PPQ Under Pressure: Designing Practical Validation Strategies for CGT Programs

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Session 5 – Innovative PPQ Strategies Supporting Accelerated Programs

Topics Discussed:

- Needing a Different Approach to PPQ
- Adaptive PPQ (APPQ) Framework
- Lessons Learned
- APPQ Framework In-Action: Allo-iPSC
- Key Takeaways

The Paradox

Strong scientific foundation – connected to substantial data – is generally expected in the traditional pathway to BLA readiness.

Logic – in order to commercialize a therapy, one demonstrates reproducibility, at scale, many times.

CONVENTIONAL APPROACH	CGT & ATMP REALITY	TAILORED - FIT FOR PURPOSE
• Process Development Batches	• Limited Data	• Intentional Data at Onset
• Clinical Manufacturing	• Few Clinical Batches	• Clinical / PPQ Blended
• High Level of Materials Control	• Variability in Starting Materials	• High Level of Risk Understanding
• 'The Magic Three (3) PPQ Lots'	• How Many? 3?	• Right Size PPQ Batches (1+)

Where is the Industry Headed –
Intensifying the PPQ Challenge

Platform Emergence

The use of platform technologies is becoming instrumental for the commercial model. Coupled with AI-driven process development, PPQ path is highly compressed.

Consequence:

- Leveraging prior knowledge only works if program is structured from the start.
- Early stage / development data may not be suitable for PPQ support

Flexible Facilities

Dedicated single-product suites are giving way to flexible facilities (clinical, commercial, and multiple modalities).

Consequence:

- Additional knowledge needed on changeovers, cross contamination, shared utilities control, shared equipment strategy.
- Expanding scope of risks and evaluating impacts ahead of PPQ.

Geographies: From One to Many

Industry shifts in play: point-of-care-manufacturing, multi-region commercialization, decentralized models. Comparability must be a significant focus.

Consequence:

- Manufacturing limitations, supply chain / material variability, quality systems must be scrutinized early.
- Lack of regulatory framework understanding and comparability can lead to delayed PPQ path.

The industry is making the right commercial and scientific advances and the PPQ challenge is intensifying as a direct consequence. The question is whether your strategy is built for where the industry is going.

FDA Final Guidance: CMC Flexibilities for CGTP – May 2026

Process Validation

FDA does not specify a minimum number of PPQ batches … 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.

PPQ protocol can be designed to release PPQ batch … before complet(ion) of the protocol.

Commercial Specifications

Flexible release acceptance criteria when robust specifications are not feasible at submission.

Analytical method validation; FDA does not specify minimum number of lots; significantly supported and demonstrated to be robust.

Post-approval re-evaluation where changes after approval must be submitted via prior approval supplement.

Additional Flexibilities

Prior knowledge leverage - FDA may consider proposals to leverage CMC knowledge across similar CGT products, including analytical methods, method validation, lot release specifications, stability / comparability data, and process validation data.

Stability data flexibility: FDA generally recommends 3 lots / 6 months but may accept alternative lot count based on risk evaluation; clinical lots and similar-product data may support initial shelf life.

Not flexible - Release testing requires predefined acceptance criteria.

