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Delivering on the promise of Prime Editing

PPQ-As-You-Go: Accumulating CMC Validation Evidence in Step with Clinical Data for Rare Genetic Disease Programs

CASSS Cell and Gene Therapy Products, June 2026

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Delivering to patients with rare disease

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Two mechanisms, two scales, one shared lesson: clinical timelines have compressed. CMC must move with them.

Baby KJ

CGD Patient 1

CGD Patient 2

"I am filled with gratitude... Thank you for giving me a brand-new normal life"

- CGD Patient on PM359 Trial

"We worry about whether we might hurt someone, but not doing something is also hurting someone."

- Scott Demarest, Children's Hospital Colorado*

"Is this [treatment] worth the risk? Who decides? I think my family decides."

- Terry Jo Bichell, COMBINEDBrain*

* Speaking at the Duke-Margolis *Individualized Therapies on the RISE* Public Meeting, Nov. 2025

Today’s Discussion

I. The patient imperative: a case study in PM359

II. The structural problem: misaligned clinical and CMC timelines

III. A Solution: PPQ-As-You-Go framework and its primary elements

IV. The path from here: points to consider and call to action

Converging patient advocacy, industry and FDA action has attempted to redefine the clinical and CMC envelope for ultra-rare therapies

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The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Patient-Specific In Vivo Gene Editing to Treat a Rare Genetic Disease

K. Musunuru, S.A. Grandinette, X. Wang, T.R. Hudson, K. Briseno, A.M. Berry, J.L. Hacker, A. Hsu, R.A. Silverstein, L.T. Hille, A.N. Ogul, N.A. Robinson-Garvin, J.C. Small, S. McCague, S.M. Burke, C.M. Wright, S. Bick, V. Indurthi, S. Sharma, M. Jepperson, C.A. Vakulskas, M. Collingwood, K. Keogh, A. Jacobi, M. Sturgeon, C. Brommel, E. Schmaljohn, G. Kurgan, T. Osborne, H. Zhang, K. Kinney, G. Rettig, C.J. Barbosa, S.C. Semple, Y.K. Tam, C. Lutz, L.A. George, B.P. Kleinstiver, D.R. Liu, K. Ng, S.H. Kassim, P. Giannikopoulos, M.-G. Alameh, F.D. Urnov, and R.C. Ahrens-Nicklas


BRIEF REPORT

Prime Editing for p47phox-Deficient Chronic Granulomatous Disease

J.L. Gori, E. Haddad, H. Frangoul, D.B. Kohn, E.C. Morris, B.N. Martin, B.A. Deary, M.K. Nickerson, R.L. Scholz, I. Fernandez, K. Leveille, S.S. De Ravin, E.M. Kang, M. Pierzynski, T. Estwick, P. Littel, D.B. Kuhns, D.A. Long Priel, P. Teira, S. Turvey, J. Arnold, M.D. Evans, M. McManus, B. Carpenter, D.P. Waterman, A.V. Anzalone, A. Petrusich, C.E. Osuna, T.T. O'Malley, J. Stewart-Ornstein, J.M. Heath, B.J. Nehilla, M. Asmal, and H.L. Malech

May 2025

FDA Hosts Roundtable on Ways to Speed CGT Reviews

July 2025

Sept 2025

FDA Issues Innovative Clinical Trials Guidance for Cell and Gene Products in Small Populations

FDA Publishes New Evidence Principles for Rare Disease

Nov 2025

Prasad and Markary Publish "FDA's New Plausible Mechanism Pathway" in NEJM

Duke MARGOLIS INSTITUTE for Health Policy

FDA Approves First Gene Therapy Treatment for Wiskott-Aldrich Syndrome, Exercising Regulatory Flexibility to Address Unmet Need for Rare, Life-Threatening Disease

Increased Flexibility on Requirements for Cell and Gene Therapies to Advance Innovation

Jan 2026

Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause

Draft Guidance for Industry

Mar 2026

Chemistry, Manufacturing, and Controls Flexibilities for Developing Human Cellular and Gene Therapy Products for a Biologics License Application

