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Leveraging Historical Data in Process Validation: Methods and Applications

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Motivation of leveraging historical information → **Bayesian linear mixed model (BLMM)** → **Family of power priors** → **Applications in process validation**

FDA 2011 Guidance

- The collection and evaluation of data from the ***process design stage throughout production,***

- Establishes scientific evidence that **a process is capable of consistently delivering quality products**.

FDA 2011➔ Approval of the process

"in consideration of the entire compilation of knowledge and information gained from the design stage through the process qualification stage".

Process validation lifecycle

Stage 1 : Process Design

- Process development
- Process characterization

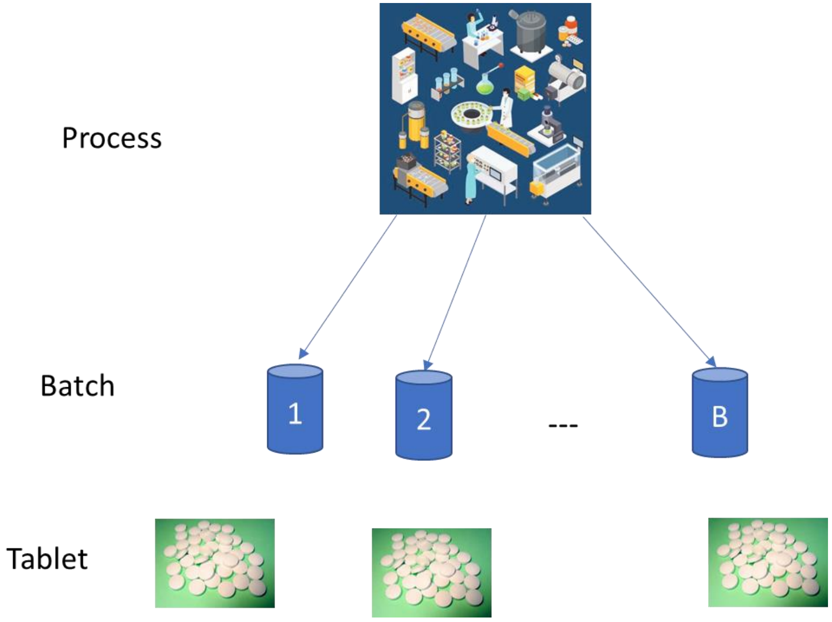
Stage 2 : Process Qualification

- Stage 2a: Design of the facility and qualification of the equipment and facilities
- Stage 2b: Process performance qualification (PPQ)

Stage 3 : Continued Process Verification (CPV)

