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# Alternative Statistical Approaches to Shelf Life Estimation

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# About the Working Group

- Formed in 2006 with the mandate to investigate current statistical methods for estimating shelf life and, if possible, to develop improved method(s)
- Composed of pharmaceutical, regulatory, and statistical scientists from industry, government, and academia

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# ICH Harmonised Tripartite Guideline

- Stability Testing of New Drug Substances and Products Q1A(R2) (2003)

**Shelf life** (also referred to as expiration dating period): The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

- Evaluation for Stability Data Q1E (2003)

The purpose of a stability study is to establish, **based on testing a minimum of three batches** of the drug substance or product, a retest period or shelf life and label storage instructions **applicable to all future batches** manufactured and packaged under similar circumstances.

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# In this talk

- Conceptual Framework
- Current Practice
  - Description
  - Small Sample Behavior
- Alternatives
  - Alignment with Q1A/Q1E mandate and conceptual framework
  - Description
- Criteria for Evaluating Proposed Alternatives
- Results & Next Steps To-Do List

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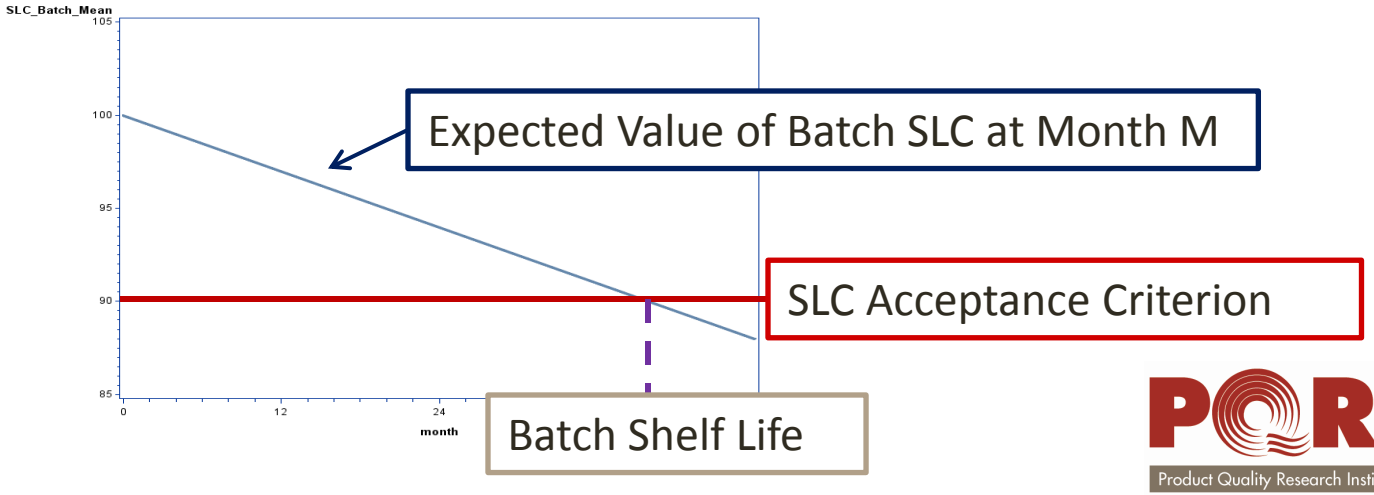
# Conceptual framework

- Big idea: stability limiting characteristic (SLC)
  - gets worse over time
  - change is monotonic
  - shelf life ≡ time after which SLC no longer acceptable
- Linear Change
  - commonly used (but more complex models are often needed)
  - Q1E uses linear to illustrate relevant issues
  - we follow Q1E's lead...

