



Comparability Assessment for Changes to Manufacturing Processes: *Industry Recommendations on Bayesian Practices*

Ji Young Kim
Takeda Pharmaceutical Company Limited

Non-Clinical Statistics Conference 2026, 24-Sep-2026



Acknowledgements



Published in Statistics in Biopharmaceutical Research (SBR)

<https://doi.org/10.1080/19466315.2026.2677711>

Co-authors (alphabetical):

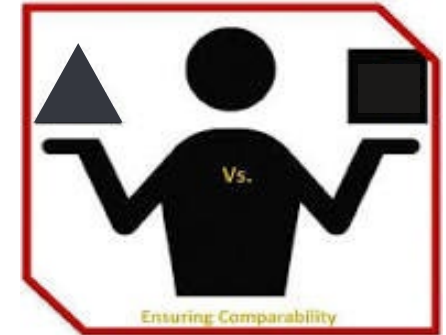
- **Takeda:** Ji Young Kim, Steven Novick (co-first authors)
- **AbbVie:** Yabing Zheng, Guodong Hui, Tony Pourmohamad, James Reynolds
- **AstraZeneca:** Chris Thompson
- **Boehringer Ingelheim:** Tobias Eilert
- **Eli Lilly:** Paul Faya
- **Fortrea:** Dwaine Banton
- **GSK:** Ray Sanchez
- **Janssen:** Stan Altan
- **Pfizer:** Jia Liu

Authors are members of

**Nonclinical Biostatistics Bayesian CMC
Scientific Working Group**
Within ASA BIOP

Goal: Addressing gaps in existing guidance for Bayesian Comparability

- Provide **industry recommendations** for applying **Bayesian** methods
 - Equivalence margin approach
 - Quality range approach
- How to **identify and use prior information** for comparability assessments



→ *Also hope to promote dialogue between industry and regulatory agencies*

With every change, we must show comparability in critical quality drug attributes



=



Declaring *comparability* means:

Manufacturing change has not adversely affected **product quality, safety or efficacy**

Examples of manufacturing changes



- Process (eg. change in purification process)
- Formulation (eg. excipient, coating composition)
- Scale (eg. pilot scale to commercial scale)
- Manufacturing sites



Pre

Post

Common Critical Quality Attributes (CQAs)



CQAs are **physical, chemical, biological, or microbiological properties**

- **Tablets**
 - Assay, content uniformity, % impurities, dissolution, hardness
- **mAbs**
 - % Purity (low aggregates), potency, low impurity (host cell proteins)
- **Injectables**
 - Sterility, pH, osmolarity, potency, reconstitution time (freeze-dried), delivered volume, injection flow rate



Regulatory Guidance for Comparability



- **1997** FDA: Changes to an approved application: biological products
- **2004** ICH Q5E: Comparability of biotechnological/biological products subject to changes in their manufacturing process
- **2007** EMA: Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process: Non-clinical and clinical issues
- **2007** EMA: Guideline on comparability of medicinal products containing biotechnology-derived proteins as drug substance: Quality issues.
- **2017** EMA: Statistical methodology for the comparative assessment of quality attributes in drug development – Scientific guideline.
- **2021** EMA: Reflection Paper: Statistical methodology for the comparative assessment of quality attributes in drug development – Scientific guideline.
- **2022** FDA: Comparability protocols for post approval changes to the chemistry, manufacturing, and controls information in an NDA, ANDA, BLA

CMC Guidelines supporting the use of prior knowledge

- ICH Q2(R2) (Analytical method validation)
- ICH Q1 draft (Stability)
- ICH Q6(R1) draft (Setting specification limits)

