Roundtable Session 2 - Table 1 - Potency Assurance Strategies

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Abstract:

Each cell or gene therapy product is typically highly unique, and each product may have a complex and poorly understood mechanisms of action. Factors like patient and donor variability, site-specific or context-dependent behavior of the product, limited product lots, and assay complexity often make selection and development of a potency assay challenging.

The FDA requires a validated potency assay for licensed drug product lot release and some measure of potency/strength for all drug product lots used in the clinical study. In 21 CFR 600.3(s), the word potency is interpreted to mean "the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result."

In December 2023, FDA CBER released the "Potency Assurance for Cellular and Gene Therapy Products" draft guidance. The draft guidance recommends a "science- and risk-based approach" that includes a multifaceted approach through "manufacturing process design, manufacturing process control, material control, in-process testing, and potency lot release assays." Despite the many CGT advances in the last decade, many sponsors still struggle with potency assay development.

Discussion Questions:

Please consider the following questions based on US FDA requirements for CGT potency assays:

1. What are some barriers to developing potency assays (e.g., real/perceived, financial, scientific, regulatory, product-specific, starting-materials, CTO, etc.)?
2. What successes (or failures) have you had/heard about in potency development and implementation? When have these events occurred on your development timeline (preclinical, early/mid/late clinical studies, at the BLA review, or post-approval?
3. Who should be involved in potency assay development, implementation, and ongoing potency assay use?
4. What have been some regulatory issues or misunderstandings or miscommunications that you have either experienced or are concerned about in the future?

5. How can sponsors implement/envision implementing a “whole process” approach for ensuring success of the final potency testing? (i.e., multifaceted approach through “manufacturing process design, manufacturing process control, material control, in-process testing, and potency lot release assays.”)

Notes:

- One of the barriers for developing potency assays discussed at the roundtable was the challenge of being able to develop a single assay to address the mechanism of action (MOA) of the product at early stages of the development. Participants agreed that a matrix approach/orthogonal method is more appropriate in the early stages of development until a MOA addressing potency assay can be developed in later stages (pre-BLA), potentially showing equivalency with the earlier methods.
- The enormous cost of developing potency assays was also identified by one of the participants as a hurdle for developing an MOA based potency assay
- One of the biggest challenges identified was to develop stability indicating potency assay. One view was that if a correlation can be shown with an assay that is stability indicating with that of a potency assay, this challenge can be successfully mitigated.
- The long time taken to generate synthetic artificial cell lines for complex processes has been identified as another challenge to develop potency assays.
- One participant emphasized the correlation of clinical efficacy with in vitro potency assay development and suggested leveraging Module 2 to put together a complete picture of the product.
- The participants agreed that having retain samples from earlier lots that can be tested at later stages of the program when a MOA based functional potency assay has been developed will be helpful. This can be used for specification setting and acceptance criteria setting at later stages.
- Having a correlation with gene signature during long term culturing of cells and the downstream product can also be leveraged in cell therapy space.
- Research/Discovery, Clinical and CMC teams should work together during early development and be involved in potency assay development, implementation, and ongoing potency assay use. Research/discovery should talk with CMC and develop different potency assays based on product understanding. In later stages, CMC should discuss with Research and select some assays that can developed further as MOA based functional potency assay suitable for release testing. Disconnect between research/discovery and CMC was identified as a bottleneck for potency assay development. Having regular meetings with representatives from different departments was proposed as a mitigation strategy.

- All the participants agreed that not developing a potency assay and hoping that it would be ok with FDA is not an option. The agency understands that the sponsors know their product the best. Presenting the scientific rationale in a lucid way to the agency and having frequent regulatory interactions will help in development of successful potency assay.