Roundtable Session 1 – Table 1 – Unorthodox Approaches to Stability Programs for Small Batch-size Cell and Gene Therapies

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Abstract:

Traditional stability frameworks fit poorly when applied to the realities of cell and gene therapies operating at small scale. Autologous constructs, limited patient populations, short shelf lives, and irreplaceable starting material create a landscape where conventional ICH Q1-aligned programs can be technically infeasible, ethically fraught, or simply uninformative.

This round table invites open discussion on pragmatic and creative departures from standard stability practice. Topics may include the use of mechanistic and predictive modeling as surrogates for real-time data, bracketing and matrixing strategies adapted for n-of-1 batch sizes, platform-based comparability as a stability bridge, and the role of real-world patient outcome data in supplementing bench stability findings. We will also examine how sponsors are engaging regulators — particularly FDA and EMA — in early dialogue to establish fit-for-purpose programs that satisfy the spirit of guidance without demanding the impossible.

Participants will be encouraged to share experience with novel container-closure systems, cryopreservation as a stability strategy, and the challenge of defining meaningful acceptance criteria for living products whose identity and potency are inherently dynamic. The discussion aims to surface emerging consensus, flag unresolved tensions, and identify where new guidance or precedent is most urgently needed.

Discussion Questions:

· Accelerated and predictive modeling for AAV stability: When is mechanistic degradation modeling — covering capsid integrity, genome titer, and empty-to-full ratio drift — sufficient to support shelf-life claims in the absence of real-time data, and what does FDA expect to see to accept it?

· Stability of ex vivo edited cell products: How are sponsors defining and measuring stability for CRISPR- or vector-modified cell products post-thaw, and what parameters — viability, editing efficiency, on-target specificity, functional potency — are proving most stability-indicating in practice?

· Defining stability-indicating parameters for cryopreserved CAR-T products: Which attributes — transduction efficiency, CAR expression level, T cell phenotype, cytotoxic potency — are proving most predictive of post-thaw clinical performance, and how are sponsors prioritizing them in lean stability panels given limited batch material? Autologous CAR-T and the n-of-1 stability problem

Notes:

Cell therapies:

- Model w/ HD cells
- In use stability studies
- Bookended stability on patient discard materials
- Small scale model of container closure
- Consider being opportunistic on material availability.
- Sampling plans must encompass stability even if its a large amount of material.
- Stability indicating parameters for CAR-T: in use study is much more telling, and it tends to be potency.
- Colony forming assays for stem cells could be stability indicating.
- Degree of gene editing or gene addition doesn't seems to change over time

Gene Therapies

- Could not have a lot on stability every year it super rare claim platform, could do just LTS and start with initial know shelf life.
- Modeling is common for protein therapeutics, but need big data set.
    - Ways to use accelerated data to predict long term if degradation profile matches
- Refer to J&Js presentation to model stability
- LNPs - stability indicating parameters: adduct formation, payload purity, potency assay
- Tox batch is very important, use it to set shelf life, test with GMP assays
- Basic validation is ok w/ ultra-rare, not needed for purity assays
- Be judicious in what you test in middle of stability
- CCIT - in beginning and annually in leu of stability microbial testing. New regulatory asks to test gene therapies within 24h of manufacture.