**No regulatory guidance specifically addressing
Bayesian methods for **CMC comparability** assessments**

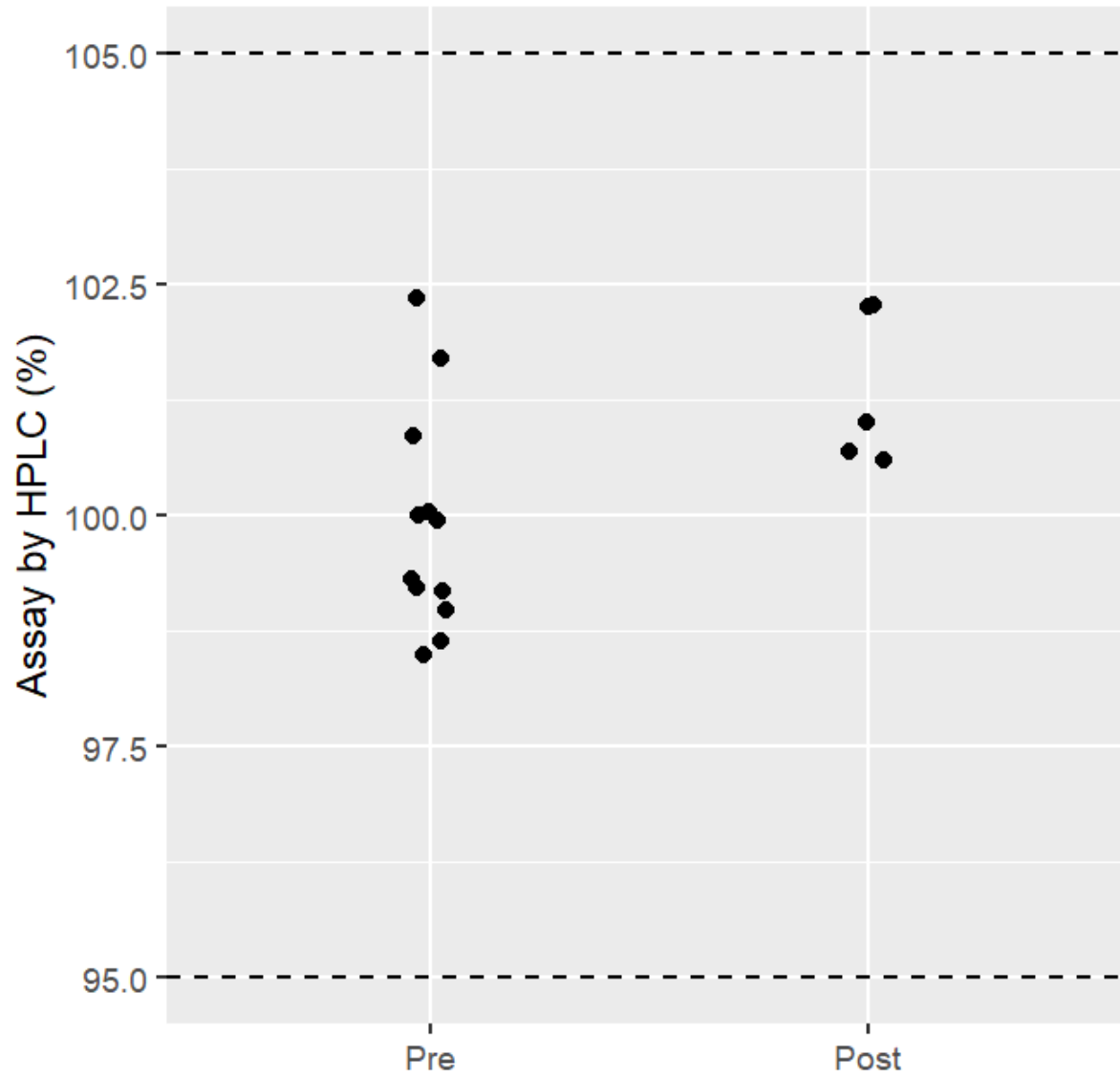


Illustration of Concept

Pre-change vs Post-change

Two questions:

- How to show comparability?
- How to set priors?

