Roundtable Session 2 – Table 2 – Risk-Based Process Validation Strategies for CGT: Applying ICH Frameworks with Limited Manufacturing Batches

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Abstract:

Conventional process performance qualification (PPQ) strategies are difficult to execute for cell and gene therapy (CGT) products. Accelerated development timelines, limited batch availability, high production costs, inherent biological variability, complex assays, and patient-specific manufacturing often make the typical three-consecutive-batch approach impractical or not relevant. Despite these constraints, developers must still demonstrate that the CGT manufacturing process is controlled and capable of consistently producing product of the intended quality.

This roundtable will examine how ICH frameworks can support PPQ validation strategies for CGT products where "traditional approaches" may not be appropriate. Discussion will focus on science- and risk-based approaches — including prior knowledge, platform data, process characterization, and comparability — as foundational components of the overall validation rationale. The session will also consider lifecycle management concepts from ICH Q12, such as established conditions, post-approval change management protocols, and continued process verification, as mechanisms for expanding process knowledge after licensure while sustaining confidence in control and product quality. Finally, the roundtable will address what body of evidence is needed to justify nontraditional PPQ validation approaches (e.g., use of surrogate, split batches, post approval verification) for CGT products.

Discussion Questions:

1. Reduced PPQ Datasets & Defensibility:

When batch numbers are inherently limited, what specific criteria should determine whether a reduced PPQ dataset (e.g., one or two batches) is scientifically defensible? What other approaches have been considered?

2. Platform Data & Cross-Jurisdiction Tools:

How much weight can platform data reasonably carry across CGT products that share a vector backbone or manufacturing platform but differ in transgene, indication, or patient population — and where does that argument break down? What are the anticipated issues related to differences in regulatory tools across jurisdictions (e.g., PTMF in EU, platform designation in US)?

3. Process Characterization & Comparability Assurance:

In the absence of traditional PPQ runs, how should developers use process characterization studies and comparability assessments to build an equivalent level of assurance, and how should that rationale be documented for regulators?

4. ICH Q12 Lifecycle Mechanisms:

Which Q12 mechanisms — established conditions, post-approval change management protocols (PACMPs), or continued process verification (CPV) — offer the most practical near-term value for CGT programs?

5. Timing of Evidence & Post-Licensure Validation:

If nontraditional PPQ validation approaches shift some validation burden into the post-licensure period, what does "enough" evidence look like at the time of filing — and how do developers avoid the perception of under-validating at regulatory application filing?

Discussion Notes & Key Takeaways

1. Reduced PPQ Datasets

- Ultrarare Diseases & Batch Limitations: In ultrarare disease contexts, producing a traditional number of PPQ batches is often unfeasible. Regulators (e.g., FDA) may accept concurrent validation approaches with a reduced number of batch(es) but can lead to request of timelines for when subsequent batches will become available.

- Single-Batch Approvals & Continued Process Verification: Cases were discussed where a single PPQ batch was supported by a commitment to a Continued Process Verification (CPV) protocol. However, some sponsors hesitate to commit to extensive post-approval CPV protocol to avoid long-term or "perpetual" regulatory commitments beyond standard validation scheme.

- Low-Frequency Production: Demonstrating process consistency is particularly challenging when only one batch is produced every few years (e.g., many years apart).

- GMP Certificate Renewals: When GMP certificates come up for renewal, multiple global inspectorates schedule inspections ahead of expiration—leading to frequent back-to-back inspections—making the leverage of regulatory reliance frameworks key to mitigating this burden.

- Batch Size & QC Constraints: Batch sizes are often small and “inherited” and can lead to significant QC sampling bottlenecks, where required testing consumes a disproportionate amount of the manufactured lot.

- Use of Surrogate Material: Surrogate material has been successfully used by some sponsors; specifically, in scientific advice for autologous products in orphan indications, healthy donor material was suggested as a surrogate for validation. It is more difficult to justify a surrogate approach for off-the-shelf therapies.

