Proposed Methodology for Shelf Life Estimation

March 18, 2009

Michelle Quinlan, University of Nebraska-Lincoln
James Schwenke, Boehringer Ingelheim Pharmaceuticals, Inc.
Walt Stroup, University of Nebraska-Lincoln

Outline

- Product Quality Research Institute (PQRI) Stability Shelf Life Working Group
- Shelf Life Estimation
  - o ICH Guidelines
  - o Random batch analysis
  - o Proposed methodology
- Simulation Results
- Example using real-life data
- Future/Continued Research

Product Quality Research Institute (PQRI) Stability Shelf Life Working Group

- Objectives
  - o Investigate statistical methods for estimating shelf life which allow the sponsor to define and manage risk
  - o Assess alternative methods for estimating shelf life
  - o Enhance safety/efficacy of pharmaceutical products through accurate estimation of shelf life
- Research efforts include developing statistical methodology to directly estimate shelf life of pharmaceutical products

Shelf Life Estimation

- ICH Guidelines
  - Q1E states the purpose of a stability study is to establish

    "*a retest period or shelf life and label storage instructions applicable to all future batches manufactured and packaged under similar circumstances*"

Shelf Life Estimation

- ICH Guidelines
  - Test for equal slopes/intercepts among batches using $\alpha = 0.25$
  - No evidence of batch-to-batch variability: labeled shelf-life is the time the 95% one-sided lower (upper) confidence bound for mean degradation curve/stability limiting characteristic of drug product intersects lower (upper) specification limit
  - Evidence of batch-to-batch variability: shelf-life for each individual batch is computed and minimum of all shelf-lives is labeled shelf-life

Shelf Life Estimation

- Problems with ICH Guidelines
  - Shao & Chow (1994) conclude the minimum approach "lacks statistical justification"
  - Estimate obtained from pooling batches applies only to batches used in analysis; inference should be made to future batches