Equivalence margin approach



- Pre- and post-change processes are similar through equivalence/non-inferiority tests

Criteria could be:

- Mean equivalence: $\Pr(|\mu_{Pre} - \mu_{Post}| < \delta) \geq 0.95$
- Individual value equivalence: $\Pr(|Y_{Pre} - Y_{Post}| < \delta) \geq 0.95$

Bayesian methods allow us to directly assess the probability of meeting comparability.

Quality range approach



- Post-change processes demonstrates **sufficient quality**
- Comparison of **post** data to **quality limits** (*Not a comparison between pre and post*)

Criteria could be:

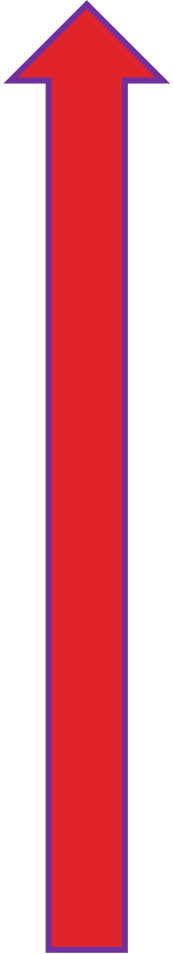
- $\Pr(LSL < Y_{post} < USL) \geq p_0$, (LSL, USL) = lower/upper specification limit
- $\Pr(\text{Shelf Life}_{post} \geq k \text{ months}) \geq p_0$

Bayesian methods allow us to directly assess the probability of meeting comparability.

How to set the priors?



