Roundtable Session 2 – Table 1 – Unorthodox Approaches to Stability Programs for Small Batch-size Cell and Gene Therapies

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Abstract:

This roundtable focuses on innovative and non-traditional strategies for designing, implementing, and evaluating stability programs tailored specifically for cell and gene therapy products manufactured in small batch sizes. Traditional stability paradigms often face significant technical and practical limitations within this context, given the highly personalized or rare nature of the product, constraints in material availability, and accelerated timelines.

Discussion will explore: creative methods for sample management, acceptance criteria adjustments, leveraging analytical platform technologies, and statistical approaches that maximize data utility from limited material. Regulatory considerations, risk-based frameworks, and real-world case studies will be considered, with the goal of identifying solutions that preserve patient safety and product quality while driving operational feasibility. Participants are invited to share their experiences, lessons learned, and perspectives on overcoming challenges unique to small-scale CGT stability programs.

Discussion Questions:

1. What are the biggest limitations of applying conventional stability program designs to small batch-size cell and gene therapies, and how have these challenges led teams to explore unorthodox strategies?

2. Have you implemented any alternative study designs or analytical methods to compensate for limited material availability in your stability programs? What were the outcomes and what lessons did you learn?

3. How have manufacturing constraints such as limited batch size, variable supply chains, or short shelf lives influenced the design of your stability studies, and what creative solutions have proven successful in these scenarios?

4. Given the regulatory expectation for robust stability data, what approaches have you used to justify abbreviated or unconventional stability programs to health authorities when working with small-scale batches?

5. Have you encountered regulatory pushback or uncertainty when proposing novel analytical or risk-based approaches to stability for small batch-size products, and how did you resolve these issues?

Notes:

In the field of CGT, while there are approved products in market, these products are not the same: there are differences such as delivery mechanisms, length of process and patient populations. For an example cell therapy product targeting multiple markets and multiple indications, questions arose on whether the stability program for this product should be therapeutic area specific or program specific even if the product is the same across indications or programs. Another point to think about is designing the stability program depending on storage requirement and indication (for example, acute oncology or not acute immunology)?

Recent relevant guidance includes FDA's May 2026 GFI on flexibility and expectation in terms of stability for marketed vs early phase products. Additionally, ICH Q1A(R2) is a useful reference for stability.

Some discussion points are:

What are the biggest limitations of applying conventional stability program designs to small batch-size cell and gene therapies, and how have these challenges led teams to explore unorthodox strategies?

Constraints with cell therapy products include small batch sizes. For bespoke therapies (such as neoantigen-based immunotherapies), there are challenges in adding samples to a stability program. The FDA is found to be flexible with respect to these types of products. For one autologous cell therapy product, the Agency was agreeable to not qualify any methods for a phase 1 product (this is not typically seen for other products and may be unique to this particular product as it is a last therapy option to patients). Other unorthodox strategies for similar products included usage of appropriate surrogate in evaluation of long-term storage stability in LN_2. The justification for using a surrogate in a CAR-T cell product was that changing the CAR may not affect the stability of the T cell.

Justification for these strategies is recommended to be through a risk assessment that covers the following points: (1) selected product is representative of the process; (2) length of time product is cryopreserved (i.e., product to be administered acutely vs. product for chronic condition); (3) utility in performing stability programs for personalized cell therapy products where scientifically, difference in transgene is not expected to affect stability of the cell. Long-term stability evaluation is also not relevant or useful for products where the patient is dosed shortly after the product is manufactured (i.e., where the product may be stored for a short amount of time prior to administration).

For gene therapies, discussion regarding stability programs focused on number of lots to place in stability, reduced availability of samples and typical questions are whether there is potential to skipping timepoints. For AAV, sterility testing is burdensome for each timepoint. Recent feedback from the FDA showed an inclination towards performance of non-destructive CCIT instead of sterility test at each timepoint. Options such as usage of a surrogate product or reduction in the number of vials allotted for sterility test in stability compared to number of vials tested for release were discussed. Another useful approach is to assess which assays are stability indicating and to provide data to justify not including an assay in the stability program.

