Risk assessments using a Bayesian approach:

Evaluation of impact from analytical method performance on process capability

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Global Statistics

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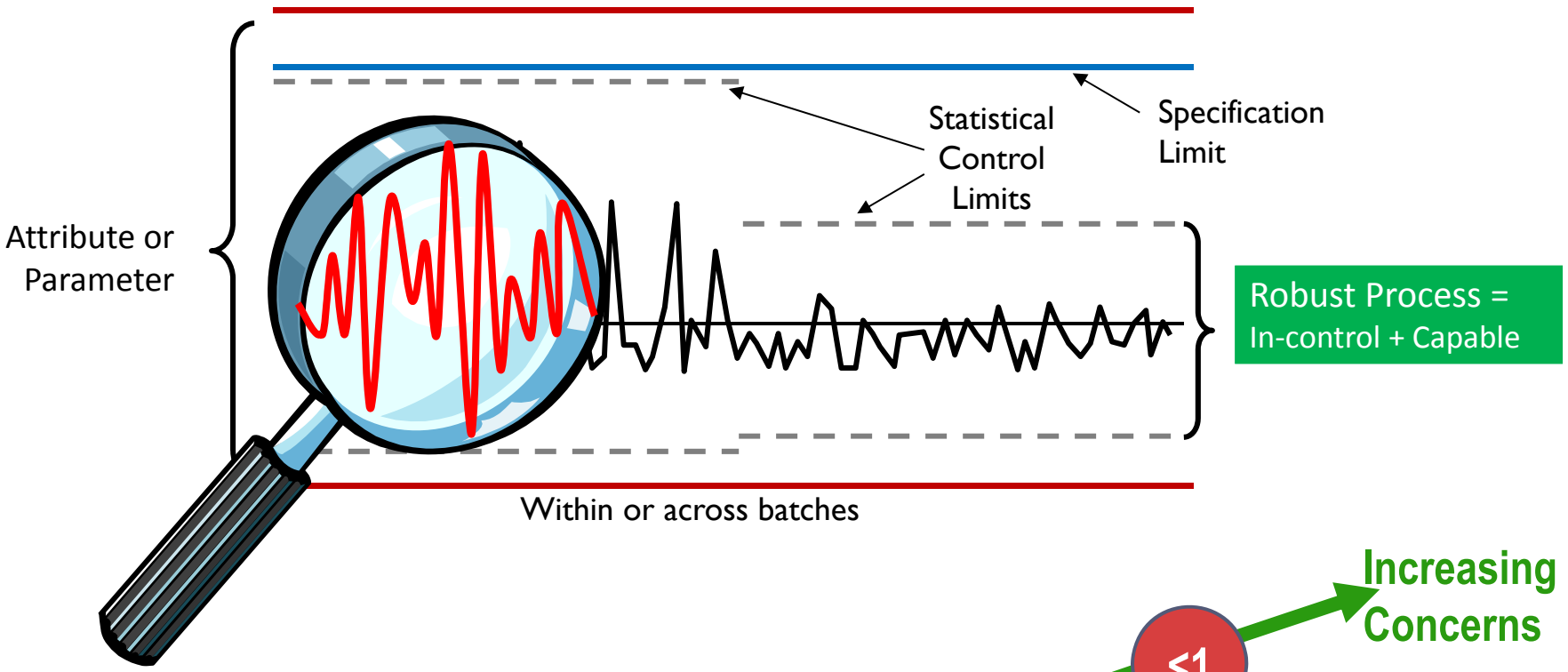
Outline

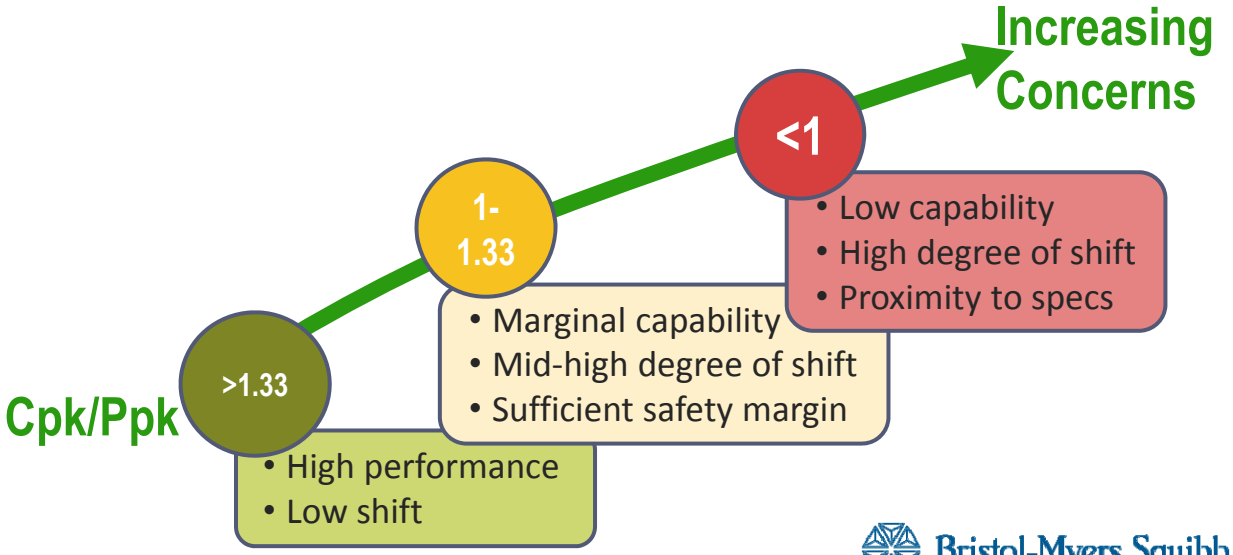
- Business needs for using advanced statistical modelling tool to build effective control strategy through life-cycle
  - Achieve robustness goal through continuous process verification
  - Control analytical performance is critical
  - BMS's vision in delivering analytical performance through continuous analytical verification
- Bayesian's advantages in establishing risk-based control strategy
- A case study on protein concentration method
- Summary and next steps

Robustness through Continuous Process Verification



Robust Process =
In-control + Capable

What is the source of variability?



