

Application of Bayesian Methodologies in CMC Statistics – Areas of Focus

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The contents of this presentation are my personal opinion.
My remarks do not necessarily reflect the official view of
HPRA, EMA, or any associated working party or committee

Disclaimer



Areas where Bayesian statistical methods would be of use in Module 3 – Quality (CMC) of the eCTD submission package

Agenda

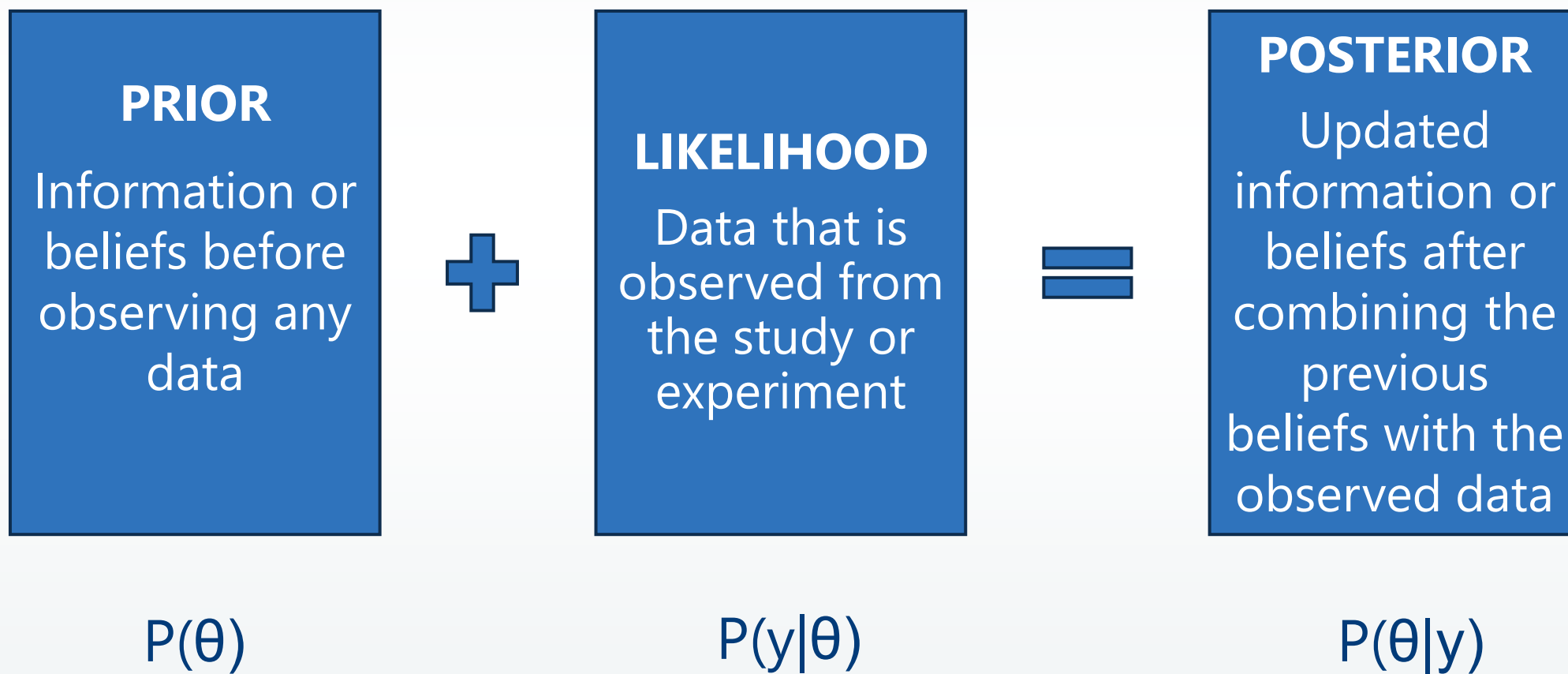
- Comparability
- Stability

Working Guidelines

- ICH Q1A(R2): Stability Testing of New Drug Substances and Products
- ICH Q1E: Evaluation of Stability Data
- ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process
- ICH Q8(R2): Pharmaceutical Development
- ICH Q9(R1): Quality Risk Management
- Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017)
- Reflection paper on a tailored clinical approach in biosimilar development (EMA/CHMP/BMWP/60916/2025)

