PPQ Sample Size Determination using Bayesian simulation

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Outline

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  - Process Validation
  - Objective
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- Methods
- Results
- Conclusions

Introduction

ICH Quality vision (2003):

"Develop a harmonized pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science."

We want to:

- ensure quality products; and
- reliable supply to patients

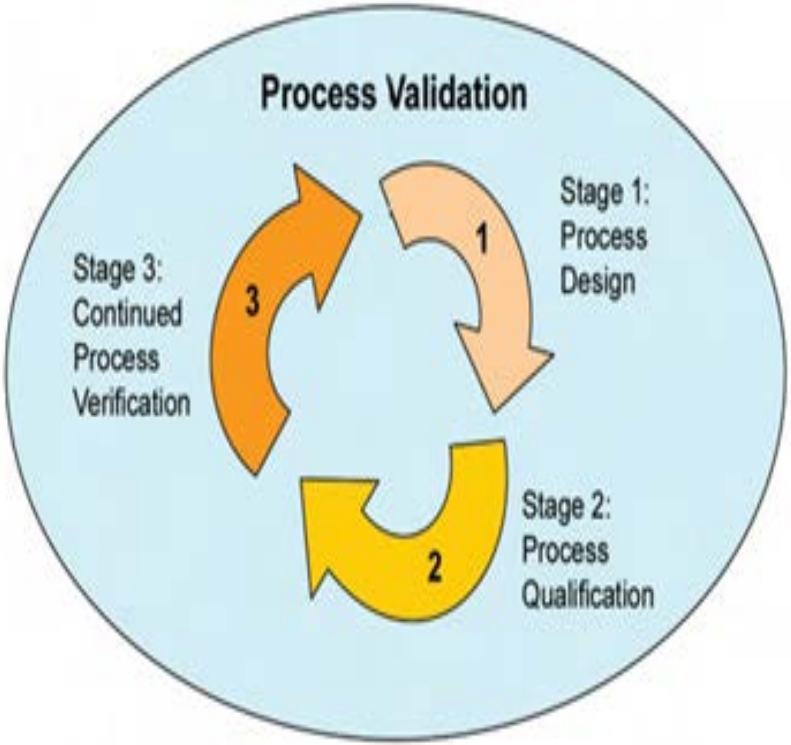
There is a need to improve execution and communication of science and risk based assessments that enable product lifecycle management

Process Validation

Process Validation: is the analysis of **data** gathered **throughout the design and manufacturing** of a product in order to **confirm** that the process can **reliably** output **quality** products.

Ensure ***varied*** inputs ⟹ ***consistent*** and ***high quality*** outputs

Quality *cannot always* be determined by *finished-product inspection!*



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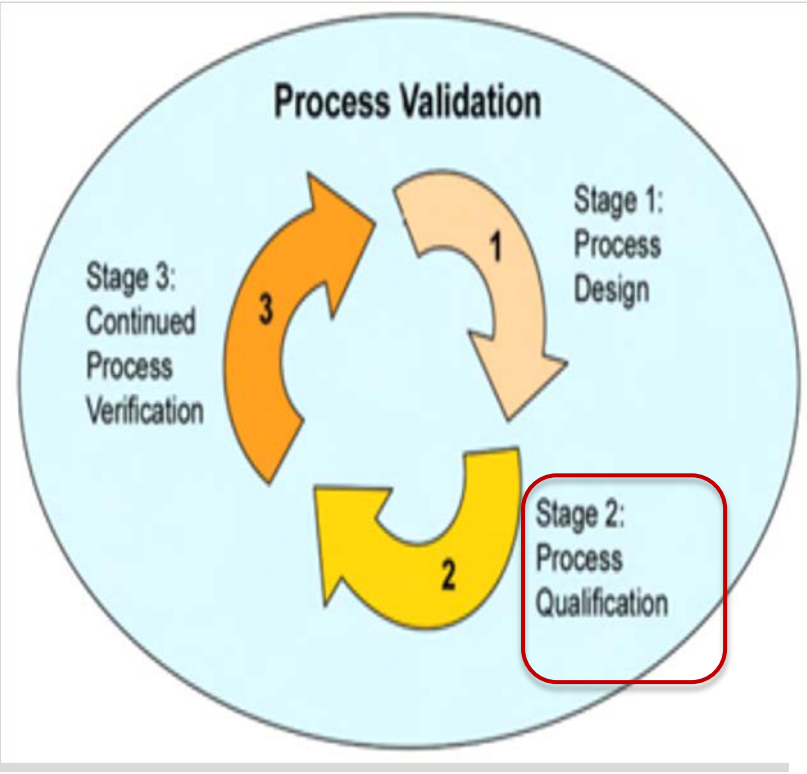


Process Qualification

Process Qualification: *During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing*

1. *Design of a Facility and Qualification of Utilities and Equipment*
2. *Process Performance Qualification (PPQ)*

Phases of PPQ

- **PPQ Sampling size**
- Evidence enough(What & How)?