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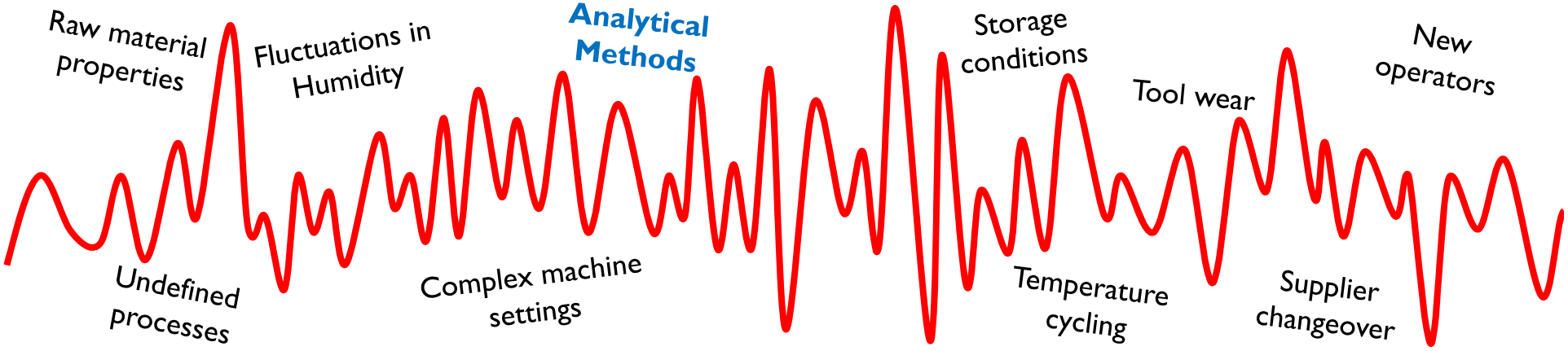
Understand Sources of Variance




Raw materials +

Processes +

Environment +

Analytical Method =

Quality Variations

To what degree should each source of variance be controlled to meet the robustness goal?

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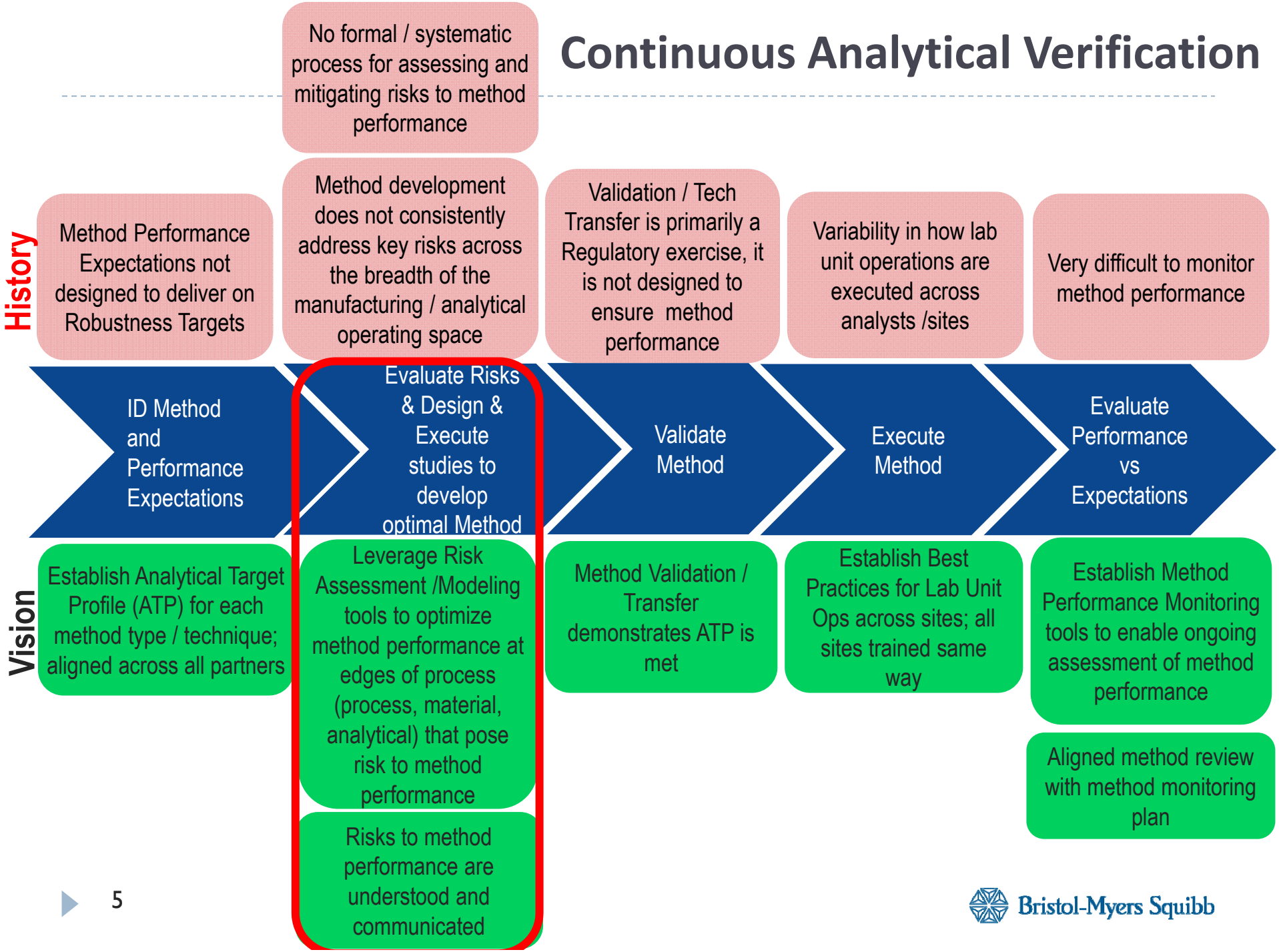
Continuous Analytical Verification