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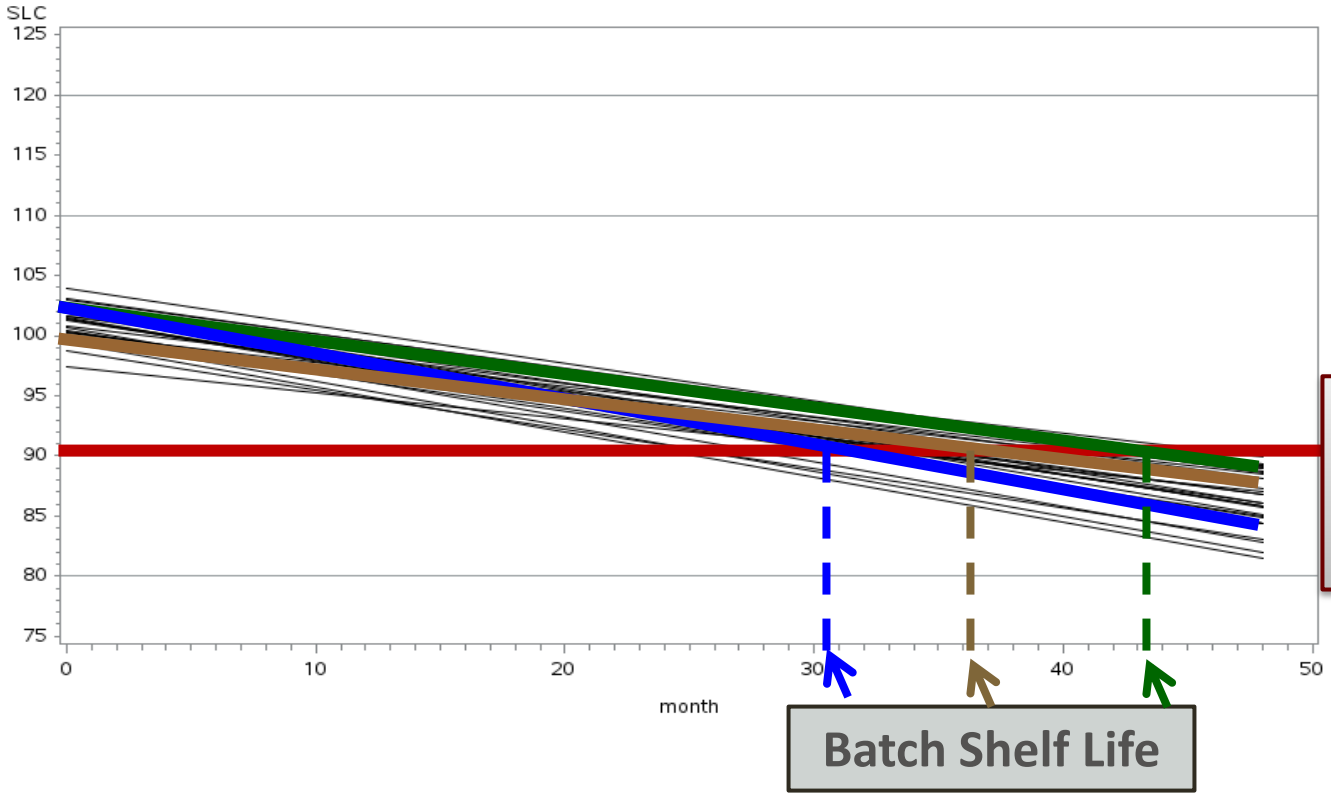
# Conceptual Framework
## Distribution of Batch Means



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# Conceptual Framework – Formal

- Batches are not identical
- Mathematical model of variability

"There are no wrong notes,
some are just more right than others."
- Thelonious Monk

There are no right models.
Some are just less wrong than others.

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# Conceptual Framework – Formal

- Batches are not identical
- Mathematical model of variability
- Description of how data arise

| Source | | Distribution |
|---|---|---|
| batch ($i^{th}$ batch) | intercept | $\begin{bmatrix} b_{0i} \\ b_{1i} \end{bmatrix} \sim N\left( \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_0^2 & \sigma_{01} \\ \sigma_{01} & \sigma_1^2 \end{bmatrix} \right)$ |
| | slope | |
| time ($j^{th}$ month) | | $\mu_{ij} = \beta_0 + b_{0i} + \left(\beta_1 + b_{1i}\right) M_j$ |
| unit of observation | | $y_{ijk} \mid b_{0i}, b_{1i} \sim N\left(\mu_{ij}, \sigma^2\right)$ |

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# Current ICH Recommendation

- Start with unequal slopes ANCOVA model

$$\beta_0 + b_{0i} + (\beta_1 + b_{1i})M$$

- Test for equality of slopes ("poolability") $H_0$: all $b_{1i} = 0$
- Possible models
  - (1) $\beta_0 + b_{0i} + (\beta_1 + b_{1i})M$
  - (2) $\beta_0 + b_{0i} + \beta_1 M$
  - (3) $\beta_0 + \beta_1 M$
- If model (1) or (2) focus on shortest-lived batch
- If model (3) use pooled regression
- $sup_M\{M: lower\ conf\ bound\ of\ \hat{Y} > AC\}$
- if batches ↑ model (1) increasingly likely

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# Current ICH Recommendation

- Current ICH: batch effects **fixed**
- However...
  - nothing special about batches observed per se
  - repeat stability trial need not (unlikely to be able to) use same batches
  - requirement: observed batches **represent** the target population
  - **Mandated inference space**: "**future batches**"
- The above are characteristics of **random** effect:
- **Current practice inconsistent with above**
- Practical Reality
  - small-sample behavior of current practice is problematic
  - see Capen, et al. 2017; Stroup & Quinlan, 2015; Quinlan, et al. 2013, Schwenke, 2010)

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# Block Effect Random ⇒ Mixed Model

- ➔ Align analysis model with process giving rise...

$$\beta_0 + b_{0i} + (\beta_1 + b_{1i})M,$$

$$\begin{bmatrix} b_{0i} \\ b_{1i} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_0^2 & \sigma_{01} \\ \sigma_{01} & \sigma_1^2 \end{bmatrix}\right)$$

- No need / reason to test equality of slopes; variation among slopes is assumed
- Focus on batch-specific regression