- Stage 3a: Short term CPV
- Stage 3b: Long term CPV

FDA 2011: Process performance criteria

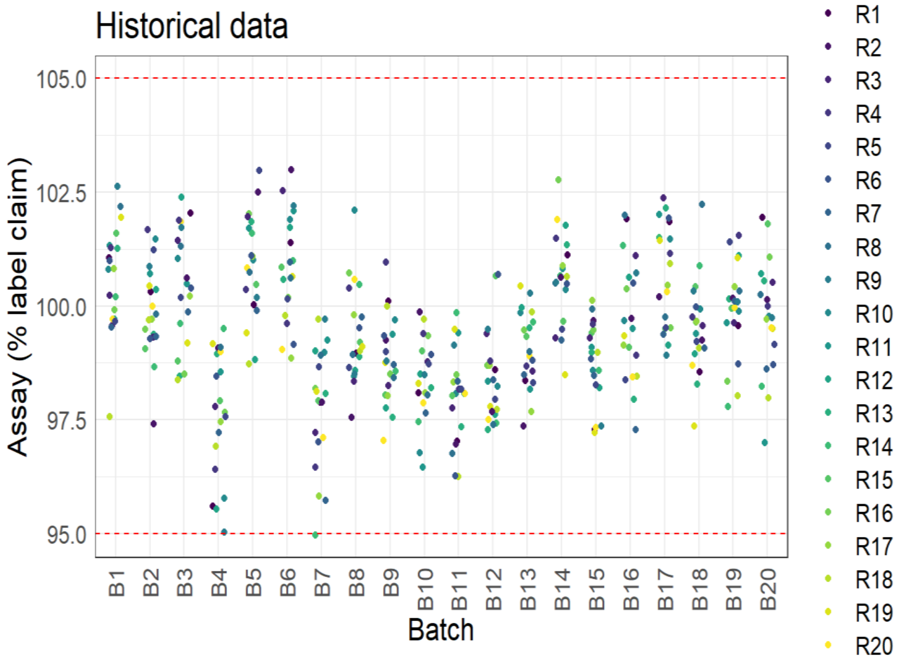


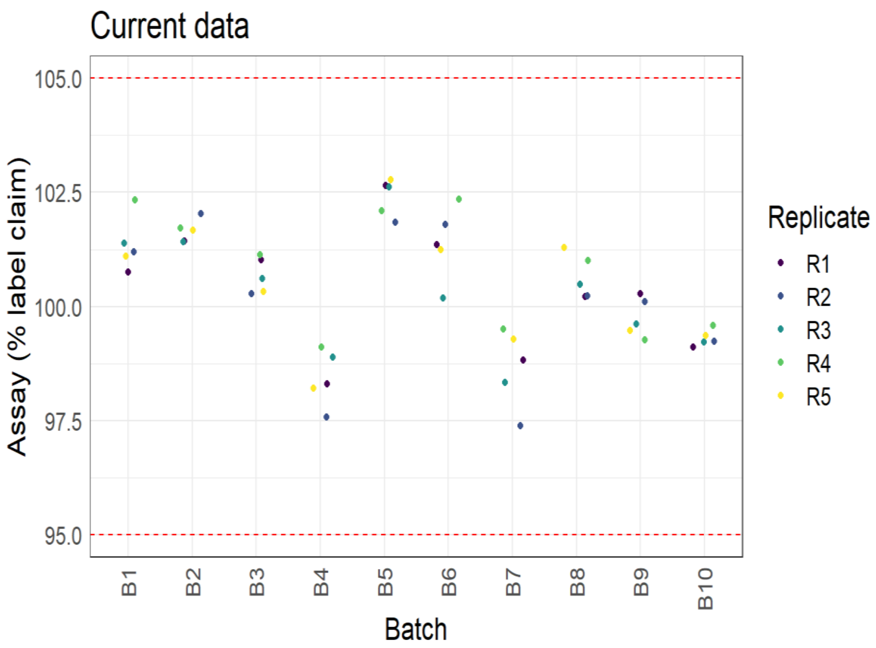
- The criteria should include statistical metrics defining both
  - intra-batch and
  - inter-batch variability

Sampling plan of PPQ

Fit an appropriate Bayesian model for the data → Generate posterior samples → Specify candidate sample size → Specify the range of true batch means → **Calculate the tolerance interval (TI) and the probability of the TI to be within specifications (PoS)** → Select a minimum sample size sufficient for PPQ

Motivating data sets





BLMM for historical data

$$y_{0ij} = \beta_{00} + b_{0i} + \varepsilon_{0ij}$$

- y_{0ij} = assay value
- β_{00} = the process mean,
- b_{0i} = the random batch effect
- $\epsilon_{0ij} \sim N(0,\ \sigma_0^2)$ the random error term

$$L(\theta_0|D_0) = \prod_{i=1}^{B_0}\prod_{j=1}^{n_{0i}} f\left(y_{0ij}|b_{0i},\beta_{00},\sigma_0^2\right) g\left(b_{0i}|\sigma_{b_0}^2\right)$$

- $f\left(y_{0ij}|b_{0i},\beta_{00},\sigma_0^2\right) = N(\beta_{00} + b_{0i},\sigma_0^2)$
- $g\left(b_{0i}|\sigma_{b_0}^2\right) = N\left(0,\ \sigma_{b_0}^2\right)$ distribution of batch random effect,
- $D_0 = (B_0,\ y_0,\ b_0)$ historical data
- $\theta_0 = \left(\beta_{00},\ \sigma_0^2,\ \sigma_{b_0}^2\right)$ vector of parameters

BLMM for current data

$$y_{ij} = \beta_0 + b_i + \varepsilon_{ij}$$

- y_{ij} = assay value
- β_0 = the process mean,
- b_i = the random batch effect,
- $\epsilon_{ij} \sim N(0,\ \sigma^2)$ the random error term

$$L(\theta|D) = \prod_{i=1}^{B}\prod_{j=1}^{n_i} f(y_{ij}|b_i, \beta_0, \sigma^2)\, g(b_i|\sigma_b^2)$$

