

PPQ Sampling plan based on Bayesian dynamic borrowing

Bayesian dynamic borrowing of within-batch variance: multiple data-sources

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Process validation stages

Process knowledge is accumulated and maintained across a lifecycle

Stage 1 | Process Design

Define the commercial process from development and scale-up knowledge.

Stage 2 | Process Qualification

Facility/equipment qualification and Process Performance Qualification (PPQ).

Stage 3 | Continued Process Verification

Maintain a state of control during routine production.

Focus: determine an appropriate PPQ sampling plan using current and relevant historical information from multiple data sources.

Kifle et al. (2025): dynamic borrowing for PPQ

Borrow historical within-batch information, not historical process means

Random-intercept model

$$y_{ij} = \mu + b_i + \epsilon_{ij}, \quad b_i \sim N(0, \sigma_b^2), \quad \epsilon_{ij} \sim N(0, \sigma_w^2)$$

- Borrow: within-batch variance σ_w^2 .
- Do not borrow: historical means or between-batch variance σ_b^2 .

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Formulating Three Classes of Partial Borrowing Power Priors to Leverage Historical Data in Process Validation

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ABSTRACT

The power prior approach has been widely used in decision-making processes across various fields where historical data is available. However, its application in process validation—a critical step in pharmaceutical manufacturing to ensure product quality and safety—remains limited, particularly in partial borrowing of historical information from early development batches. This article addresses this gap by formulating and evaluating three classes of partial borrowing power priors: (PBPP1) a partial borrowing power prior with a fixed discounting parameter, (PBPP2) an unnormalized partial borrowing power prior with a random discounting parameter, and (PBPP3) a normalized partial borrowing power prior with a random discounting parameter. A Bayesian linear mixed model is employed for each class to account for both intra-batch and inter-batch variability in drug product potency. These methods are illustrated with simulated data based on real drug product data to provide a framework for leveraging historical data in process validation and to determine the number of samples per batch required to adequately characterize intra-batch variability for process performance qualification (PPQ). By modeling relevant data and conducting a simulation study, we confirm the limitations of PBPP1 and PBPP2 in addressing discrepancies between historical and current data, while demonstrating that PBPP3 effectively handles potential incompatibilities between historical and current data and makes inferences regarding the discounting parameter.

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Kifle et al. (2025): dynamic borrowing for PPQ

Borrow historical within-batch information, not historical process means

Random-intercept model

$$y_{ij} = \mu + b_i + \epsilon_{ij}, \quad b_i \sim N(0, \sigma_b^2), \quad \epsilon_{ij} \sim N(0, \sigma_w^2)$$

- Borrow: within-batch variance σ_w^2 .
- Do not borrow: historical means or between-batch variance σ_b^2 .

Decision criterion

Use the posterior predictive probability that a tolerance interval for future PPQ data lies within specification limits.

Select the minimum number of observations per PPQ batch that meets the target probability of success.

Extension

- More than 1 historical data set
- Close form normalizing constant

Extending to multiple historical datasets

Historical evidence can come from process history or another site

Current pre-PPQ

Target process

Historical 1

Historical process data
Same process or site

Historical 2

Related evidence
For example, another site

Separate source-specific discounting factors

$$a_1, a_2 \in [0, 1], \quad a_1 + a_2 \text{ need not equal } 1$$

A conflicting source can be discounted without discarding a compatible source.

Simulated datasets (assay specs 95.0-105.0%)