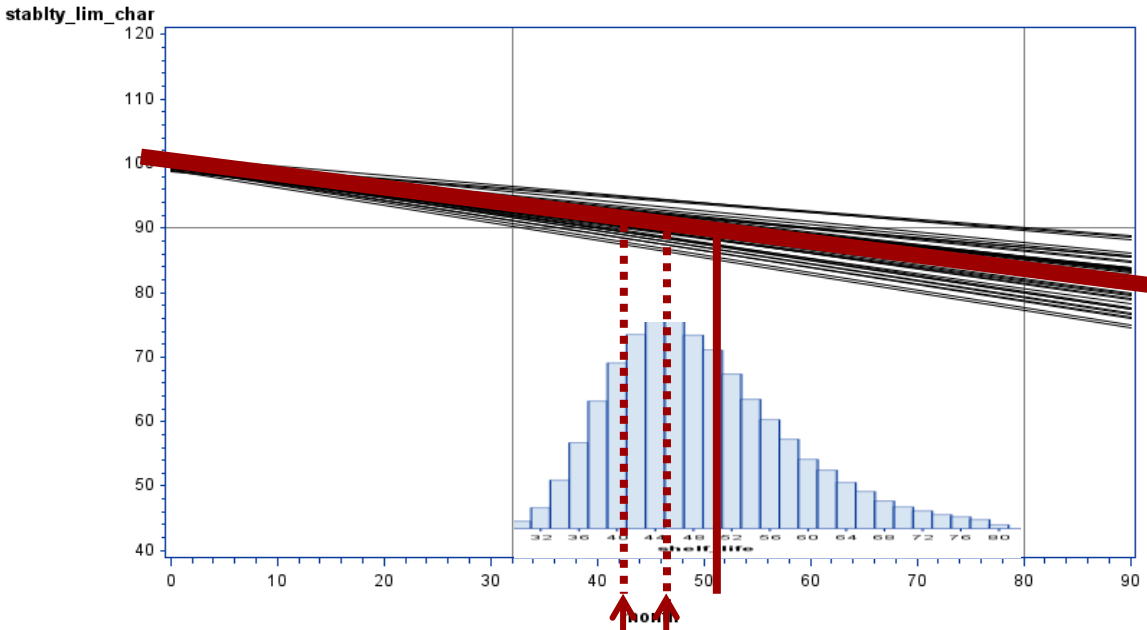
# “Naive” Application of Mixed Model

- Use random coefficient regression
- Obtain 95% lower confidence bound $\hat{Y}|M$
- Use $sup_M\{M: lower\ conf\ bound\ of\ \hat{Y}|M > AC\}$

```
proc glimmix data=stability_demo;
class batch;
 model y=month / ddfm=kr2 s cl;
 random intercept month / subject=batch;
  estimate 'yhat at 31' intercept 1 month 31/ cl;
  estimate 'yhat at 32' intercept 1 month 32/ cl;
```

- **Why “naive”?**: **wrong inference space** - fails to address “all future batches” objective of shelf-life estimation

# Why Do We Say "Naive"?




mean of batch mean distribution

"Naive"
Mixed Model
Expected Estimate, 3 batches

"Naive"
Mixed Model
E(Estimate), >3 batches

as batches ↑
E(estimate)→ mean

area to left of estimate
= Pr{future batch SLC < AC before labelled shelf life}
if mean is target, this probability is 0.5

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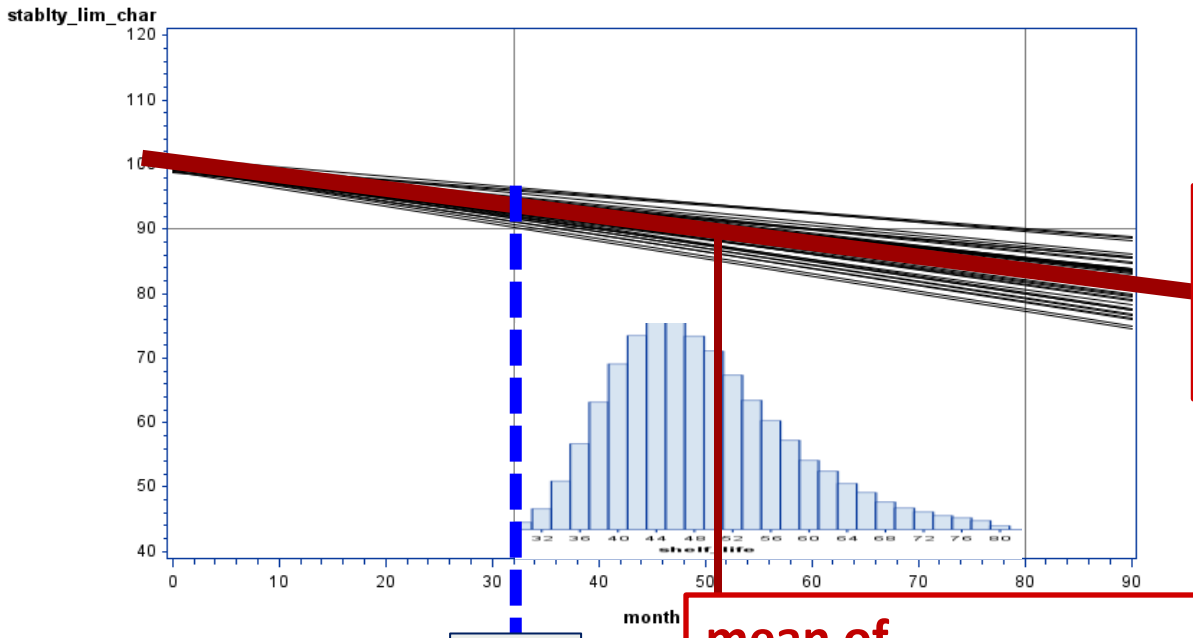
# What does "all future batches" mean?




