Bayesian Shelf Life and Internal Release Limit incorporating Storage Excursions

Ji Young Kim
CMC Statistics
QS, SQS, Data and Quantitative Sciences
Takeda Pharmaceutical Company Limited

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Acknowledgement

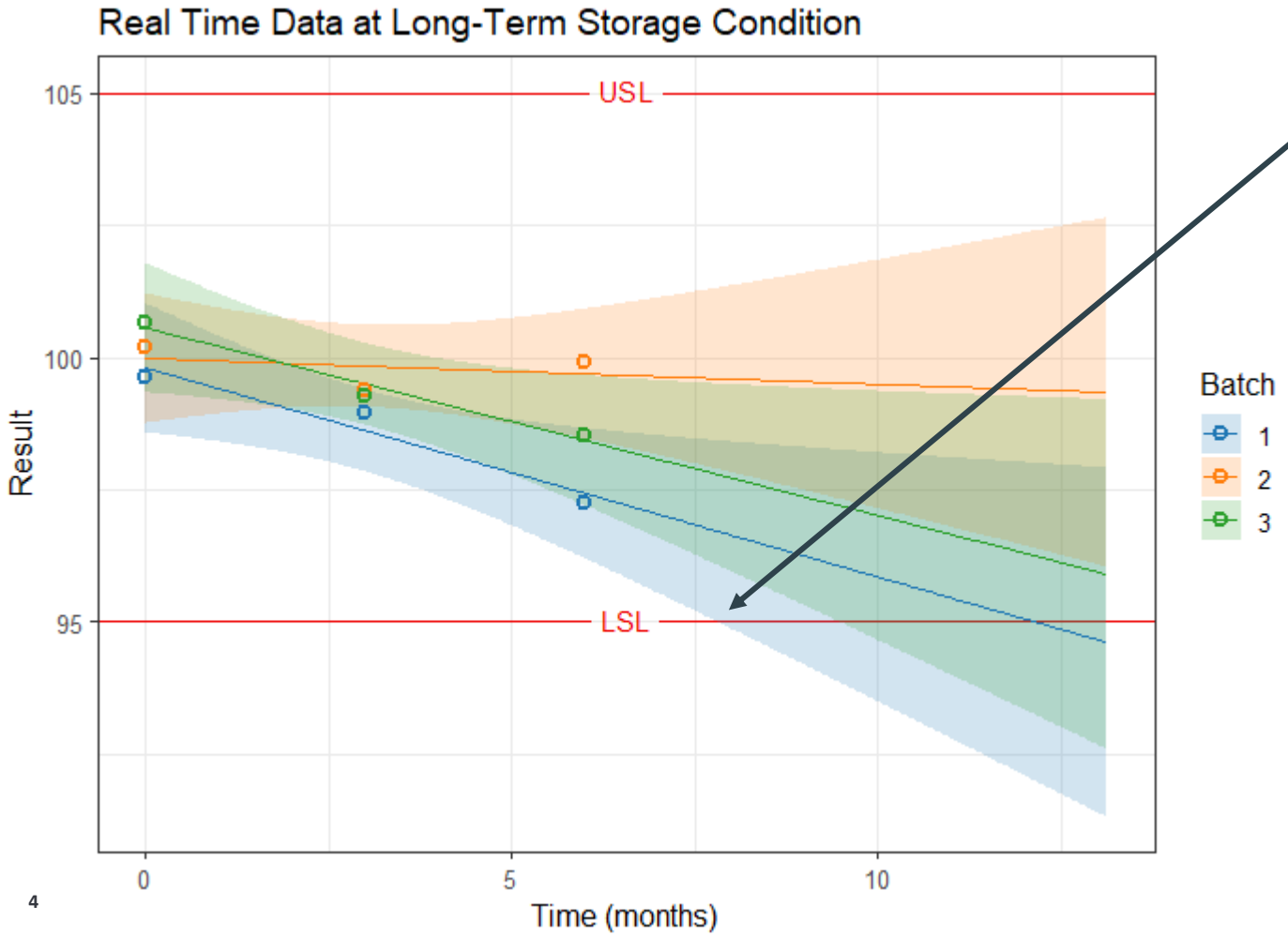
This is a joint work with

Steve Novick
Head of Nonclinical Statistics, QS, SQS,
R&D Data and Quantitative Sciences
Takeda Pharmaceutical Company Limited

Shelf-Life

- For every drug product, an **expiration date (shelf-life)** should be indicated on the container label.
- Inaccurate shelf-life estimate or releasing batches that could go OOS before expiry is a risk both for patients and producers.

Shelf-life = Maximum duration at the **long-term storage** during which the mean of the attribute remains within stability specification

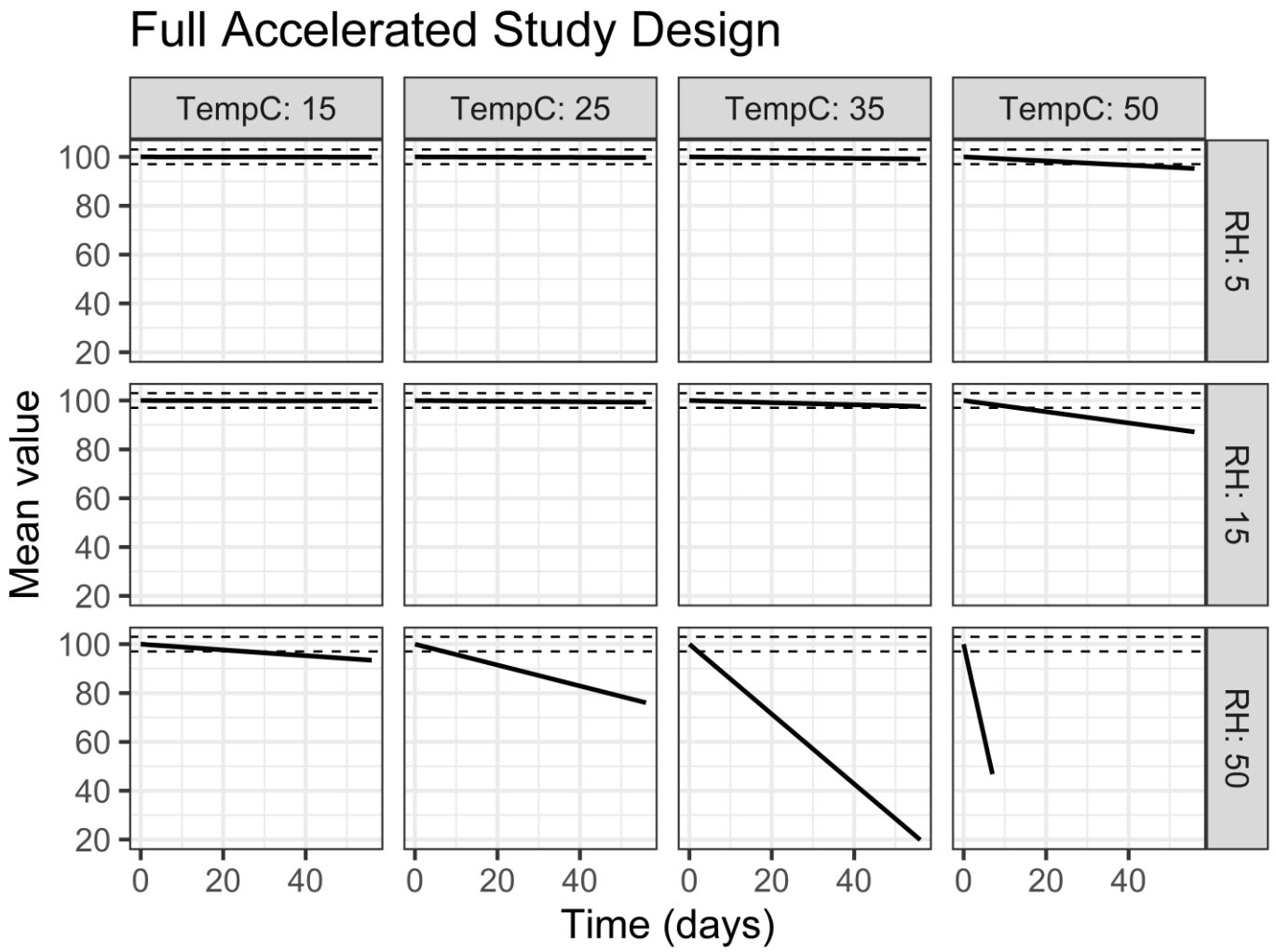


Mean is expected to go beyond spec from here: Shelf-life around 8 month.

"Long term condition" is chosen at the best storage condition for the product (differ widely by drug product class; e.g., tablet/capsule vs mAb).

Eg.
Long-Term Storage at
Temperature of 5C
Relative Humidity of 30%

Accelerated Stability Studies



Accelerated stability studies are conducted to expedite the degradation to estimate the trajectory faster.