The evaluation uses deliberately different current and historical sources

Current data set

10 batches

10 measurements

$$\mu = 100.0$$

$$\sigma_b = 1.95; \sigma_w = 0.60$$

Hist 1 data set

20 batches

20 measurements

$$\mu = 98.8$$

$$\sigma_b = 1.49; \sigma_w = 1.11$$

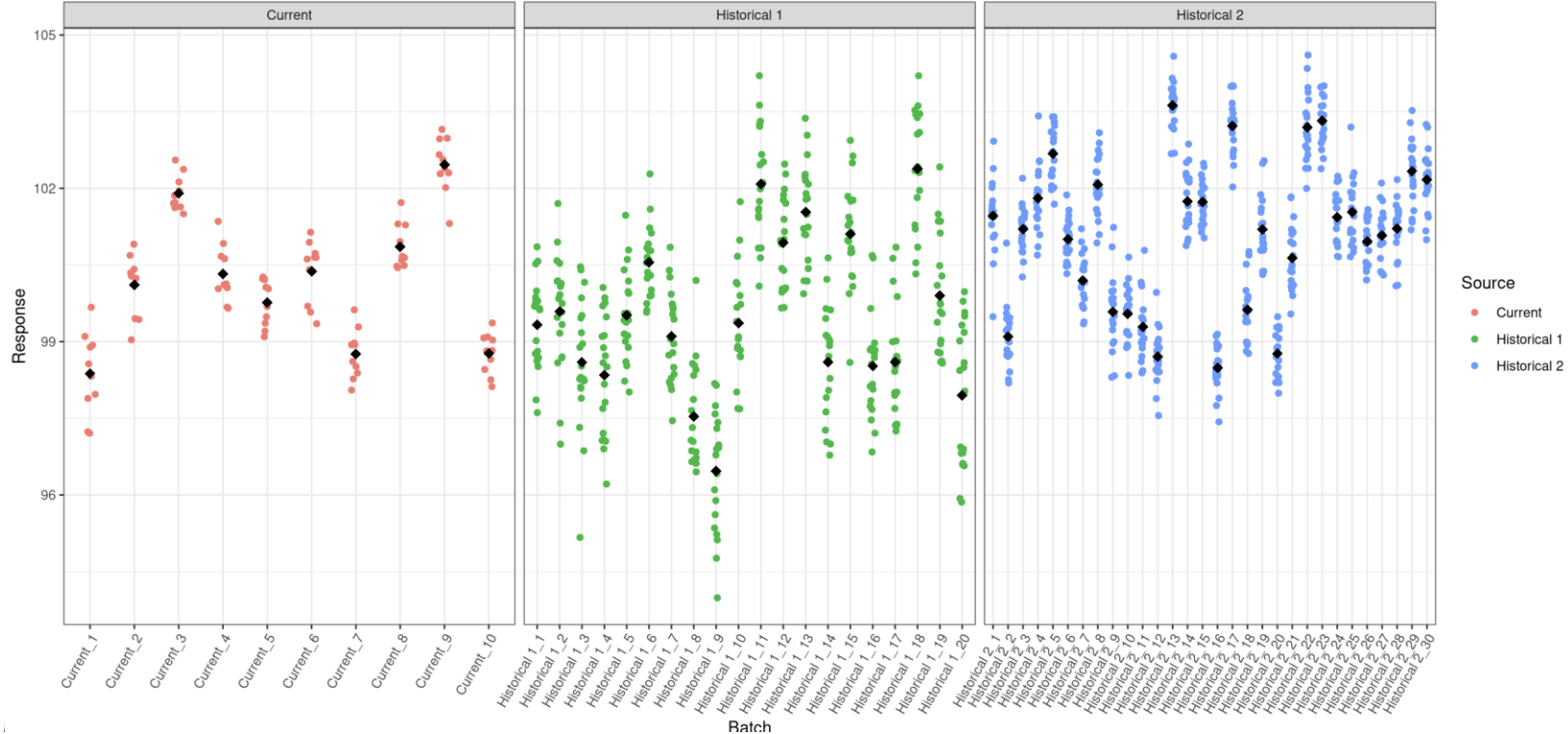
Hist 2 data set

30 batches

20 measurements

$$\mu = 101.2$$

$$\sigma_b = 1.70; \sigma_w = 0.55$$



Likelihood based on sufficient statistics

Batch centering isolates residual information per source

$$S_k = \sum_i \sum_j (y_{kij} - \bar{y}_{ki\cdot})^2, \quad \nu_k = N_k - B_k$$

$$L_k(\tau_w) = (2\pi)^{-\nu_k/2} \tau_w^{\nu_k/2} \exp(-\tau_w S_k/2)$$

Two-source powered contribution

$L_1(\tau_w)$ raised to a_1 and $L_2(\tau_w)$ raised to a_2 .