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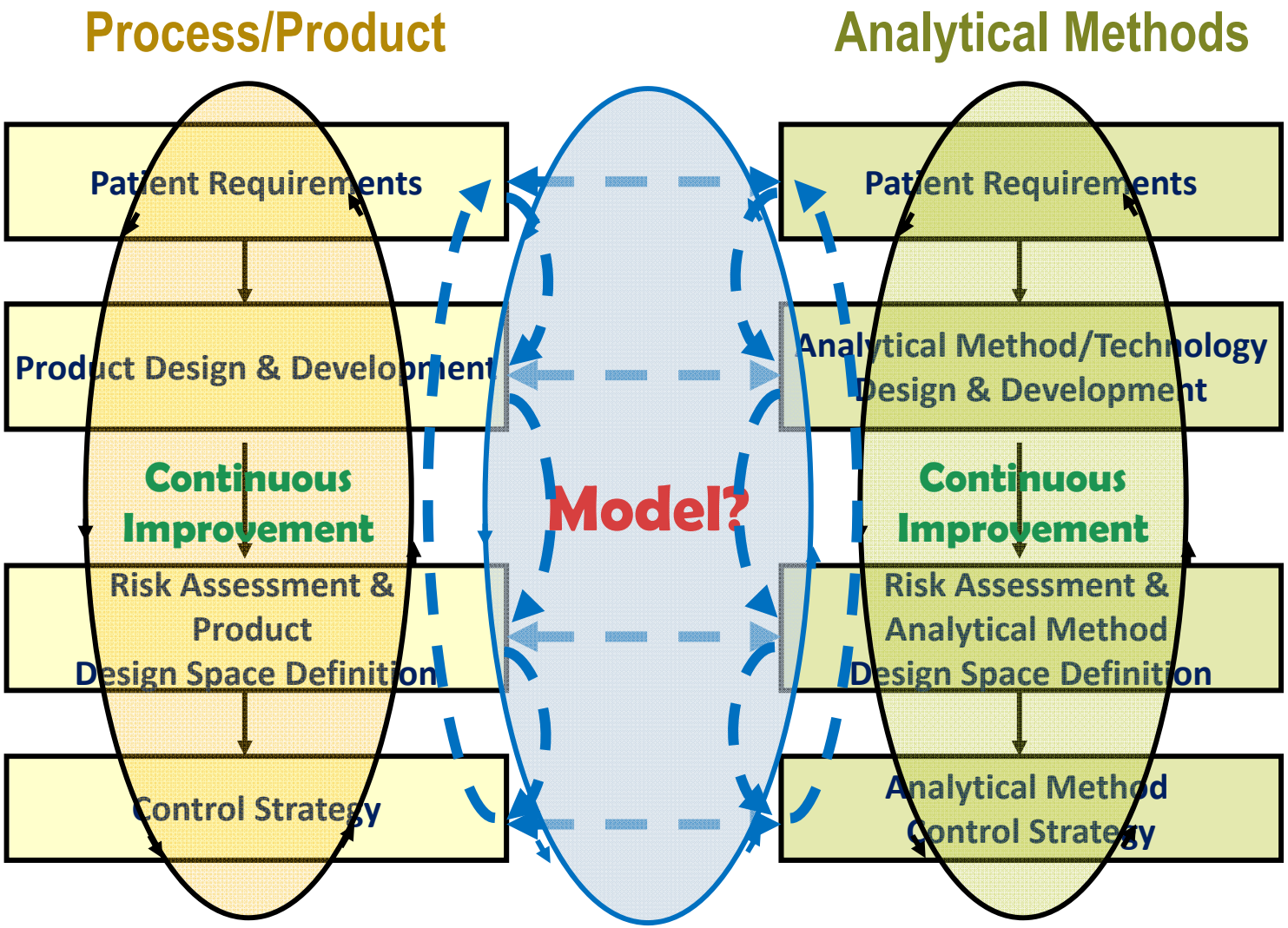
Need for Advanced Statistical Modelling

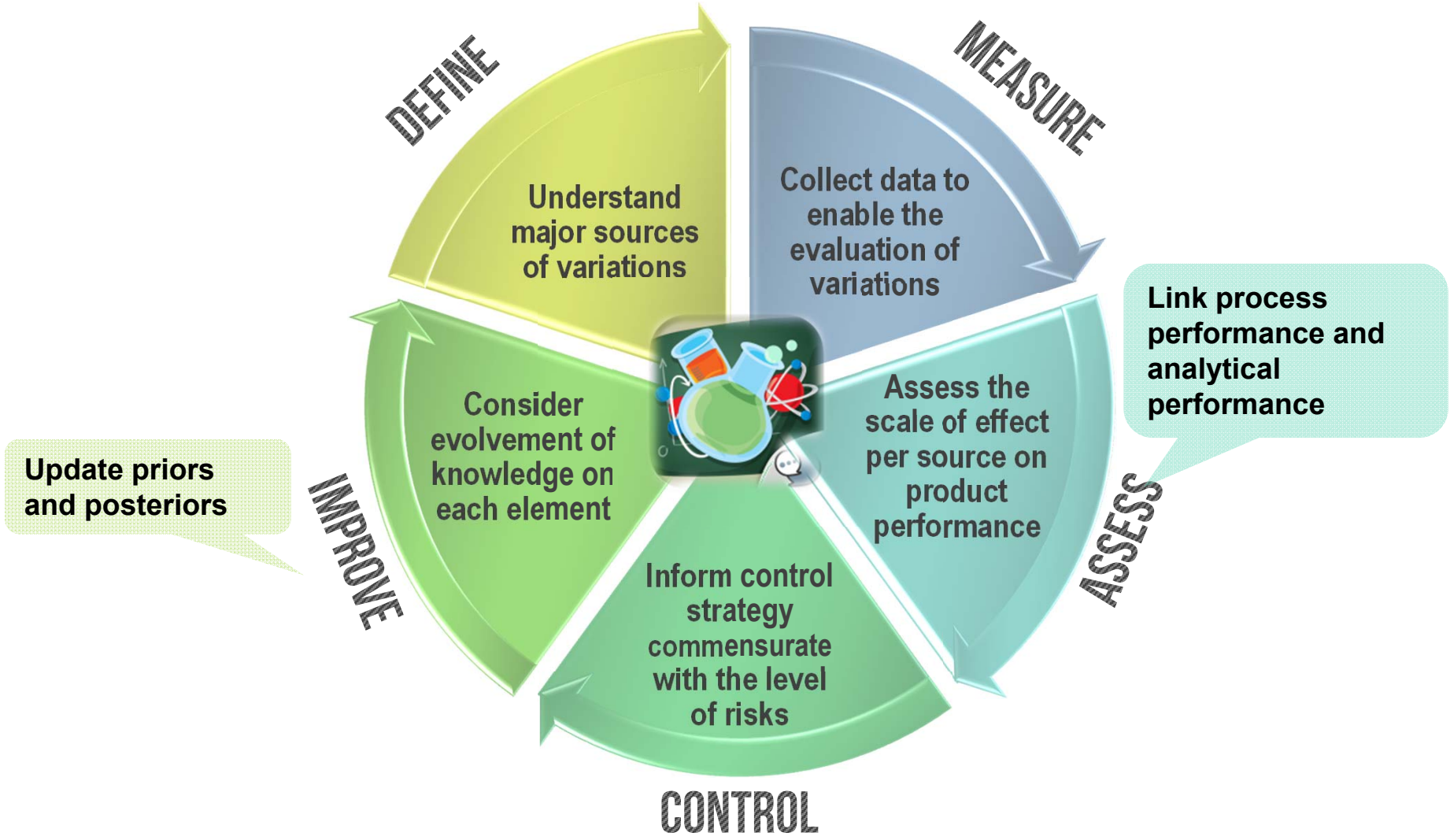


Bayesian Hierarchical Modeling

Frequentist	vs.	Bayesian
P(data | performance)		P(performance | observed data + prior information)

