MEDIUS CONSULTING, LLC

Holistic Thinking for PPQ Strategy

Lessons Learned and Future Opportunities

Mary Rodley
Medius Consulting, LLC

Modality-Specific Considerations & Challenges for PPQ

Autologous Cell Therapy

Living cells from the patient, often engineered to deliver genetic modifications (e.g. CAR T)

CONSIDERATIONS

High number of clinical manufacturing batches; high variability in starting material

CHALLENGES

Process consistency confounded by starting-material variability; PPQ runs cannot be used commercially

Allogeneic Cell Therapy

Living cells from a donor, often engineered to deliver genetic modifications (e.g. CAR T)

CONSIDERATIONS

Low number of clinical manufacturing batches; donor selection and/or cell banking

CHALLENGES

Low number of commercial batches required to meet demand

Gene Therapy

Introduces, removes, or alters genetic material (DNA or RNA) within the patient's cells

CONSIDERATIONS

Low number of clinical batches; multiple critical drug-substance components

CHALLENGES

Small batch sizes (limited sampling); drug substance vs. drug product runs & interconnection

CASE STUDY

Autologous CAR T PPQ: Variance Component Analysis

Process consistency is impossible to demonstrate with a traditional 3-run approach — inherent variability in starting material confounds it.

Between-batch variability — and therefore consistency — can be estimated with a variance-components model:

$$\sigma^2_{Total} = \sigma^2_{Donor} + \sigma^2_{Process} + \sigma^2_{Analytical}$$

Donor	How much does starting-material variability contribute to total variance?
Process	How consistent is the manufacturing process itself?
Analytical	How much do the analytical methods contribute to measurement variability?

Adapted from Ashton, R. — BioPhorum CGT 2021

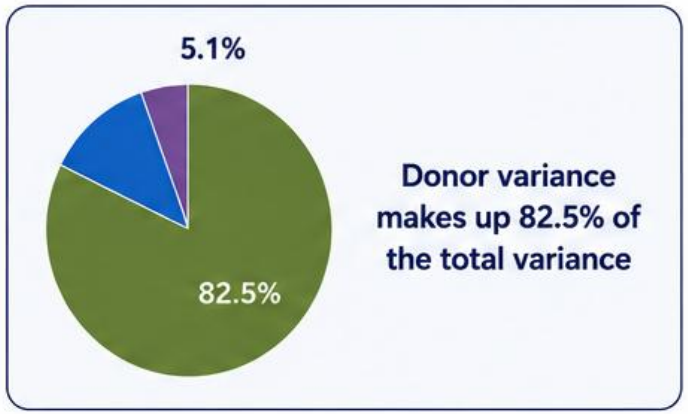
Example Variance Components (CQA 1)

Example Variance Components (CQA 1)

Derived from nested (split-run) PPQ study

Source	Variance	Std Dev (σ)
Donor variability	0.00621	0.0788
Process variability	0.00093	0.0305
Analytical variability	0.00038	0.0195
Total variability	**0.00752**	**0.0867**

Variance Component	% of Total Variance
Donor variability	82.5%
Process variability	12.4%
Analytical variability	5.1%
Total	**100%**