$$\tau_w = 1/\sigma_w^2 \text{ [precision parameter]}$$

$$\tau_w \sim \text{Gamma}(\alpha_o, \beta_o)$$

$$L_1(\tau_w)^{a_1} L_2(\tau_w)^{a_2}$$

Defining terms

PBPP – Partial Borrowing Power Prior

PBPP1	The fixed discounting approach
PBPP2	The unnormalized random-discounting approach
PBPP3	The normalized random-discounting approach
PBPP3A	Normalized random-discounting — closed-form normalizing constant
PBPP3B	Normalized random-discounting — normalizing constant via bridge sampling

Two-source PBPP formulation

Two independent discount parameters, one per historical source

Assign independent discount parameters $a_1, a_2 \in [0, 1]$. Use the proper initial prior

$$\tau_w \sim \text{Gamma}(\alpha_0, \beta_0).$$

PBPP2 omits the normalizing constant:

$$p(\theta, a_1, a_2 \mid D, D_{01}, D_{02}) \propto L(D \mid \theta) L_1(\tau_w)^{a_1} L_2(\tau_w)^{a_2} \pi_0(\theta) \pi(a_1) \pi(a_2).$$

PBPP3 includes

$$C(a_1, a_2) = \int L_1(\tau)^{a_1} L_2(\tau)^{a_2} \pi_0(\tau) d\tau.$$

PBPP2 and PBPP3 differ by a single term: the normalizing constant $C(a_1, a_2)$.

Normalizing constant in closed form

A closed-form expression from batch-level sufficient statistics

Let

$$A = \alpha_0 + \frac{a_1 v_1 + a_2 v_2}{2}, \quad B = \beta_0 + \frac{a_1 S_1 + a_2 S_2}{2}.$$

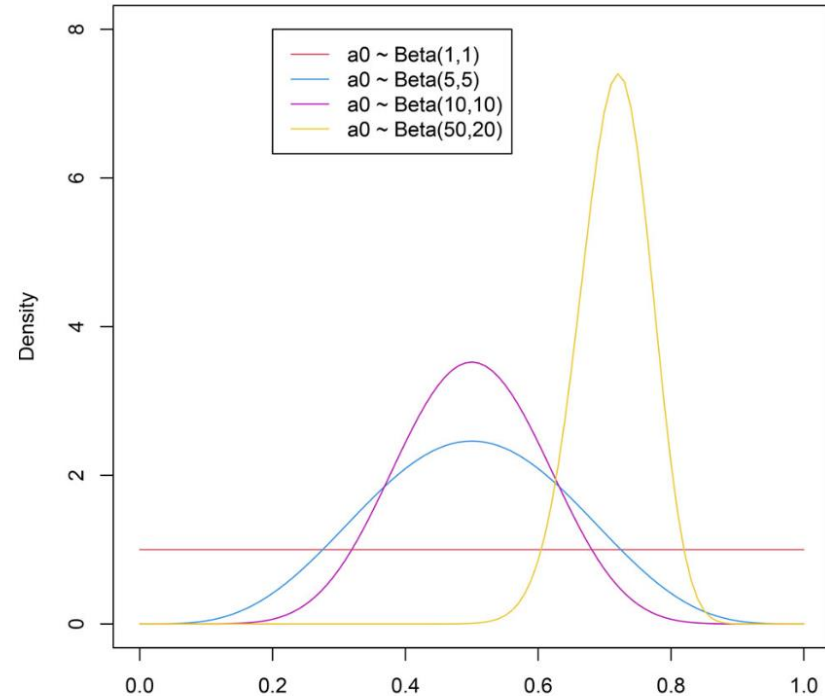
Then

$$\log C = -\frac{a_1 v_1 + a_2 v_2}{2} \log(2\pi) + \alpha_0 \log \beta_0 - \log \Gamma(\alpha_0) + \log \Gamma(A) - A \log(B).$$

log C is available in closed form — no bridge sampling required.