Guidance for Industry

May 2026

FRIENDS of CANCER RESEARCH

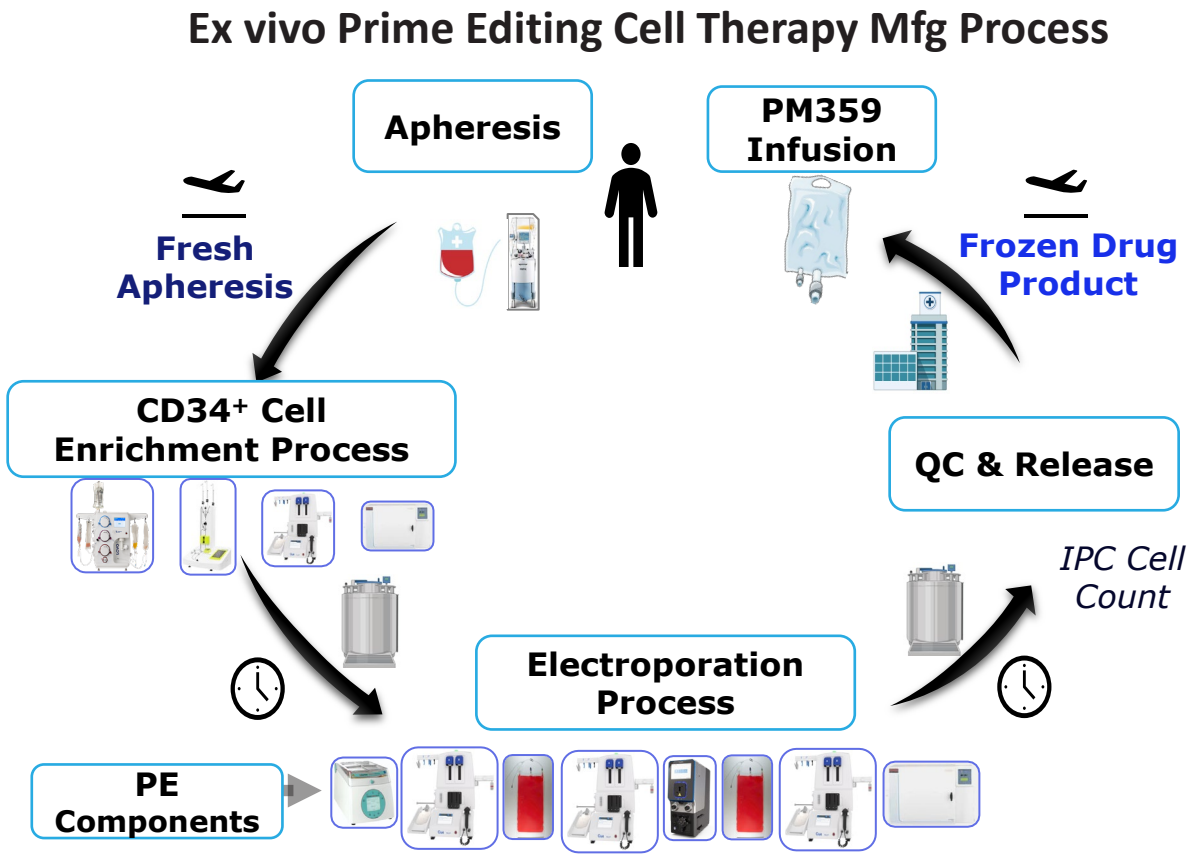
Regulatory and Operational Considerations for Cell-Based Therapies

Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing

Draft Guidance for Industry

PM359 for Chronic Granulomatous Disease (CGD) – Disease Context and Approach

- Life-threatening childhood – onset immune disorder
- Prime Editing corrects p47phox mutation in CD34+ HSCs
- mRNA, peg and ng RNAs considered critical materials, not DS
- Closed GMP platform for *ex vivo* autologous cells: enrichment, electroporation and cryopreservation



Breakthrough Clinical Data: PM359 Establishes Proof-of-Concept for Prime Editing as the Foundation for a New Class of Curative Therapies

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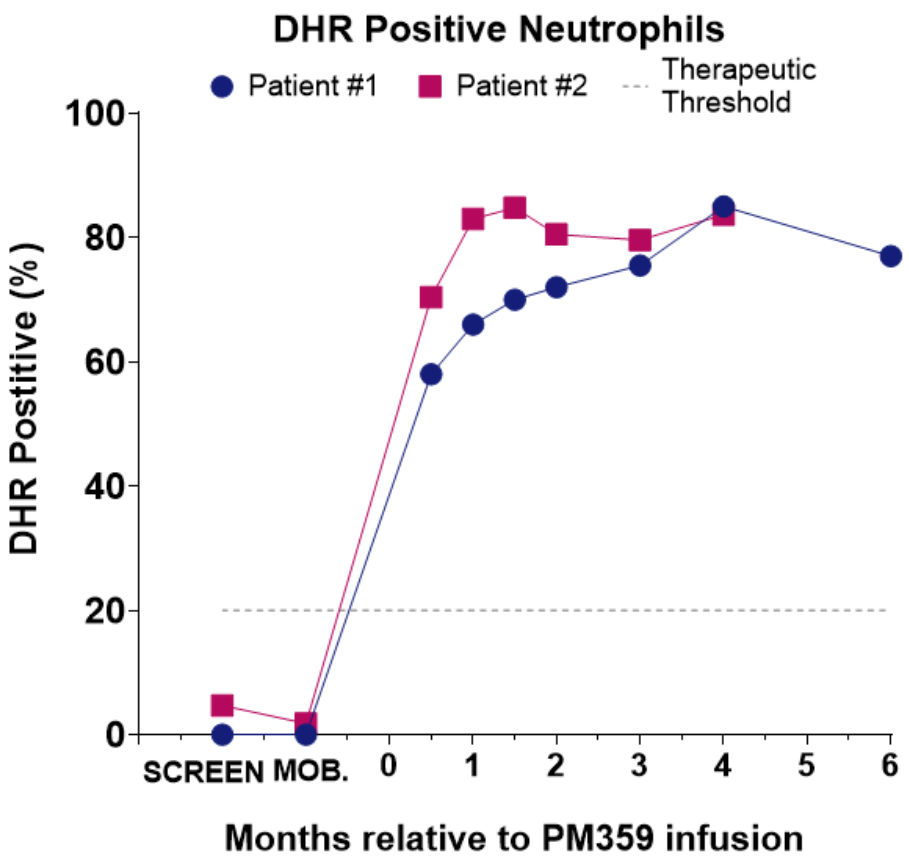
Observed rapid engraftment, restored DHR positivity and improvement in inflammatory markers, with acceptable safety