assuming estimate ⇒ labelled shelf life, area to right
= Pr{future batch SLC remains > AC for ≥ labelled shelf life}
don't we want this to be >>0.5??

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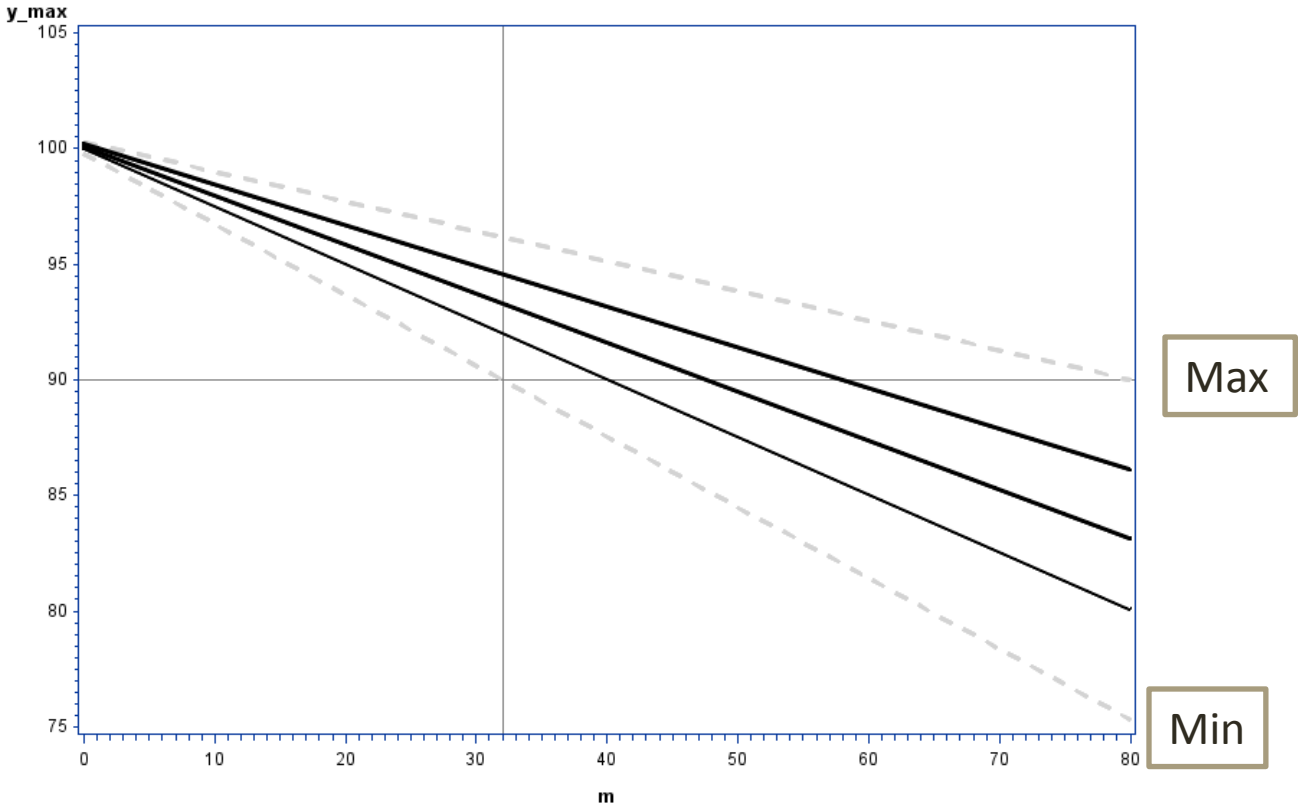
# What does each batch target?