The Adaptive PPQ Approach

Adaptive PPQ Approach
Accelerating a CGT PPQ Program

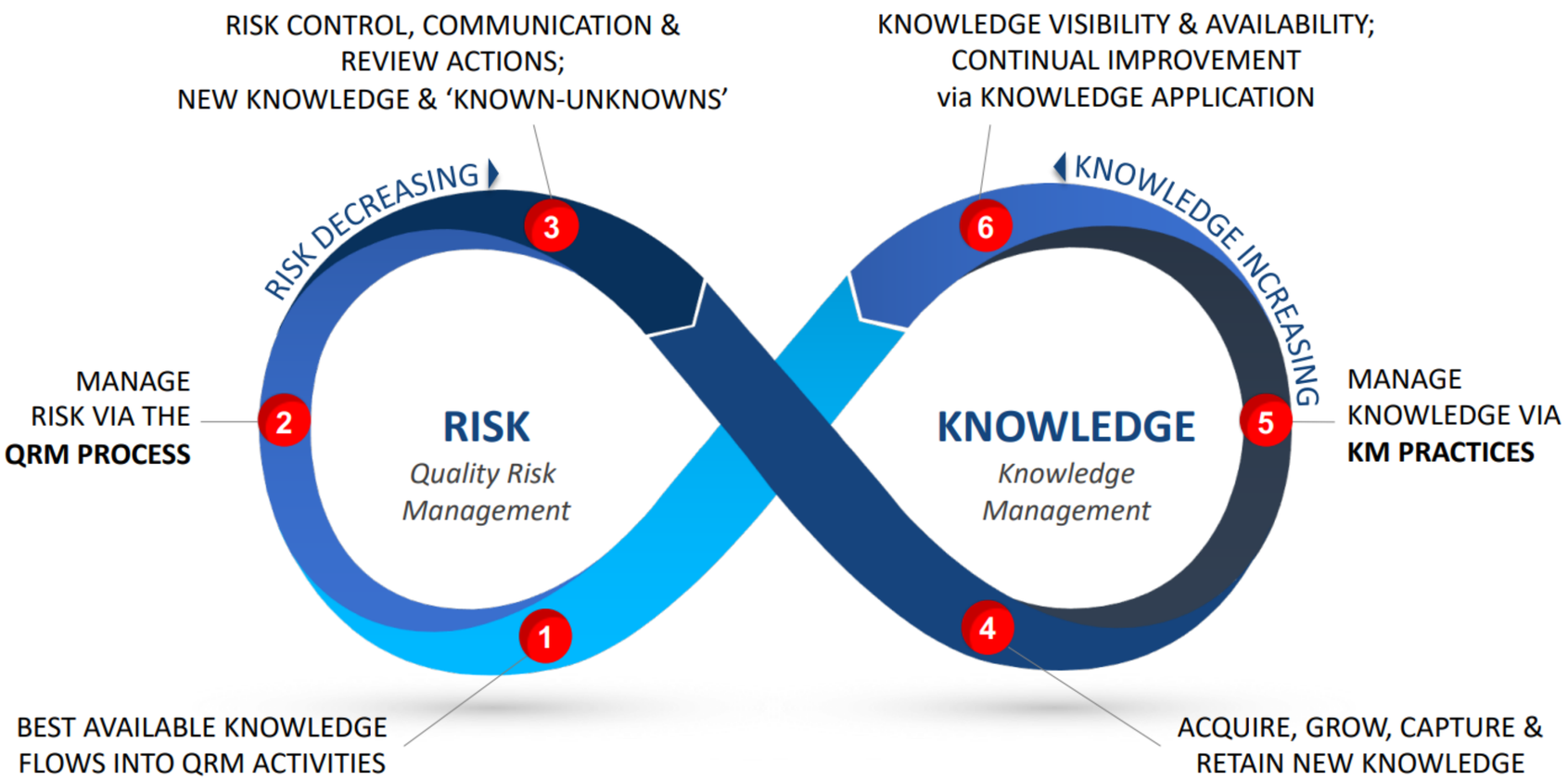
	Data Priority	PPQ Value	Stage Gate Support
Phase I	• Critical Process Parameters tied to Critical Quality Attributes • Assay Development • Process Ranges	• Building the Foundational Knowledge	• Predefined acceptance criteria • Risk-ranked CQA/CPP Map
Phase II	• Platform Comparison • DoE Completion • Scale Confirmation	• Building Prior Knowledge	• Commercial Readiness – Technology Transfer Evaluation • Qualified Facility / Equipment
Phase III	• Process Lock • Engineering Runs • Comparability	• Accelerating by PPQ contribution • Surrogate Batches	• Runs meeting predefined Criteria • Failures Resolved • Demonstrated CPP Control
PPQ	• RTRT Strategy • Protocol Execution	• Commercial Readiness	• Informed CPV Plan • Regulatory Alignment
Post-PPQ / CPV	• Enhanced / Continuous Monitoring • Specification Refinement • Lifecycle Management	• Sustained Manufacture • Post-Approval Learning	• Post-BLA Commitments Satisfied • Expansion Activity