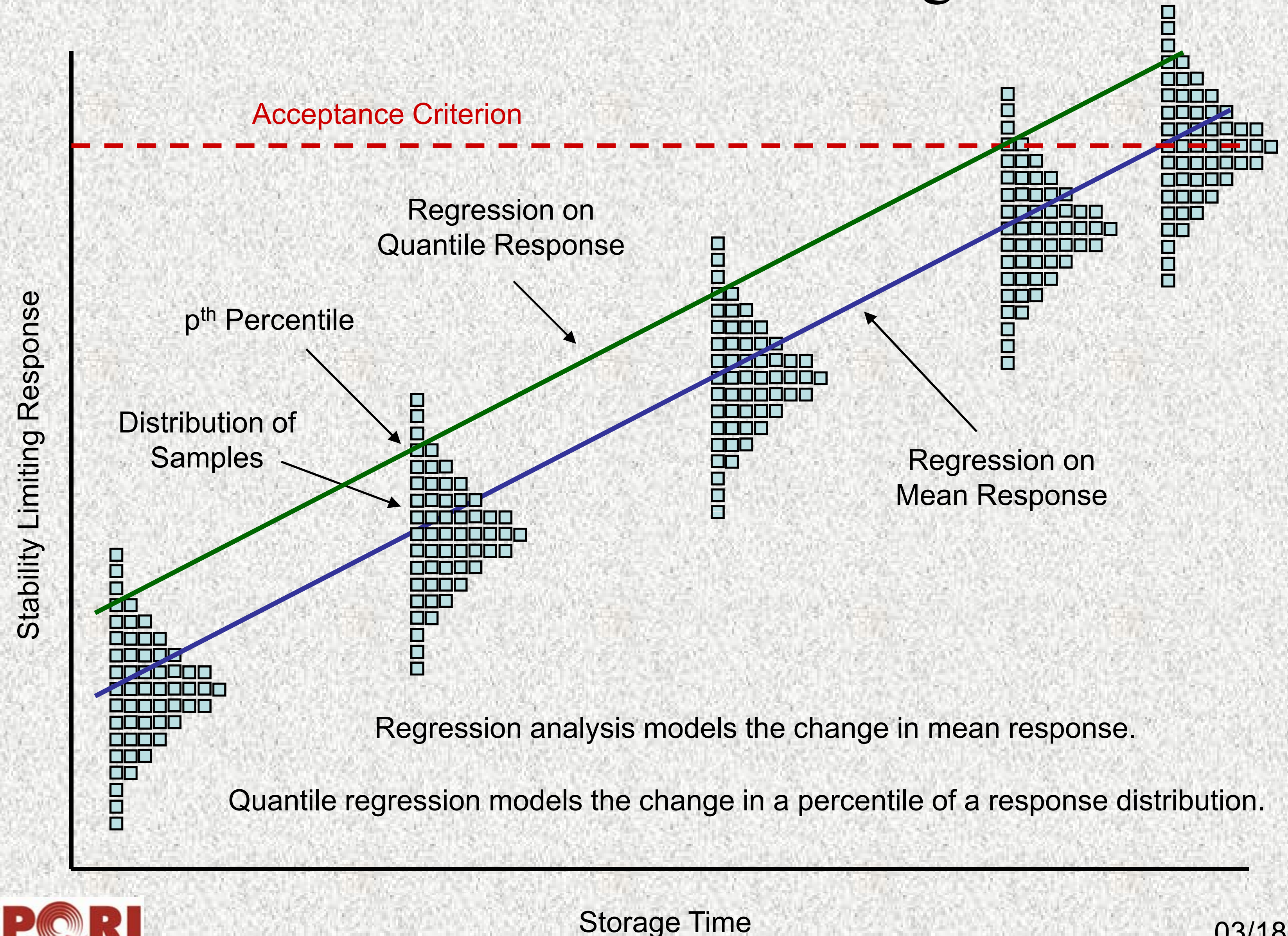
Random Batch Analysis

- Our proposed statistical analysis takes into account batch-to-batch variation via random batch effects
  - o Same approach by Chow & Shao (1991) for marketing stability studies
- By appropriately accounting for batch-to-batch variation, the question of batch "poolablity" is eliminated
- Including batch-to-batch variation allows for more straightforward estimation and interpretation of shelf life
- Inference can be made to future batches

Proposed Methodology

- Provides a consistent, flexible methodology for directly estimating shelf life
  - Consistent with how acceptance criteria is defined
  - Can be implemented using overall mean response or percentile of response distribution
  - Involves lower interval estimate on calibrated point
  - Examples presented are using overall mean response among batches of a pharmaceutical product