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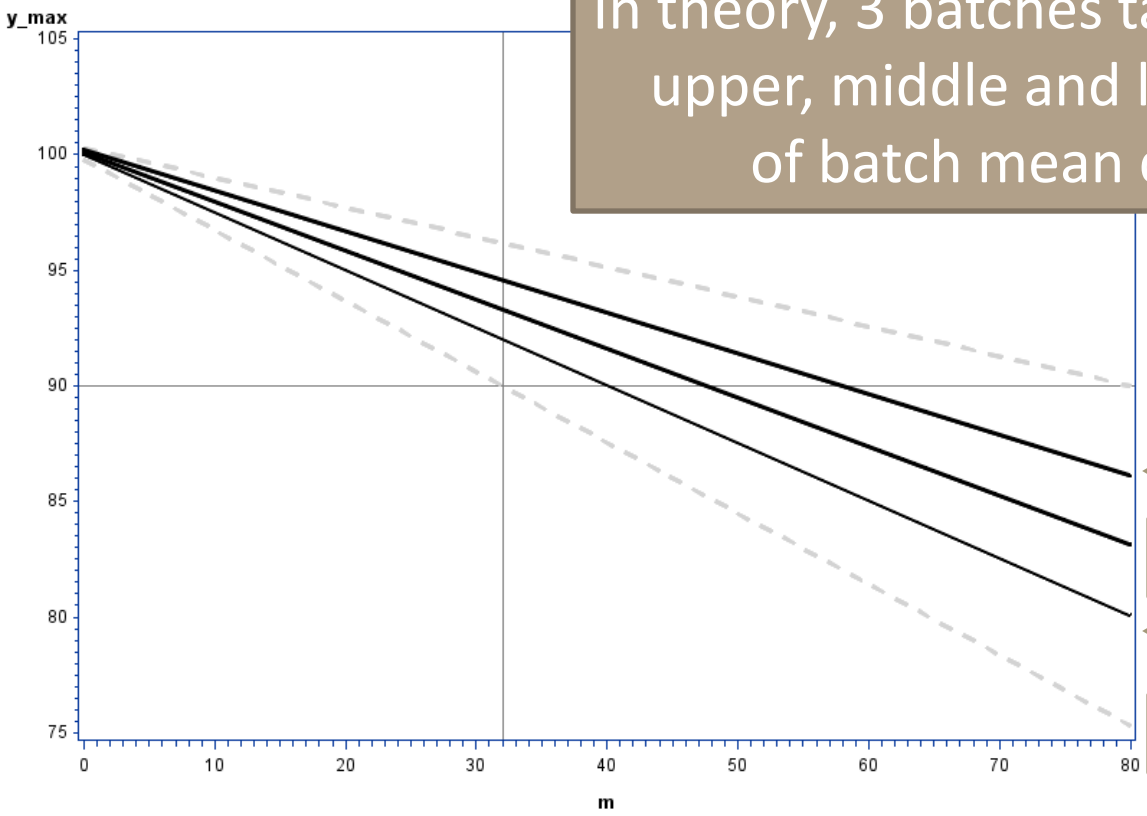
# What does each batch target?

In theory, 3 batches target
upper, middle and lower 1/3
of batch mean distribution




Max

Median of
Upper 1/3
Q 83-1/3

Q50

Median of
Lower 1/3
Q 16-2/3

Min

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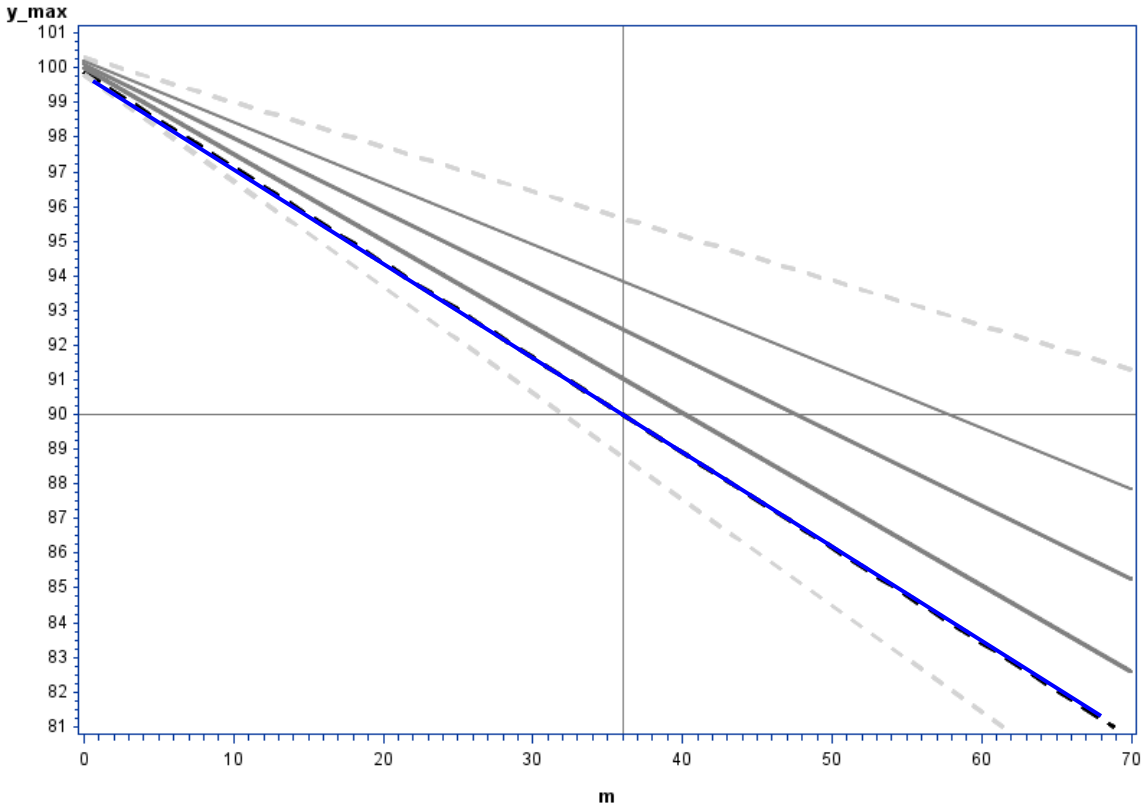
# Mixed Model BLUP – Quantile Regression




Goal: Predict M corresponding to desired Quantile

Mixed Model quantile regression?