APPQ Enablers

Risk – Based PPQ Readiness Scorecard

	Key Questions
Process Understanding	• Is the CPP/CQA Mapping Complete? • Sufficient data / DOEs at scale?
Analytical Readiness	• Can methods be easily validated and transferred? • Is potency fit-for-purpose? Justifications applicable?
Depth of Batch History	• Is there a surrogate strategy planned and justified? • How many batches available and supportive of PPQ?
Platform Leveraging	• Do we understand comparability needs?
Facility & Equipment	• Is there a knowledge audit completed? • Equivalence of systems / equipment confirmed?
Regulatory Alignment	• Strategy for phase appropriate work agreed to? • Predefined acceptance criteria is working?
Control Strategy	• Is it clearly documented and sufficiently linked to CPV plans?
Change Management	• Are changes from early to late phase assessed and part of comparability impact evaluation?
Cross-Functional Alignment	• Clinical / Regulatory / Manufacturing / QA Teams understand strategy and aligned on PPQ scope and timeline?

APPQ Enablers
Risk – Knowledge Continuum



PPQ Readiness is a knowledge state – not a compliance milestone. As you accumulate knowledge, you decrease process risk.

Continuum Stages

- **Stage 1** – Prior knowledge, process/product knowledge
- **Stage 2** – QRM Process: perspectives, historical, best practices
- **Stage 3** – QRM Outputs – the known-unknowns become prior knowledge for managing risk
- **Stage 4** – New knowledge proactively acquired (tacit and explicit)
- **Stage 5** – Managing new knowledge
- **Stage 6** – Deploying knowledge for re-evaluation

Lipa, Martin J.; et al. (2020). doi:https://doi.org/10.21427/

APPQ Enablers – Strengthening the CPV Strategy

The Five Pillars – From Residual Uncertainty to Lifecycle Assurance

	Risk-Based Monitoring	Analytical Lifecycle Management	Process Evolution Management	Biological Performance	Long-Term Performance
PRIORITIES	Focused attention on known uncertainty: • Potency Variability • Operator Variability • Transduction Consistency	Leaning in to flexibilities through: • Reference Standards • Drift Analysis • Inter-lab Variability	Closing the knowledge gaps: • Characterization of Changes • Expansion Activity • Mixing / Hold Studies	Residual uncertainty surveillance: • Stability Studies • Longitudinal Studies • Orthogonal Measurements	Consistency is verified by: • LTFU Integration • Safety Signals • Clinical Outcomes
ELEMENTS	• Multivariate Trend Review • Batch Trends • Potency Correlation	• Orthogonal Methods • Ref. Standard Lifecycle • Assay Lifecycle	• Change Impact • Knowledge Transfer • Scale-Up/Out	• Attribute Trending • Function Mapping • Emergent CQAs	• Registry Strategy • Product-Clinic Correlation • Real World Outcomes
VALUE	**Not an exercise to generate data, but monitor uncertainty**	**Maturity of assays evolves alongside commercial operations**	**Unlock justifications with new knowledge**	**CGT Risk tradeoff transitions to lifecycle performance**	**Strong integration leads to product confidence**

Lessons Learned

Case Study – Gene Therapy CDMO Tech Transfer

Background

- Gene therapy program, supported by first generation data (Clinical / Commercial)
- Limited development data using second generation platform technology
- To meet BLA submission deadline, CDMO selected with PPQ hard date (<12 months)

Problem

- Multiple accountable stakeholders – CDMO, CDMO Vendors
- Limited Guidance from Sponsor
- Robust Gen 1 Data, Limited Gen 2
- No evaluation of Gen 2 process prior or during CDMO transfer.
- CDMO capability via general process knowledge, new process equipment / training would be needed to accommodate scale-up.
- Immediate priority to assign 'default' tasks related to PPQ readiness (batch records, new equipment, new changeover procedures, all associated validation / qualification activities, sample handling and testing support)
- Priorities were based on business feasibility (people, equipment, long lead time / difficult to source materials).