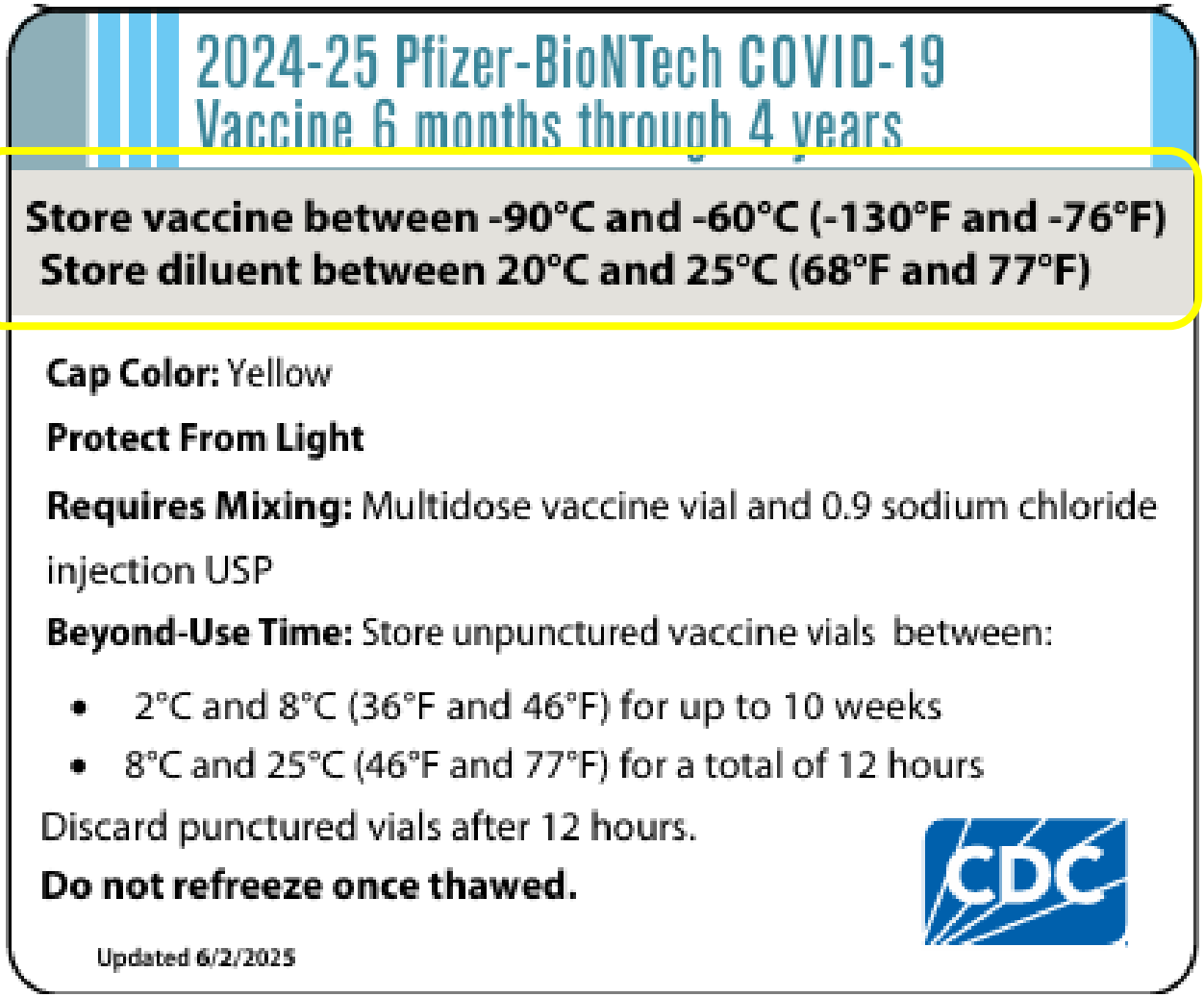
Typically, **under elevated temperatures and varied levels of relative humidity**

Consider a full factorial of accelerated conditions: **Unlikely that anyone would run all the conditions due to cost.**

Storage Excursions

Example of storage conditions on the product labels

Vaccine Labels: Storage and Beyond-Use Date Tracking
Source: US Centers for Disease Control and Prevention



2024-25 Spikevax (COVID-19) 12 years and older

Store between -50°C and -15°C (-58°F and 5°F)

Protect From Light

Beyond-Use Time: Store between:

- 2°C and 8°C (36°F and 46°F) for up to 60 days
- 8°C and 25°C (46°F and 77°F) for up to 12 hours

Do not refreeze once thawed

Updated 6/2/2025

2024-25 FluMist (Influenza)

Store between 2°C and 8°C (36°F and 46°F)

Protect From Light

Do Not Freeze

CDC

Nirsevimab Monoclonal Antibody 50 mg Manufacturer-filled Syringe

Store between 2°C and 8°C (36°F and 46°F)

Color: Purple plunger

Protect From Light

Do Not Freeze

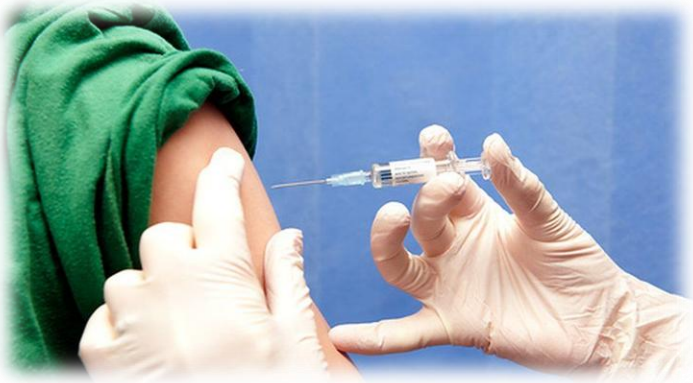
Beyond-Use Time: May be kept between 20°C and 25°C (68°F and 77°F) for a maximum of 8 hours.

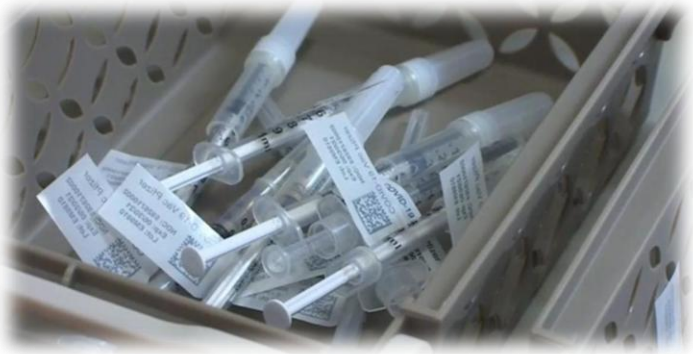
Updated 6/2/2025

CDC

Excursions can occur during shipping or storage

Over 50% vaccines wasted annually
Loss of billions of doses! (**Conditions**!)





Could be different sets of excursions for different markets!

Market-Specific Excursion scenarios should be identified

- Need to better understand the excursions and their effects on shelf life and internal release limit
- Use real-time and accelerated stability data to model the whole stability system and to predict effect of excursions

Market	Temperature	Relative Humidity (%)	Duration of Storage (months)
All: Long-Term	5C	30%	15m
A	15C	15%	**0.4m**
B	25C	5%	**0.3m**
C	25C	15%	**0.2m**
D	35C	30%	**0.1m**

Suppose that a shelf life of 15m was set for long-term storage. Can we claim that shelf life is 15 month **for all these markets**?

Excursions dramatically reduce shelf life

Real excursions could be more complex

Excursion could be a “**Series**” of events during shipping or storage such as

1 week at 15C/15% +

1 day at 25C/30% +

5 hours at 50C/50% .

Vaccine dosing in Yemen

Total Degradation after 15 months = Long-term degradation + Sum of all degradations