Bayesian Methodology

Mechanism to update our beliefs in light of new evidence



Bayesian Methodology

Prior	Likelihood	Posterior	Posterior Predictive Distribution
• Distribution of parameter (θ) before observing any data • Can be based on available data and/or justifiable knowledge • Can deliberately be non-informative to allow observed data to dominate	• Conditional probability of the data given the hypothesis on the parameter (θ) • Based solely on observed data	• Distribution reflecting the combined evidence of observed data and prior beliefs • Inference on parameter of interest (θ) with uncertainty described in terms of probability	• Given the model and posterior distribution of its parameters, distribution of plausible values for a future observation • Random draws from the posterior distribution of mean and posterior distribution of variance given the mean

Comparability

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Precedence

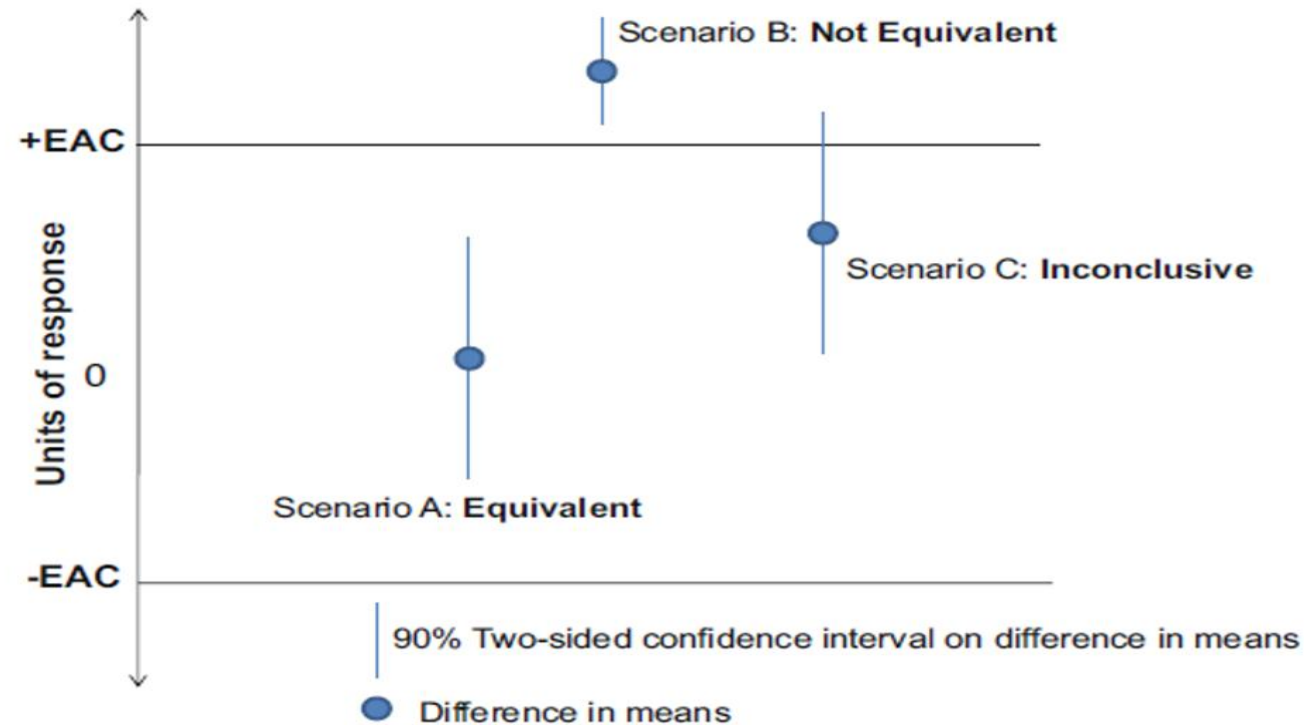
Statistical Approach

- ➞ Risk Assessment: CQAs classified according to uncertainty and impact on quality
- ➞ Range of statistical methodologies to assess equivalence:
 - Quality Range / Statistical Intervals
 - Min-Max
 - $\bar{x}$ -SD
 - Tolerance Intervals
 - Prediction Intervals
 - Bayesian Credible Intervals
 - Equivalence Testing / Inference
 - Two One-Sided Test (TOST)

Precedence

Two One-Sided Test (TOST) Approach

- Aim to have post-change attribute mean to fall within a pre-defined equivalence margin
 - $H_0: \mu \leq -\Delta$
 - $H_0: \mu \geq \Delta$



Bayesian TOST

A Bayesian approach for evaluating equivalence over multiple groups, and comparison with frequentist test (Weusten et al, 2024)