One viable approach...

...LCL of BLUP of shortest-lived batch – align with desired Quantile

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# LMM Quantile via LCL BLUP

- Let $S_i$ denote shelf life of $i^{th}$ batch
- $AC = \beta_0 + b_{0i} + (\beta_1 + b_{1i})S_i$
- therefore $S_i = \frac{AC-(\beta_0+b_{0i})}{\beta_1+b_{1i}}$
- Using BLUP of shortest lived batch targets Q16-2/3
- Using LCL of confidence interval with $\alpha = 0.30$ targets Q05 (5th percentile of batch mean distribution)
- $\Rightarrow$ use $\hat{S}_i = \frac{AC-(\hat{\beta}_0+\hat{b}_{0i})_{LCL}}{(\hat{\beta}_1+\hat{b}_{1i})_{LCL}}$



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# Another Approach – Direct LMM-based

- Assuming $\sigma_{01} = 0, y_{ij}|M \sim N\left(\mu_{ij}, {\sigma_0}^2 + M^2{\sigma_1}^2 + \sigma^2\right)$
- $\mu_{ij} = \beta_0 + \beta_1 M$
- Given *M*, proportion of distribution between $\beta_0 + \beta_1 M \pm Z_{\alpha/2}\sqrt{{\sigma_0}^2 + M^2{\sigma_1}^2 + \sigma^2}$ is $(1 - \alpha)$
- Shelf life is *M* such that *AC* = $\beta_0 + \beta_1 M - Z_{\alpha/2}\sqrt{{\sigma_0}^2 + M^2{\sigma_1}^2 + \sigma^2}$
- With estimated regression coefficients and variance components, use *t* rather than *Z*

# Bayesian

- Fit Random Coefficient LMM
- Shelf Life Definition 1: $\hat{S} = \frac{AC - \hat{\beta}_0}{\hat{\beta}_1}$
- Shelf Life Definition 2:
  - $y_{ij}|b_{0i}, b_{1i} \sim N(\beta_0 + b_{0i} + (\beta_1 + b_{1i})M, \sigma^2) \Rightarrow$
  - $\alpha = Pr\{AC < Y\} = Pr\left\{\frac{AC-\mu}{\sigma} < Z_\alpha\right\}$, where $\mu = \beta_{0i} + \beta_{1i}S$
  - Solving for S $\Rightarrow \hat{S}_i = \frac{AC - \hat{\beta}_{0i} - \hat{\sigma} Z_\alpha}{\hat{\beta}_{1i}}$
- Use MCMC to obtain posterior distributions
- Use lower credible interval bound corresponding to Q

# Criteria for Assessing Performance

- All future batches mandate
  - how to interpret
  - needed: operating definitions
    - of target of shelf life estimator / predictor
    - of "good" estimator / predictor
- Example: suppose target is 5th percentile (Q05)
  - $\hat{S}$ should target Q05 of the shelf-life distribution
  - "Price is Right" criterion (as close to target without going over)
    - with regard to patient and Prob {product "fails" before stated lifetime}
    - $\hat{S}$ > Q05 **unacceptable**
    - $\hat{S}$ = Q05 **ideal**
    - $\hat{S}$ < Q05 (but close) **good**
    - $\hat{S}$ << Q05 (especially below Q$\epsilon$ where $\epsilon \to 0$) **not good**