Strategies

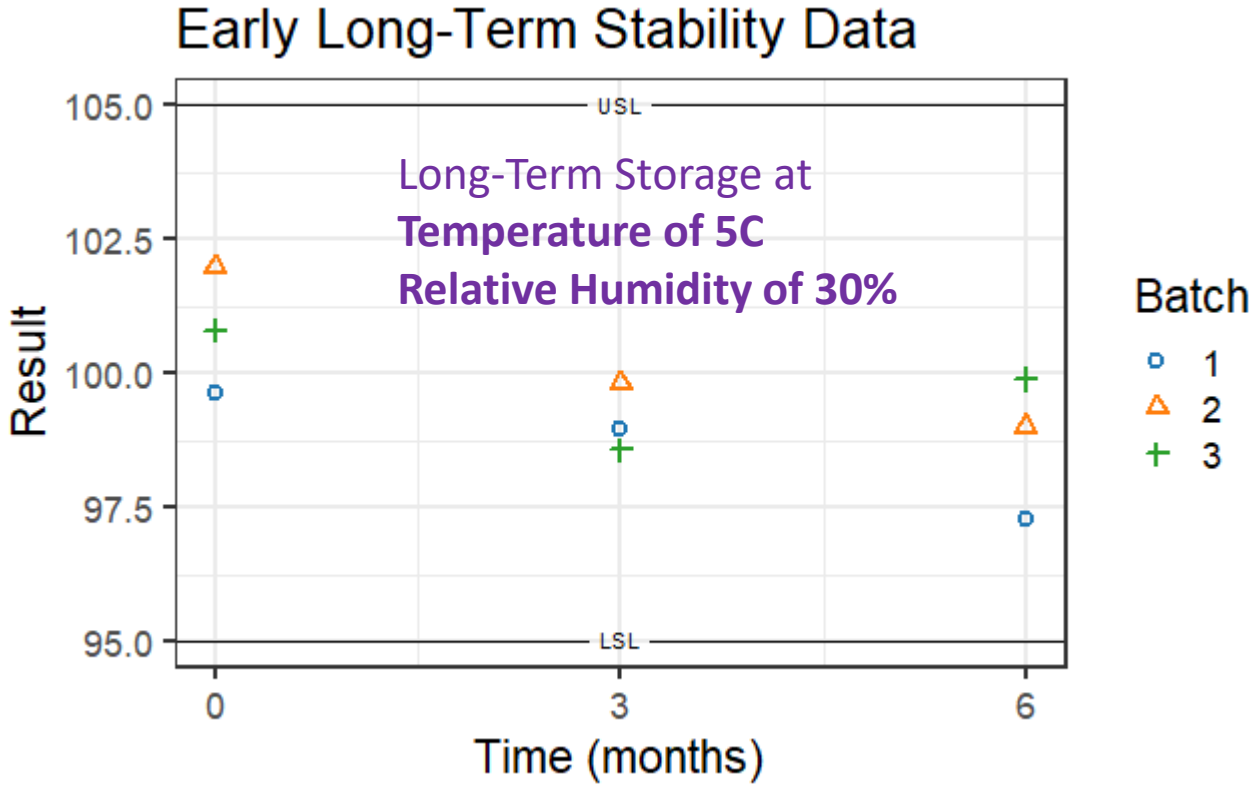
- Identify market-specific shipping process and storage conditions
- Market-specific shelf-life and internal release limit (IRL)
  - Optimal accelerated stability study design and Study Size
  - Robust statistical method to obtain the shelf life and IRL
  - Prior knowledge
- Strictly control shipping and storage to reduce excursions.

Example

Early-stage long-term stability study with accelerated stability studies

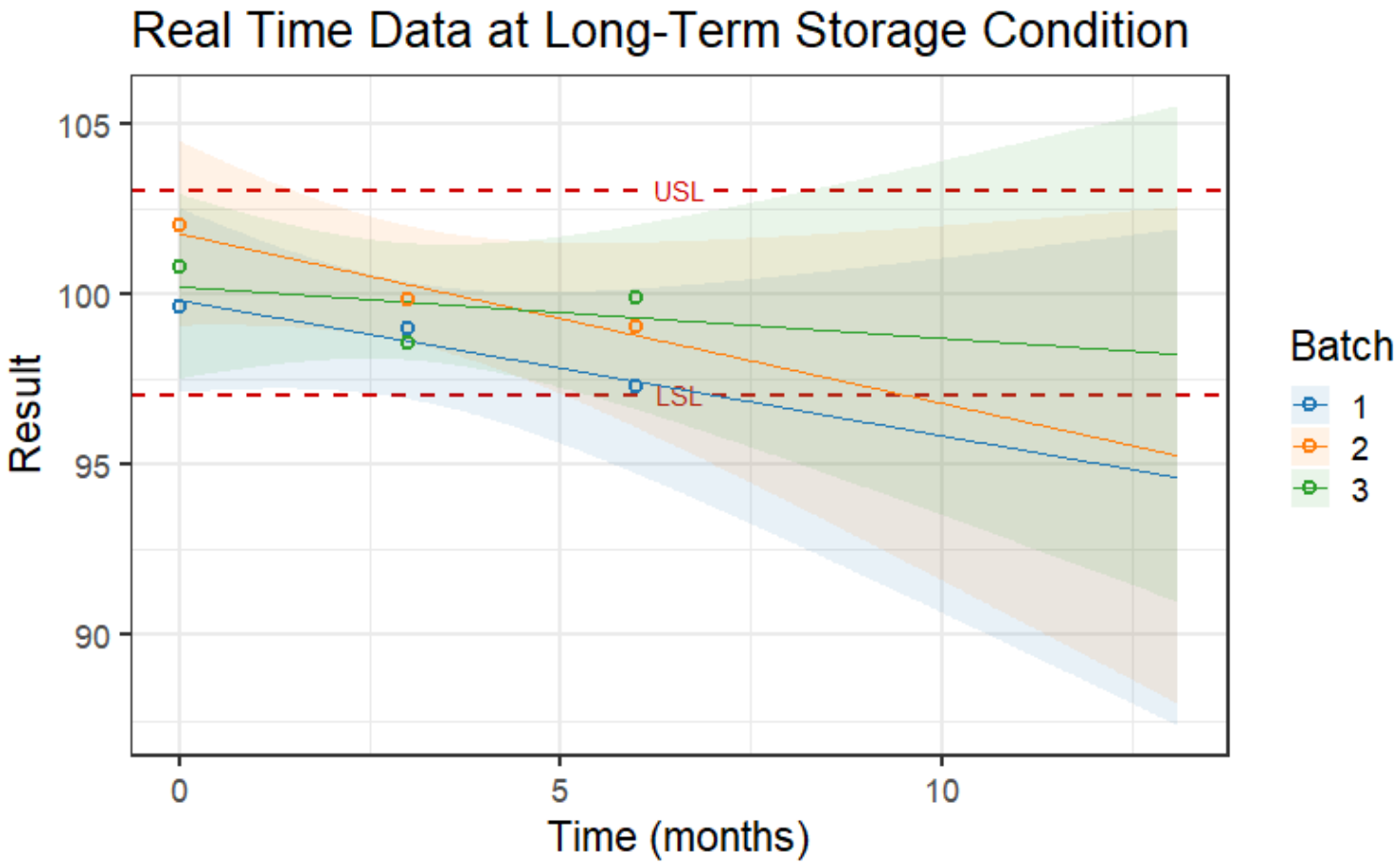
Early Stage
Real Time Stability Study at Long-term Storage

- In early stage of drug development, stability study may have progressed only a little.
- Could be only **3 batches measured up to 3 time points in the long-term storage**.
- An accurate shelf-life estimation is critical for regulatory submissions as well as to assess the manufacturability of the drug.



If this is all the data we have,
It would be difficult to obtain a quality shelf-life estimate for excursion.

Estimate only based on long-term stability data = 0m



95% CI for mean already goes outside spec at time zero.

Accelerated stability study increases estimation precision and allows modeling for excursions.

3 steps of analysis

1. Determine a good **accelerated stability design**

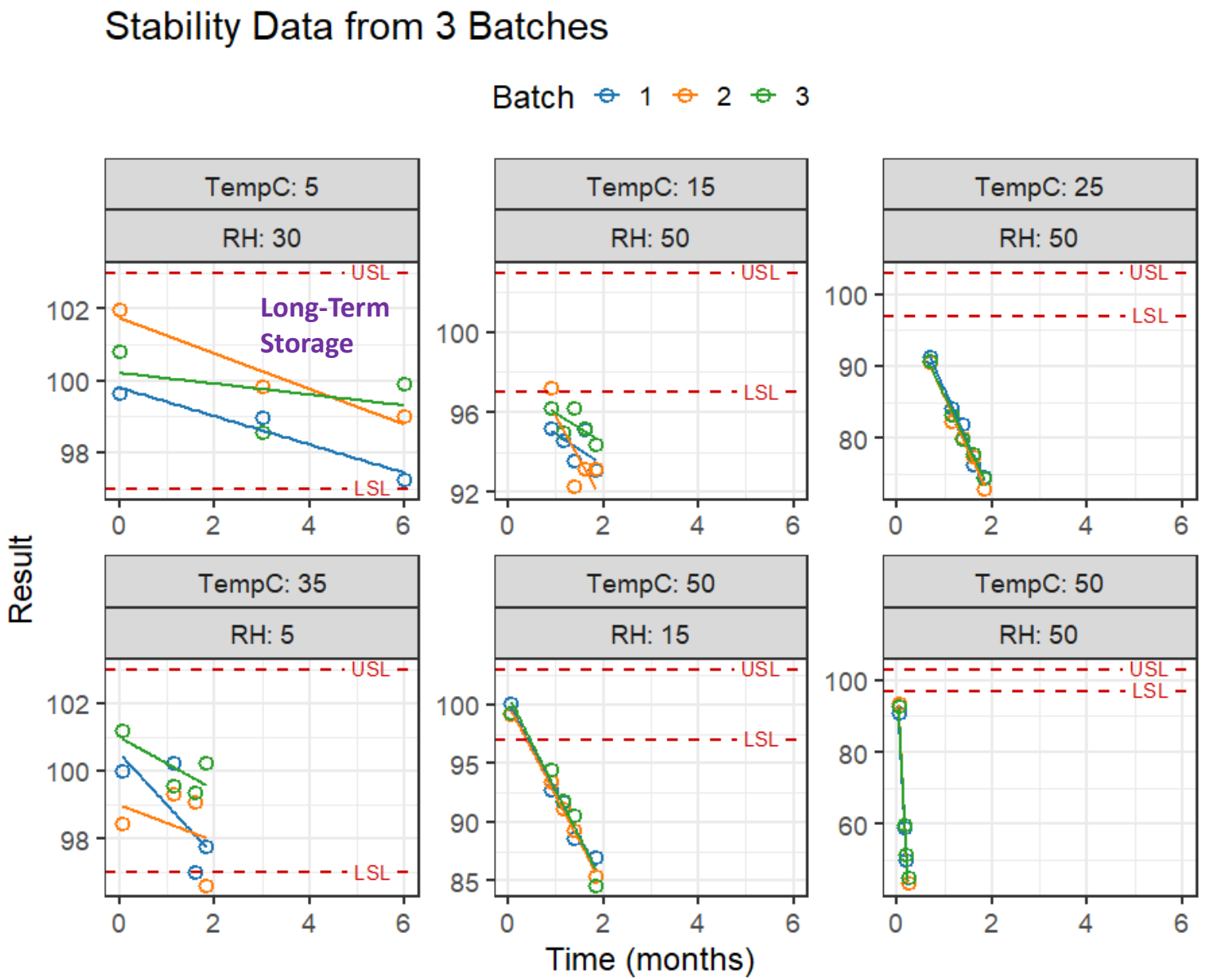
2. Estimate the mean at different conditions with credible intervals.