- ➞ Bayesian estimate of standardized mean difference (SMD, Cohen's d) between pre- and post-change CQAs
 - $\delta = \frac{\mu_{post} - \mu_{pre}}{\sigma_{pooled}}$
- ➞ Equivalence: $P(E_L < \delta < E_U | data) > Threshold$
- ➞ Prior distribution for SMD informs expectation of declaring equivalence based on true unknown SMD

Prior Specification

Prior distribution for SMD

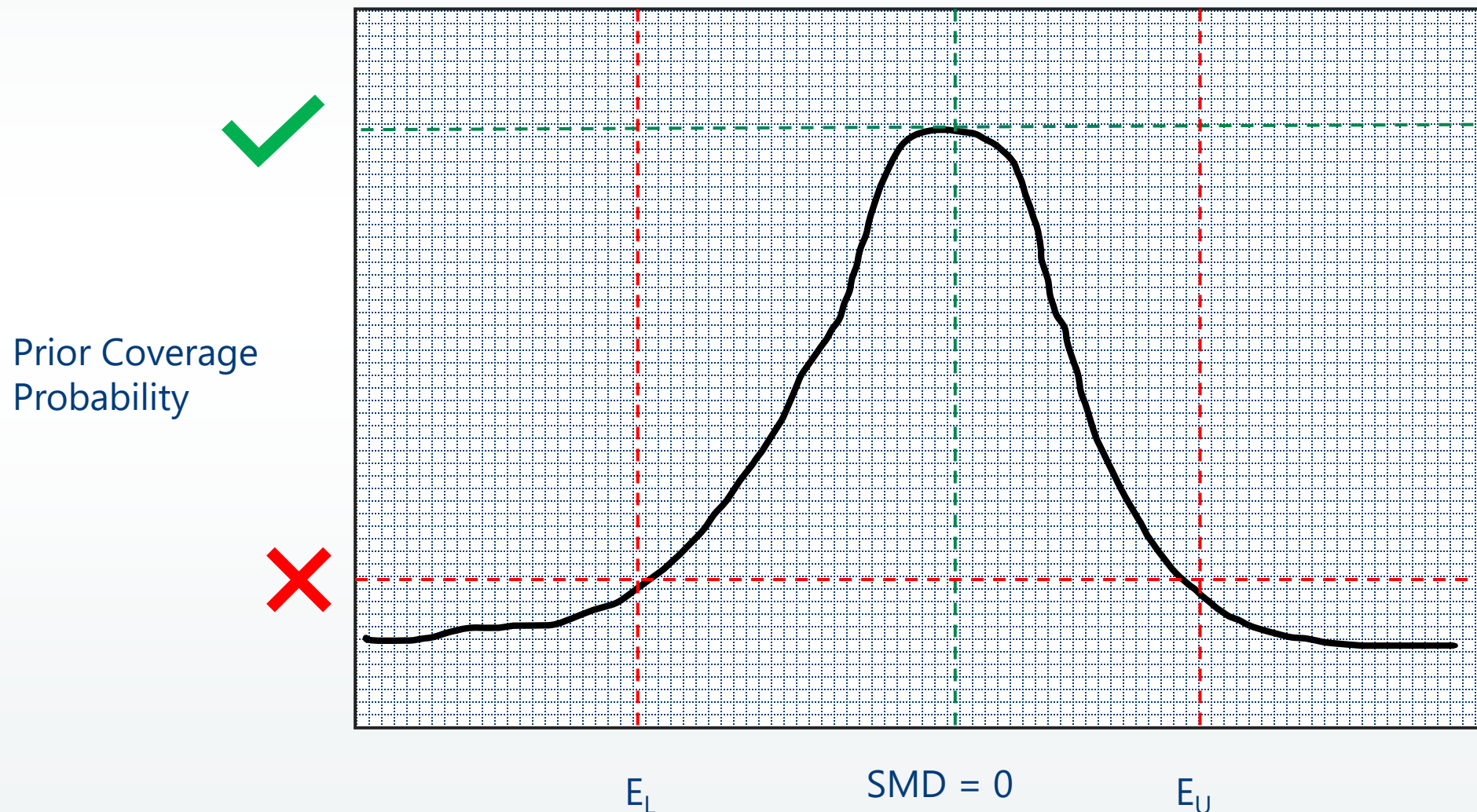
- Cauchy prior very typical for Bayesian analysis as it is weakly informative and allows data to dominate posterior
- $\Delta \sim \text{Cauchy}(\text{Location}, \text{Scale})$
- Location parameter can be set to zero, therefore centred on no difference
- Scale parameter controls how spread out the prior is