- $f(y_{ij}|b_i, \beta_0, \sigma^2) = N(\beta_0 + b_i,\ \sigma^2)$
- $g(b_i|\sigma_b^2) = N(0,\ \sigma_b^2)$ distribution of b_i
- $D = (B, y, b)$ historical data
- $\theta = (\beta_0,\ \sigma^2,\ \sigma_b^2)$ vector of parameters

Basic formulation of power prior

- Ibrahim and Chen (2000) defined power prior:

$$\pi(\theta \mid D_0, a_0) \propto L(\theta \mid D_0)^{a_0} \pi(\theta)$$

- Assumption $\theta_0 = \theta$
- a_0 is a parameter that weights the historical data relative to the likelihood of the current data.
- Range of a_0 : $0 \leq a_0 \leq 1$.

Family of power priors

Partial borrowing power prior with **fixed** discounting parameter

Partial borrowing **unnormalized** power prior with **random** discounting parameter

Partial borrowing **normalized** power prior with **random** discounting parameter

Partial borrowing power prior with fixed discounting parameter

$$\pi(\boldsymbol{\theta} \mid D_0, a_0) \propto \frac{\left\{\int L\left(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0 \mid D_0\right)^{a_0} \pi(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0) d\boldsymbol{\theta}_0\right\}}{\int\left\{\int L\left(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0 \mid D_0\right)^{a_0} \pi(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0) d\boldsymbol{\theta}_0\right\} d\boldsymbol{\theta}_c} \pi(\boldsymbol{\theta}_1)$$

$$\propto \left\{\int L\left(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0 \mid D_0\right)^{a_0} \pi(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0) d\boldsymbol{\theta}_0\right\} \pi(\boldsymbol{\theta}_1)$$

- $\boldsymbol{\theta} = (\boldsymbol{\theta}_c, \boldsymbol{\theta}_1)$ the parameters of current data,
- $(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0)$ the parameters of historical data,
- $\boldsymbol{\theta}_c = (\sigma^2)$ the common parameters,
- $\boldsymbol{\theta}_1 = \left(\beta_0, \sigma_b^2\right)$ the parameters only for the current,
- $\boldsymbol{\theta}_0 = \left(\beta_{00}, \sigma_{b0}^2\right)$ the parameters only for the historical

a_0=0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1

Partial borrowing unnormalized power prior with random discounting parameter

$$\pi(\boldsymbol{\theta}, a_0 \mid D_0) \propto \frac{\left\{\int L(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0 \mid D_0)^{a_0} \pi(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0) d\boldsymbol{\theta}_0\right\}}{\int \left\{\int L(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0 \mid D_0)^{a_0} \pi(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0) d\boldsymbol{\theta}_0\right\} d\boldsymbol{\theta}_c} \pi(\boldsymbol{\theta}_1) \pi(a_0)$$

$$\propto \left\{\int L(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0 \mid D_0)^{a_0} \pi(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0) d\boldsymbol{\theta}_0\right\} \pi(\boldsymbol{\theta}_1) \pi(a_0)$$

- $\pi(a_0)$ is the initial prior for a_0
- a_0 : the heterogeneity (compatibility) between current and historical data.

