-based assay suitable for lot release. Must be:
        - Stability Indicating: Capable of detecting product degradation over time.
        - Able to Detect Sub-Potency: Sensitive enough to identify batches falling below acceptable potency limits.
        - Robust & Feasible: Suitable for routine GMP testing within release timelines.
    - Secondary (Characterization) Potency Assay(s): Complementary assays providing deeper mechanistic understanding or orthogonal measurement of potency. Used for characterization, stability trending (supporting primary assay), and comparability assessments.

- Develop Multiple Assay Candidates: Invest in developing several potential potency assay formats early. Evaluate their performance and, crucially, correlate results with clinical outcomes as data becomes available to select the most predictive assays.
- Prioritize Surrogate Assay Development: The industry needs robust, standardized surrogate methods as alternatives to complex, highly variable, and time-consuming functional assays (e.g., co-culture-based proliferation or killing assays).

III. Addressing Key Challenges & Refining Methods

- Functional Assays May Not Predict Clinical Efficacy: Commonly measured endpoints (e.g., IFN-γ release, *in vitro* cytotoxicity) do not necessarily correlate with clinical durability or response.
- Consider Antigen Density Impact: Recognize that target cell antigen density significantly influences functional readouts (e.g., killing, cytokine release). Commercially available beads with defined antigen densities offer potential as controls or standards for proliferation/cytokine release assays.
- Manage Reference Standard Lifecycle:
    - Early development involves Interim Reference Materials.
    - Transition to fully characterized Formal Reference Standards is critical but presents significant challenges, especially for autologous products. Early variability in standards is acknowledged as a key difficulty.

IV. Correlation, Comparability & Long-Term Strategy

- Correlate Potency with Clinical Outcomes: Continuously strive to correlate potency values (from both primary and secondary assays) with clinical efficacy and safety data. This is vital for assay relevance and setting specifications.
- Leverage Characterization Assays for Comparability: Utilize secondary (characterization) potency assays to support demonstration of product comparability during process changes. Release assays alone may be insufficient.
- Strategic Assay Placement: Carefully determine which assays belong in the release panel vs. the characterization panel based on robustness, clinical correlation, and purpose.
- Implement a Robust Retain Strategy: Maintaining sufficient retain samples from clinical and pivotal batches is non-negotiable. This enables:
    - Retesting with new or refined methods.
    - Critical comparability studies post-change.
    - Addressing regulatory questions (especially at BLA filing).
    - Generating comprehensive datasets over the product lifecycle. Failure to have an adequate retain strategy jeopardizes the ability to demonstrate comparability and poses significant regulatory risk.