Equivalence margin (EM)

- Expressed as difference in SD due to estimate being SMD
- Can be set via simulation to achieve desired operating characteristics
- $f_{(EM, Scale)}(y) = x$
 - Probability according to the prior that the SMD is equivalent
- EM and Scale can be altered until satisfactory prior probability of equivalence reached

Prior Coverage Probabilities

Prior distribution hyperparameters and equivalence margin optimised for OC



Probabilistic Determination

Comparability Exercise

- ➔ Likelihood for observed SMD can be represented as a non-central location-scale t-distribution with known degrees of freedom
 - $d = \delta \sqrt{\frac{n_1 n_2}{n_1 + n_2}}$
- ➔ t-statistic describes how far the observed difference is from zero relative to its uncertainty
 - $t = \frac{\text{observed difference}}{SE}$
 - $|t| \uparrow \Rightarrow P(\text{equivalence} \mid \text{data}) \downarrow$

Probabilistic Determination

Posterior Coverage Probability

- Posterior distribution represented as t-distribution with known degrees of freedom
- Posterior probability threshold for equivalence can be calibrated to t-statistic values producing a frequentist one-sided 5% type I error
 - 95th percentile of t-distribution with k degrees of freedom
- $P(E_L < \delta < E_U | t = x) = \textit{Threshold}$
- **Can now be considered counterpart to a frequentist TOST approach**

Bayesian TOST Parameters

Parameter	Value
Prior distribution for SMD (Δ)	Cauchy with location hyperparameter set to 0 and scale hyperparameter not fixed
Prior distribution scale parameter	Optimized with equivalence margin to desired prior probability of equivalence
Equivalence margin (EM)	Difference between pre- and post-change means expressed as SD Optimized with prior distribution scale hyperparameter to desired prior probability of equivalence
Likelihood of observed SMD	Non-central location-scale t-distribution with $N_{\text{pre}} + N_{\text{post}} - 2$ degrees of freedom (d.f.)
Decision criteria (N, d.f.)	Equivalent if posterior probability of equivalence exceeds specified threshold, $P(\Delta \in \text{EM} \mid H1, \text{data}) > x$
Posterior probability of equivalence	Calibrated to one-sided 5% type I error using 95 th percentile of t-distribution

Tailored Biosimilar Approach: Special case of comparability

EMA/CHMP/BMWP/60916/2025

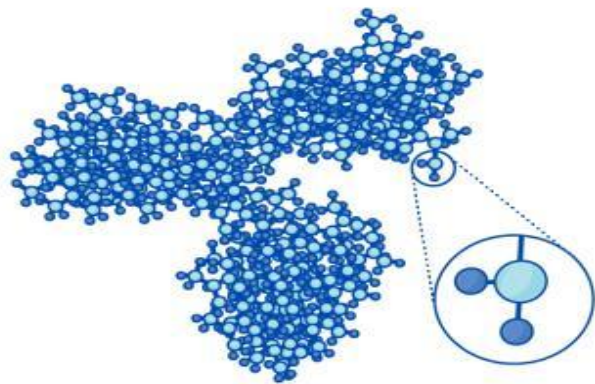
Protein
structure



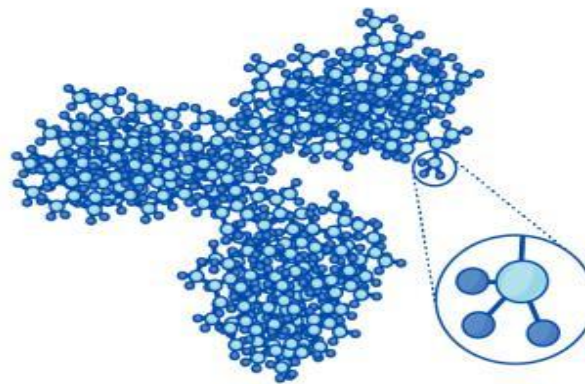
Pharmacological
properties



Clinical efficacy



Biologics
Example: infliximab



Biosimilars
Example: infliximab-dyyb

*Comparison of
physicochemical/functional
similarity (CQAs) and PK*

*No clinical efficacy study
required*

Bayesian Highest Density Intervals (HDI)