- Convenient connection of complex analytical and process components
- Natural and principled way of combining **prior information** (e.g. historical process and analytical data)
- **Continuous learning** capability based on accumulated knowledge
- **Predictive inference** (posterior distribution) based on varied hypotheses
- **Uncertainty** about future performance

Build Risk-based Control Strategy



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A Case Study

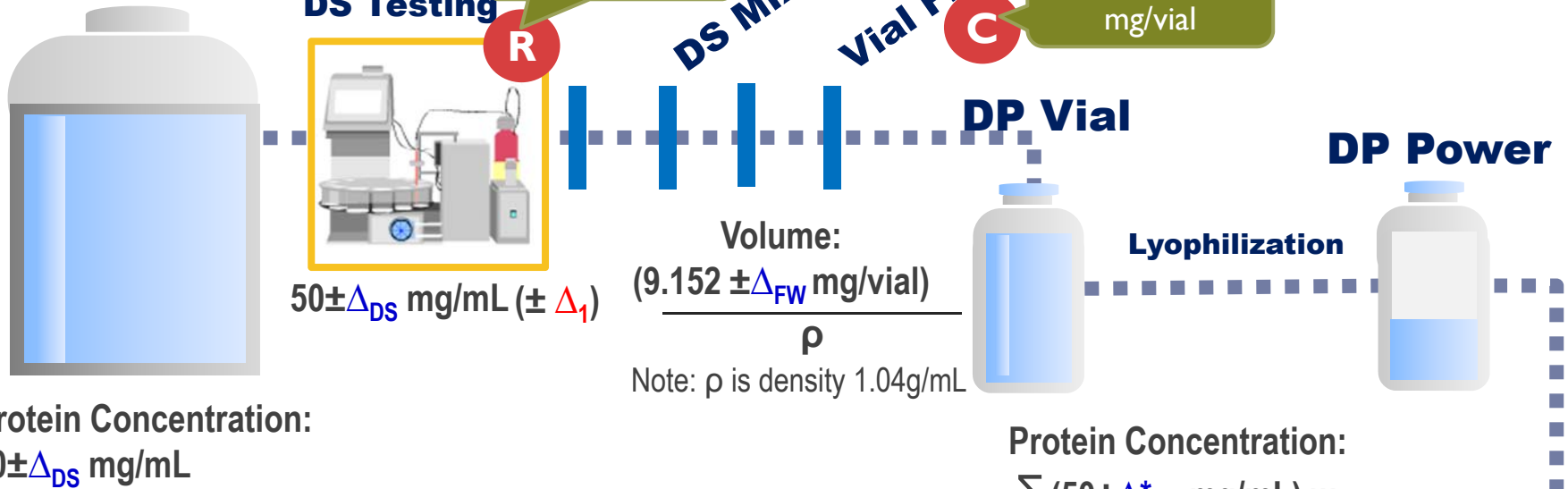
Background

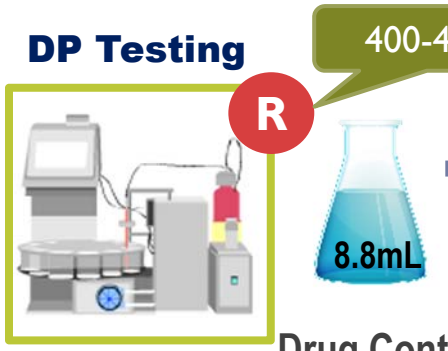
- CQA: **Drug Content (DP) / Protein Concentration (DS)**
- Target of Control

Elements of Control	Acceptance Criteria
DS Protein Concentration	• 45.0-55.0 mg/mL
DP Drug Content	• 400-480mg
DP Fill Weight	• 8.923 - 9.381 mg/vial
Analytical Variability (DS & DP)	System Suitability (SS): 3 tests on Reference Material (RM) i. RSD of the three ≤2.0% ii. Average of the three within **± 2.5%** difference from the RM lot release value (49.7%) *Note: same method for DS and DP with different execution labs*

- **Problem:** To what degree the analytical method should be controlled, such that process performance of DS and DP won't be significantly impacted?

Understanding the Variabilities





Δ_{DS}: DS Mfg Variability
Δ_{FW}: Filling Weight Variability
Δ_1 , Δ_2: Analytical Variability, Δ_1 for DS lab, Δ_2 for DP Lab

R Release testing

C In-process control

Drug Content:

$$\left\{\frac{(\Sigma(50\pm\Delta^*_{DS}\ \text{mg/mL})\cdot w_i)\cdot(9.152\pm\Delta_{FW}\ \text{mg/vial})}{\rho\cdot 8.8\text{mL}}(\pm\ \Delta_2)\right\} * 8.8\text{mL}$$