NEJM 2026; 394:1195-1203

- **Successful manufacturing** from single mobilizations
- **Tolerable myeloablative conditioning** at fully therapeutic exposures with expected adverse events (transitory mucositis, pancytopenia)
- **No serious adverse events** attributed to PM359
- **Rapid neutrophil and platelet engraftment** confirmed within 2-3 weeks post transplant, markedly faster than current benchmarks
- **Rapid recovery of NADPH oxidase activity**: ~3-4x therapeutic threshold by day 30, sustained out to six months post infusion
- **Both patients remain free of new CGD-related complications or significant intercurrent illness post-infusion;** patient 2 demonstrated improvement in inflammatory markers of CAC

Regulatory paradigm with new clinical reality

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Despite ‘flexibilities,’ CMC may still be a bottleneck

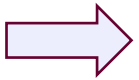
THE CONVENTIONAL PARADIGM

Trials run for years; clinical data precede commitment to late-stage PD; PPQ, method validation, and stability run sequentially after clinical readout.

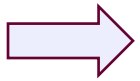
THE NEW CLINICAL REALITY

Pivotal data from two to forty patients; plausible-mechanism approvals; AI-enabled real-time clinical monitoring; one-trial standard as the new default.

FDA’s May 2026 CMC Flexibilities guidance largely reflects existing policy and practice.



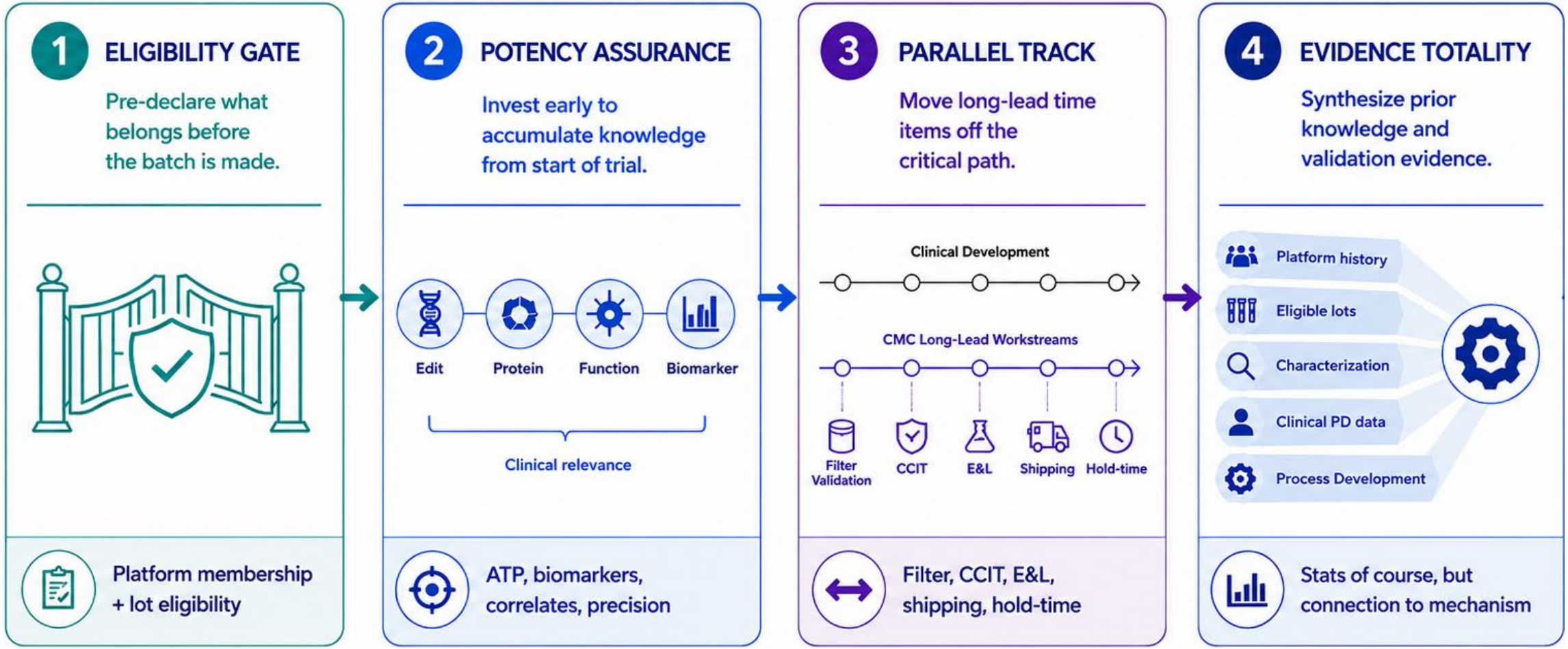
The June 2026 Prior Knowledge draft guidance gives sponsors a pathway to leverage platform evidence.