- **PPQ Validation**
- Presenting evidence/your case

Phases of PPQ

- **PPQ Sampling size**
- Evidence enough(What & How)?
- Pre-PPQ batches, Process Design, etc

- **PPQ Validation**
- Presenting evidence/your case

Objective

Sample size determination for the API of drug X

In other words,

Quantify the amount of evidence needed to **confirm** that the process can **reliably** output **quality** products

Data

- **Simulated data for API of drug product X**
  - 10 batches
  - 10 within batch observations
- **Specification limits:**
  - 95.0%-105.0%
- **Criticality analysis (Severity & occurrence of harm)**
  - Content: 99% (Beta)
  - Confidence: 95% (Gamma)

Methods: Statistical tools

- **Beta-Gamma Tolerance interval -** provides limits within which at least a certain proportion (Beta) of the population falls with a given level of confidence (Gamma)

- **Simulation** – based on the current data, scientific knowledge and the criticality analysis create expected future scenarios

Approaches: Optimization

- **Inputs**: pre-PPQ data - “Representative” statistics (Mean, SD)
- **Functions**: norm.ss() in the R package tolerance
- **Output**: n – within batch sample size for the validation batches

Approaches: Bayesian simulation

- Inputs: pre-PPQ batches data
- Fit the following mixed effects model [**brms** package]

$$Y_{ij} = \beta + b_i + \varepsilon_{ij}$$

where Y_{ij} is the j-th assay observation from the i-th batch

β is the process mean

b_i is the random intercept for the i-th batch: $b_i \sim N(0, \sigma_b^2)$

ε_{ij} is the residual error term: $\varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2)$

Approaches: Bayesian simulation

- **Output**: Posterior summaries, process tolerance interval and prediction interval for the batch means
- **Simulation**:
  - Generate samples of size K based on a normal distribution with a mean of 0 and the standard deviation equal to the posterior residual SD
  - Calculate the beta-gamma tolerance intervals for samples of size 3-K
    - Normtol.in() function
  - Consider the true batch means which span the entire specification range
  - Add the tolerance intervals to the true batch means
  - Calculate the number of tolerance intervals which are within specifications

