Roundtable Session 1 – Table 6 – Development of Phase Appropriate Specifications

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Abstract:

Cell and gene therapy (CGT) products, including autologous and allogeneic CAR-T cell therapies, lentiviral and AAV-based gene therapies, and emerging genome-editing modalities, pose specification challenges that existing frameworks, such as ICH Q6B, were not designed to address. Limited batch history, heterogeneous starting materials, patient-to-patient donor variability, which may account for up to 75% of total product variability, compressed timelines, and evolving analytical capabilities all limit the data available at each development stage. For viral vector products, attributes such as vector copy number, genome integrity, and empty/full capsid ratio may shift in regulatory relevance as process understanding matures, raising a persistently unresolved question: which attributes belong in formal release specifications versus characterization testing, in-process controls, or continued process verification trending?

The regulatory landscape is actively responding. FDA's January 2026 flexible CMC framework explicitly permits permissive, descriptive acceptance criteria at IND and acknowledges that final commercial specifications cannot be expected from small investigational datasets. The ICH Cell and Gene Therapy Discussion Group (CGTDG) endorsed harmonized ATMP-specific annexes in November 2025, including a revised ICH Q1 stability annex (Step 2b, April 2025) and the forthcoming Q6(R1), to address gaps left open by current guidelines across FDA, EMA, and PMDA jurisdictions.

Despite this progress, key tensions remain: when and how should quantitative limits replace reporting-only criteria? How should potency strategies evolve from orthogonal surrogate matrices toward MoA-linked commercial assays? And how can post-approval manufacturing experience and pharmacovigilance data inform baseline specifications that prevent batch failure rates of 30–40% in some commercial CGT programs, which undermine patient access?

This roundtable convenes CMC scientists, analytical leads, regulatory strategists, and quality professionals to share decision frameworks and lessons learned across modalities, from first-in-human specification design through pivotal, commercial, and post-approval lifecycle management.

Discussion Questions:

1. What is the minimum evidence package needed to justify first-in-human release specifications for CGTs when patient-batch data are unavailable, and how should sponsors use healthy donor

material, engineering-run data, or cross-platform prior knowledge to set initial acceptance criteria for autologous or highly individualized products, while anticipating patient-to-patient variability in later phases?

2. Which product attributes should sit in formal release specifications versus characterization testing, in-process controls, stability-indicating protocols, or continued process verification trending, and how does the answer change as product and process understanding mature from Phase 1 to commercial?

3. For autologous cell therapy products, patient/donor variability may dominate total product variability. How do you incorporate donor-to-donor biological variability into acceptance criteria for release specifications, and how should sponsors justify widening, narrowing, or replacing these criteria as patient-batch data, manufacturing history, and clinical correlations accumulate?

4. Potency specification setting remains one of the highest-stakes challenges in CGT CMC. When is an orthogonal or matrix-based assay strategy acceptable at early development stages, and what evidence is needed to justify the transition toward a mechanism-of-action-linked commercial potency assay? How do you manage potency specifications across modalities (e.g., CAR-T cytotoxicity vs. AAV relative potency)?

5. How should acceptance criteria be set when clinical relevance is uncertain, assay variability is high, or batch numbers are too limited for traditional statistical derivation — and what role should risk assessments, statistical methods (tolerance intervals, Bayesian priors, equivalence testing), and clinical linkage studies play in justifying limits that are both regulatorily credible and operationally workable?

6. How are you designing stability programs to support phase-appropriate specification setting, and what role should engineering-run material, retain samples, forced degradation studies, and in-use stability data play at each development stage? What minimum stability evidence is acceptable at IND filing, given ICH Q1's new ATMP annex (Step 2b, April 2025), and how do you structure stability commitments as you approach BLA?

7. The ICH CGTDG recommendations paper (November 2025) calls for harmonized guidance on specification setting across FDA, EMA, and PMDA. Where are the most significant divergences you have encountered in global regulatory expectations for CGT specifications, considering FDA's evolving flexibility, EMA's ATMP framework, pharmacopoeial expectations, and region-specific requirements, and how do you manage a single control strategy that must satisfy multiple health authorities simultaneously?

