**Roundtable Session 2 – Table 5 – Nontraditional Process Validation Approaches**

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**Abstract:**

Cell and gene therapy products often do not fit neatly into traditional process validation models. Limited batch numbers, individualized manufacturing, compressed development timelines, high batch costs, evolving potency assays, and complex biological variability can make conventional PPQ strategies difficult to execute or justify. Yet sponsors must still establish a robust, science-based demonstration that the process is controlled and capable of consistently producing product of acceptable quality.

This roundtable will examine nontraditional process validation approaches for cell and gene therapies, with emphasis on risk-based PPQ strategies, use of prior knowledge and platform data, process characterization, comparability, continued process verification, and validation packages for accelerated or low-batch-number programs. Participants will discuss how to define "sufficient evidence" when conventional validation models are not feasible, how to communicate the rationale to regulators, and how to maintain patient-centric flexibility while preserving confidence in process control, product quality, and clinical safety.

**Discussion Questions:**

1. When traditional PPQ expectations are impractical, what types of evidence can provide sufficient confidence that a cell or gene therapy manufacturing process is validated?

For example: process characterization data, engineering runs, clinical manufacturing history, platform knowledge, small-scale models, comparability data, or continued process verification.

2. How should sponsors justify the number of PPQ or validation batches for individualized, autologous, ultra-rare, or very high-cost therapies?

What factors should influence the justification: patient risk, process complexity, prior manufacturing experience, batch success rate, process variability, or clinical benefit?

3. What role should continued process verification play when pre-licensure batch experience is limited?

How much reliance on post-approval monitoring is appropriate, and what commitments, triggers, or acceptance criteria should be included?

4. How can platform manufacturing experience be leveraged to support validation of a new cell or gene therapy product?

What elements are most transferable, such as vector platform, cell-processing steps, analytical methods, equipment, facility design, raw materials, or control strategy?

5. How can sponsors balance process evolution with validation readiness in accelerated development programs?

At what point should the process be considered sufficiently locked, and how should late-stage changes be handled without delaying patient access?

**Notes:**

The roundtable attendees discussed emerging regulatory flexibility for process validation in cell and gene therapies, particularly for rare and ultra-rare indications where traditional PPQ expectations may not be practical. While the traditional three-batch PPQ paradigm remains a reference point, there is increasing acceptance of alternative approaches. The use of a single pre-licensure PPQ batch combined with post-approval commitments, supported by a strong analytical package, platform knowledge, and manufacturing experience, was discussed. Overall, the attendees agreed that success hinges on a risk-based approach, early regulatory engagement, and a well-supported validation strategy that ensures patient safety and product quality without unnecessarily delaying access.

1. Alternative Evidence When Traditional PPQ Is Impractical

- There is growing regulatory flexibility, especially for rare and ultra-rare diseases.
- Traditional PPQ expectations may be adapted with sound justification.
- Non-traditional approaches must be clearly framed as risk-based strategies to reduce burden and not as “shortcuts”.
- Regulators expect a scientifically justified, totality-of-evidence approach, not a reduction in rigor.
- Engage with regulators early and proactively. Present well-reasoned proposals for non-traditional strategies.
- Be prepared for possible rejection, regulators must balance access to therapy with protection of vulnerable patients.

2. Number of PPQ Batches

- Three consecutive batches remain a benchmark, but there is increasing flexibility in how those batches are defined and achieved.
- Not all batches/data may be required pre-licensure.
- One PPQ batch prior to licensure with additional batches committed post approval was proposed as an emerging model.
- Flexibility “depends” on factors including the rarity of the indication, manufacturing complexity and variability, prior knowledge/platform experience, clinical benefit, and patient risk.
- PPQ batches may not need to be consecutive. Validation protocols for cell therapies should account for batch failure scenarios.
- Regional insights:
    - FDA and EU are open to flexible approaches if justified
    - Health Canada has shown flexibility, especially in some rare disease cases

3. Role of Continued Process Verification

- Experience from the group indicates that post approval data is additive, not a replacement.
- CPV can become an added burden instead of providing flexibility if layered on top of reduced PPQ.

4. Leveraging Platform Manufacturing Experience

- Platform knowledge is highly valued, especially for lentiviral vector production and standardized cell processing steps.
- A single verification batch may be sufficient for lentiviral vectors if platform and CDMO data are strong. In some cases, PPQ may not be required for drug substance but is still required for drug product manufacture.
- Access to platform validation data is critical. This may be a challenge depending on the CDMO.
- A strong control strategy and comparability data are required.
- An emerging trend from the EU is that critical starting materials (mRNA etc.) are being considered as drug substances, requiring deeper characterization.

5. Balancing Process Evolution versus Validation Readiness

- Process should be sufficiently stable and understood before PPQ to avoid changes close to submission.
- Develop comparability and bridging studies.
- Analytical methods must be validated prior to PPQ. This is non-negotiable. Consider submitting method validation data with IND/CTA for early feedback.
- Comparability will require retains for testing. Bridging with clinical material may be expected. Build this into plans early.
- It is recommended to stage changes strategically rather than implementing multiple changes simultaneously. This includes adding additional manufacturing sites. Too many changes increase review complexity. A clear “story” outlined in the submission is preferred. Changes can be made post licensure, including adding additional manufacturing sites.
- Methods may also be changed, but there needs to be a clear justification and a bridging strategy. Retains are required for these studies.