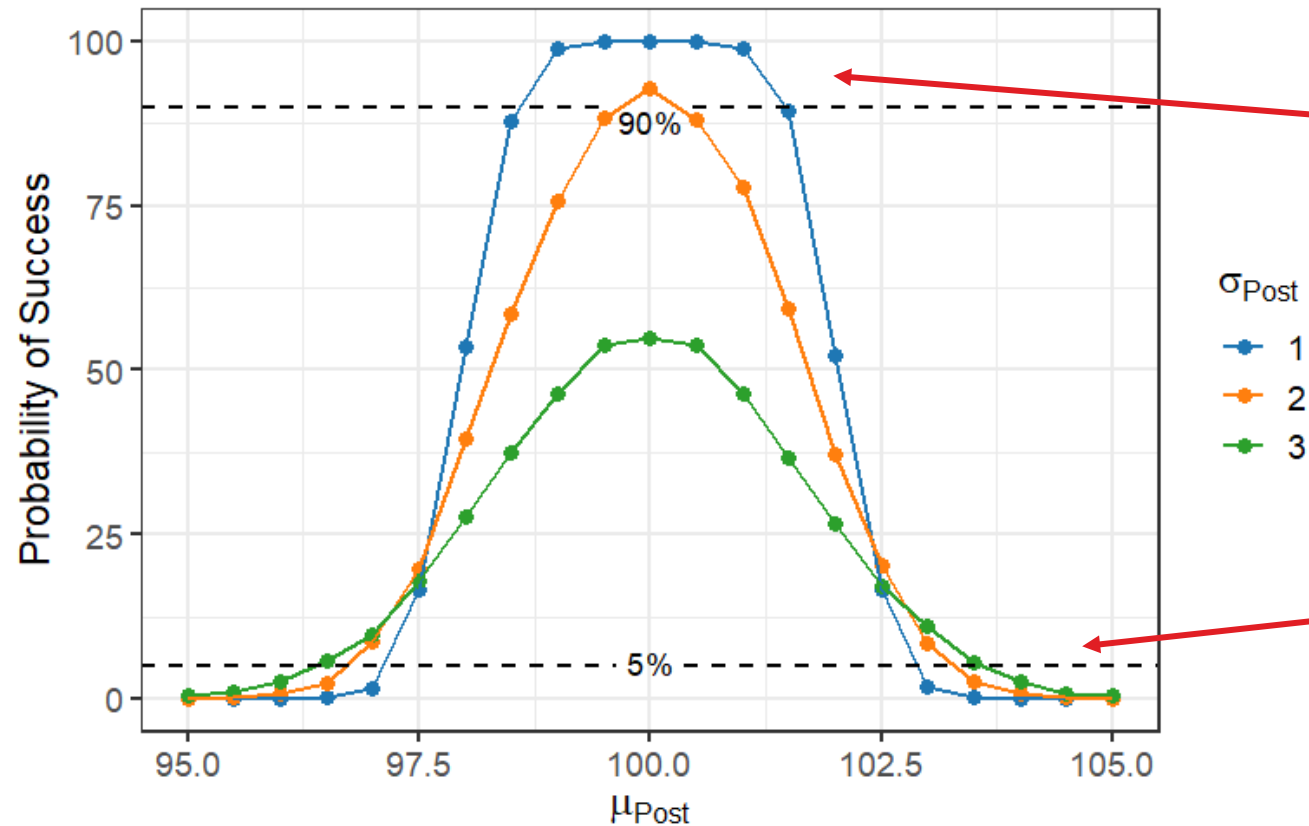
More information



- **Data-driven**
 - Based on development data from same molecule
 - Based on platform data from similar molecules
- **Subject-area knowledge**
 - Process mean falls inside spec limits
 - Total %CV < 100%