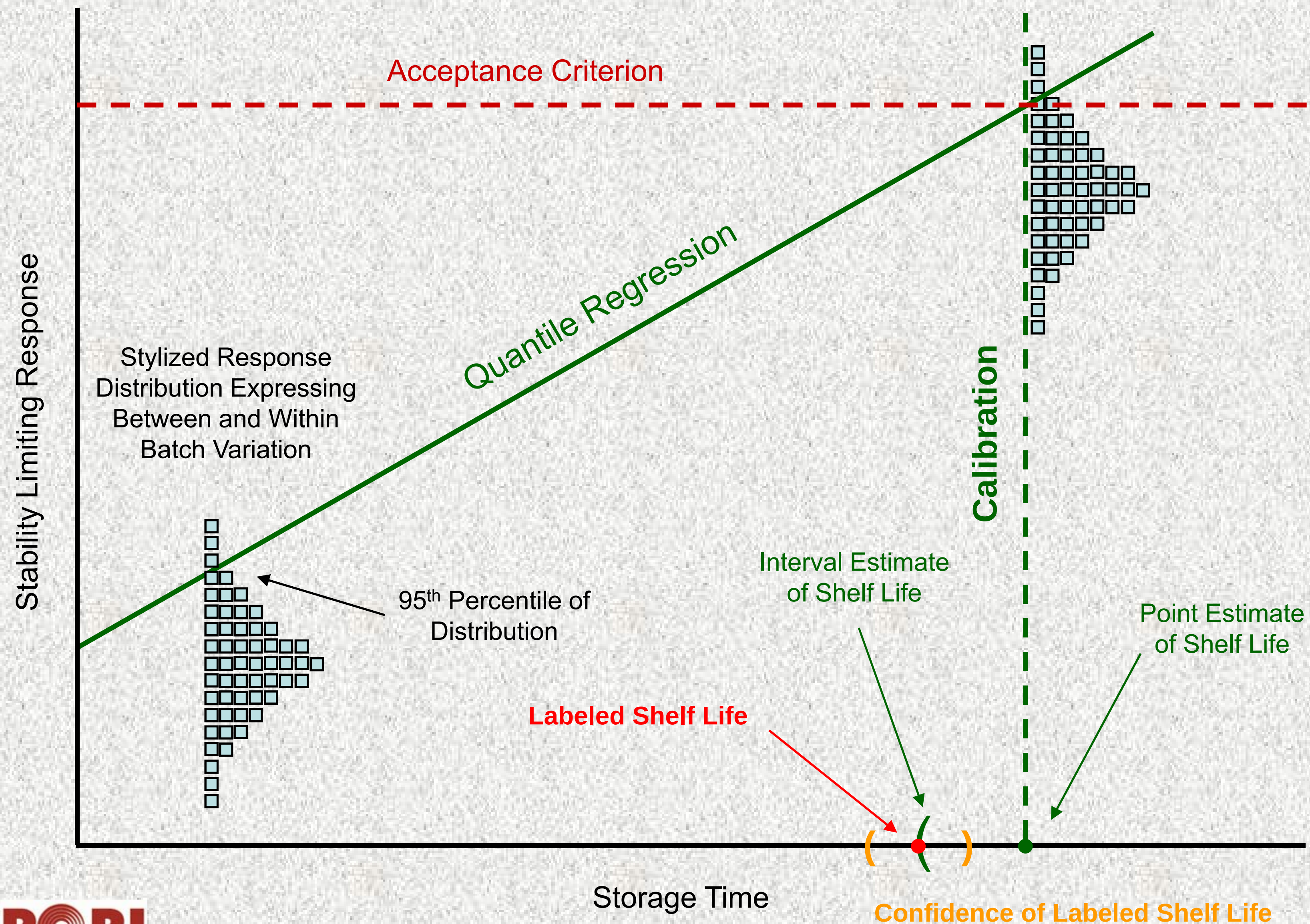
The Shelf Life Paradigm



Regression analysis models the change in mean response.

Quantile regression models the change in a percentile of a response distribution.

Proposed Shelf Life Estimation Procedure



PQRI Product Quality Research Institute

Proposed Shelf Life Estimation Procedure

- Use mixed model (random batch effects) on stability limiting response
  - Estimated shelf life is then "applicable to all future batches" (ICH Q1E)
- Estimated shelf life is storage time corresponding to the point where predicted mean (or quantile) response intersects specification limit or acceptance criteria
- Lower interval estimate is constructed around calibrated point to determine labeled shelf life
  - Similar to Shao & Chow's (1994) 1-α lower confidence bound for ε^{th} quantile of true shelf life

Proposed Shelf Life Estimation Procedure

- As added information on the quality of the labeled shelf life estimate, 2-sided interval estimate (e.g. CI, PI, TI) is obtained about labeled shelf life
  - o 2-sided interval estimate is a diagnostic tool
  - o Analogous to Chow's (2007) *safety margin* which provides useful information regarding drug safety beyond labeled shelf life
  - o Similar to Chow & Shao's (1991) tolerance correction to estimate the 95% lower bound for individual shelf lives

Interval Estimates on Calibrated Point

- 3 methods to obtain interval estimate about calibrated point:
  - 1) Using distribution of x_0
  - 2) Using distribution of estimated parameter values ($\hat{\beta}$)
  - 3) Reflection method
    - Equal to 1) in linear case
- Method 2 produces less conservative estimates (usually greater than or equal to other methods in linear case)

PQRI Product Quality Research Institute

Simulation Example

- Data simulated for 36 months using 3 and 6 batches
- Acceptance criteria is 95-105% of label claim
- Assay follows simple linear response decay
- Model: $y_{ij} = b_0 + batch_{0i} + (b_1 + batch_{1i})x_{ij} + \varepsilon_{ij}$

$batch_{0i} = random\ batch\ effect\ on\ intercept$

$batch_{1i} = random\ batch\ effect\ on\ slope$

$\varepsilon_{ij} = error\ associated\ with\ response\ for\ i^{th}\ batch,\ j^{th}\ month$

$\varepsilon_{ij} \sim N(0,\sigma_e^2) \quad batch_{0i} \sim N(0,\sigma_b^2) \quad batch_{1i} \sim N(0,\sigma_{b*m}^2)$

- NLMIXED was used to analyze mean response and is compared with ICH approach

PQRI Product Quality Research Institute

Simulation Results (3, 6 batches)
$\alpha = 0.05$

- Percentage of time true shelf life is captured (*labeled* ≤ *true*)
  - **ICH method: 98%, 99%**
  - **Mixed Model method: 98%, 95%**
- Percentage of time true shelf life is overestimated (*labeled* > *true*)
  - **ICH: 2%, 1%**
  - **Mixed Model: 2%, 5%**
- Average difference between true and estimated shelf life
  - **ICH: 4.7 months, 5.7 months**
  - **Mixed Model: 4.6 months, 2.4 months**