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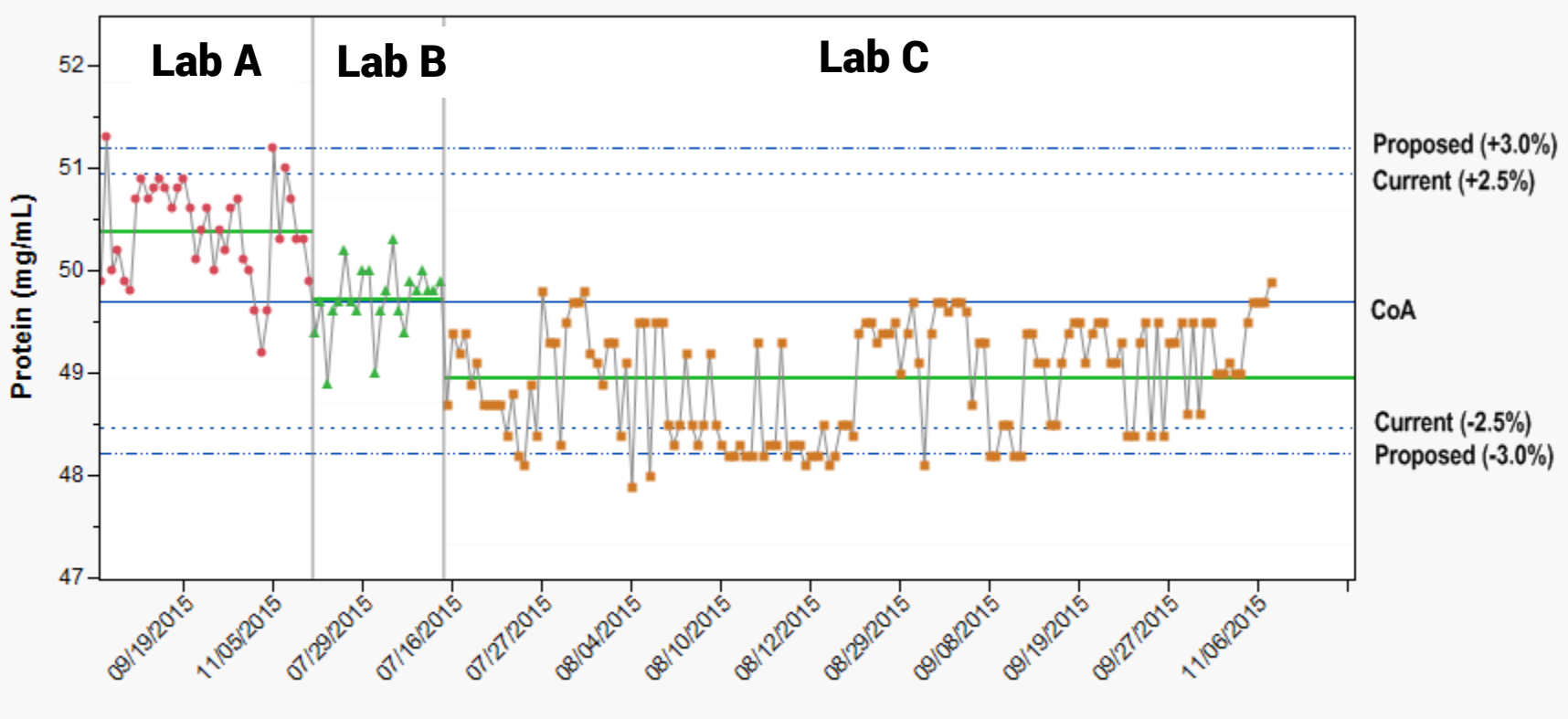
Reference Material Trends



Consideration of the lab factor into the risk assessment.

Modeling Flow

***Model 1*: Predict the analytical variability from DS lab (Δ_1)**

Historical Data: Observed DS results and corresponding SS results (N=34)

Output: analytical variability (Δ_1) and true manufacturing variability (Δ_{DS})

***Model 2*: Predict the individual vial weight**

Historical Data : Fill weight batch mean, within batch SD (N=10)

Output: individual vial weight (n= 10,000x200 vials)

***Model 3*: Predict the analytical variability from DP lab (Δ_2)**

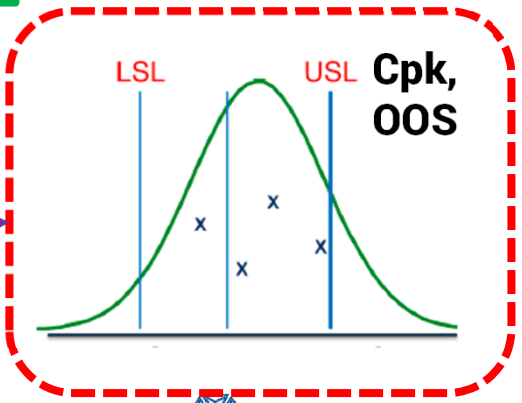
Historical Data: Observed DP results and corresponding SS results

Output: analytical variability (Δ_2)

***Model 4:* Predict measured DP drug content per vial**

Input:

Output: measured DS protein concentration and DP drug content for each simulated vial



Model 1: Analytical Variability of DS Lab

Objective:
- Obtain predictive inference for true DS protein concentration.
- Obtain predictive inference for analytical variability from DS lab.

Data: Measured DS and the matching SS results (average of three RM). N=34

$$PC_i^{DS.Obs} \sim PC_i^{DS} + \Delta_1$$

$$PC_i^{DS} \sim N(\mu_{DS}, \sigma_{DS})$$

$$\Delta_1, SS_1, SS_2, SS_3 \sim N(\mu_i^{DS}, \sigma_i^{DS})$$

$$SS_{report}^{DS} \sim \sum_{k=1,2,3} SS_k /(3 \cdot CoA) \cdot I(LowerCriteria, UpperCriteria)$$

SS criteria on mean

$$\mu_i^{DS} \sim N(\mu_{M\mu}^{DS}, \tau_{M\mu}^{DS})$$

Priors:

$$\mu_{DS} \sim N(50,100) \qquad \sigma_{DS} \sim U(0,100)$$

$$\mu_{M\mu}^{DS} \sim N(0,100) \qquad \tau_{M\mu}^{DS} \sim U(0,10) \qquad \sigma_i^{DS} \sim U(0,1)$$

where PC_i^{DS} is the protein concentration for the ith DS lot (i= 1, 2, …, 34); $\mu_i^{DS}, \sigma_i^{DS}$ is the population mean and standard deviation for analytical error under the same testing circumstance in DS lab (repeatability); $\mu_{M\mu}^{DS}, \tau_{M\mu}^{DS}$ is the population mean and standard deviation for analytical error under varied testing circumstance in DS lab (intermediate precision); μ_{DS}, σ_{DS} DS process mean and process standard deviation

Model 2: DP Fill Weight

Objective: Obtain predictive inference for filling weight of individual vials
Data: Fill weight batch mean, and within batch standard deviation $(N = 10)$

$$FW_{ij} \sim N(FW_i, \sigma_i)$$
$$FW_i \sim N(\mu_g, \sigma_g)$$
$$\tau_i = \frac{1}{\sigma_i^2} \sim \Gamma(\alpha, \beta)$$

Priors:

$$\mu_g \sim N(9.152, 100) \qquad \sigma_g \sim U(0, 10)$$
$$\alpha \sim \Gamma(0.001, 0.001) \qquad \beta \sim \Gamma(0.001, 0.001)$$

where FW_{ij} is the fill weight for the jth vial (j = 1, 2, …, 200) from the ith lot (i = 1, 2, …, 10) .