 - Shelf life target is at least 12 months
- *No longer recommending vague or vaguely-informative priors*

Operating Characteristics Curve

A Curve to display how a test performs



$$\mu_{pre} = 100$$

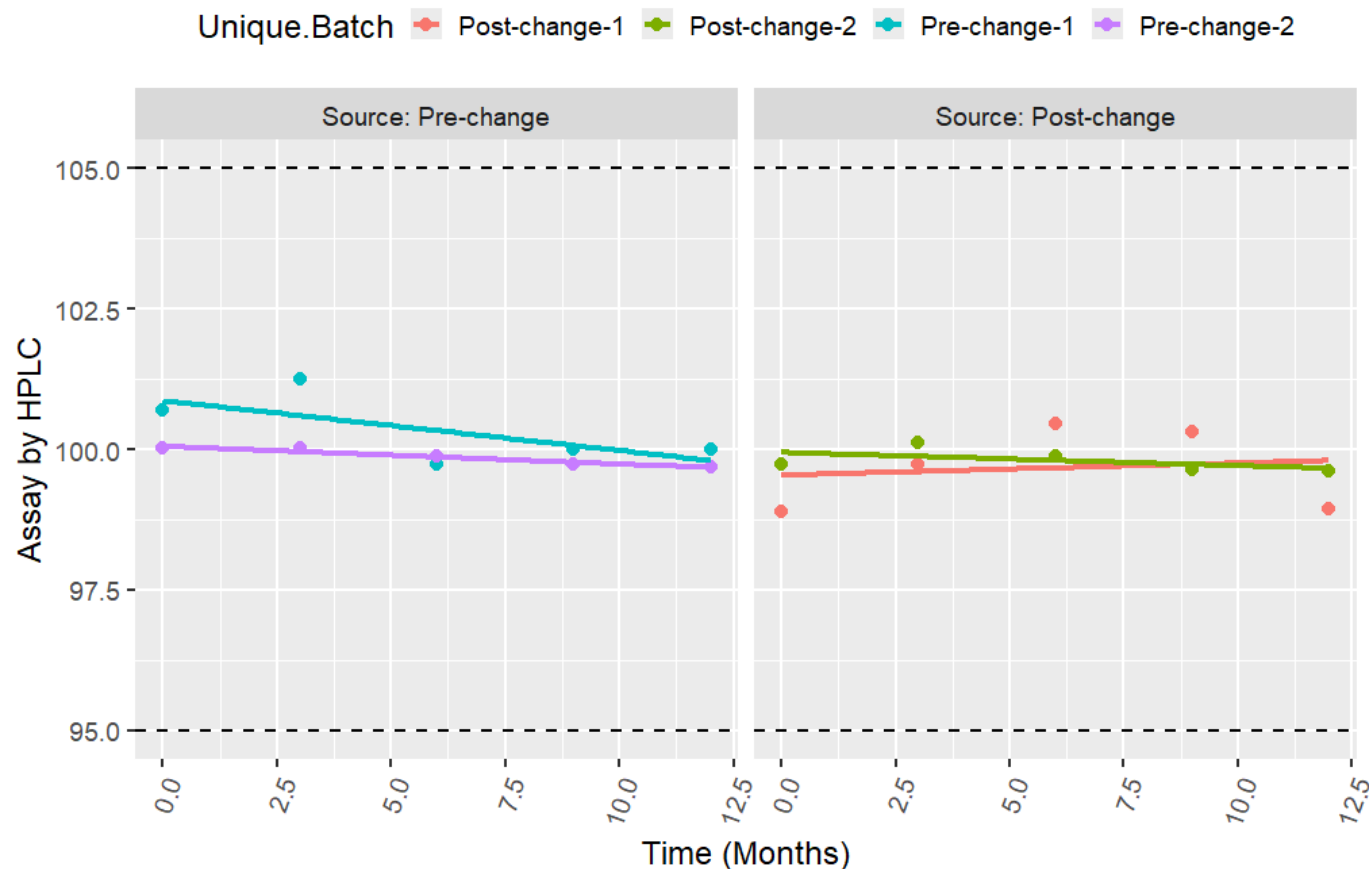
We want
high success rates when
pre and post are close