Bayesian Evaluation and Monitoring of Process Comparability, Wang & Cheng, 2023

- ➞ Comparison of quality attributes between EU-sourced reference product and proposed biosimilar
 - 10 batches of RMP
 - Subject to availability and manufacturing changes
 - 6 batches of biosimilar
- ➞ Bayesian HDI can act as interval for this comparison that can be updated as more reference batches are collected
- ➞ Two distributions to be defined:
 - Likelihood – RMP (Student's t-distribution)
 - Prior – Distributions assigned to parameters of RMP Student's t-distribution (hyperparameters allow for scientific knowledge)

Bayesian Highest Density Intervals (HDI)

Bayesian Evaluation and Monitoring of Process Comparability, Wang & Cheng, 2023

- ➔ Once RMP data is available posterior simulated samples from combining prior and likelihood are generated from MCMC sampling algorithm
- ➔ Posterior predictive distribution generated from posterior for a full distribution of unobserved CQA
- ➔ HDI is constructed as a form of credible interval where it is the narrowest interval with the same probability of the distribution for a unimodal probability distribution
- ➔ The calculated HDI from the posterior predictive distribution of RMP becomes the biosimilarity criterion
- ➔ If all biosimilar batch data falls within the determined HDI then biosimilarity has been demonstrated
- ➔ The posterior predictive distribution can be updated when new RMP batch data becomes available
 - *"Today's posterior becomes tomorrow's prior"*

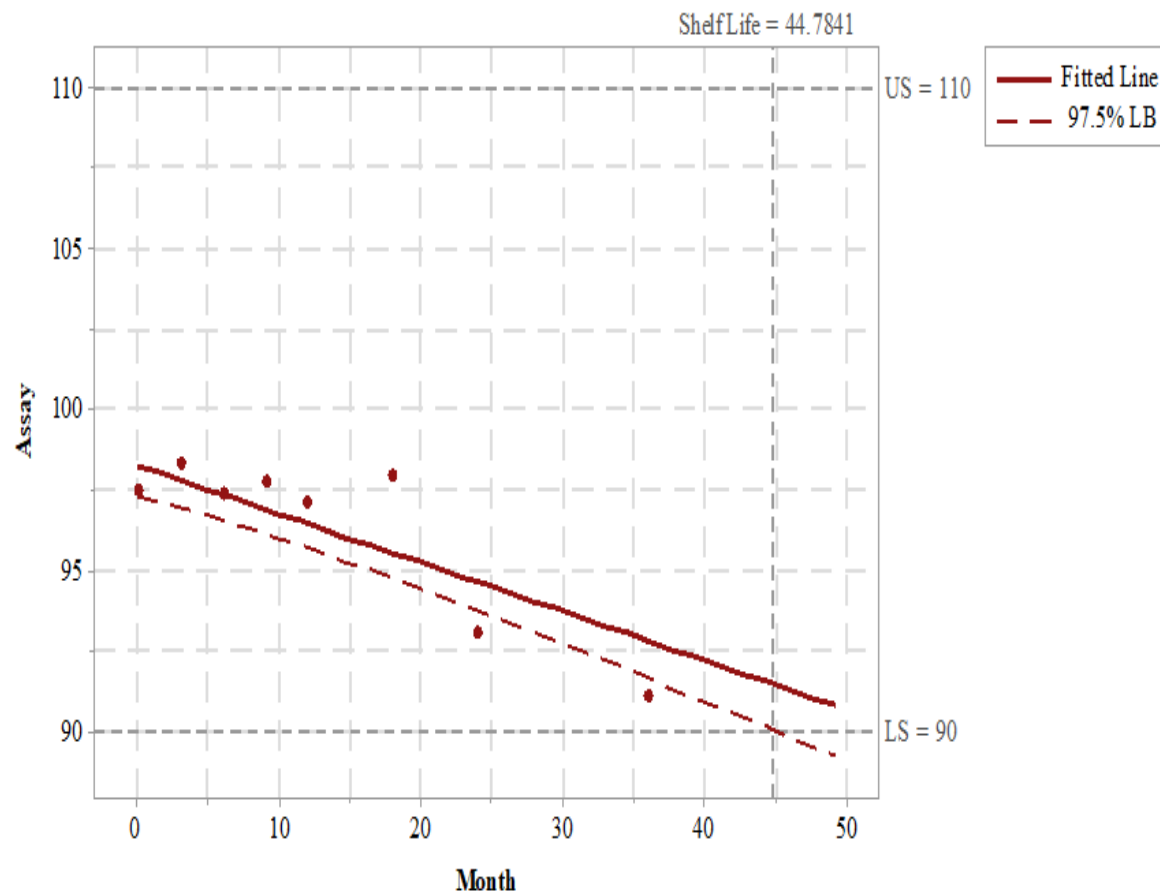
Stability

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Shelf-Life Estimation

Frequentist Approach

- Stability data for CQAs can be used in a linear regression model to estimate shelf-life
- Shelf-life is determined as the point at which the lower/higher bound of the 95% CI of model-predicted attribute value over time crosses the specification