3. **Incorporate excursions** in the prediction of the shelf life.

Let’s discuss from step 2:

2. Estimate the mean at different conditions with credible intervals.

All data (Real-time and Accelerated) from 3 batches



Given a good DOE with the accelerated stability data, let's get the shelf life for excursions!

Simulated with:
SD(batch effect on μ_0) = 0.3
SD(batch effect on K) = 0.2
SD(error) = 1

Arrhenius model

Zero-order was used in this presentation,

But same strategy can be applied to other models.

$$k_{T,RH} = \exp\left(\ln(A) - \frac{E_a}{RT} + B \cdot RH\right),$$

with parameters:

- $\ln(A)$, the natural logarithm of the pre-exponential factor A.
- E_a, the Arrhenius activation energy in kJ/mol.
- B, the moisture sensitivity of the relative humidity.
- $R = 0.0083144$ (kJ/mol/K), the gas constant.

Kinetic model	Differential form $f(\alpha)$	Integrated form $\alpha(t)$
Zero-order	1	kt
First-order	$1-\alpha$	$1-\exp(-kt)$
Second-order	$(1-\alpha)^2$	$1-(1+kt)^{-1}$
Third-order	$(1-\alpha)^3$	$1-(1+2kt)^{-1/2}$
Power-law ($m = 1/2, 2, 3, 4$)	$m \cdot \alpha^{(m-1)/m}$	$(kt)^m$
Avrami-Erofeyev ($m = 2, 3, 4$)	$m(1-\alpha)[-\ln(1-\alpha)]^{(m-1)/m}$	$1-e^{-(kt)^m}$
Truncated Šesták-Berggren	$\alpha^m(1-\alpha)^n$	✗

Chau, J., Altan, S., Burggraeve, A. et al. (2023)

Hierarchical Zero-Order Kinetic Arrhenius model

Ki

$$y_{ij} = (\mu_0 + b_{1i}) + t_{j(i)} \times \left[D \times \exp\left\{ -\left(\frac{E_a}{1.987}\right)\left(\frac{1}{T_i} - \frac{1}{T_{Ref}}\right) + B\left(RH_i - RH_{Ref}\right) + b_{2i} \right\} \right] + e_{ij}$$

$$\text{At Long-Term Storage}: y_{ij} = (\mu_0 + b_{1i}) + t_{j(i)} \times \left[D \times \exp\{b_{2i}\} \right] + e_{ij}$$

Parameters

- μ_0 = initial content (t=0)
- D = degradation
- E_a = activation energy
- B = relative humidity term

T_{Ref} = Long-Term Temp
RH_{Ref} = Long Term RH

Appropriate true parameter values should be chosen priori through discussions with scientists.

Data

- y_{ij} = Content (%) from i^{th} batch and j^{th} time point
- $t_{j(i)}$ = j^{th} day within i^{th} batch
- T_i = temperature (K) condition of i^{th} batch
- RH_i = rel. humidity condition of i^{th} batch

- b_{1i} = batch intercept error term
- b_{2i} = batch slope error term

$$\begin{pmatrix} b_{1i} \\ b_{2i} \end{pmatrix} \sim MN\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{bmatrix} \sigma_{1b}^2 & \sigma_{12} \\ \sigma_{12} & \sigma_{2b}^2 \end{bmatrix} \right)$$

- e_{ij} = residual error term $\sim N(0, \sigma_e^2)$

Why Bayesian?

- Flexible modeling
- Exact, not approximate
- Direct probabilistic assessment of hypotheses
- Opportunity to include prior information
- Allows for interpretable posterior inference
- Robustness when the data are sparse or of limited quality.

Chau, J., Altan, S., Burggraeve, A. et al. ***A Bayesian Approach to Kinetic Modeling of Accelerated Stability Studies and Shelf Life Determination.*** AAPS PharmSciTech 24, 250 (2023). https://doi.org/10.1208/s12249-023-02695-5

Bayesian Hierarchical Zero-Order Kinetic Arrhenius model

Vaguely Informative Priors, mimicking the early stage of drug development

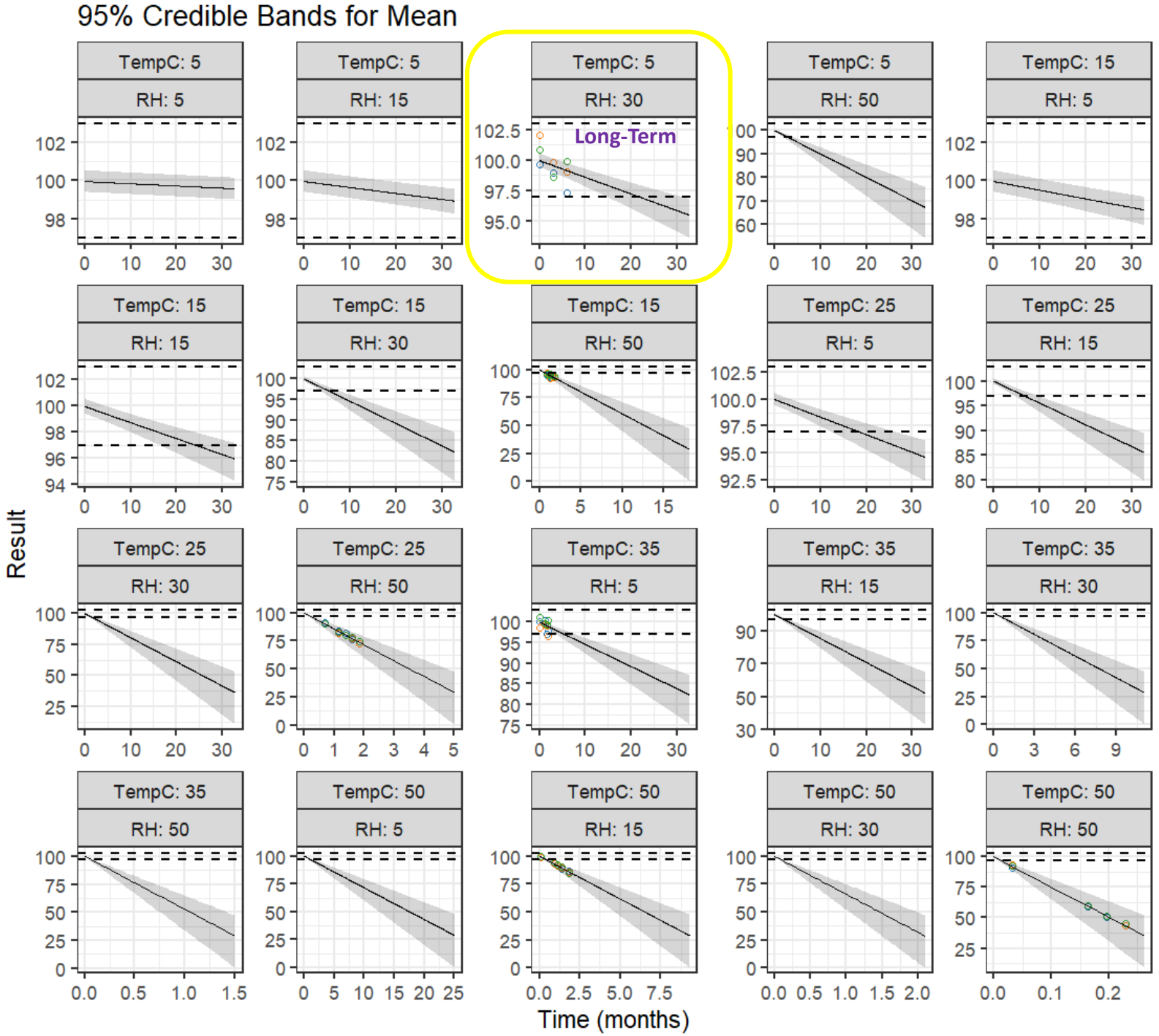
- $\mu_0 \sim N(100,\ 10)$
- $D \sim N(-0.0037,\ 1)$
- $\ln E_a \sim N(10.007,\ 10)$
- $B \sim N(0.1024\ , 10)$
- $\sigma_e^2 \sim \text{half-Cauchy(Scale = 0.1)}$
- $$\begin{bmatrix} \sigma_{1b}^2 & \sigma_{12} \\ \sigma_{12} & \sigma_{2b}^2 \end{bmatrix}^{-1} \sim \text{Wishart}\left(Scale = \begin{bmatrix} \sigma_{1b}^2 & \sigma_{12} \\ \sigma_{12} & \sigma_{2b}^2 \end{bmatrix},\ df = 3 \right)$$

Estimates obtained from fitted zero-order Kinetic Arrhenius model (using the optim_fit function in the OptimModel library).