Simulation Results – 3 batches

True Shelf Life: *33.3* months

Method	Sim. #	Average	Avg. diff	Under %	Over %	Under diff	Over diff	Min	Max
ICH	1	28.6	-4.7	0.980	0.020	-4.8	0.8	21.7	35.0
ICH	2	28.6	-4.7	0.978	0.022	-4.8	0.9	20.5	35.6
ICH	3	28.6	-4.7	0.982	0.018	-4.8	1.2	20.5	35.9
ICH	4	28.7	-4.7	0.982	0.018	-4.8	0.6	22.0	35.1
ICH	5	28.6	-4.8	0.980	0.020	-4.9	0.6	22.7	35.1
LMM_B_hat	1	29.2	-4.2	0.965	0.035	-4.3	0.9	22.0	35.9
LMM_B_hat	2	29.1	-4.2	0.965	0.035	-4.4	1.0	20.7	36.6
LMM_B_hat	3	29.2	-4.2	0.966	0.034	-4.3	0.8	20.6	35.5
LMM_B_hat	4	29.2	-4.1	0.970	0.030	-4.3	0.8	18.6	36.4
LMM_B_hat	5	29.1	-4.3	0.969	0.031	-4.4	0.5	22.2	35.7
LMM_Reflect/x_0	1	28.8	-4.6	0.973	0.027	-4.7	0.7	21.3	35.6
LMM_Reflect/x_0	2	28.7	-4.6	0.972	0.028	-4.8	0.8	19.7	36.1
LMM_Reflect/x_0	3	28.8	-4.6	0.981	0.019	-4.7	0.9	20.4	35.2
LMM_Reflect/x_0	4	28.8	-4.5	0.982	0.018	-4.6	0.9	17.4	36.0
LMM_Reflect/x_0	5	28.7	-4.7	0.984	0.016	-4.7	0.5	22.0	35.0

Simulation Results – 6 batches

True Shelf Life: *33.3* months

Method	Sim. #	Average	Avg. diff	Under %	Over %	Under diff	Over diff	Min	Max
ICH	1	27.5	-5.8	0.997	0.003	-5.9	0.9	20.5	35.4
ICH	2	27.6	-5.7	0.998	0.002	-5.7	0.2	20.3	33.6
ICH	3	27.6	-5.7	0.999	0.001	-5.8	0.3	21.0	33.7
ICH	4	27.7	-5.7	0.999	0.001	-5.7	0.3	22.0	33.6
ICH	5	27.6	-5.7	0.998	0.002	-5.8	0.5	19.2	34.2
LMM_B_hat	1	30.9	-2.4	0.951	0.049	-2.6	0.6	26.6	36.2
LMM_B_hat	2	31.0	-2.3	0.948	0.052	-2.5	0.6	26.2	35.4
LMM_B_hat	3	31.0	-2.3	0.945	0.055	-2.5	0.7	25.8	36.2
LMM_B_hat	4	31.1	-2.3	0.941	0.059	-2.5	0.7	27.0	36.3
LMM_B_hat	5	31.1	-2.3	0.945	0.055	-2.5	0.7	27.0	35.9
LMM_Reflect/x_0	1	30.8	-2.6	0.961	0.039	-2.7	0.6	26.9	36.0
LMM_Reflect/x_0	2	30.9	-2.4	0.951	0.049	-2.6	0.5	26.5	35.2
LMM_Reflect/x_0	3	30.9	-2.4	0.949	0.051	-2.6	0.6	25.7	36.1
LMM_Reflect/x_0	4	30.9	-2.4	0.951	0.049	-2.6	0.6	26.9	36.1
LMM_Reflect/x_0	5	30.9	-2.4	0.952	0.048	-2.6	0.7	26.9	35.8

Simulation Results

- Adding more batches
  - **ICH method:**
    - **increases bias (farther away from true shelf life)**
    - **overestimation rate approaches 0**
  - **Mixed Model method:**
    - **decreases bias (closer to true shelf life)**
    - **overestimation rate approaches α**

- On average Mixed Model method produces longer, more accurate shelf life

Simulation Results
True Shelf Life: 33.3 months

- 3 batches: **ICH** and **Mixed Model** methods produce on average equal estimated shelf lives, but estimate is not good (<< true shelf life)
- 6 batches: **ICH method: 27.6 months**