LS = Lower Specification, US = Upper Specification

Equation for fitted line: Assay = 98.3 - 0.152 Month

Bayesian Hierarchical Model

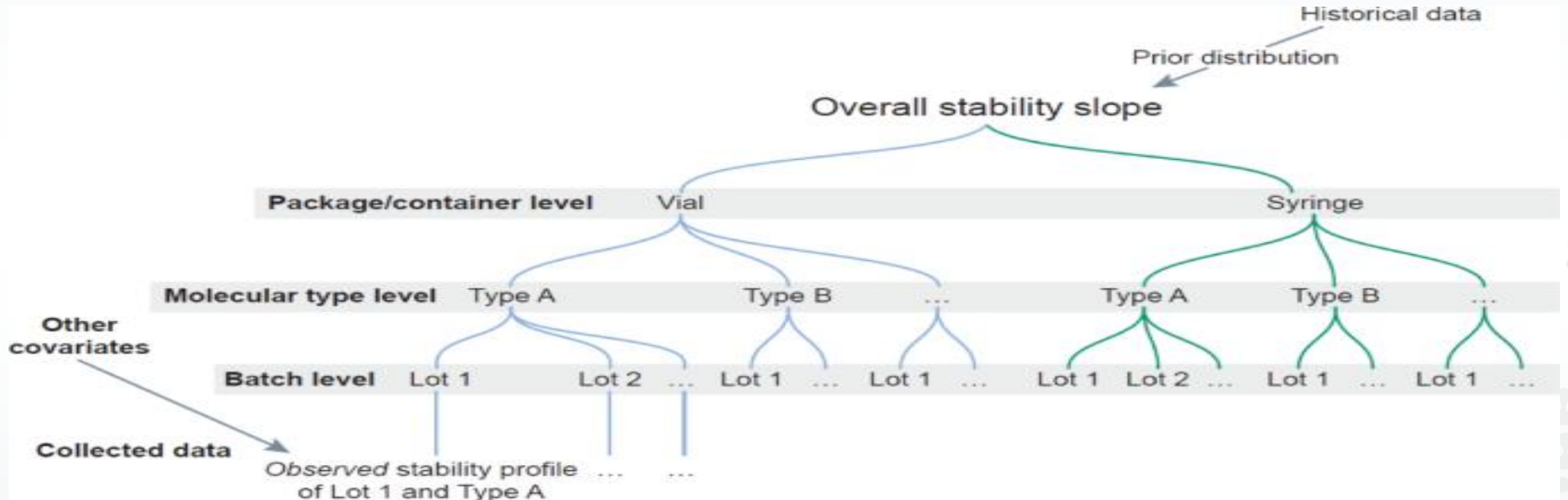
Predictive Stability Modelling

- ➔ BHM can incorporate prior knowledge and multiple levels of information
- ➔ Structure can capture process or analytical method changes
 - Specific long-term stability predictions
- ➔ BHM estimate distributions for all included variables
 - Stability-indicating variable
 - Slope (Rate of degradation/accumulation)
- ➔ Calculation of prediction intervals give a range within which a future, unobserved value is expected to fall
 - Accounts for uncertainty around model-predicted mean
 - Multiple batches incorporate process variability



Graphical representation of BHM

Bayesian hierarchical model predicts biopharmaceutical stability indicators and shelf life with application to multivalent human papillomavirus vaccine (Ferrari, Berger, Lemieux et al, 2025)