Model 3: Analytical Variability of DP Lab

Objective: Obtain predictive inference for analytical variability from DP Lab
Data: Measured DP and the matching SS results

$$\Delta_2, SS_1, SS_2, SS_3 \sim N(\mu_k^{DP}, \sigma_k^{DP})$$

$$SS_{report}^{DP} \sim \sum_{k=1,2,3} SS_k / (3 \cdot CoA) \cdot I(LowerCriteria, UpperCriteria)$$

SS criteria on mean

$$\mu_k^{DP} \sim N(\mu_{M\mu}^{DP}, \sigma_{M\mu}^{DP})$$

Priors:

$$\mu_{M\mu}^{DP} \sim N(0,100) \qquad \sigma_{M\mu}^{DP} \sim U(0,5) \qquad \sigma_k^{DP} \sim U(0,1)$$

where $\mu_k^{DP}, \sigma_k^{DP}$ is the population mean and standard deviation for analytical error under the same testing circumstance in DP lab (repeatability); $\mu_{M\mu}^{DP}, \sigma_{M\mu}^{DP}$ is the population mean and standard deviation for analytical error under varied testing circumstance in DP lab (intermediate precision).

Model 4: Predict DP drug content

Objective:

- Obtain predictive inference on true DP drug content.

Data: predicted true DS protein concentration (Model 1), predicted DP fill weight per vial (Model 2), analytical errors for DS and DP lab (Model 1, 3)

$$PC_{ij}^{DP*} = \frac{FW_{ij}^{*} * PC_{i}^{DS*}}{\rho}$$

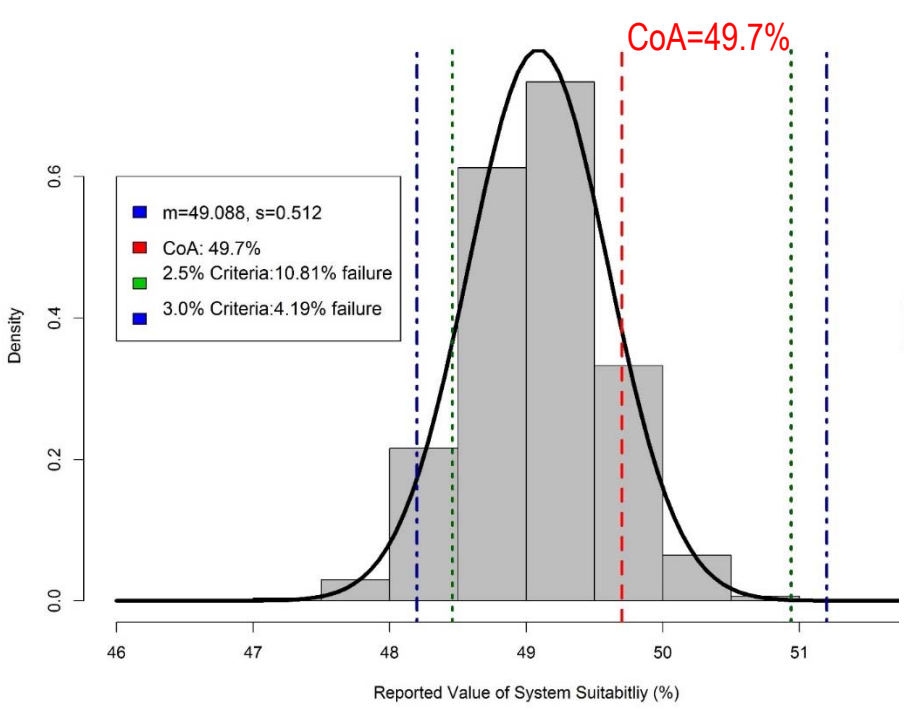
$$PC_{ij}^{DP.Obs*} = PC_{ij}^{DP*} + \Delta_{2}^{*}$$

$$| SS_{report}^{DP*} | \leq \text{WRS Criterion}$$

where PC_i^{DS*} is predicted true protein concentration for the i^{th} DS lot from Model 1; PC_{ij}^{DP*} is simulated true protein concentration for the jth vial (j = 1, 2,…, 200) produced from the ith DS lot (i= 1, 2, …, N) ; $PC_{ij}^{DP.Obs*}$ is the estimated tested protein concentration for the jth vial produced from the i^{th} DS lot.

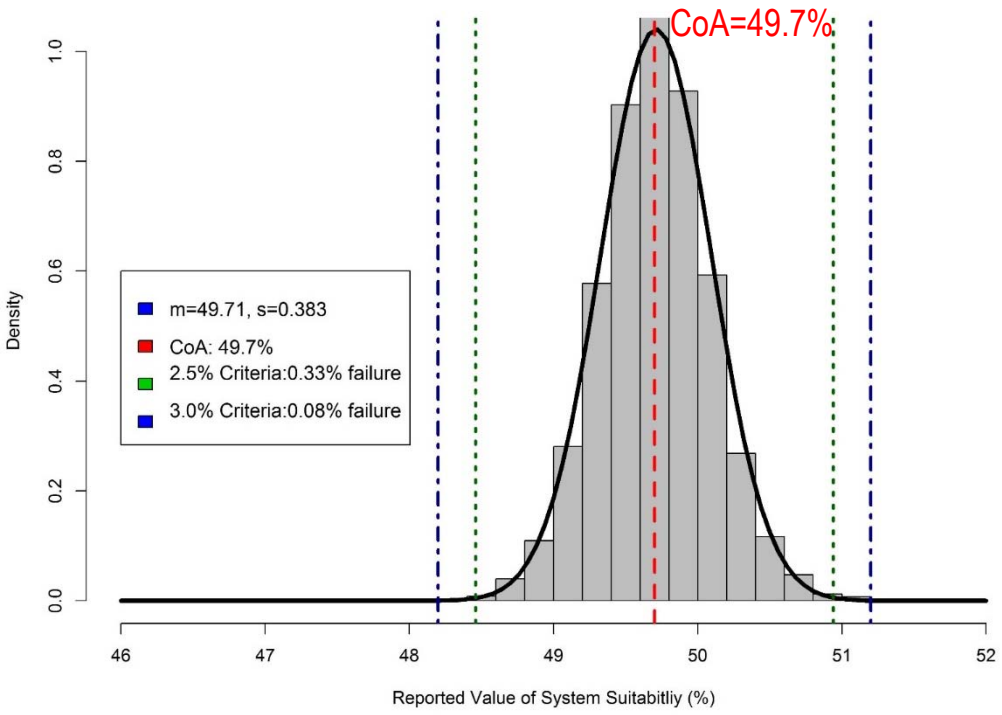
Prediction: Distribution of System Suitability Results