8. Post-approval variability in CGT products has led to high batch failure rates in some programs, with reports of 30–40% failure against commercial acceptance criteria. How should the field approach the concept of data-informed baseline specifications, using longitudinal manufacturing and pharmacovigilance data, statistical methods (tolerance intervals, Bayesian priors), AI/ML tools, or platform designation frameworks to prospectively set acceptance criteria

that ensure safety and efficacy without creating unworkable failure rates, and how can this approach be built into a phase-appropriate specification strategy from IND onward?

Notes:

- In early stage of development: specifications are typically set using engineering run data. Could be wide. Data is limited or near non-existent in early stage. Expected to tighten in later phase with more data. Don't want to unnecessarily fail lots (especially since some OOS lots could be beneficial to patients).
- One participant shared using healthy donor material and setting wide specs. So far, the batches have fallen into these ACs but can already tell will need to narrow those specs. Have committed to narrowing limits after completion of Phase 1/2 trial.
- Much knowledge from earlier programs at the company can be leveraged, so it is helpful when a program is not the first one at the company.
    - Although may have platform knowledge to be able to set initial specs, if the therapy is autologous cell therapy you may not know how the starting material (from various donors) will play a role in potential differences. There could also be differences between different constructs for different disease indications.
    - Importance of investing in analytical development: if you have good quality assays in early stage, you can ~~can~~ better interpret process data.
- One participant shared their experience with two regulatory agencies giving different feedback on release assays. One of the agencies was stricter, so the company has to manage two different sets of specifications for different regions/~~-~~agencies.
- If there is a focus on efficacy early on, regulators will expect a higher standard.
- One participant shared their experience from a parallel scientific advice meeting with two regulatory agencies. The company received conflicting feedback in the same live meeting. The company now has to manage how to move forward in both regions.
- One participant's experience in a Phase 1 company: report results for some critical materials. But now there are expectations to have release specs for critical materials. Also, expectation to set DP impurity limits even though it is difficult right now to figure it out. In such a situation, leveraging GLP tox data can help set impurity limits.
- What is the minimal for your Phase 1 test panel?
    - Expected to have a potency assay even if it is an expression test in the initial phase and not your ultimate potency assay.
    - One participant has seen a regulatory authority ask for a functional, quantitative bioassay for potency, even though the other regulators were OK with the proposed potency tests.
    - FDA Guidance for Potency Assurance. Some potency at early stages to at least improve chances that patient will benefit (in addition to being safe).
    - Singular potency assay? May be easier for gene therapy and genome editing products than for a cell therapy.

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    - One participant has seen regulators request additional characterization testing (even with a robust initial release panel); perhaps can become CQAs in the future.
    - Consider using some available clinical material for early-stage assays that are currently not part of the testing plan (not even as characterization) as they need further development.
    - Companies often reluctant to invest a lot into additional tests in early stages. Time is also another constraint.
    - In-process controls could serve as orthogonal tests to fill gaps. E.g. RNA sequence: can use in-process controls to help assure sequence by the time you can include sequencing test.
    - For an LNP product, one participant has seen a regulatory agency request quantitative spec on impurity limit for truncated RNA species, as well as lipid adduct information even at early stage.
    - Start trending data as soon as you can.
- Importance of availability of materials:
    - Save retains to accommodate future studies when process and/or analytical methods change.
    - As part of analytical method development/qualification, lesser quality batches can help ascertain that the methods are dependable, e.g. for impurity assays. Also, importance of good assay controls.
- Have any roundtable participants seen specs shift?
    - One participant saw this with a cell-based assay that was transferred from another lab. Same product but couldn't get same results.
    - Another participant saw range had to be updated when a process target changed.
    - A participant cited mAb therapeutic as an example, where the reference standard shifted over time. The company had to apply a correction factor.

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