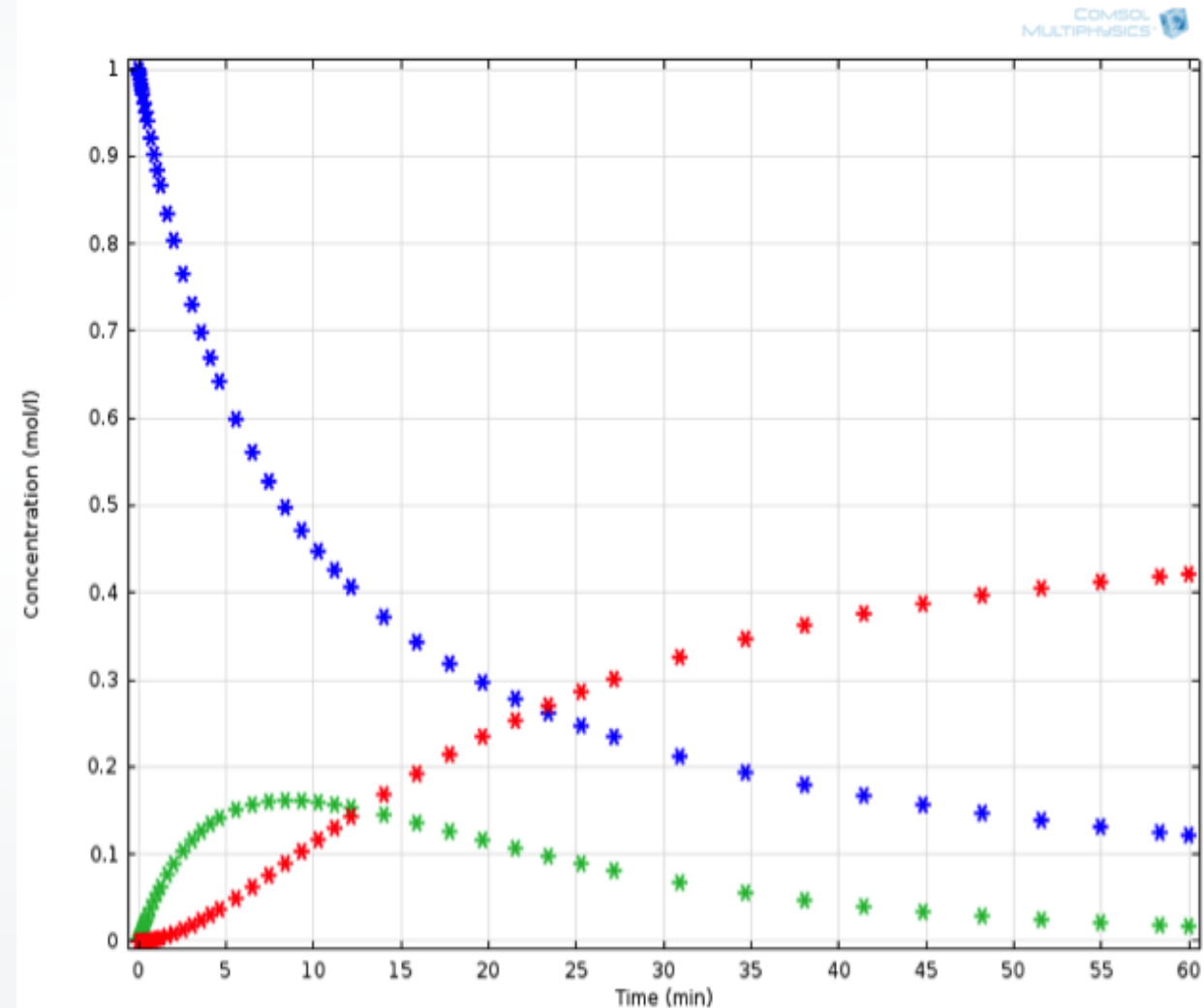


$$p(y, \theta, \phi \mid data) = p(y|\theta) p(\theta|\phi) p(\phi)$$

Kinetic Models

Arrhenius-like Equations

- Allow for nonlinear relationships
 - Single Degradation
 - Parallel Reaction
- Priors incorporate scientific knowledge
 - Activation energy
 - $E_a \sim N(\mu_{Ea}, \sigma_{Ea})$
 - Reaction rate constant
 - $k \sim N(\mu_k, \sigma_k)$



Prior Specification

- ➔ Priors to be specified for every level of the hierarchical model
- ➔ Priors for intercept terms can be based on the measured values of CQAs at the beginning of stability studies
- ➔ Priors can be specific to:
 - CQA knowledge
 - Intercept $\sim N(\mu, \sigma)$
 - Effect of process changes
 - Slope (reaction rate constant): $K_p \sim N(K, sd_{Kp})$
 - Unknown variability of change to analytical method
 - Slope (reaction rate constant): $K_{p,m} \sim N(K_p, sd_{Kp,m})$