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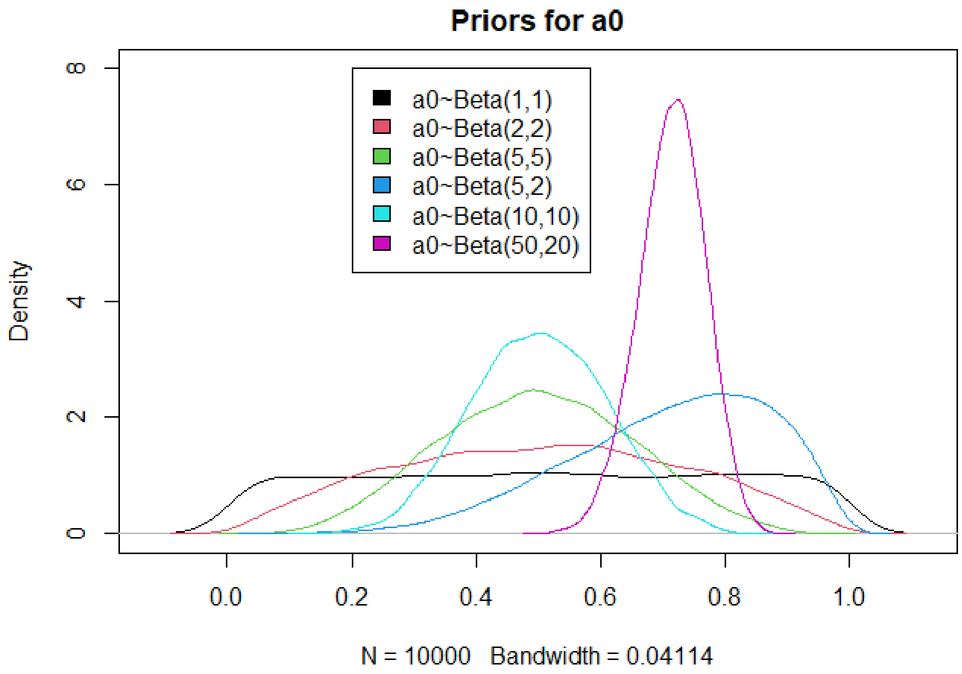
Partial borrowing normalized power prior with random discounting parameter

$$\pi(\boldsymbol{\theta}, a_0 \mid D_0) \propto \frac{\left\{\int L(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0 \mid D_0)^{a_0} \pi(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0) d\boldsymbol{\theta}_0\right\}}{c(a_0)} \pi(\boldsymbol{\theta}_1) \pi(a_0)$$

- $c(a_0) = \int \left\{\int L(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0 \mid D_0)^{a_0} \pi(\boldsymbol{\theta}_c, \boldsymbol{\theta}_0) d\boldsymbol{\theta}_0\right\} d\boldsymbol{\theta}_c$ the normalsing constant.