Outcome

- Delays due to lack of materials, and no policies / procedures to risk-assess and identify creative solutions (data leveraging, scale down models, engineering runs versus PPQ lots)
- PPQ timing based on business needs with limited knowledge transfer (Gen 1 → Gen 2, Sponsor → CDMO, CDMO → Vendor) prevented parallel / prerequisite activities that may have alleviated deadlines.
- Both Sponsor and CDMO very familiar with GMP knowledge, well established, but missed acceleration opportunity due to rigid quality systems.
- Ultimately the transfer was not successful, and CDMO was not selected for Gen 2 cGMP manufacturing.

Case Study – Gene Therapy CDMO Tech Transfer
Lessons Learned

Communication

- Governance was driven by default ‘must-have’ deliverables.
- Risk-based planning was not an option without unified go / no-go criteria.

Knowledge Transfer

- The Gen 2 process required more data before it was ready to move to a CDMO.
- Define what sufficient means before the transfer.
- If the answer reveals the process is not transfer-ready, that is the most valuable output of the assessment.

Readiness

- Build the risk-based qualification plan first. Sequence high-risk activities to the front.
- Deprioritize what is not critical to PPQ readiness. Then read the projected completion date as an output of that plan.

Case Study – Allogeneic Cell Therapy Research-to-GMP

Background

- Allogeneic Cell Therapy
- History of minimally manipulated donor material
- Transition from early phase to late-phase GMP
- Aim to have internal GMP capabilities and PPQ support, no partnerships

Problem

- Process knowledge existed almost entirely as tribal knowledge
- Multiple manual steps performed across varied instruments with no standardization.
- The program had grown organically from academic research practice. No structured quality system existed.
- Data integrity controls, reproducibility documentation, and audit trails were absent or inconsistent. The team was confident in their science
- Client maintained a strict separation between research operations and GMP manufacturing.

Outcome

- Systematic identification of critical to quality activity for phase appropriate laboratory
- Evaluated the research-to-GMP transition, developed unified model to organize Team+Facility+Instruments
- Knowledge Management was employed to explore reproducibility of workflows, build methods development plans.
- Evaluations and frameworks as direct inputs to define areas of risk and update segregation strategy.
- Due to limited scope and independent treatment of space, numerous challenges to leveraging into legacy systems.

Case Study – Allogeneic Cell Therapy Research-to-GMP
Lessons Learned

Tacit Knowledge

- Characterizing tribal knowledge was critical
- Reliance on multiple manual steps and little standardization addressed, not forced.

Phase Appropriate

- Quality frameworks appropriate to each phase without imposing stringent policy too early.
- Ph. 1 required structured data capture and formal procedures for critical steps.
- Ph. 2 required method validation and a formalized comparability framework.

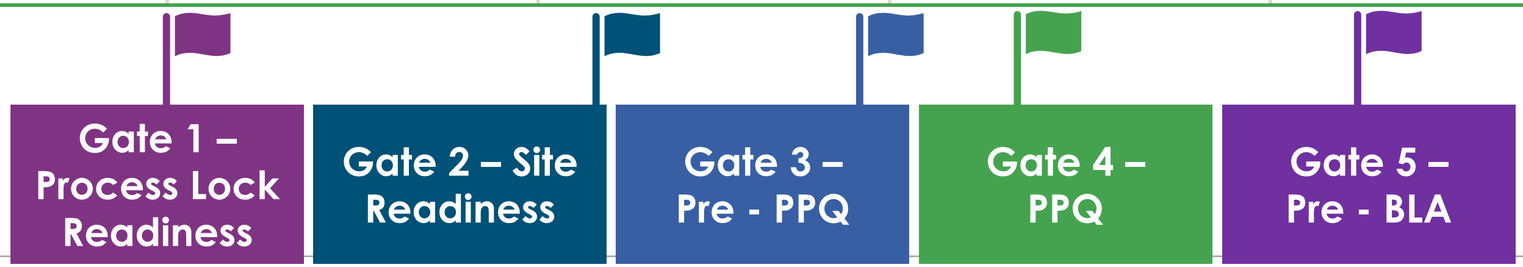
Siloed Effort

- Within the bubble, strong potential for leveraging and accelerating PPQ.
- Outside the bubble, data/knowledge not amenable to legacy organization, leading to disconnect.