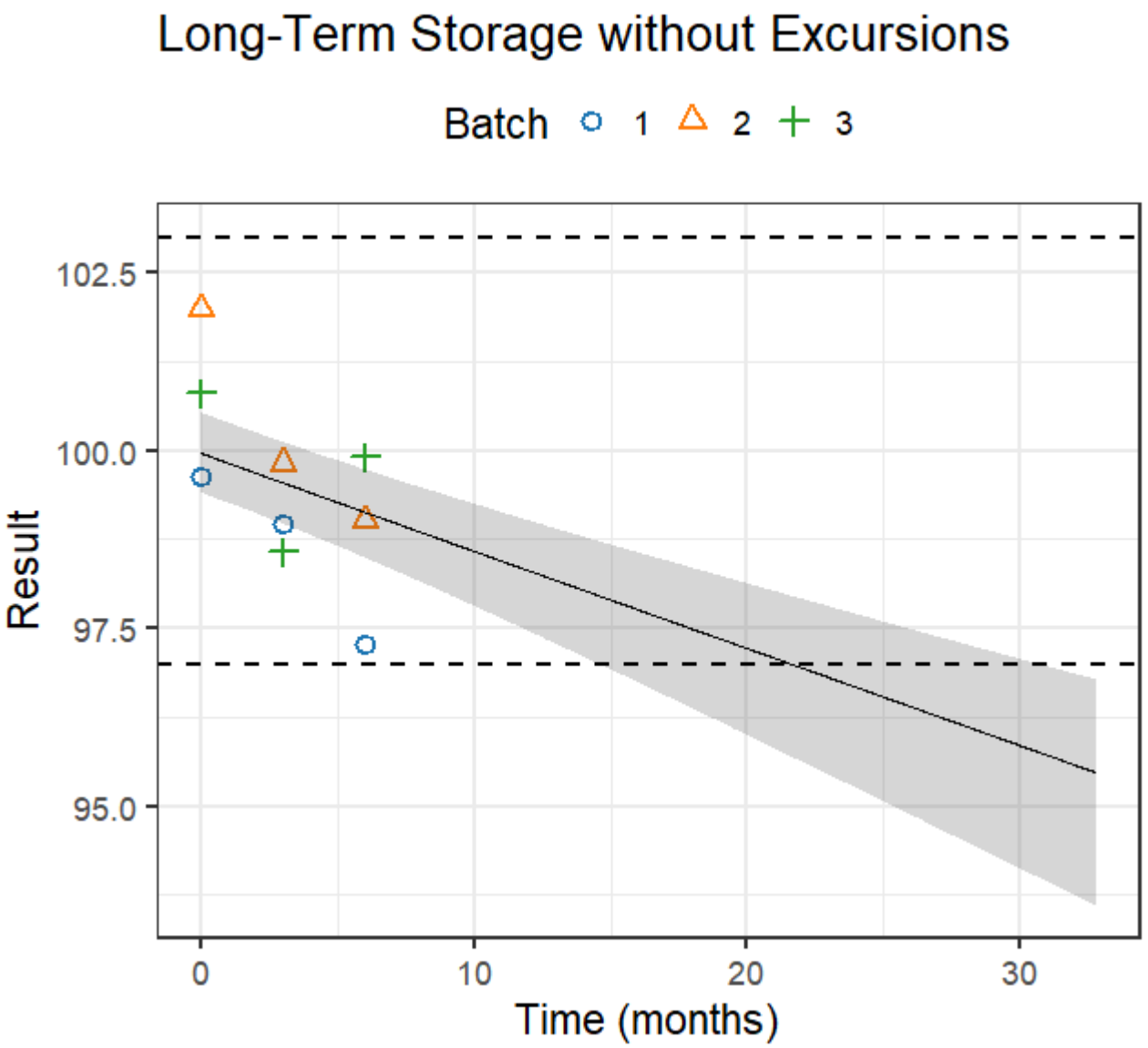
These estimates could be replaced with informative priors when available.

Predicted Stability Profiles

The design was able to estimate the mean with a 95% credible band at all conditions.



Long-term storage zoomed in



Shelf-life estimate based on long-term storage = **15 months**

But..

What is shelf life with excursions?

3. Incorporate Excursions in the Prediction of the Shelf life.

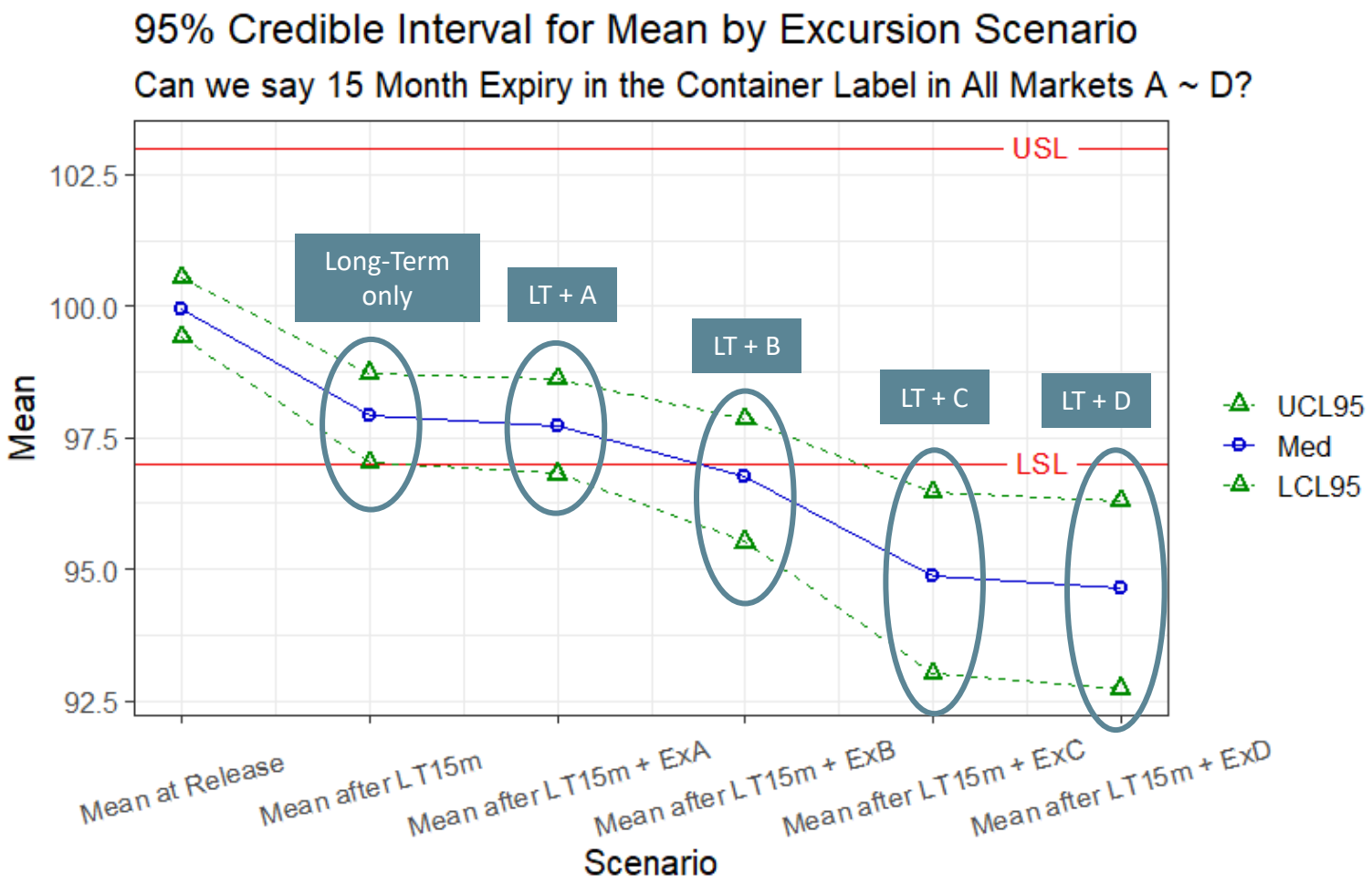
Market-Specific Excursion scenarios should be identified

- Need to better understand the excursions and their effects on shelf life and internal release limit
- Use real-time and accelerated stability data to model the whole stability system and to predict effect of excursions

Market	Temperature	Relative Humidity (%)	Duration of Storage (months)
All: Long-Term	5C	30%	15m
A	25C	5%	1.2m
B	35C	15%	0.8m
C	50C	15%	0.6m
D	35C	50%	0.1m

Can we say shelf life is 15 month for all these markets?