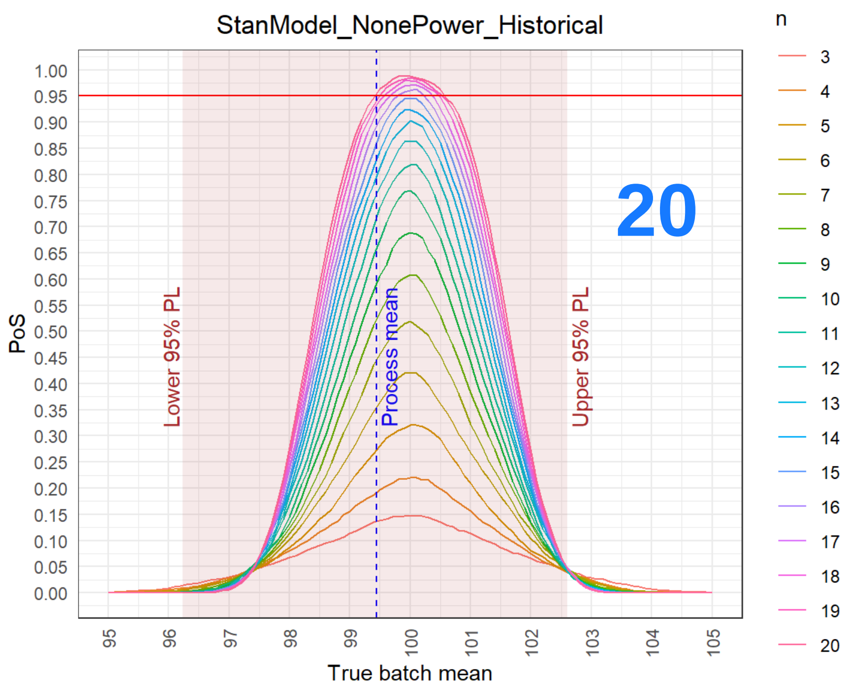
Priors for discounting parameter

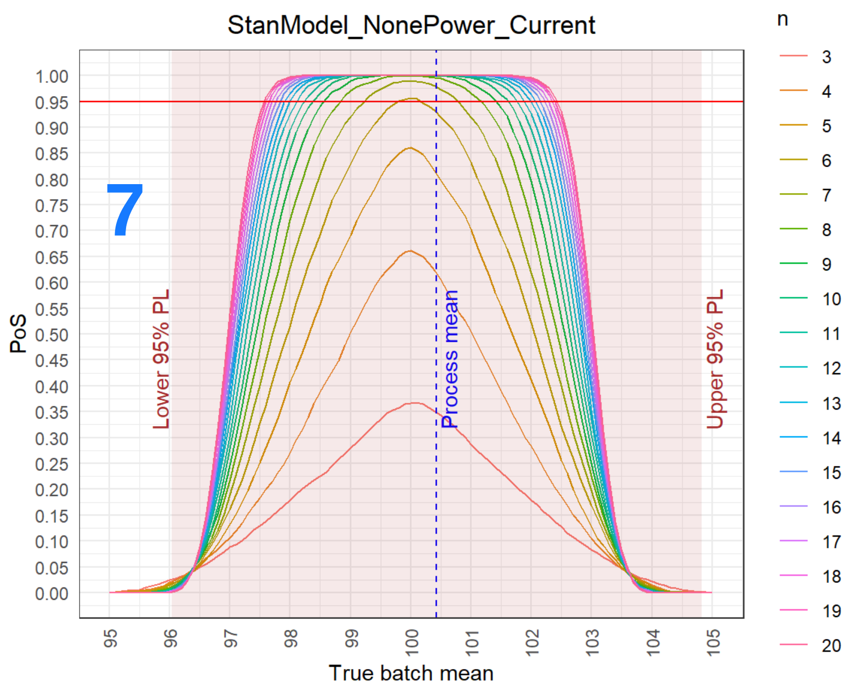


Modeling results for historical and current data separately

Model		Process Mean (β_0)	Within-batch SD (σ)	Between-batch SD (σ_b)
Historical	Estimate	99.4	1.11	1.49
	Lower	99.0	1.04	1.08
	Upper	100.0	1.20	2.15
Current	Estimate	100.4	0.55	1.96
	Lower	99.5	0.45	1.27
	Upper	101.4	0.71	3.38

Estimating sample size for historical and current data separately

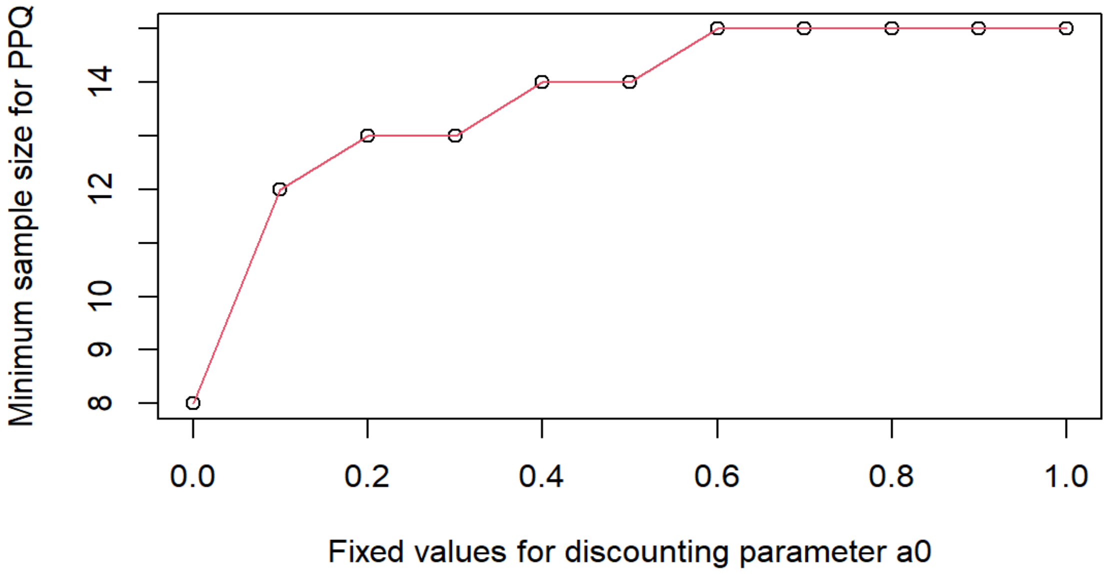




Modeling results using the partial borrowing power prior with fixed discounting parameter