What are some practical ways to leverage and operationalize prior knowledge that keeps pace with the clinical clock?

A Proposal: PPQ-As-You-Go

Embedding validation evidence from the start of clinical development



Pillar 1: Platform Membership

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Products on the same platform contribute to validation evidence

PLATFORM ELIGIBILITY BOUNDARY

Site & equipment	Raw materials	Unit operations	Quality attributes
SAME	**SAME**	**SAME**	**SAME**
Manufacturing site. Equipment train.	Core bill of materials.	Sequence. In-process control strategy.	Panel, Methods, Specifications.
FLEX	**FLEX**	**FLEX**	**FLEX**
Scale-up to within equipment capability	*Product-specific inputs (e.g., IVT template, amidites).*	*Parameter settings within platform ranges.*	*Product-specific ID or mechanism-linked attributes.*

Flex items carry a documented risk assessment: failure modes identified, prior knowledge mapped to each, residual risk mitigated by additional controls

Pillar 1: PPQ Lot Eligibility

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Establishing validation intent prior to manufacturing:

EXR-368 v1.0 PPQ Lot Eligibility Declaration Effective DD-MMM-YYYY

Material: mRNA Drug Substance Lot: Unique ID

SECTION 1 Prospective Lot Requirements

- ☑ Quality System Requirements
  Raw material specs · Component specs · MBR · SOPs
- ☑ Equipment Qualification & Facility Commissioning
  IQ/OQ current · Good Engineering Practices · Single-use systems
- ☑ Analytical Method Readiness
  Method qualification reports approved · Sampling and testing plans defined
- ☑ Contamination Controls
  EM program operational with acceptance levels · Control strategy defined

SECTION 2 Joint Sponsor/CDMO Approval

Pillar 2: Potency Assurance

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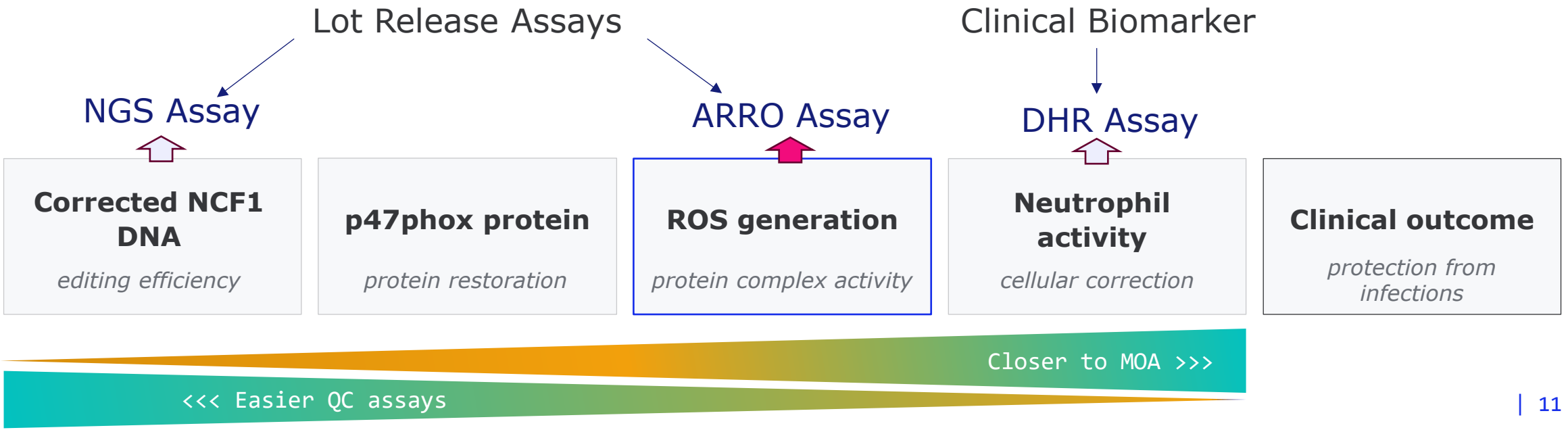
Early investment in this CQA is essential for potential acceleration

- Potency Assurance is a five-element strategy that includes release assays
- Reflect mechanism of action in Analytical Target Profile, invest in data infrastructure, and make assays automation-friendly to improve their precision.
- Qualification package may draw on data from method development runs



NGS = Next Generation Sequencing; ARRO = Amplex Red Reactive Oxygen; DHR = Dihydrorhodamine