We want
low success rates when
pre and post are far



Example – Comparability in Stability

Assay by HPLC (%) on stability



- Twelve months of stability data
- Spec limits: 95 – 105%
- **Only two batches each for pre- and post-change!**

Linear mixed model (random intercept/slope)

$$y_{Pre} = (a_{Pre} + a_i) + (b_{Pre} + b_i) \times t_j + e_{ij}$$

$$y_{Post} = (a_{Post} + a_i) + (b_{Post} + b_i) \times t_j + e_{ij}$$

Assume common variance structure

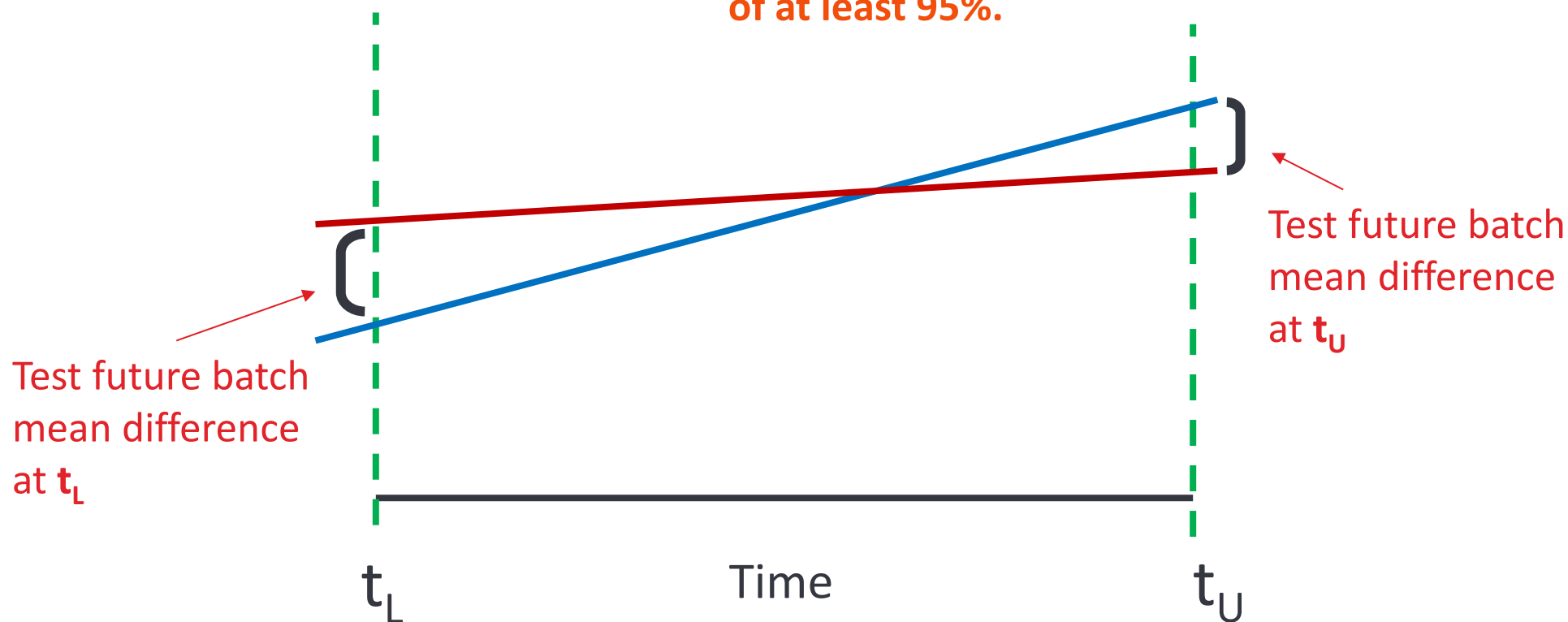