Predicted Mean after 15-month LT storage + excursions



No market can claim 15-month expiry when excursions are likely to occur!

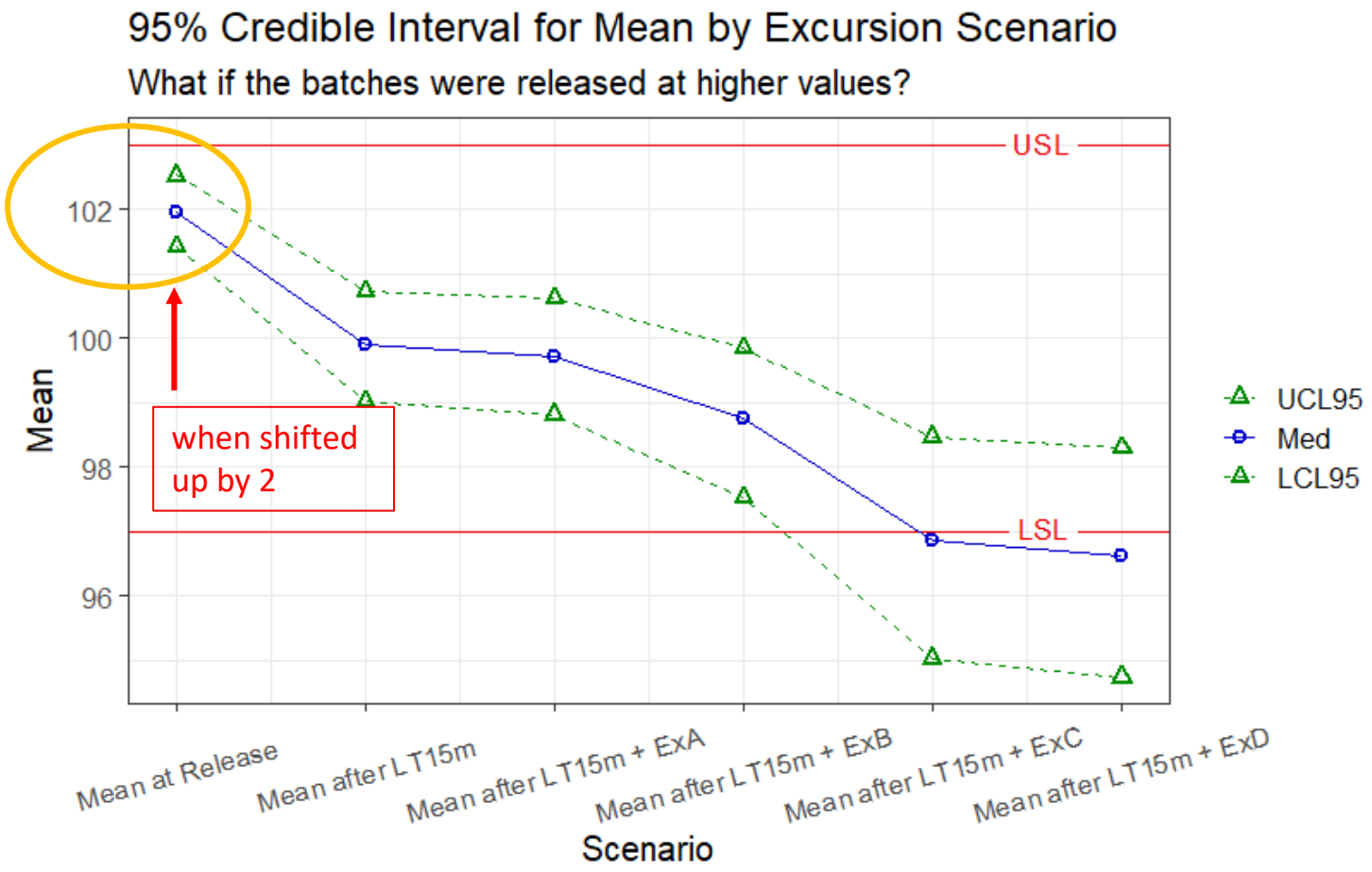
- Different expiry dates across markets?
- Or, different release limits across markets keeping the same expiry?

Setting different internal release limits

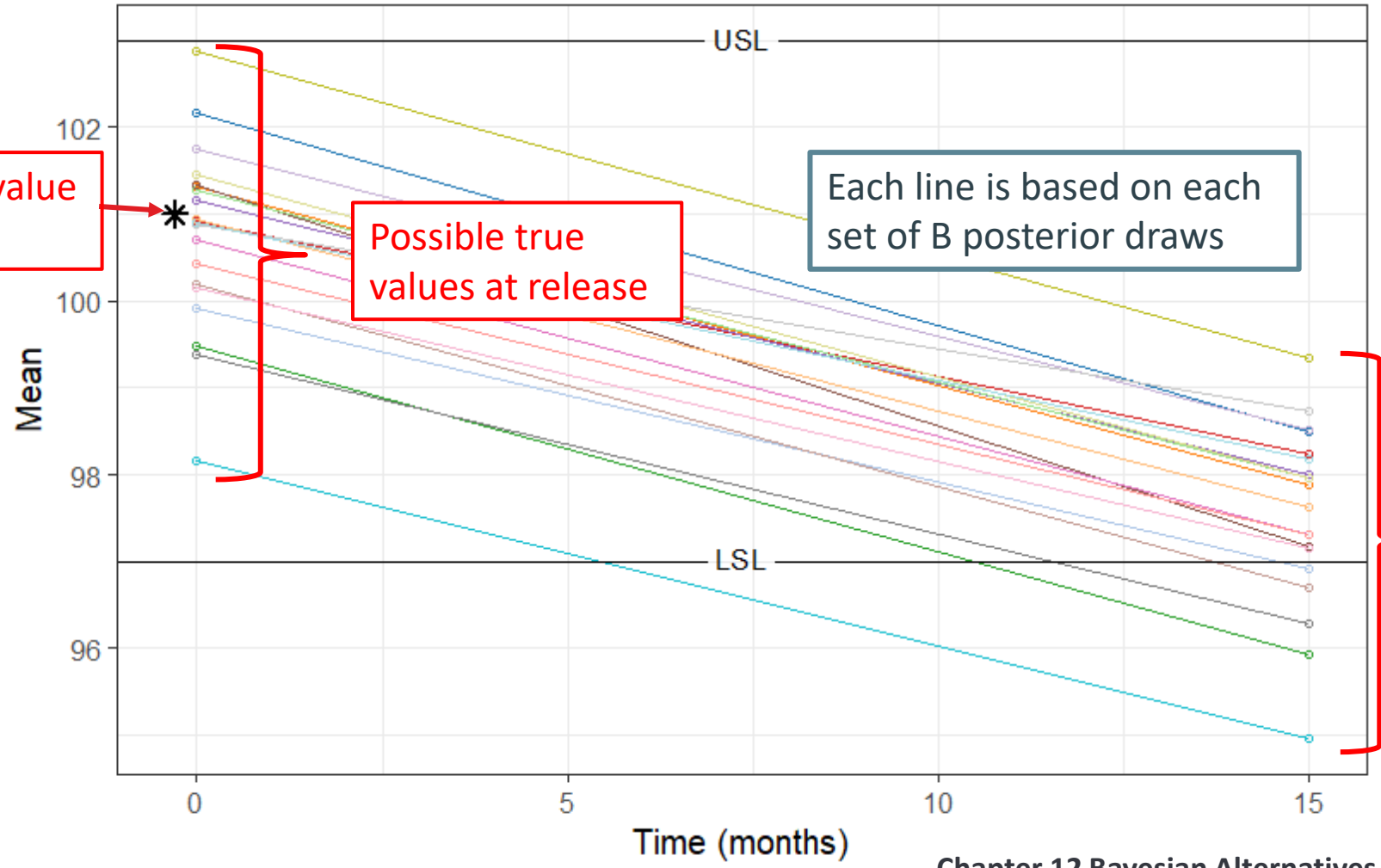
Only release high-enough batches!

Set **Internal Release Limits (IRL)** for each market based on specific excursion series.

If a batch fails to fall within IRL for a market, it may still pass IRL for another market with less excursions.