Automated Potency Assay Development

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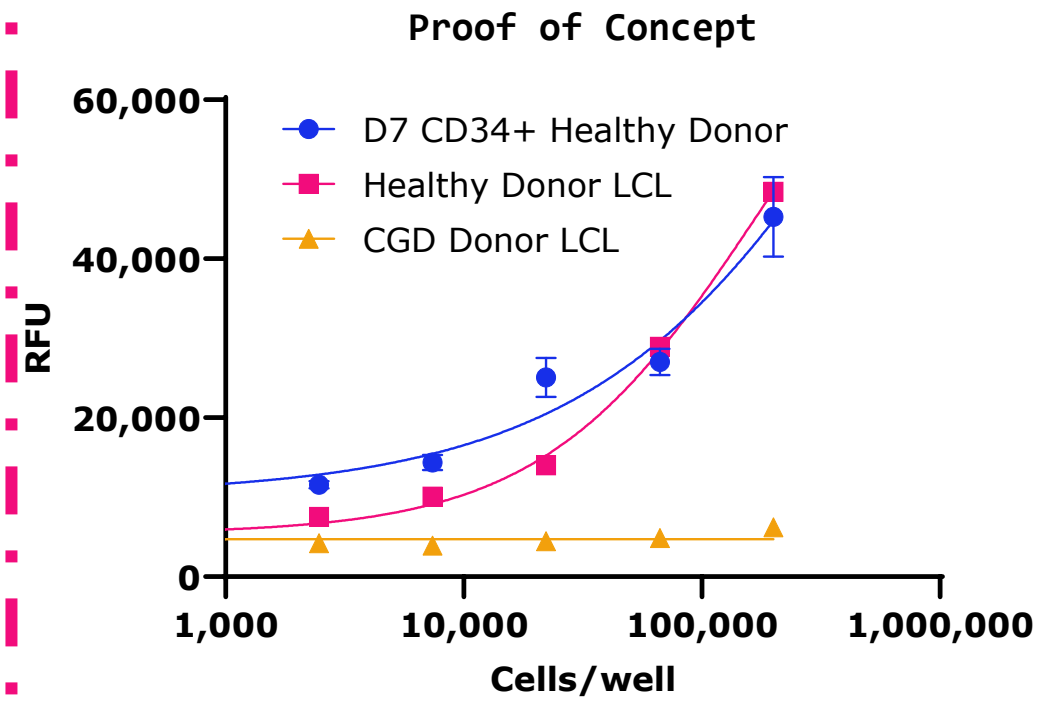
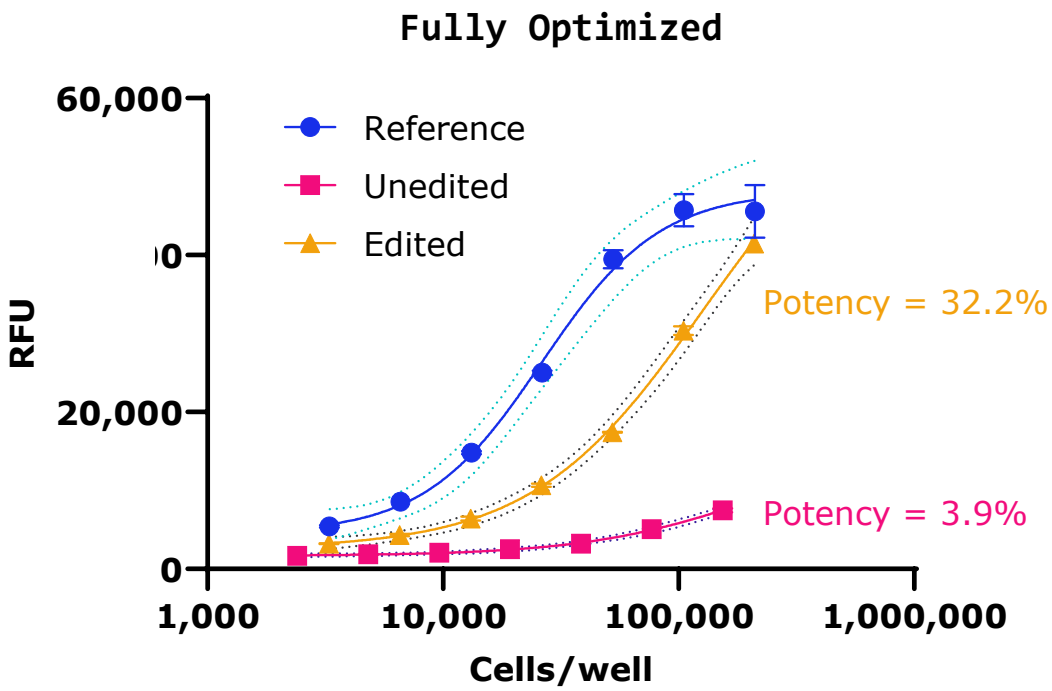
Corrected CD34+ cell can *differentiate* and *produce reactive oxygen*