The APPQ Framework In Action:
Use Case – Allo-iPSC

Representative Use Case – Novel Allogeneic iPSC
Rare Disease Indication

	Pre-IND	Phase 1	Phase 2	Phase 3	PPQ / Filing	Approval / CPV
Knowledge Maturity Level	• Less is known, • Assessments Critical	• Knowledge Foundation, • Communication Critical	• Deeper knowledge, • Iteration of Program / Process	• Foundational Knowledge Brings Benefit	• Process knowledge at scale	• Knowledge / Risk re-assessed • CPV Evolution
CMC & Manufacturing	• MCB Creation • Reprogramming Protocol – CQA Definitions	• Phase-appropriate release criteria, • CQA-CPP RR • Scalable DOE	• Comparability • Platform Potential • Strong CDMO Transfer	• Platform Data / Prior Knowledge • Donor Strategy	• Fit-for-Purpose Monitoring • Proactive Controls • Right-Size CPV Plan	• CPV Data Accumulation • Safety • LTFU Protocol
Regulatory	• Pre-IND Meeting • Fast Track/ RMAT • Dedicated PMDA Coordination	• Acceptability of Data / Safety	• PMDA Consultation • Ph1/Ph2-Dossier	• Pre-BLA (Type C) • PMDA Data	• Clear BLA CPV Path • MAA Study Protocols	• Real-time Validation • Knowledge Share • Inspection Readiness



Representative Use Case – Novel Allogeneic iPSC
Rare Disease Indication – Phase Gate Playbook

Gate 1 – *Before IND*

Fully Characterized Master Cell Bank?

Cell Differentiation Protocol Defined?

Critical CQAs versus flexible to-be characterized?

Regulators aligned on intentional approach?

① Assay Approach

Gate 2 – *Mid-Ph.2*

Tech Transferability considered?

Analytical Methods transferable?

Eligibility of manufacture for multiple geographies?

Comparability and prior knowledge defined?

② Commercial Mindset

Gate 3 – *Pre-PPQ*

Surrogate / engineering runs meet performance indicators?

Differentiation efficiency, viability, SC purity in range of historical data?

Is surrogate strategy aligned with FDA?

U.S. Ph.1/Ph.2 data supportive of PMDA MAA?

③ Comparability Alignment

Gate 4 – *PPQ*

All protocol acceptance criteria defined?

Approach aligned to Type C strategy?

Cell Differentiation Protocol Defined?

Is CPV Plan of appropriate design?

④ Leverage Position

Gate 5 – Pre-BLA

All deviations to CQA impact resolved?

Acceptance criteria satisfied?

Prepared to satisfy post-PPQ commitments?

Is knowledge bank feeding risk re-evaluation?

Leveraging for seamless expansion?

⑤ Strong Readiness Scorecard

What Do You Take Back Today

- **PPQ Scientific Narrative Starts with IND**

  Early stage activities are an **OPPORTUNITY** to begin PPQ preparations through prior knowledge strategy, surrogate approaches, and probable CPV commitments long before Phase 3 begins.

- **Revisit Risk Assessments Regularly**

  PPQ Readiness is part of the lifecycle and should be a standing agenda item during CMC governance discussions and should inform decisions as you go. If possible, utilize QMS for automated re-assessment, and build maturity in your KM / RM programs as you go.

- **Start talking to the agency(ies) early and specifically**

  Make the most of early interactions and be prepared to discuss strategies and guidance interpretations to get actionable recommendations in good time.

- **Establish QRM in as many functional areas as possible**

  Data management is an integral component to not delay knowledge transfer and changes to evaluated risk. As flexibilities are leveraged, a comprehensive CPV will be needed. Consider risks to assumptions – any anticipated commitments can compromise approval if they ultimately cannot be met.

Organizations that are successful at expedited PPQ for advanced therapies are the ones who decide readiness begins at Phase 1, not at BLA filing.

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