DS Lab



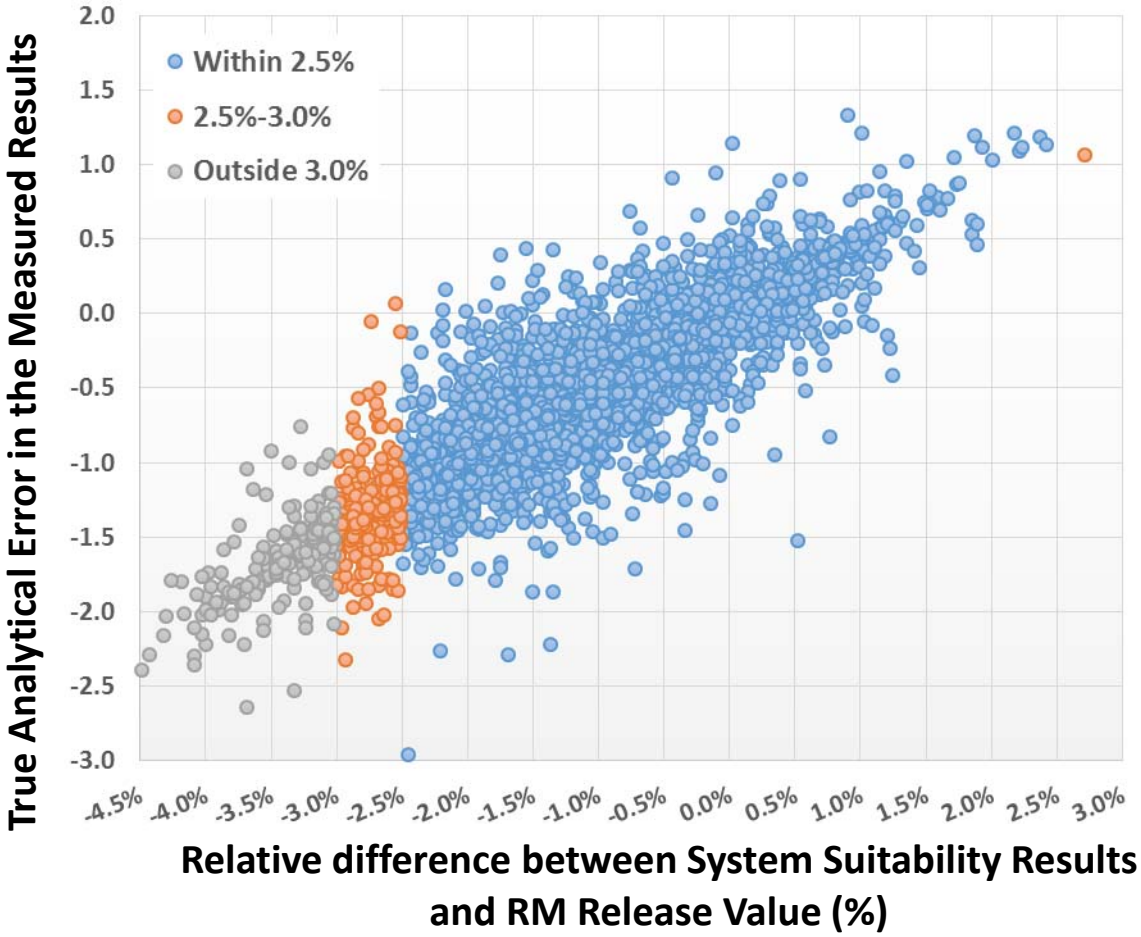
Widening the SS criteria will reduce the failure rate by > 6%

DP Lab



RM has small chance of failing either SS criteria

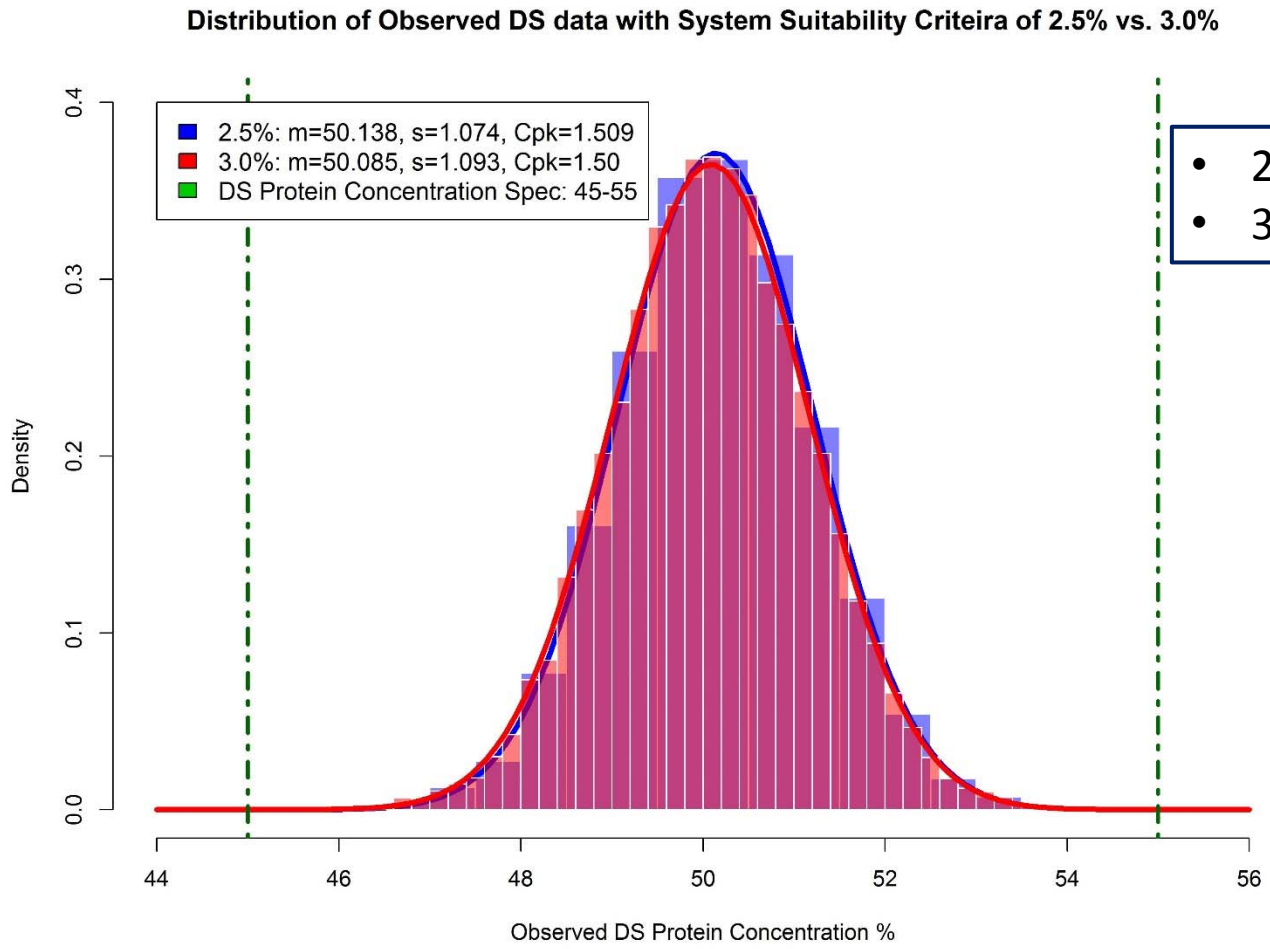
Simulation Result: SS vs. Analytical Error (DS)