Discount-factor priors

Four Beta priors span uniform to strongly informative

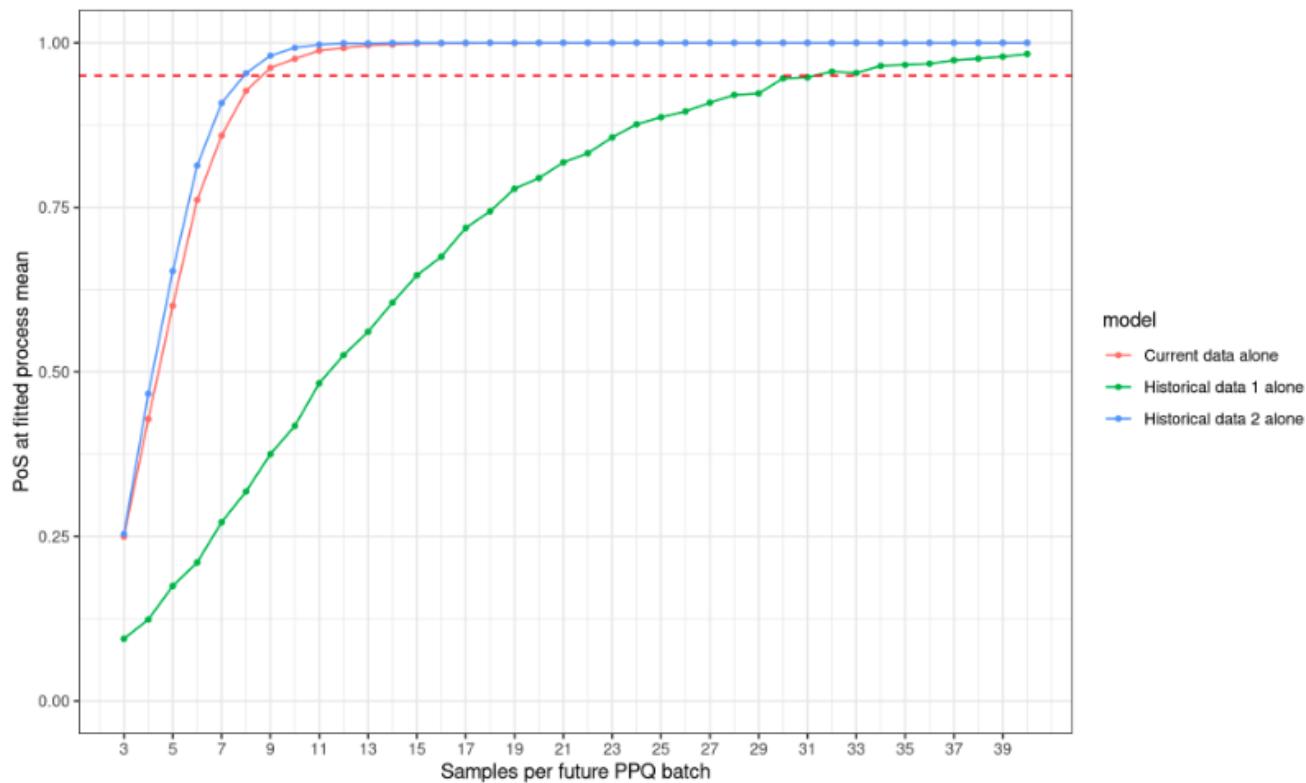


Prior for a_1 and a_2	Interpretation
Beta(1,1)	Uniform
Beta(5,5)	Moderately concentrated at 0.5
Beta(10,10)	More concentrated at 0.5
Beta(50,20)	Concentrated above 0.5

The prior controls how much discounting is allowed before the data speak.

Results: One data source

Data Source	μ	σ_w	σ_b	Min Sample Size
Current	99.17 (97.93, 100.42)	0.62 (0.54, 0.72)	1.90 (1.27, 3.24)	9
Hist 1	99.48 (98.67, 100.36)	1.09 (1.02, 1.17)	1.86 (1.38, 2.67)	32
Hist 2	101.20 (100.56, 101.81)	0.54 (0.50, 0.57)	1.71 (1.34, 2.27)	8



PBPP2: Unnormalized power prior

Ignoring the normalizing constant drives both discount factors to zero

DF Prior	a_1	a_2	Minimum Sample Size
Beta(1,1)	0.00 (0.00, 0.01)	0.00 (0.00, 0.01)	9
Beta(5,5)	0.00 (0.00, 0.02)	0.01 (0.00, 0.03)	9
Beta(10,10)	0.01 (0.01, 0.02)	0.02 (0.01, 0.04)	10
Beta(50,20)	0.07 (0.05, 0.09)	0.10 (0.07, 0.13)	11

Negligible borrowing

Minimum sample size barely moves (9 to 11) across all four discount-factor priors.

