Roundtable Session 1 – Table 5 – Nontraditional Process Validation Approaches

Facilitator: John Kerwin, *Ascidian Therapeutics*
Scribe: Isabella Palazzolo, *Intellia Therapeutics*

Abstract:

Let's be real: trying to fit advanced therapies into a "three-consecutive-batches" box is like trying to fit a square peg into a viral vector—it's just not happening. Fortunately, the latest FDA guidance confirms that we can ditch rigid checklists for a flexible, risk-based approach to Process Validation (PV) that favors process understanding over arbitrary batch counts. Join us to geek out over how to justify your validation strategy using prior knowledge and platform magic to keep your timelines moving. We'll brainstorm ways to navigate concurrent release of PPQ batches and leverage post-approval experience to refine those initial, less-than-statistically-robust specifications. It's all the rigor of high-quality clinical science, just with the non-traditional flexibility needed to reach patients faster.

Discussion Questions:

1. Since the FDA doesn't specify a minimum number of PPQ batches, what "context-specific factors" do you find most persuasive when justifying a lean validation run to regulators?
2. The new guidance mentions "concurrent release" of PPQ batches for commercial distribution—how are you planning to handle the risk of distributing a batch before the full validation protocol is technically complete?
3. When leveraging prior knowledge from "sufficiently similar" products, where do you draw the line between a "representative" process and one that requires its own fresh validation data?
4. The FDA now considers analytical method validation using as few as a single representative lot—what are the biggest hurdles in proving such a method is "sufficiently robust" for its intended use?
5. Do you think we've reached a point where US and EU expectations for PPQ are actually aligned, or is the FDA's new CMC Flexibility guidance just a different flavor of the EMA's PRIME toolbox?
6. With the enhanced flexibility that is depicted in the new FDA guidance, how would a sponsor ensure that PPQ effort have used sufficient variability to vet the robustness of the process?
7. Other than a lifetime of post-approval changes, what are the biggest technical "regrets" or supply chain risks we face by performing less than three PPQ runs before licensure?

Notes:

Q1 – Justifying a lean PPQ run: context-specific factors

Example of justification that were reported helpful in justifying an lean PPQ campaign included: 1) prior product experience and platform in broader terms,

2) Rare indications which would result in commercial demand may be too limited, and product may expire before use; very short shelf life may also preclude multiple runs. If PPQ runs involve healthy donors, running three batches may be wasteful.

3) Simplicity of the process (e.g., single unit step, straightforward cell culture).

4) When multiple complex drug substances are already subject to extensive PPQ, one PPQ for the drug product may be justifiable.

5) Emergency authorization scenarios were discussed as another context-specific factor.

6) The maturity of GMP factors, facility readiness, QMS, and CAPA systems in place were considered relevant to the overall justification.

The table agreed that success is more likely when the strategy is aligned early enough that some process characterization (PC) studies can be designed to support a one-PPQ strategy.

Q2 – Concurrent release of PPQ batches before full validation protocol closure

Discussion around what needs to be in place to release a batch for human use before PPQ is complete (e.g., in a 3-PPQ protocol not closed until post-licensure). Suggestions included having an interim report in place to include in the initial BLA, or potentially negotiate with FDA the possibility to obtain informed consent from patients for the sale of PPQ material was raised.

For small molecules it was acknowledge that it’s more common practice, and leveraging prior knowledge and scale-down model data to support the PPQ protocol were considered important elements

---

Q3 – Drawing the line between "representative" process and fresh validation data

Incorporating concepts of process lock, scalability, and representative process into protocol development was recommended.

Leveraging a platform designation can reduce the number of required PPQ batches. Recently in the 2026 guidance for flexibility, FDA recommends using the small P platform to reduce PPQ runs. In principle the table agrees that PPQ acceptance criteria should ensure the product delivers the same results as claimed on the label — therefore all batches supporting the label claim should be leverageable to reduce the scope of PPQ. The plausible mechanism may also support batch reduction.

However as a cautionary message, the table acknowledges that a CDMOs' prior knowledge cannot be leveraged in a sponsor's BLA; DMFs for DS and DP cannot be leveraged in a BLA submission and the actual data needs to be included in the BLA. This may limit the ability to leverage that prior knowledge. Analytical comparability alone was also noted as insufficient to justify use of a prior product, based on FDA feedback — even with equivalence testing for individual claims, the totality of small changes may still trigger the need for clinical studies.

In general the table acknowledge the challenge derived from applying small molecule templates to non-well-characterized products such as AAV. Running a PPQ protocol with some runs in the

PD lab and some at GMP scale has been done for AAV. Assessing the magnitude of process changes between batches was also discussed — above a certain threshold would trigger a repeat of PPQ; below it, fewer than three runs may be acceptable. Adding orthogonal or characterization assays was proposed as a way to strengthen risk assessments.

Assessing process robustness against variability in non-GMP runs could support justification for fewer PPQ runs. The tradeoff: more PPQ/less characterization at scale vs. more characterization/less PPQ. Would the company like to prioritize more PPQ work, since that material could also be used for sales, vs non GMP work?

Q4 – Proving analytical method robustness using a single representative lot

When using a single lot, picking samples from beginning, middle, and end of the lot was suggested to mitigate the risk about it not being representative of the overall variability, and also combining multiple drug substances into one drug product could increase the variability observed. Other approaches to maximize the representativeness of the single lot included using different batches as reference standards and assay controls, or leveraging pre-characterizing method variability before validation could justify fewer than three batches.

This approach was reported to be a common practice with mAb, where representative lots are easier to identify. The approach relies on a robust qualification report and many lots generated during assay development; robustness studies during development were suggested. For less characterized product, significant effort would be required to identify critical materials for method execution and a risk was flagged around locking the process based on a limited analytical dataset. Using routine data to estimate intermediate precision before approaching validation was recommended. AI tools were suggested as potentially helpful for analyzing accumulated data; structuring data in an AI-processable format was noted as a forward-looking practice.

Q5 – US and EU alignment on PPQ expectations

EMA has not published a platform definition, but the PRIME toolbox has always existed and included several flexibility mechanism.

Sharing feedback across EMA and FDA could be beneficial. Examples were shared where EMA wanted looser specifications and FDA agreed, and vice versa — in both cases, agencies ultimately agreed to the wider limits justified by science.

Q6 – Ensuring sufficient variability in PPQ under enhanced flexibility

- *(No detailed notes recorded for this question, as previously addressed in other questions)*

Q7 – Technical "regrets" and supply chain risks from fewer than three PPQ runs

Regrets discussed and agreed by the table includes:

1) Raw material variability may not be adequately assessed and results in failures post approval

2) Post-approval changes may be more burdensome. Further process transfers with only one pre-change PPQ may be challenging.

3) In the absence of strong characterization data, proven acceptable ranges (PARs) will likely be extremely tight. Similarly, specifications may end up too tight if not adequately informed by PC runs.

- Counterpoint: if one PPQ is justified by strong historical data, there may be little unknown variability going forward.