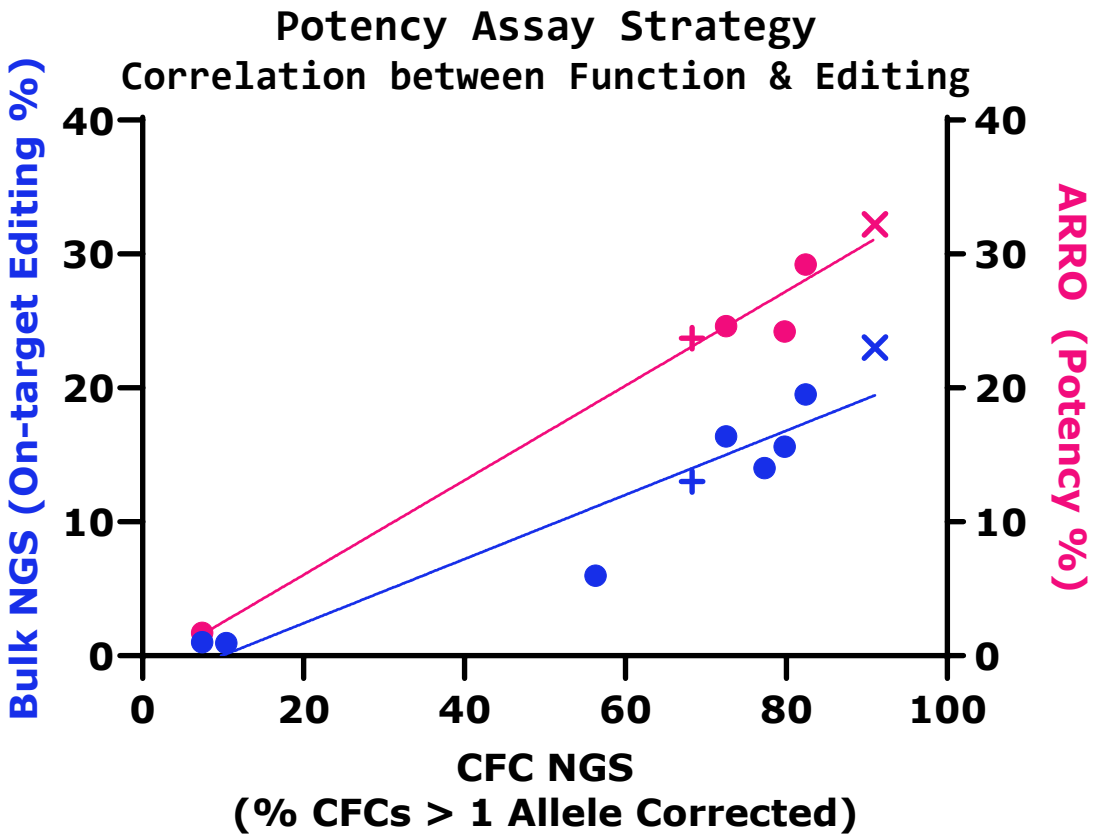




Automation enabled trial and error with 10 assays, screening 441 combination of conditions, and >100 plates in 5 months time/17 assay runs

ARRO for DP Release

We established correlation between functional potency and editing, from drug product development through clinical release



Bulk NGS
ARRO
\+ Patient #1
x Patient #2

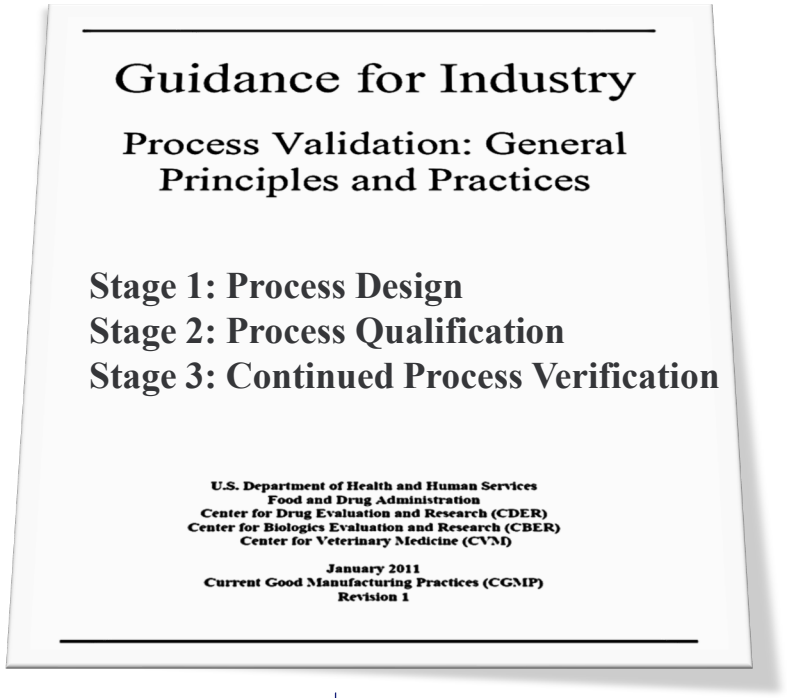
	Bulk NGS	ARRO
Best-fit values		
YIntercept	-2.368	-1.024
Slope	0.2397	0.3531
Goodness of Fit		
Degrees of Freedom	7	4
R squared	0.8867	0.9801

Results for unique research scale (•) and clinical GMP (**+**/**x**) patient lots. Low responding lots were investigational and are shown to indicate the complete correlation with batches that both pass and fail release specifications, across all assays.