PBPP3A: Normalized power prior

DF Prior	a_1	a_2	Minimum Sample Size
Beta(1,1)	0.13 (0.01, 0.49)	0.71 (0.16, 0.99)	10
Beta(5,5)	0.28 (0.11, 0.57)	0.62 (0.36, 0.85)	12
Beta(10,10)	0.36 (0.19, 0.59)	0.59 (0.39, 0.77)	12
Beta(50,20)	0.69 (0.57, 0.80)	0.74 (0.63, 0.83)	14

- **Substantial borrowing**
 - Higher borrowing from Historical data set 2 (compatible)
 - Increased borrowing from Historical data set 1 (less compatible)
- **Higher minimum sample size than the no-borrowing**

PBPP3A: Normalized power prior

A **higher minimum sample size than the no-borrowing design** can indicate the borrowing procedure is working correctly and guarding against erroneous borrowing.

- **Robustness:** dynamic borrowing aims to borrow when appropriate and limit bias when historical data conflict with current data, not to always reduce sample size.
- **Quality and safety:** in conflict scenarios the method requires more new evidence before process performance is deemed acceptable.
- **“Pay for uncertainty”:** the method accounts for uncertainty about the relevance of historical information.

PBPP3: Normalized power prior

Closed Form: PBPP3A

DF Prior	a_1	a_2	Minimum Sample Size
Beta(1,1)	0.13 (0.01, 0.49)	0.71 (0.16, 0.99)	10
Beta(5,5)	0.28 (0.11, 0.57)	0.62 (0.36, 0.85)	12
Beta(10,10)	0.36 (0.19, 0.59)	0.59 (0.39, 0.77)	12
Beta(50,20)	0.69 (0.57, 0.80)	0.74 (0.63, 0.83)	14

Bridge sampling: PBPP3B

DF Prior	a_1	a_2	Minimum Sample Size
Beta(1,1)	0.19 (0.01, 0.50)	0.79 (0.26, 0.99)	10
Beta(5,5)	0.29 (0.14, 0.53)	0.62 (0.35, 0.85)	11
Beta(10,10)	0.35 (0.21, 0.55)	0.58 (0.38, 0.76)	12
Beta(50,20)	0.70 (0.57, 0.80)	0.74 (0.63, 0.83)	14

- **Similar results** – closed form solution reduces the computational burden

PBPP2 falls short

Without the normalizing constant, the power prior is uninformative

Ignores $C(a_1, a_2)$

The unnormalized power prior drops the normalizing constant.

Discounting collapses

Estimated discount factors sit near zero for every prior.

No compatibility signal

Cannot distinguish a compatible source from a conflicting one.

PBPP2 borrows almost nothing, whatever the discount-factor prior.

PBPP₃ remains the preferred approach

Normalization restores meaningful, interpretable borrowing

Correctly normalized

Accounts for $C(a_1, a_2)$, so discount factors are estimated honestly.

Closed form scales it

Sufficient statistics remove the computational burden of extra historical sources.

Interpretable diagnostic

Discount factors quantify compatibility or discrepancy per source.

Scientifically defensible borrowing, now practical for multiple historical sources.

Conclusion

Several historical data sets helps:

- consistent sources add strength and can reduce the new samples needed, while a single odd source carries less weight.

A larger sample size is not a failure of the method: it is the method protecting the decision.

- When past and current data disagree, the approach relies less on history and asks for more new evidence.
- This keeps both risks in balance: patient risk (accepting a process that is not performing) and producer risk (rejecting a process that is actually fine).
- The result is greater reliability, fewer wrong conclusions, and stronger confidence in process performance.

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Thank you!

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Questions welcome