Model		β_0	σ	σ_b
$a_0 = 0.0$	Estimate	100.4	0.55	1.41
	Lower	99.5	0.45	0.90
	Upper	101.3	0.69	2.47
$a_0 = 0.1$	Estimate	100.4	1.01	1.35
	Lower	99.4	0.85	0.82
	Upper	101.3	1.23	2.42
$a_0 = 0.2$	Estimate	100.4	1.04	1.34
	Lower	99.5	0.91	0.81
	Upper	101.3	1.20	2.41
$a_0 = 0.3$	Estimate	100.4	1.05	1.34
	Lower	99.5	0.93	0.80
	Upper	101.3	1.19	2.35
$a_0 = 0.4$	Estimate	100.4	1.06	1.34
	Lower	99.4	0.96	0.80
	Upper	101.3	1.18	2.43
$a_0 = 0.5$	Estimate	100.4	1.06	1.35
	Lower	99.5	0.97	0.82
	Upper	101.3	1.17	2.39
$a_0 = 0.6$	Estimate	100.4	1.07	1.34
	Lower	99.5	0.98	0.80
	Upper	101.4	1.16	2.42
$a_0 = 0.7$	Estimate	100.4	1.07	1.34
	Lower	99.5	0.98	0.81
	Upper	101.3	1.16	2.45
$a_0 = 0.8$	Estimate	100.4	1.07	1.36
	Lower	99.4	0.99	0.80
	Upper	101.4	1.15	2.45
$a_0 = 0.9$	Estimate	100.4	1.07	1.33
	Lower	99.5	1.00	0.81
	Upper	101.3	1.15	2.40
$a_0 = 1.0$	Estimate	100.4	1.07	1.34
	Lower	99.4	1.00	0.81
	Upper	101.3	1.15	2.38

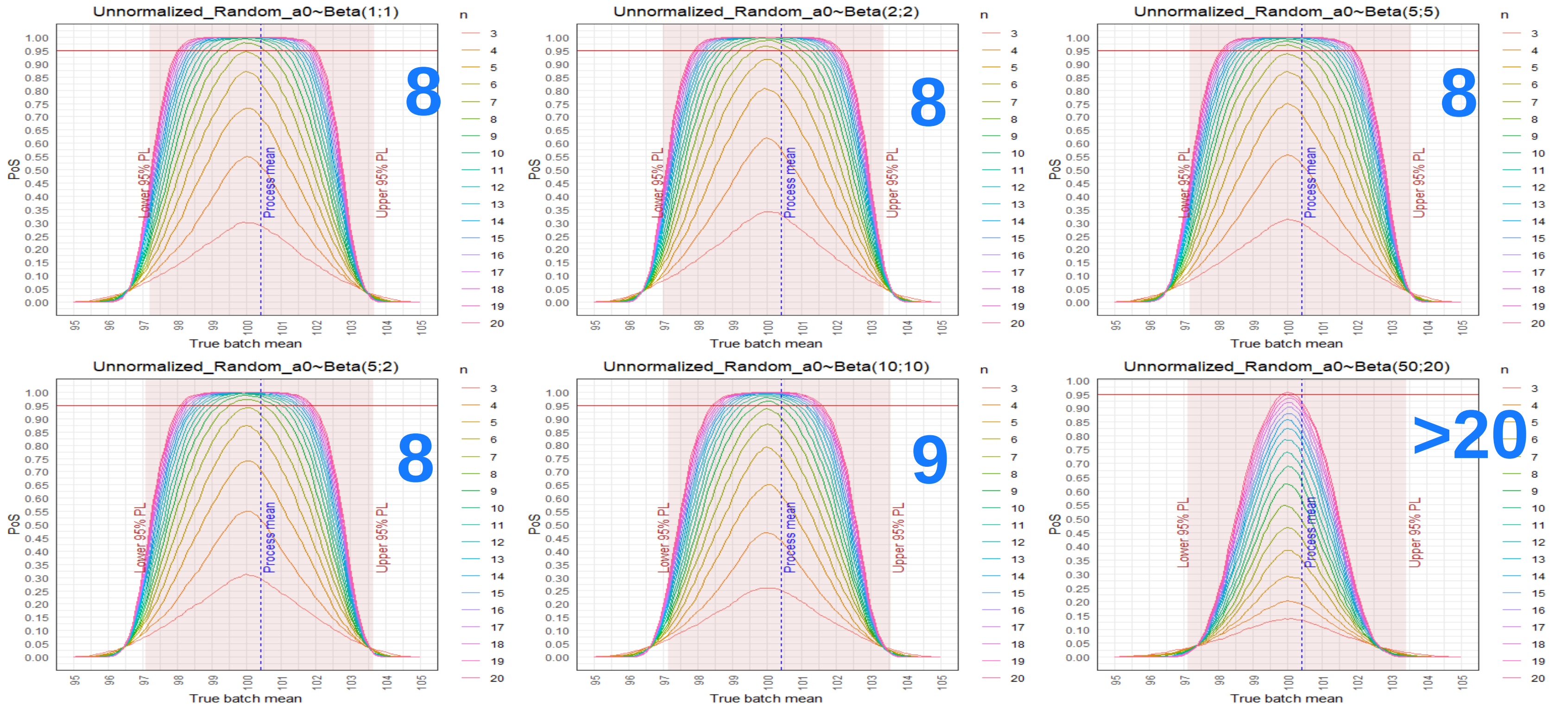
Sample size using the partial borrowing power prior with fixed discounting parameter