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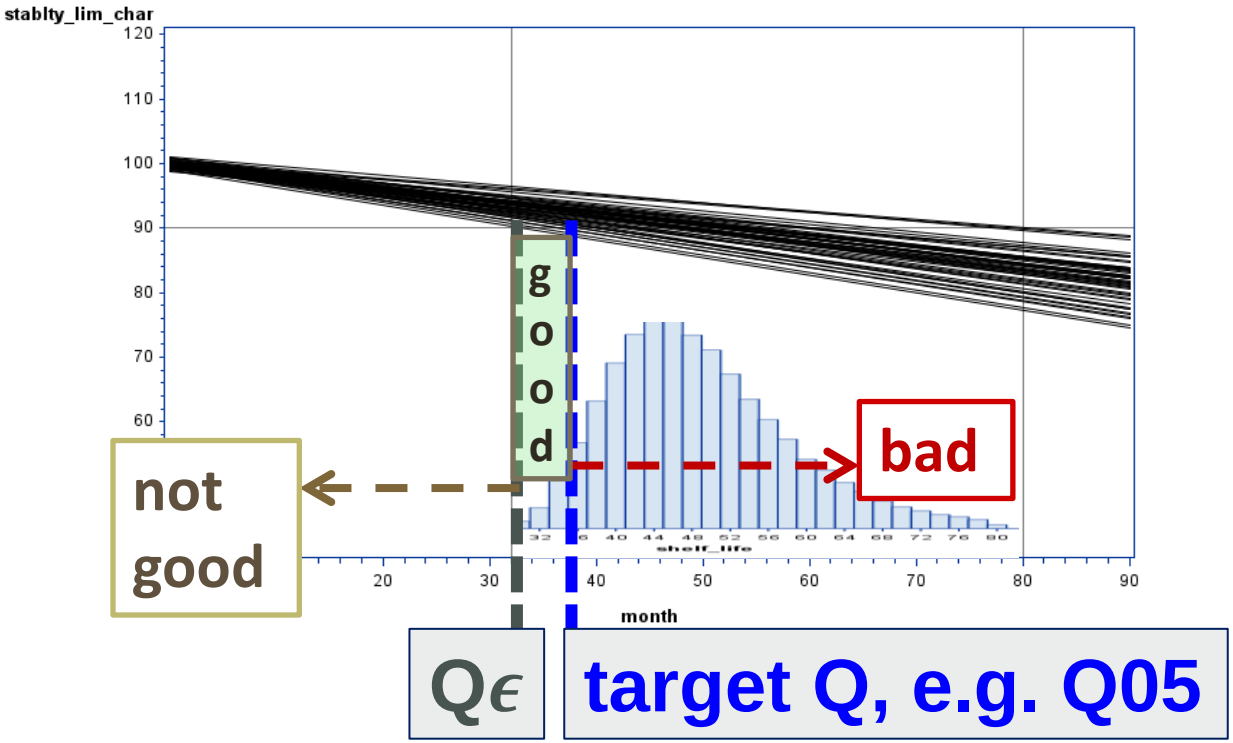
# Visualize Criteria

- Coverage




- Truncated Mean Square Prediction Error (MSPE)
  - Good: $\propto \sum I(\widehat{SL} \leq Q05)(\widehat{SL} - Q05)^2$
  - Bad: $\propto \sum I(\widehat{SL} > Q05)(\widehat{SL} - Q05)^2$

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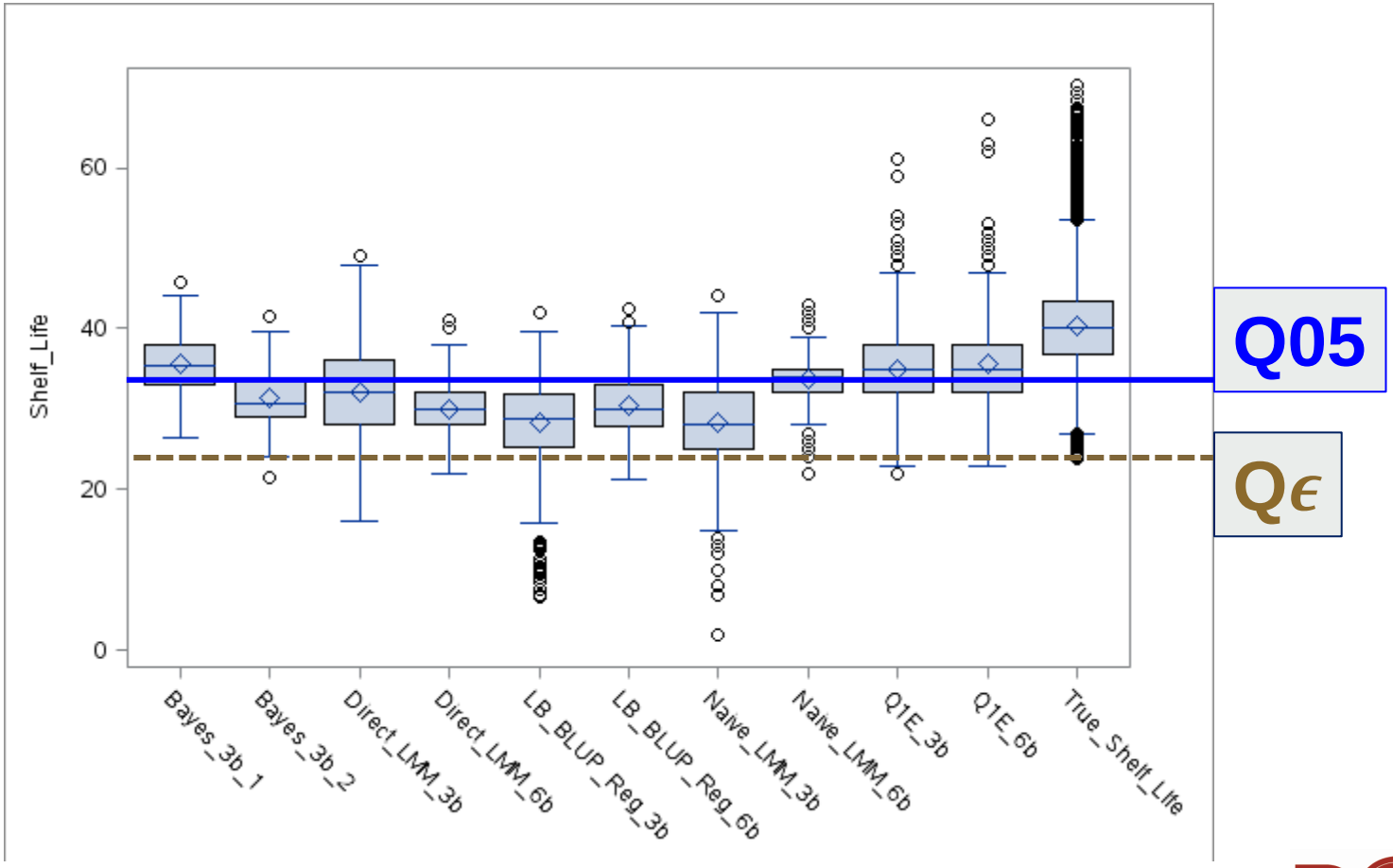
# What we know to date