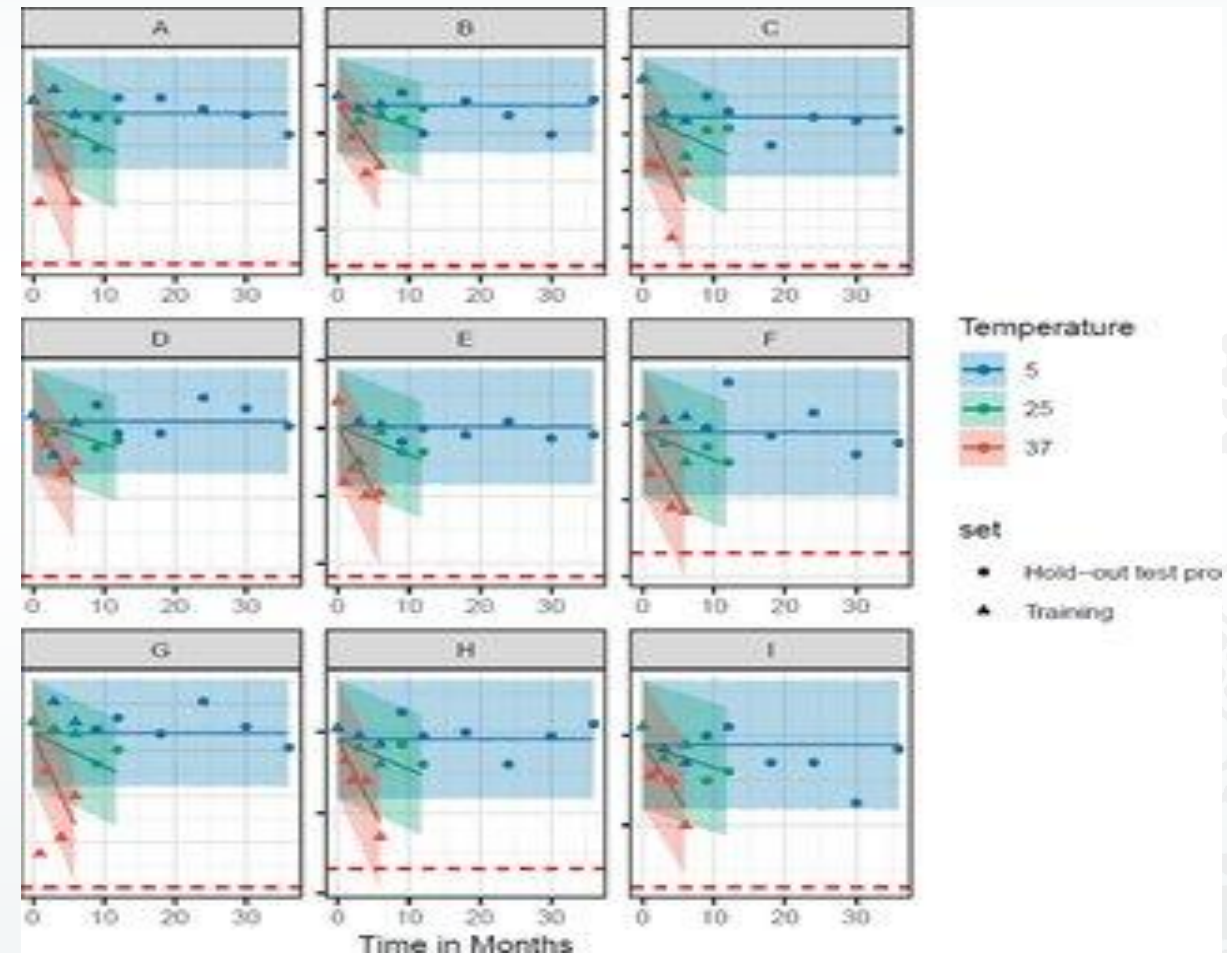
Model Fitting

- Depending on the CQA, stability data are fitted to a type of Bayesian kinetic model
- All available stability data for each level of the hierarchy can be used
 - Long-Term, Accelerated, Stressed etc.
- This data is combined with the prior distributions to generate posterior distributions for the kinetic model parameters via MCMC simulations
- The posterior distribution for the unknown slope parameter of the kinetic model can be integrated out to provide a posterior predictive distribution of future observations of data
 - **CQA values**

Predictive Stability

Supporting a Shelf-Life

- Model-predicted median CQA values from the posterior predictive distribution are calculated and a 95% prediction interval constructed around this median
- Model predictions can be supportive of stability if this 95% prediction interval is contained within relevant specification for the proposed shelf-life



Pros & Cons



Helpful where there is a lack of data

Able to handle process and/or method changes implicitly

Specification of priors allow knowledge to be leveraged

Quantifiable probability

Requires specialist statistics knowledge

Computationally intensive

Priors can be considered subjective

Going against established precedence





Thank you! Questions?

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