Modeling results using partial borrowing unnormalized power prior with random discounting parameter

Model		β_0	σ	σ_b	a_0
$a_0 \sim Beta(1,1)$	Estimate	100.4	0.56	1.40	0.0003
	Lower	99.5	0.46	0.91	0.0000
	Upper	101.3	0.72	2.46	0.0014
$a_0 \sim Beta(2,2)$	Estimate	100.4	0.58	1.42	0.0009
	Lower	99.5	0.47	0.90	0.0001
	Upper	101.3	0.73	2.49	0.0029
$a_0 \sim Beta(5,5)$	Estimate	100.4	0.62	1.40	0.0031
	Lower	99.4	0.49	0.90	0.0008
	Upper	101.4	0.79	2.41	0.0071
$a_0 \sim Beta(5,2)$	Estimate	100.4	0.61	1.41	0.0032
	Lower	99.5	0.49	0.91	0.0008
	Upper	101.4	0.80	2.53	0.0075
$a_0 \sim Beta(10,10)$	Estimate	100.4	0.68	1.38	0.0079
	Lower	99.4	0.54	0.88	0.0035
	Upper	101.3	0.88	2.44	0.0146
$a_0 \sim Beta(50,20)$	Estimate	100.4	0.98	1.35	0.0634
	Lower	99.5	0.80	0.82	0.0455
	Upper	101.4	1.20	2.46	0.0849