Pillar 3: Parallel Long Lead Activities

Removing Select Stage 2 Process Qualification Activities

→ Traditional Approach:



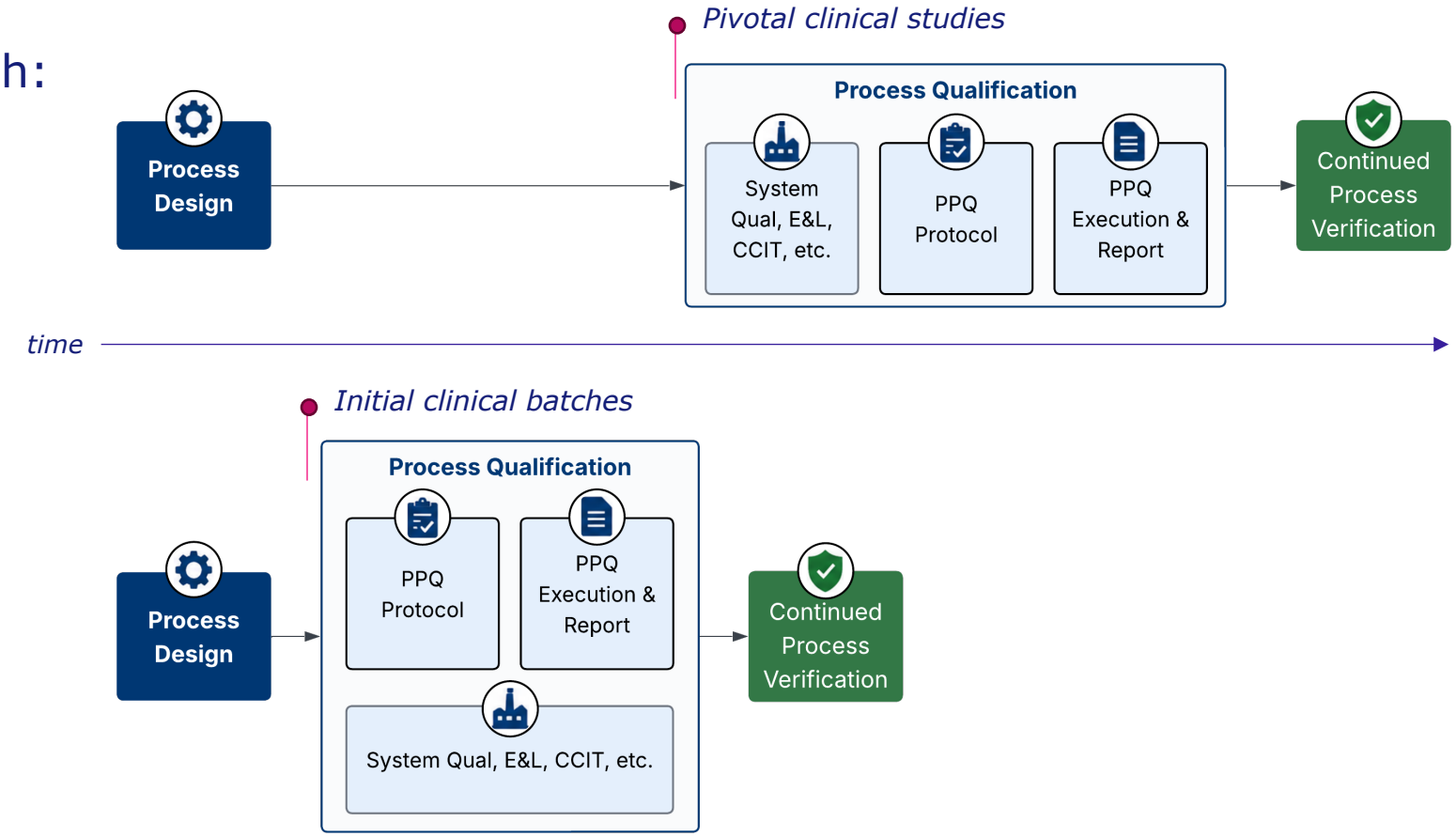
Guidance for Industry

Process Validation: General Principles and Practices

Stage 1: Process Design
Stage 2: Process Qualification
Stage 3: Continued Process Verification

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1



→ PPQ-As-You-Go Approach:

Pillar 3: Parallel Long Lead Activities

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Parallel execution better aligns PPQ with the clinical clock

Parallelization of long-lead activities should be risk based, tailored to the platform and tracked in a formal long-lead risk and activity register subject to scheduled review and approval.

Long-lead activities must be completed before BLA submission.

Example activities

- Filter validation
- Container closure integrity testing
- Extractables and leachables studies
- Hold-time and in-process stability studies
- Shipping validation
- Materials qualification
- Equipment PQ for platform-specific configurations
- Computer software assurance for platform systems
- Reference standard qualification

Risks associated with parallelization of long-lead activities should be mitigated in part by leveraging prior knowledge

Pillar 4: Totality of Evidence in Practice

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Validation evidence arises from five different sources