2. Platform Data & Prior Knowledge

- Scope: Platform data and prior knowledge are valuable for enhancing process understanding. It could be applied to specific unit operations or sub-components (e.g., plasmid production) rather than the entire manufacturing process.

- Data Volume Requirements: Leveraging platform concepts still requires a substantial history of lots to adequately substantiate knowledge claims across different products which are often not available.

3. Scale-Down Models (SDMs) & Process Characterization

- Scale Down Models (SDM): Scale-down models can justify operating ranges, but qualifying them requires significant effort. Companies must balance the investment in qualifying SDMs against running additional full-scale batches.

- Representativeness of SDM: Unlike traditional monoclonal antibody (mAb) processes where x thousand L fermenters are scaled down to a few hundred mL, CGT scale-down models involve scaling down from liter-scale processes to benchtop mL volumes.

4. Lifecycle Management tools (e.g., ICH Q12, PACMP, CPV)

- PACMP: Post-Approval Change Management Protocols (PACMPs) are generally not realistic for initial process validation itself. PACMPs can be useful for negotiating reduced PPQ batch requirements for subsequent process change. However, PACMP may carry high regulatory risk in initial submission when initial dataset sizes are very limited.

- Established conditions and Product Lifecycle Management document (PLCM): EC and PLCM may be helpful in clarifying what elements would need to be reported if changed from those that do not need to be reported, however, these tools have not been consistently implemented around the world and is unlikely going to support significant reduction of PPQ dataset.

- Continued Process Verification (CPV): Lower amount of PPQ dataset could be achieved with a commitment to follow a CPV protocol (see discussion above). However, CPV concept was traditionally designed for larger commercial campaign sizes (e.g., 30+ lots) and would require some adaptation for low-volume CGT programs.

- Bracketing Approaches: Bracketing validation strategies are well-established for non-ATMP products, but experience in the ATMP/CGT space remains limited.

5. Regulatory Pathways

- Conditional Approvals: Conditional Marketing Authorizations may be leveraged to submit verification data at a later stage. Conditional pathways may not be intended for CMC data (often intended for clinical data) and may always be accepted.

- Scientific Advice (Scientific Advice / ScAd): Early engagement with regulators provides valuable guidance, though non-binding advice remains a challenge. Experience with joint or parallel advice programs (e.g., EMA and FDA) is still limited.

- PRIME Scheme (EU): Early access pathways such as the EMA PRIME (PRIority MEdicines) scheme provide enhanced interaction and accelerated assessment for products

targeting major public health needs, helping align process validation strategies earlier in development.

- Clinical Data & LTFU: No experience was shared regarding the use of post-approval clinical data or long-term follow-up (LTFU) to justify a lack of initial validation data.

- Benefit-Risk & Unmet Need: Regulatory flexibility on PPQ datasets is strongly tied to the benefit-risk profile and unmet medical need. The bar for validation rigor is significantly higher if alternative treatments are already available.

Key Takeaways

1. Flexibility Requires Strong Rationale: Regulators accept reduced PPQ batch numbers when duly justified. Benefit/risk, unmet-medical need and post-market verification can be used to support the claim.

2. Surrogate Materials: Surrogate material (e.g., healthy donor cells) can support validation for autologous products in orphan indications, whereas justifying surrogates for off-the-shelf therapies may be more challenging.

3. Regulatory Reliance & GMP Renewals: Leveraging regulatory reliance frameworks is essential to mitigate the inspection burden caused by frequent back-to-back GMP certificate renewal audits across global inspectorates.

4. Platform Data for Unit-Operation: Platform knowledge may be easier to introduce to shared unit operations (e.g., vector or plasmid production) rather than full end-to-end processes and still requires sufficient supporting data.

5. SDMs Present Scale-Up Trade-offs: Scale-down models are valuable for defining operating ranges, but the burden of SDM qualification must be carefully weighed against performing full-scale runs.

6. Early Regulatory Dialogue & Priority Pathways: Utilizing early scientific advice and priority regulatory pathways (such as the EU PRIME scheme) helps align validation expectations, surrogate material use, and post-licensure verification plans early in development.