CDMOs can support sponsors with stability burden by placing a platform product (with same equipment, same vial size, same fill) on a stability program.

When there is no sufficient demand to manufacture at least one batch per year, the result is that a batch cannot be placed on stability each year. In such a situation, discussion may be made with Agency input to manufacture a defined number of lots by a given duration. The Agency has been flexible based on justification provided but, on the flipside, sponsors must not push the envelope too far. As long as the justification for the unorthodox method is not compromising patient safety and is not just about preserving the cost, sponsors have found the Agency willing to listen. The justification in the example product discussed in the roundtable included a summary of a thorough risk assessment that covered the stability of the virus along with prior engineering batch data from formal stability programs where the product was determined to be stable for up to 36 months. The sponsors of the discussed program had frequent interactions with the Agency where feedback indicated that manufacturing additional batches solely for long-term stability was not time well spent, as the sponsor could spend efforts on other aspects of the program such as development of appropriate potency assays.

For a case study product that was not shelf stable after a few days, there was no potency in the proposed stability program and the Agency strongly encouraged adding potency. This required qualifying a characterization assay that posed challenges to the sponsor.

While the burden of proof is always on the sponsor, there was agreement in the roundtable that more involvement of CDMOs will be helpful, particularly in finding a way to share data to prevent redundancies. The best practice is to collect all data and understand which aspects can be leveraged for other programs.

From a CDMO point of view, there has been success in defining broad attributes and being creative in establishing robust platform assays for analytics such as residual assays. The classification of assays that can be made into a platform method for the purpose of stability is important. With regards to a platform process, if there is similarity in vector and transgene size, as well as the same host cell, it would be easy to predict and pick timepoints where stability might be expected to drop off. This information may be used to justify a reduced stability program based on prior CDMO experience with a certain number of clients. It was agreed that this justification may be easier to do for early-stage products compared to products at BLA stage. It was expected to be harder to justify a platform though in situations where a transgene is 50% larger.

Ultimately, the question is: for the product where an unorthodox stability program is proposed, is the sponsor willing to administer this product to a relative or loved one? If the answer is a yes, the justification is in the right direction.

In a situation where the product is in Phase 2, and there are not enough PPQ batches, is there experience/ideas in addressing the fact that there will be limited stability at the time of BLA?

If the Agency agrees to one PPQ batch, DP sub-lots cannot be made to bolster numbers as this would be considered pseudo replication.

A justification for limited stability in this situation is that resources utilised to make 3 PPQ lots result in the resources not being available to patients. Examples: resources for shipment, customs, transport to clinical site, need for facilities in multiple regions.

In an islet cell product example, it is not practical for the clinic to take a sample from the patient dose and ship back to the manufacturer to evaluate stability due to the need to administer the product fresh and the strict temperature requirements of the fresh product. Agreement with the Agency for this product was to use an engineering batch for stability and no GMP batch to be on stability for Phase 1. The sponsor's proposal was to also perform limited testing such as viability alone for stability, but the Agency wanted additional assessments added. In this product example, cell banks (MCB and WCB) were also on stability. Considerations for adding stability indicating assays included developing a protein based functional assay and using characterization assays to propose not adding potency for future phases.

Taken together, this roundtable conversation indicated that there is no one answer for designing stability programs. The strategy depends on product type and product requirements. In addition to using Agency guidances that are available, it would be useful to leverage CDMO data. The product examples discussed today indicate that unique solutions can be developed and that the Agency may be flexible, provided they are presented with solid justifications and data. Consideration should be made to not only provide the optimal data to bolster justification but also show negative data to demonstrate ways that did not work. The key message reiterated in ICH and FDA's guidance is to engage early with regulators. Ultimately, sponsors should think of patients first and know that it is not ethical to push for a product that is unsafe for the patients.