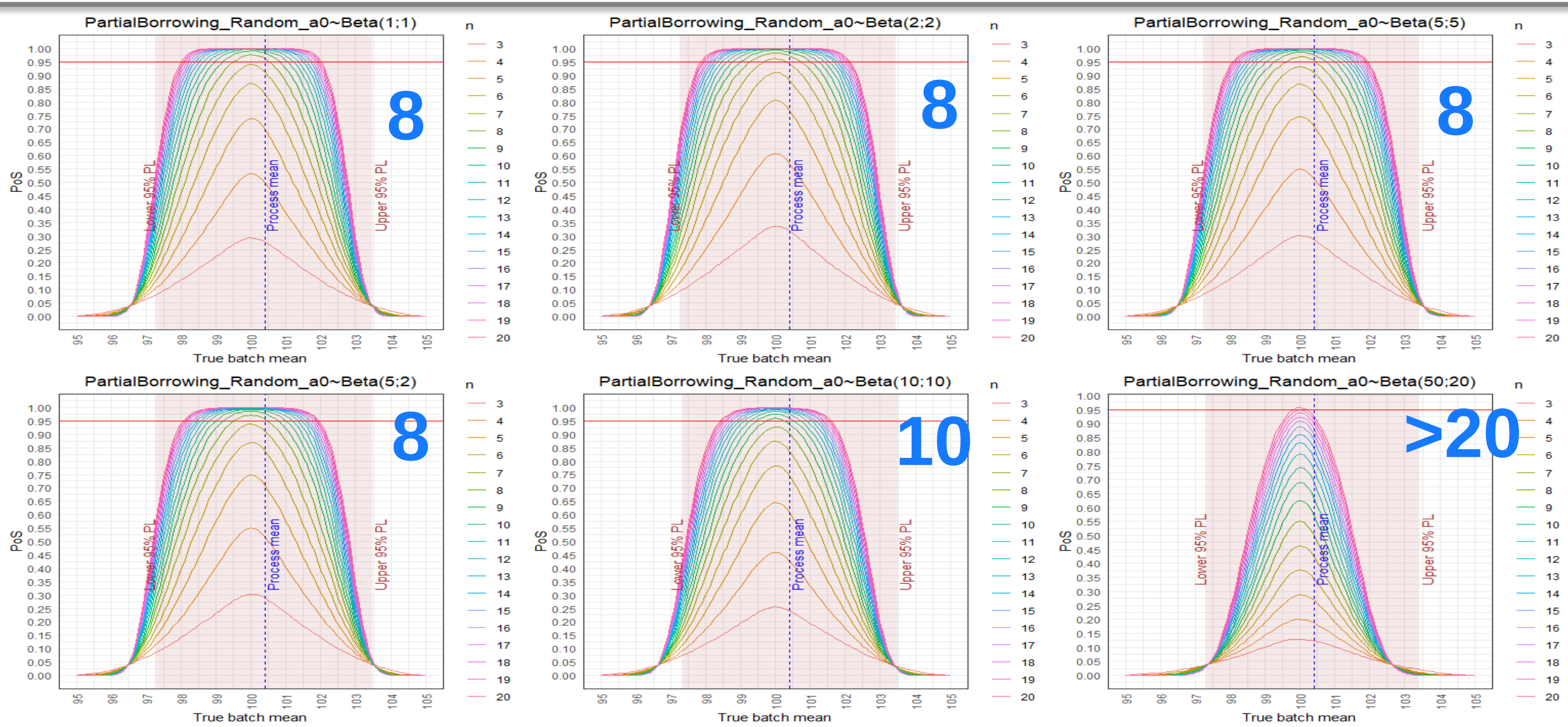
Sample size using partial borrowing unnormalized power prior with random discounting parameter



Modeling results using partial borrowing normalized power prior with random discounting parameter

Model		β_0	σ	σ_b	a_0
$a_0 \sim Beta(1,1)$	Estimate	100.4	0.59	1.40	0.0926
	Lower	99.4	0.47	0.89	0.0000
	Upper	101.4	1.11	2.45	0.8819
$a_0 \sim Beta(2,2)$	Estimate	100.4	1.06	1.35	0.5594
	Lower	99.4	0.67	0.81	0.0038
	Upper	101.3	1.16	2.49	0.9136
$a_0 \sim Beta(5,5)$	Estimate	100.4	1.06	1.33	0.5344
	Lower	99.5	0.96	0.80	0.2691
	Upper	101.3	1.17	2.46	0.8054
$a_0 \sim Beta(5,2)$	Estimate	100.4	1.07	1.35	0.7332
	Lower	99.5	0.99	0.81	0.3943
	Upper	101.3	1.16	2.44	0.9584
$a_0 \sim Beta(10,10)$	Estimate	100.4	1.06	1.35	0.5156
	Lower	99.5	0.97	0.82	0.3199
	Upper	101.3	1.17	2.40	0.7176
$a_0 \sim Beta(50,20)$	Estimate	100.4	1.07	1.35	0.7184
	Lower	99.4	0.98	0.81	0.6032
	Upper	101.3	1.16	2.45	0.8174

Sample size using partial borrowing **normalized** power prior with **random** discounting parameter



Summary

- Why do we need to validate a manufacturing process?
  - To assure drug quality
- Why sampling plan for PPQ is so important?
  - To be cost effective
- Informative priors to leverage historical data in process validation?
  - Power priors
- Discounting parameter Vs Sample size?
  - Increasing (not always)
- Unnormalized Vs Normalized?

References

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Thank You!

What is next?

Simulation study

PPQ validation

Dissolution

Joint modeling

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