Bayesian Internal Release Limits



Observed value at release

Possible true values at release

Each line is based on each set of B posterior draws

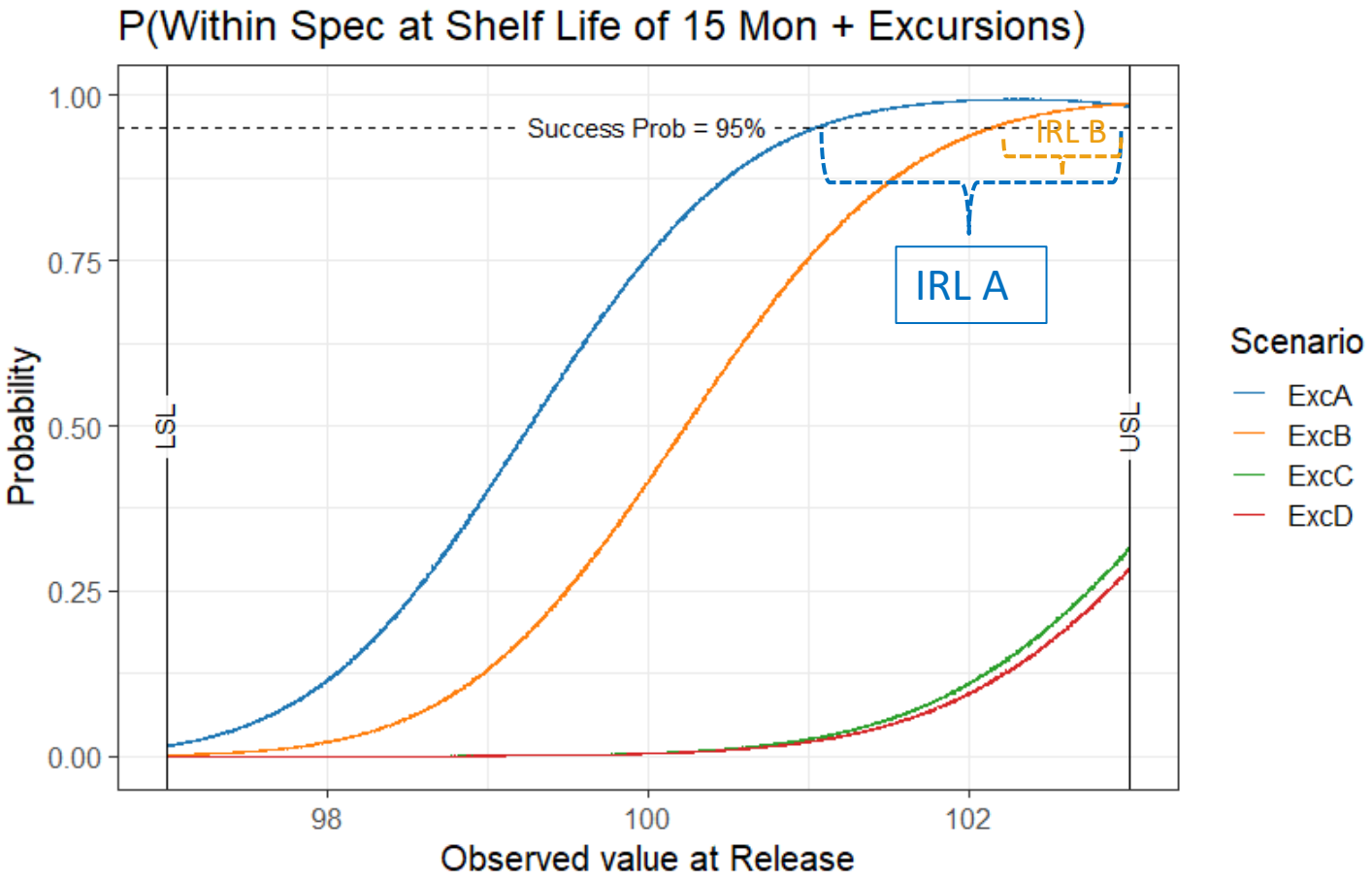
Possible range of the mean after 15m and excursions (B lines)

What proportion of these lines did not cross spec here? (= Success prob)

Internal Release Limit (IRL): The limit for observations at Time 0 that gives a good probability (eg. 95%) of being within stability specification at the shelf life + Excursions.

Chapter 12 Bayesian Alternatives to Traditional Methods for Estimating Product Shelf Life and Internal Release Limits, *Perceval Sondag, Ji Young Kim, Laurent Natalis, and Tara Scherder.* Case Studies in Bayesian Methods for Biopharmaceutical CMC. 10.1201/9781003255093. Edited by *Faya, Paul & Pourmohamad, Tony.* (2022).

Internal Release limits



To be within spec with 95% probability after 15m and excursions,

Market A:
Batches should be released between [101.0 103.0].

Market B:
Batches should be released between [102.1 103.0].

Markets C and D:
15-month shelf-life cannot be claimed.
Or excursions should be strictly controlled.

Chapter 12 Bayesian Alternatives to Traditional Methods for Estimating Product Shelf Life and Internal Release Limits, *Perceval Sondag, Ji Young Kim, Laurent Natalis, and Tara Scherder.* Case Studies in Bayesian Methods for Biopharmaceutical CMC. 10.1201/9781003255093. Edited by *Faya, Paul & Pourmohamad, Tony.* (2022).

Let’s circle back to step 1:

1. Determine a good accelerated stability study design

Step 1. Determine a good accelerated stability design

Choosing Optimal Stability Study Conditions and Time Points

Long-term Storage Condition

Temperature = **5C**

Relative Humidity = **30%**

Data from 3 batches at the time points of **0, 3, 6 months** will be available at the time of regulatory submission

Accelerated Conditions

Temperature: **15C, 15C, 35C, 50C**

Relative Humidity: **5%, 15%, 50%**

Time Points: **0, 1, 2, 3, 4, 5, 6, 7, 14, 21, 28, 35, 42, 49, 56 Days**

Assumption

Data from each batch are assumed to follow a ***Zero-Order Kinetic Arrhenius Model***

Full Accelerated Stability Study Design:

12 conditions×15 time points = 180 combinations

True parameters assumed

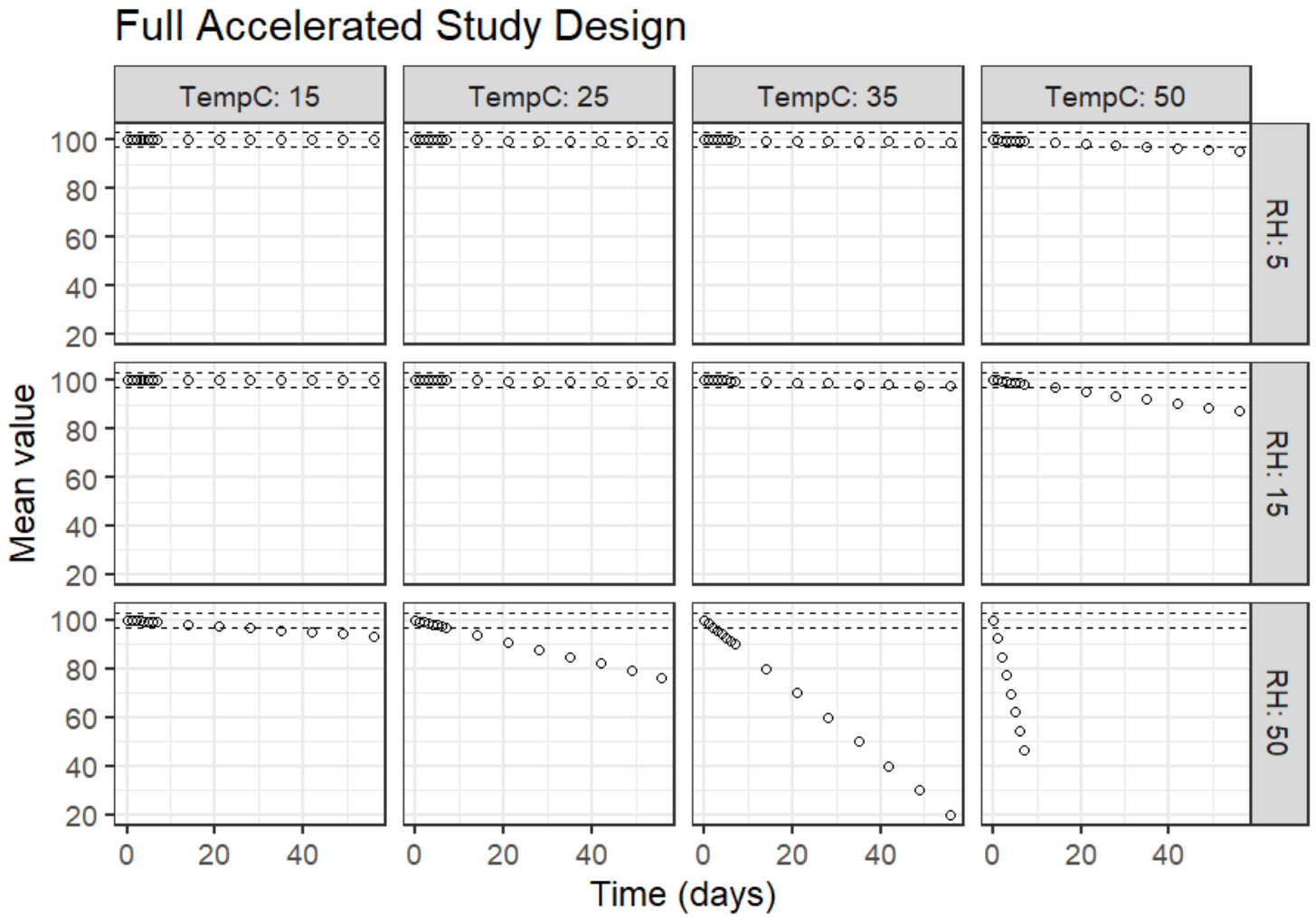
- μ_0 = initial content (t=0) = 100
- D = degradation = - 0.004
- E_a = activation energy = e^{10}
- B = relative humidity term = 0.1