01
Process development
DoE, scale-up models, characterization, robustness studies.

02
Manufacturing history
All prior lots across every platform member, full CQA and CPP records.

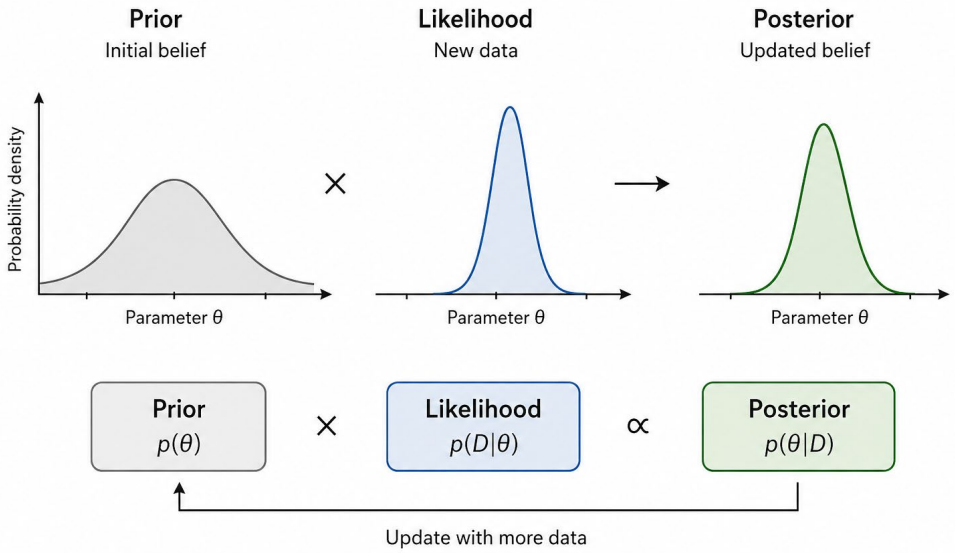
03
PPQ lots
Lots designated under initial and successor protocols.

04
Enhanced characterization
Orthogonal methods, deeper analytics

05
Clinical data
Biomarkers tied to mechanism (e.g., NADPH oxidase activity for PM359).

Evidence integration models

1. **Bayesian hierarchical models**
   Informative priors from platform history. Posteriors update after each lot.
2. **Variance components analysis**
   Decomposes total variance into platform, product, lot, and within-lot terms.
3. **Tolerance intervals**
   Applied to the aggregate dataset, with coverage tuned to per-CQA residual risk.
4. **Mixed model analysis**
   Separates process effects from biological and analytical sources of variation
5. **Process understanding**
   Mechanism-based understanding informs validation conclusions



Pillar 4: Totality of Evidence

Bayesian application within the PPQ-As-You-Go framework

01

Bayesian credibility

Pre-specification and calibration

Can the model support a regulatory-quality claim?

Pre-specify priors, borrowing rules, sensitivity analyses, and operating characteristics.

02

Process confirmation

Continued Process Verification

Is this batch behaving as the model predicted?

Forecast residual in posterior-σ units. Large residuals trigger investigation.

03

Process diagnosis

Control strategy attribution

Why did this batch land where it did?

CPP/CMA-attributable component vs. unexplained residual. Support investigation, experimentation.

04

Analytical comparability

ICH Q14 method transfer

Does the new method give equivalent or better assurance?

Model method bias, precision, and attribute uncertainty; apply equivalence margins.

05

Stability

Shelf-life and post-approval refinement

What is the posterior on shelf-life now?

Hierarchical pooling across lots. Each timepoint refines the degradation rate posterior.

06

Specification updates

Post-approval commitments

When does accumulated evidence justify a limit change?

Commercial lots update predictive reliability under pre-specified criteria and change control.

Aligned with FDA lifecycle process validation principles and the January 2026 FDA draft guidance, “Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products.”

Leveraging AI Capabilities

Prime uses an AI-powered platform from Benchling that accelerates every phase of the analytical method and process development lifecycle

EVIDENCE ANALYSIS

Recommend parameters from a body of evidence

SCHEMATICS AND VISUAL AIDS

Build visual workflows from protocols

ENTITY COMPARISON

Surface similarities and differences across datasets

DOE PLANNING

Design experiments from context and questions

DATA INGESTION

Integrate new data into the evidence base

VALIDATION READINESS

Map data to ICH guidelines and flag gaps

Where PPQ-As-You-Go Fits and Doesn't

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A framework designed for specific applications

BOUNDARY CONDITIONS

Fits where these conditions hold

- Platform gene editing programs treating ultra-rare diseases
- Manufactured at commercial-intent scale from early (Phase I/II) development
- Sponsor and CDMO quality systems mature enough for prospective eligibility and joint governance
- Accelerated clinical pathway is the operative regulatory strategy

Does not fit in these circumstances

- No meaningful platform precedent for the membership assessment to anchor on
- Processes with high-risk failure modes not yet characterized
- Organizations lacking quality infrastructure for joint governance and data management
- Programs where the accelerated clinical pathway is not the operative strategy

What the Field Might Do Next

Opportunity for sponsors to collaborate on a consensus framework that keeps CMC in sync with clinical development timelines

01 **A consensus framework for comparability at small-n**

Industry working group chartered to publish risk-tiered "comparability" guidance that incorporates mechanistic understanding and prior knowledge to complement empirical approaches

02 **A field standard for the adoption of Bayesian statistics in a CMC setting**

Industry consensus on updating models to incorporate what we learn from residuals to strengthen prior knowledge

03 **A precompetitive platform data commons**

A neutral-host repository for de-identified platform manufacturing data, governed by a sponsor consortium (e.g., BioPhorum) with data contribution as the price of access.

04 **AI-assisted CMC in the context of computerized software assurance**

Data mining, data verification, and prior knowledge assistance are entering practice. How should we align FDA's 2025 AI credibility framework to their finalized software assurance guidance?

Acknowledgements

- Our patients and their families
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