$$\begin{pmatrix} a_i \\ b_i \end{pmatrix} \sim N(0, \Sigma), e_{ij} \sim N(0, \sigma^2)$$

Equivalence margin testing for two straight lines



Criterion:

Two future straight lines (pre and post) stay less than 1.5% apart up to 12 months, with a probability of at least 95%.



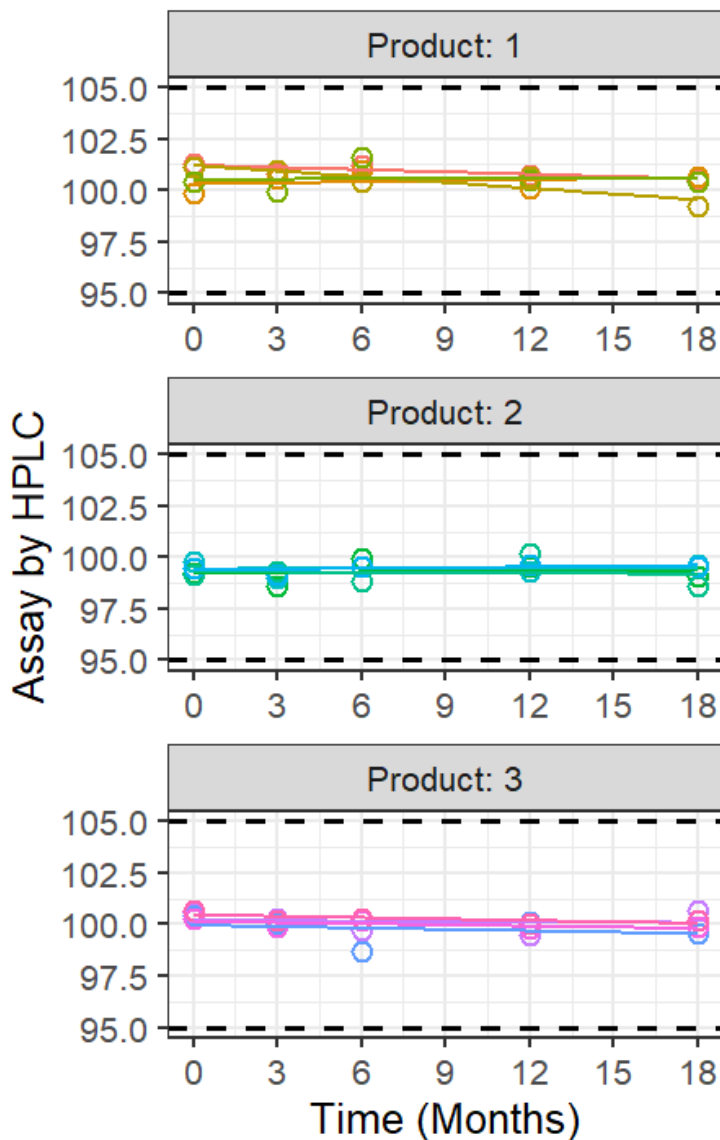
Zeng L, Novick S, Yu B, Yang H (2019). General framework for equivalence testing over a range of linear outcomes with CMC applications. *Stat Biopharm Res.* 11(2):182-190.