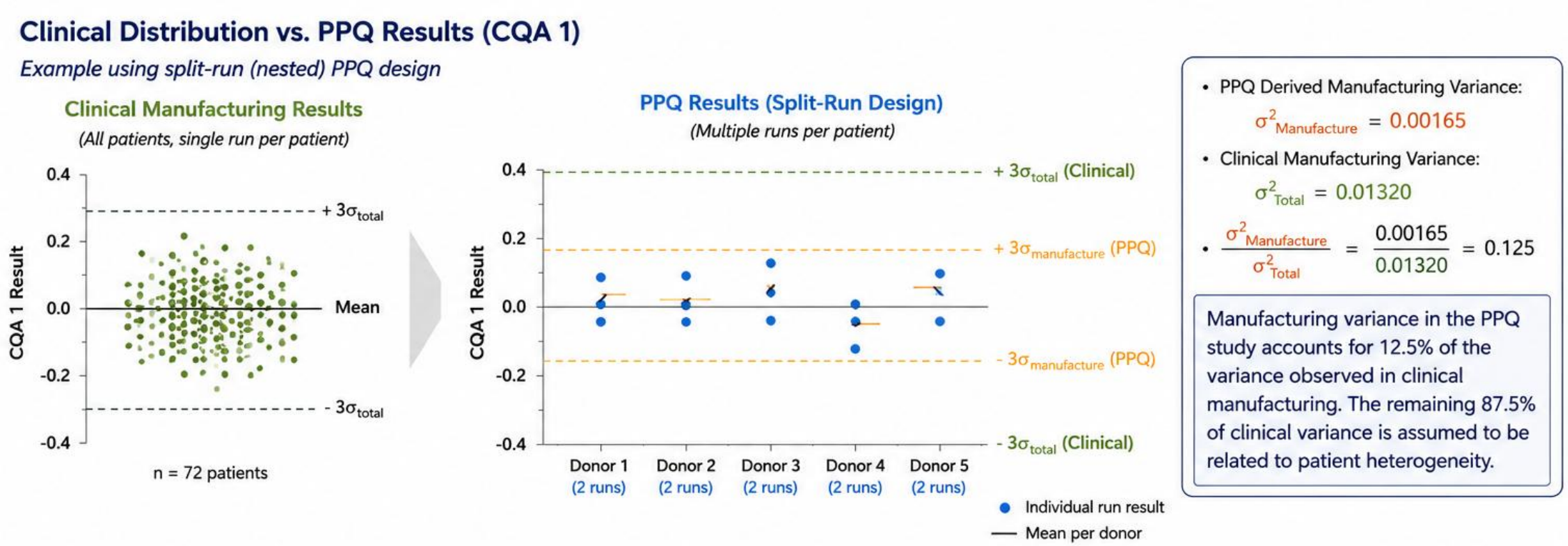


$$\sigma^2_{Total} = \sigma^2_{Donor} + \sigma^2_{Process} + \sigma^2_{Analytical} = 0.00621 + 0.00093 + 0.00038 = 0.00752$$

Donor variability dominates total variance (82.5%) — confirming the process itself is highly consistent.

Adapted from Ashton, R. — BioPhorum CGT 2021

Clinical Distribution vs. PPQ Results (CQA 1)



Manufacturing accounts for just 12.5% of observed variance; the remaining 87.5% reflects patient heterogeneity.

Adapted from Ashton, R. — BioPhorum CGT 2021

CRITICAL APPRAISAL

Variance Component Analysis: A Better Characterization Tool

STRENGTHS

- Quantifies where variability originates — letting you state confidently that the process is consistent when its contribution to total variance is low.
    - Profoundly useful for both validation and for prioritizing resources toward future optimization.

LIMITATIONS

- Estimating variance can demand a large sample size, especially as variables (raw-material lot, hold times) are added.
    - With a realistic number of runs, uncertainty in the calculated variances is high.
- Between-batch variability understanding before PPQ heavily influences the statistical basis for run number and acceptance criteria.
    - Hard to set acceptance criteria for variance without a large development data set.

THE PATH FORWARD

The future = codified flexibility

> *FDA recommends that sponsors justify the appropriate number of PPQ batches based on **context-specific factors**, such as the overall level of understanding of the product and process, complexity of the manufacturing process, and levels of control in place.*

U.S. FDA · Chemistry, Manufacturing, and Controls Flexibilities for Developing Human Cellular and Gene Therapy Products for a Biologics License Application Guidance, May 2026

No more "rule of 3."

Liberating — and a huge white space to fill.

When options seem endless,

where do you start?

REWRITING THE PLAYBOOK

With codified flexibility, it's time to rewrite the playbook.

Autologous Cell Therapy

Context-Specific Factors

- Substantial clinical experience (>100 runs)
- Highly variable starting material
- PPQ material cannot be released for commercial use

Justification for PPQ Approach

- Well-characterized sources of variability through development and PC
- Rigorous PC with DOE studies supporting risk-based parameter classification
- Commercial control strategy in place pre-PPQ, set to evolve with PPQ & CPV

Potential PPQ Design

- Run PPQ as 'concurrent validation' during the latter half of pivotal-study manufacturing
    - Add PPQ-level testing during the first X years / lots of CPV

REWRITING THE PLAYBOOK

With codified flexibility, it's time to rewrite the playbook.

Gene Therapy

Context-Specific Factors

- Limited clinical experience (<10 runs)
- High cost for full-scale GMP runs; lots would expire before commercial use
- Platform process

Justification for PPQ Approach

- Robust SDM with qualification — used for PC and most supportive validation studies
- Rigorous PC with DOE studies; results + platform data support risk-based classification
- Commercial control strategy in place pre-PPQ, set to evolve with CPV

Potential PPQ Design

- Use SDM & platform data to justify small-scale PPQ, with N justified by statistics
    - Commit to PPQ-level testing during the first X years / lots of commercial manufacturing

A HOLISTIC FRAMEWORK

The Inputs to a Robust PPQ Strategy

Looking Forward: Building the Foundation for the Next Generation of PPQ

1 Start Earlier. Learn Faster. Use Data Better.

The quality of a PPQ strategy is determined long before PPQ begins.

- Design process characterization, development studies, and validation activities with the end PPQ strategy in mind.
- Establish a robust data management and analysis framework early.
- Integrate development, manufacturing, analytical, and validation data into a connected knowledge base.
- Leverage advanced analytics and AI-enabled tools to identify variability drivers, quantify uncertainty, and maximize learning from every run.

Goal: *Transform isolated data points into actionable process understanding.*

2 A Bold Idea for Our Industry

Can we validate smarter together?

Many CGT programs face similar challenges:

- Limited clinical manufacturing experience
- High development costs
- Expensive process characterization studies
- Shared critical raw materials, platforms, and technologies
- Time to patients

What if we explored *pre-competitive partnerships* to build broader *process understanding*?

- Shared process characterization datasets
- Cross-sponsor studies of common raw materials or platform technologies
- Industry consortia focused on validation science
- Cross-referenced evidence packages supporting regulatory submissions

Challenge to the audience:
How can we work together to reduce the burden of generating evidence while increasing confidence in process understanding?

Confidence in Process. Assurance in Quality. Faster Access for Patients.

The future of PPQ is not more runs—it is better understanding.