Widening the SS criteria from 2.5% to 3.0% will potentially introduce more negative analytical error into the DS results.

But, is this of critical impact to the product performance?

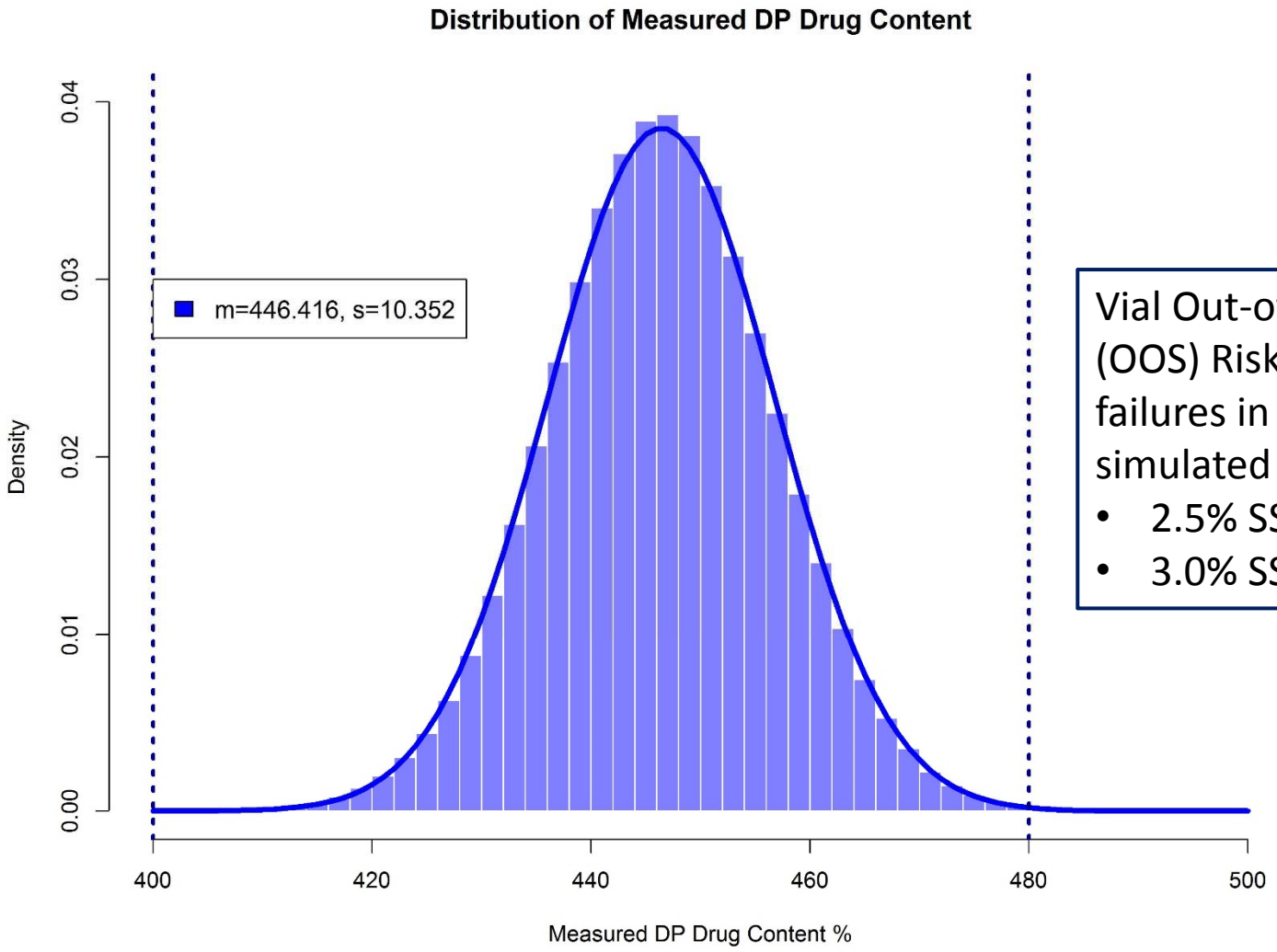
Simulation Result: DS Protein Concentration



- 2.5% SS: Cpk=1.509
- 3.0% SS: Cpk=1.50

Impact of SS criteria on DS Cpk is relatively small.

Simulation Result: DP Drug Content



Vial Out-of-Specification (OOS) Risks (proportion of failures in 200x10,000 simulated vials):

- 2.5% SS: 0.114%
- 3.0% SS: 0.114 %

Impact of SS criteria on DP OOS risk is small.

Summary and Next Steps

- Connecting process and analytical performances in a life-cycled manner is critical when establishing risk-based control strategy.
- Bayesian is a proper modeling tool for risk-based control:
  - Convenient connection of analytical and process components
  - Proper leverage of prior information
  - Predictive inferences about future results
  - Continuous learning capability.
- A case study illustrated the Bayesian method in modeling the impact of system suitability criterion on capability performance for a protein concentration method.
- Model potentials:
  - Update the model with accumulated knowledge
  - Expanding to other sources of variances

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Questions?