Specification Limit = [97, 103]

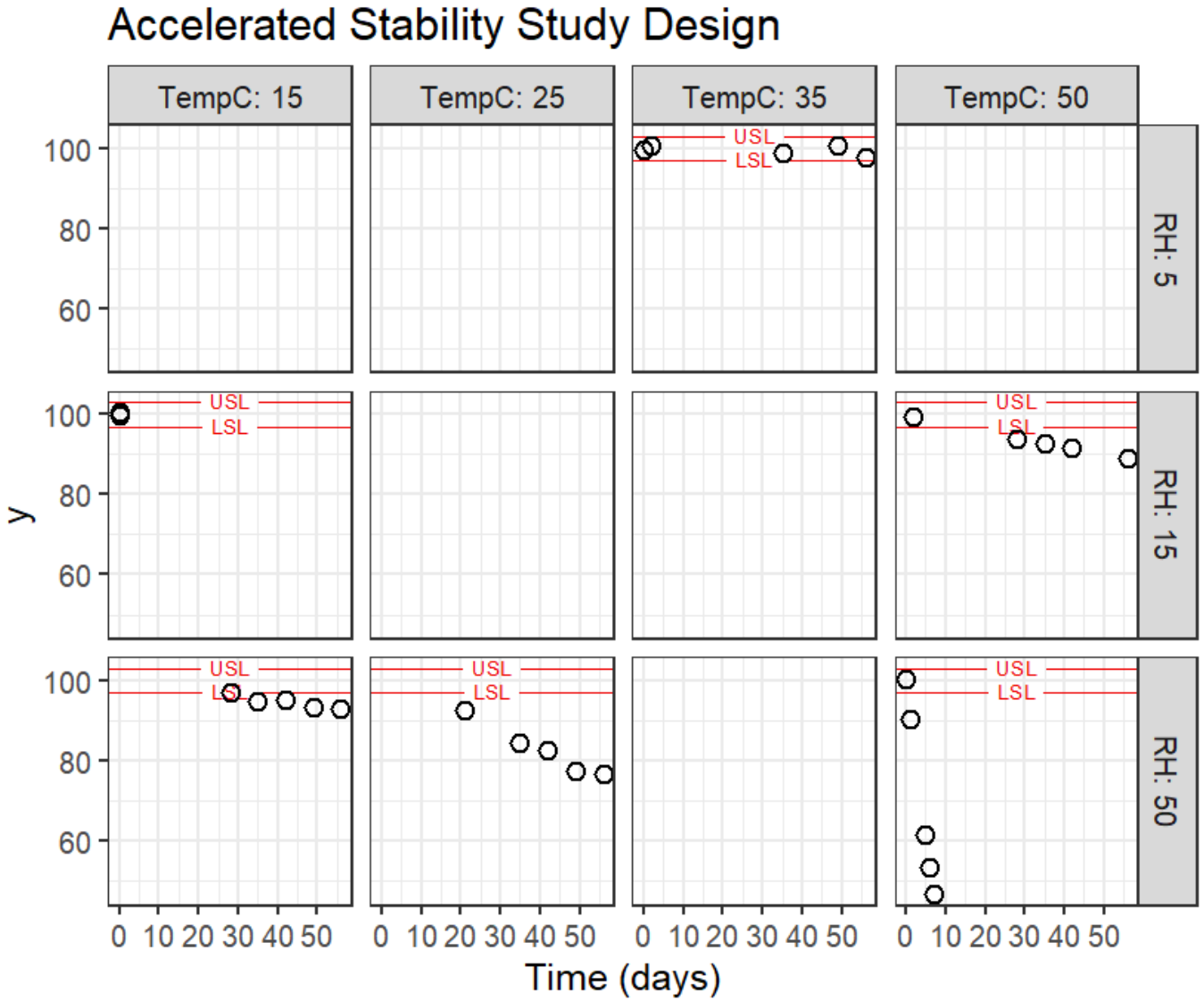
True Shelf Life (with no batch-to-batch variations) = 750 Days (About 24 months)
(by solving 100 - 0.004×Time = 97)

Response is simulated:
173 total combinations among 180

Need 6 conditions × 5 time points



Optimal Accelerated study design minimizing the prediction variance at the shelf life



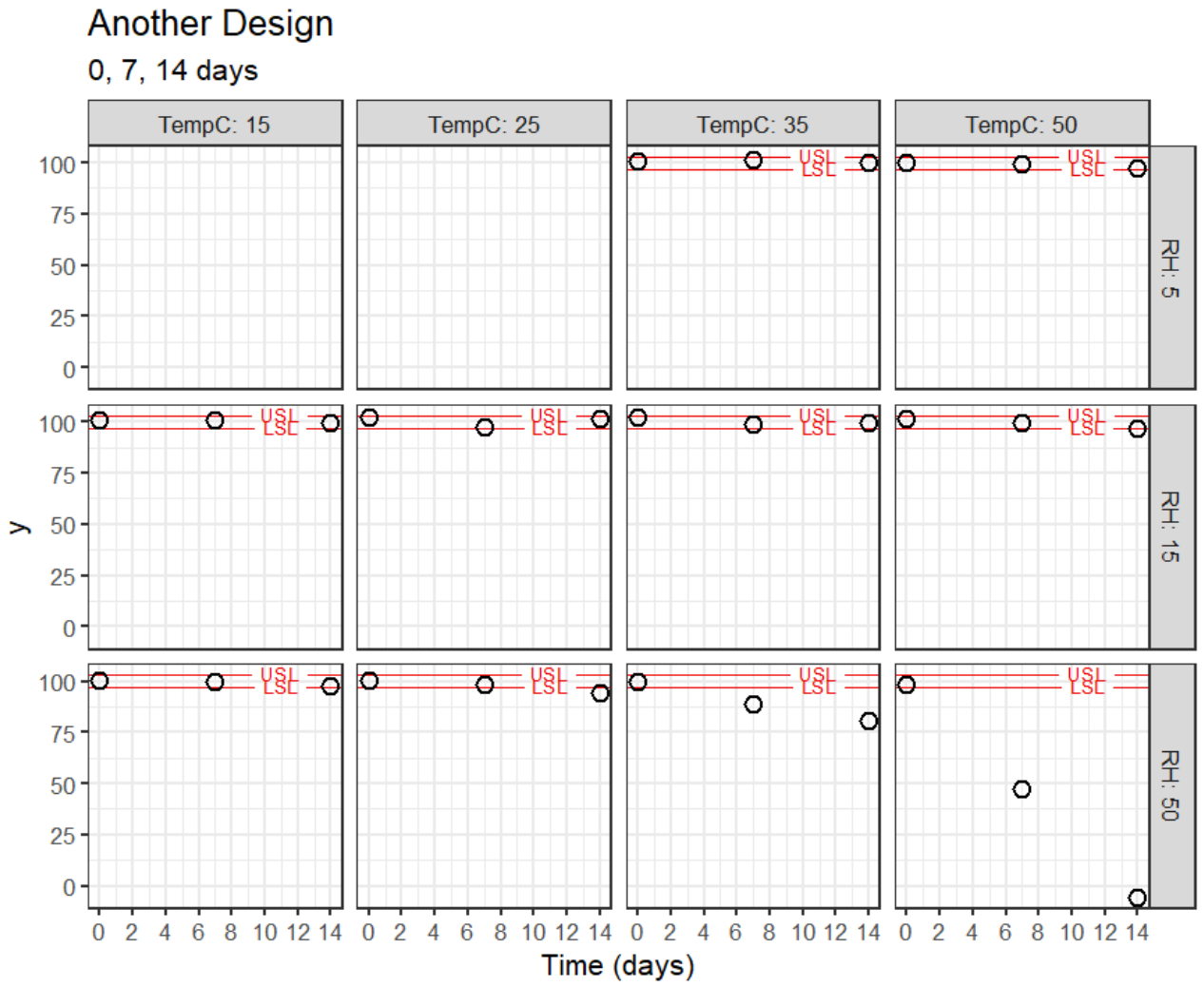
Design that minimizes

Objective: $\mathrm{Var}(\widehat{\mu_0} + t_{SL} \times \widehat{D})$

Same design applied to each batch

Why DoE is important

What if this design was used for accelerated studies?



- Same set of time points in every condition:

  0, 7, 14 days

- **N=30 combinations total**

- SE(Shelf life) > 2.6 times SE(shelf life) from optimal design

  ➔ **Less precise**

  (eg. only 11 month shelf life from a simulated data)

Summary

- Design of accelerated stability studies
- Kinetic modeling of all conditions enhances shelf-life estimation
- As more data become available, estimation precision will improve ➔ excursion effects can be re-assessed
- Patient and producer risk greatly reduced with refined shelf-life or shipping/storage instructions
- Manuscript in progress: DoE for stability study and shelf-life/IRL considering storage excursions

Thank you!

Ji-young.kim@takeda.com

Better Health, Brighter Future