Tricky part: requires posterior Σ from $\begin{pmatrix} a_i \\ b_i \end{pmatrix} \sim N(0, \Sigma)$ with four batches!

Platform solution: Borrow information from other products



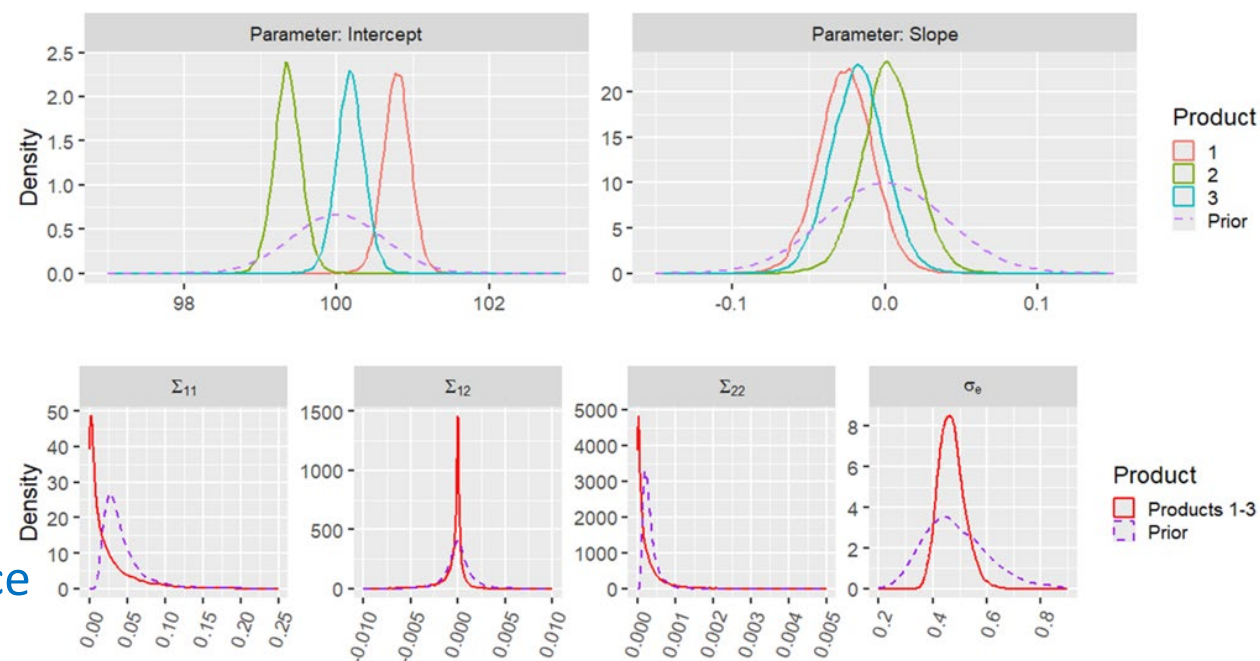
Platform data: 3 products



Prior for lines

Prior for variance

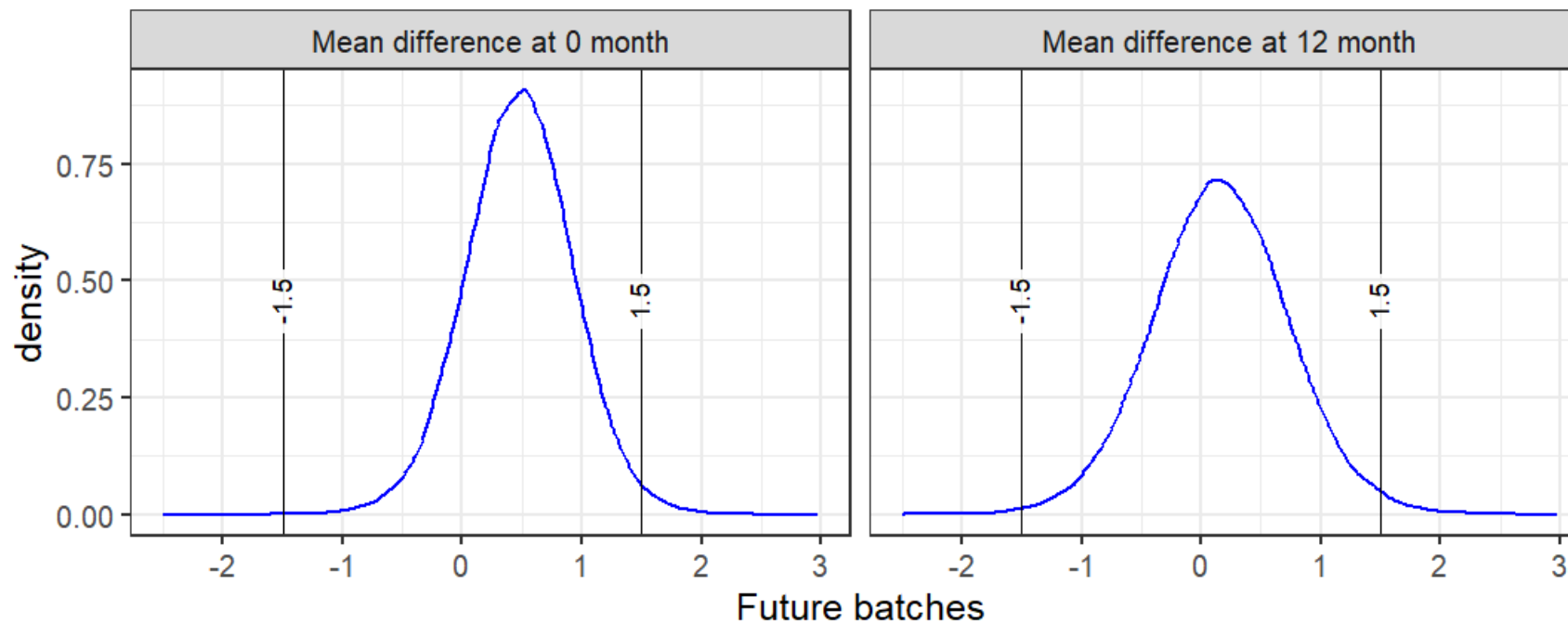
Priors derived from platform data



Posterior predictive probability of equivalence



Posterior predictive distributions of differences between lines



Prob [Differences between lines both at 0 month and 12 month ≤ 1.5] = **0.98**

➔ Declare equivalence (comparability)

Summary



- We provided industry recommendations for applying **Bayesian** methods to **CMC comparability**, addressing gaps in existing guidance.
 - Equivalence margin approach
 - Quality range approach
- **We covered a broad range of comparability exercises** encountered in industry and illustrated how to identify and use prior information for comparability assessments
- We hope this will promote further dialogue between industry and regulatory agencies toward establishing **comprehensive guidelines for Bayesian analyses**.



Thank You!