Results: EDA

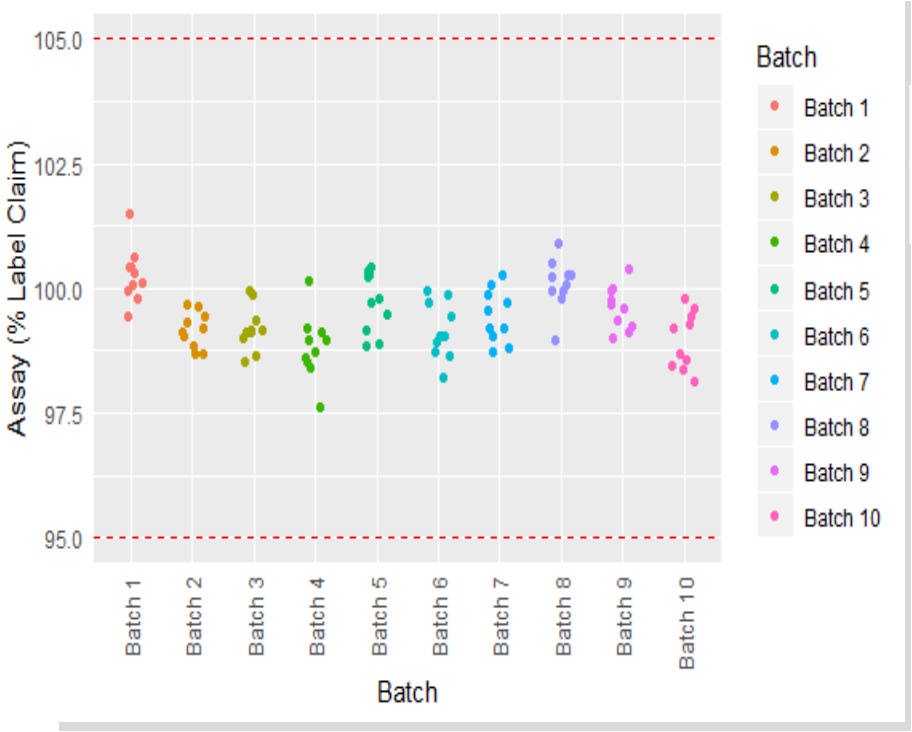


Table: Summary Statistics

Mean (SD)	Minimum	Maximum
99.4 (0.68)	97.6	101.5

Results: Posterior summaries

Process mean

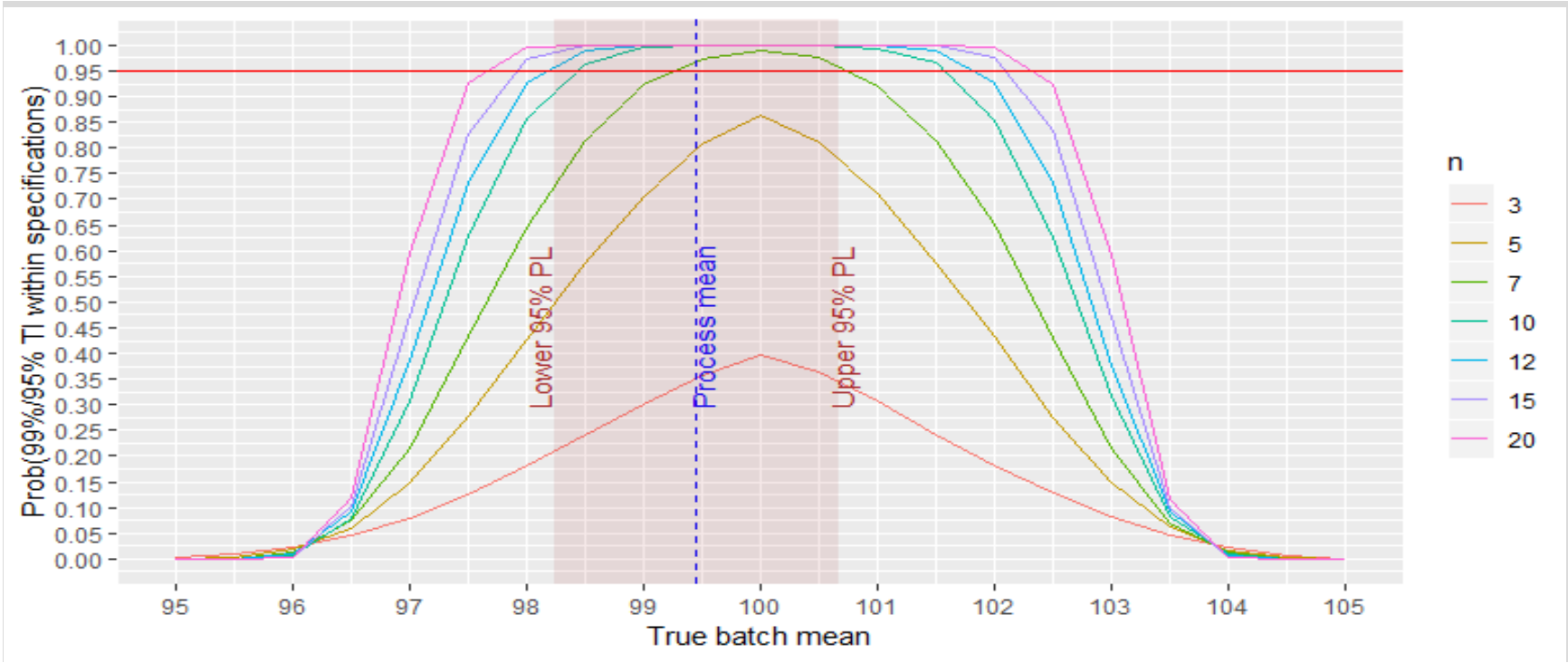
Mean	95% CI	99%/95% TI
99.4	(99.0; 99.8)	(97.0; 101.9)

Variance components (SD)

VC	Median	95% CI
Batch	0.49	(0.30; 0.96)
Residual	0.47	(0.47; 0.63)

- **Process mean**
  - Lower than the label claim
  - Range of future observations **97.0%-101.9%** [process TI]
  - Range of future batch means **98.2%-100.7%**
- **Variance components**
  - Within- and between-batch sd are similar

Sample size determination



Sample size determination

Samples	Process Mean	Lower 95% PL
3	0.35	0.21
5	0.80	0.50
7	0.97	0.74
10	>0.99	0.92
12	>0.99	0.97
15	>0.99	0.99
20	>0.99	>0.99

- **@Process mean:**
  - n = 3 (norm.ss() function)
  - n = 7
- **@Worst case scenario:**
  - n = 4 (norm.ss() function)
  - n = 12

Conclusion

- For a batch mean == process mean : n=3 vs n= 7
- For a batch mean == lower 95% PL : n=4 vs n=12
  - Which estimate would you take?
  - If you present these two estimates to the scientist, which estimate are they going to take?

- Bayesian approach:
  - Larger sample sizes (conservative sample sizes)
  - Risk assessment of various sampling plans
  - Incorporating parameter uncertainty / various scenarios
  - Overall costs of sampling plans based on Bayesian simulations are less (Less investigations)

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3/08/2018

Rhonda Fenwick, *Time is Now I*
Through her art, Rhonda has explored psoriasis, a chronic skin disorder she has lived with since the age of six.

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