- Simulation study, Stroup and Quinlan, 2015
- Characteristics drawn from
  - Alton, et al. 2013, survey of stability trial parameter estimates
  - Capen, et al. 2017, industry data provided to PQRI SSL WG
- Simulation Description
  - 1000 simulated trials with 3 batches and 1000 with 6 batches
  - $\beta_0 = 100, \beta_1 = -0.25, {\sigma_0}^2 = 0.5, {\sigma_1}^2 = 0.000625,\ \sigma^2 = 0.5, \sigma_{01} = 0$
  - Assume one assay per batch at each time of measurement
  - $\hat{S}$ computed from Q1E, naive LMM, LB BLUP, Direct and Bayes
  - **Plot** distribution of $\hat{S}$ relative to $Q05$ and $Q\epsilon$
  - **Table**
    - MS(prediction error)
    - "Coverage" – proportion $Q\epsilon < \hat{S} < Q05$

# What we know to date

- distribution of $\hat{S}$ by method and number of batches



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# What we know to date

- Performance of $\hat{S}$ by method and number of batches

| Method | Number Batches | MSPE | | | Coverage % |
|---|---|---|---|---|---|
| | | Good | Bad | Net* | |
| **Q1E** | 3 | 3.22 | 28.35 | -25.12 | 49 |
| | 6 | 2.73 | 35.78 | -33.04 | 42 |
| **Naive LMM** | 3 | 39.06 | 3.72 | 35.34 | 67 |
| | 6 | 2.17 | 8.30 | -6.14 | 64 |
| **LB BLUP** | 3 | 40.31 | 1.87 | 38.44 | 72 |
| | 6 | 11.61 | 2.93 | 9.38 | 83 |
| **Direct** | 3 | 14.27 | 16.64 | -2.36 | 60 |
| | 6 | 11.76 | 1.43 | 10.33 | 89 |
| **Bayes – Defn 1** | 3 | 1.06 | 26.24 | -25.18 | 31 |
| **Bayes – Defn 2** | 3 | 8.57 | 4.76 | 3.81 | 78 |

* Net MSPE should be positive and small

# Summary

- All future batches mandate $\Rightarrow$ predictor for $\hat{S}$
- Q1E Current Practice
  - Inconsistent with how data arise and mandated inference space
  - Small sample behavior disquieting
- Alternatives
  - LMM
  - But LMM with attention to mandated inference space
- Assessment of Alternatives
  - simulation
  - criteria – we use Good/Bad MSPE and “coverage” --- other ideas?
- With 3 batches
  - upper limit on ability to predict future performance
  - but LB BLUP and Bayes, Definition 2 show promise

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# Future Work

- More simulation scenarios
- Other Methods Under Consideration
  - Tolerance Interval
  - Refine BLUP and Bayes
  - Other Bayes Methods, e.g. Predicted Probability Distribution
- Eventual Goal: propose method(s)
  - that show consistently desirable behavior
  - can be implemented with available software
  - e.g all computations in this presentation used SAS® PROC GLIMMIX or PROC MCMC

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# References


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# Acknowledgements

| PQRI Stability Shelf-Life Working Group Membership (2017) | | |
|---|---|---|
| Member Name | | Affiliation |
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| Capen | Robert | CMC Statistics, Merck & Co., Inc., West Point, PA |
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| Patterson | Nate | Bayer U.S., Berkeley, CA |
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| Rajagopalan | Radhika | FDA/CDER/OPQ/OLDP/Quality Assessment Lead, Silver Springs, MD |
| Schwenke | Jim | Applied Research Consultants, New Milford, CT |
| Stroup | Walter | Statistics, University of Nebraska-Lincoln, Lincoln, NE |
| Ptukhina | Marina | Mathematics and Computer Science, Whitman College, Walla Walla, WA |

*All research work supported under the direction of PQRI*

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# That’s all - thanks

## Questions?

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