  Mixed Model method: 30.9 months
- 9 batches: **ICH method: 26.9 months**

  Mixed Model method: 31.4 months
- 12 batches: **ICH method: 26.5 months**

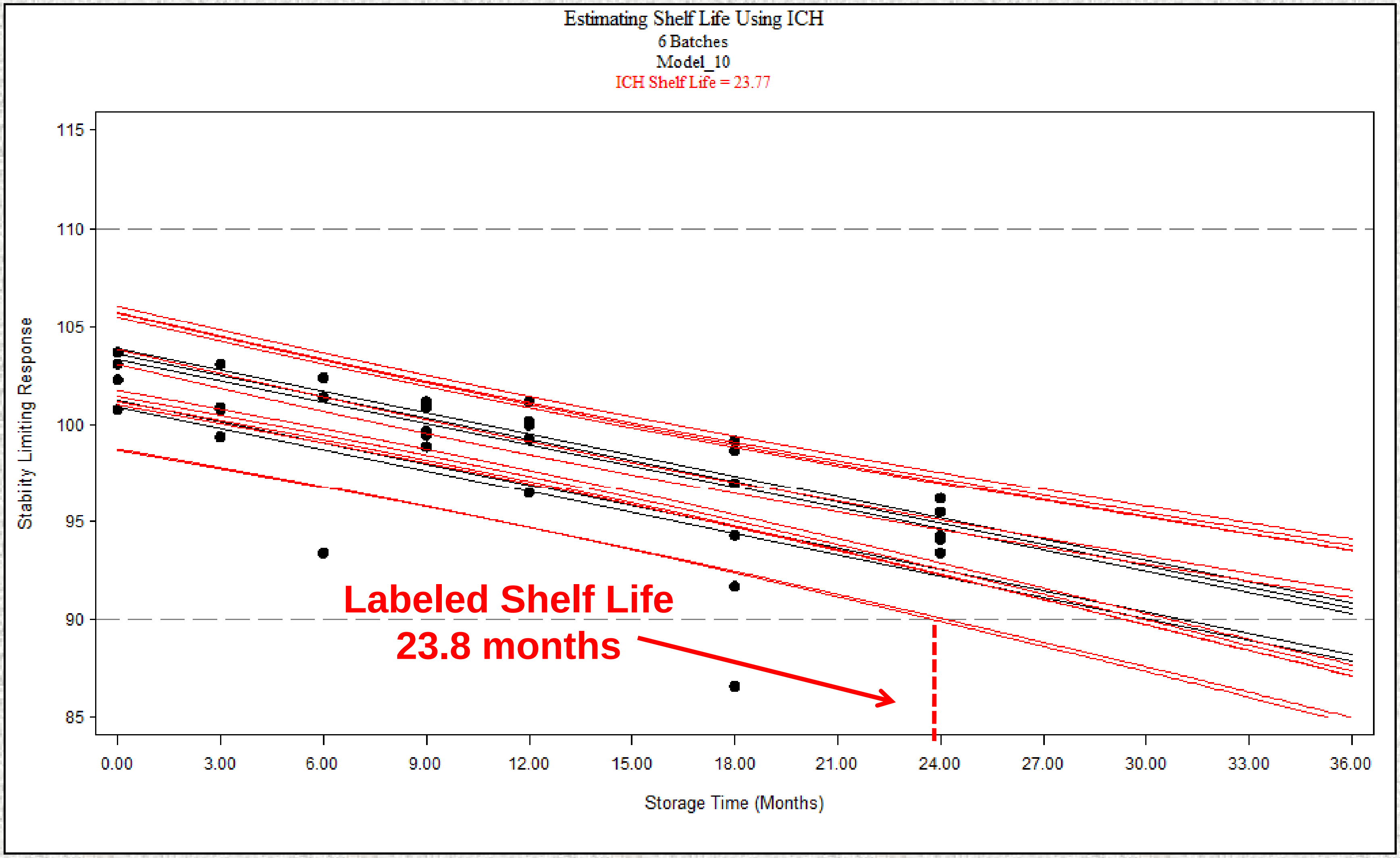
  Mixed Model method: 31.7 months
- Do we want an estimator whose bias increases as $n \to \infty$ (**ICH**) or whose bias $\to 0$ as $n \to \infty$ (**Mixed Model**) ???

PQRI Product Quality Research Institute

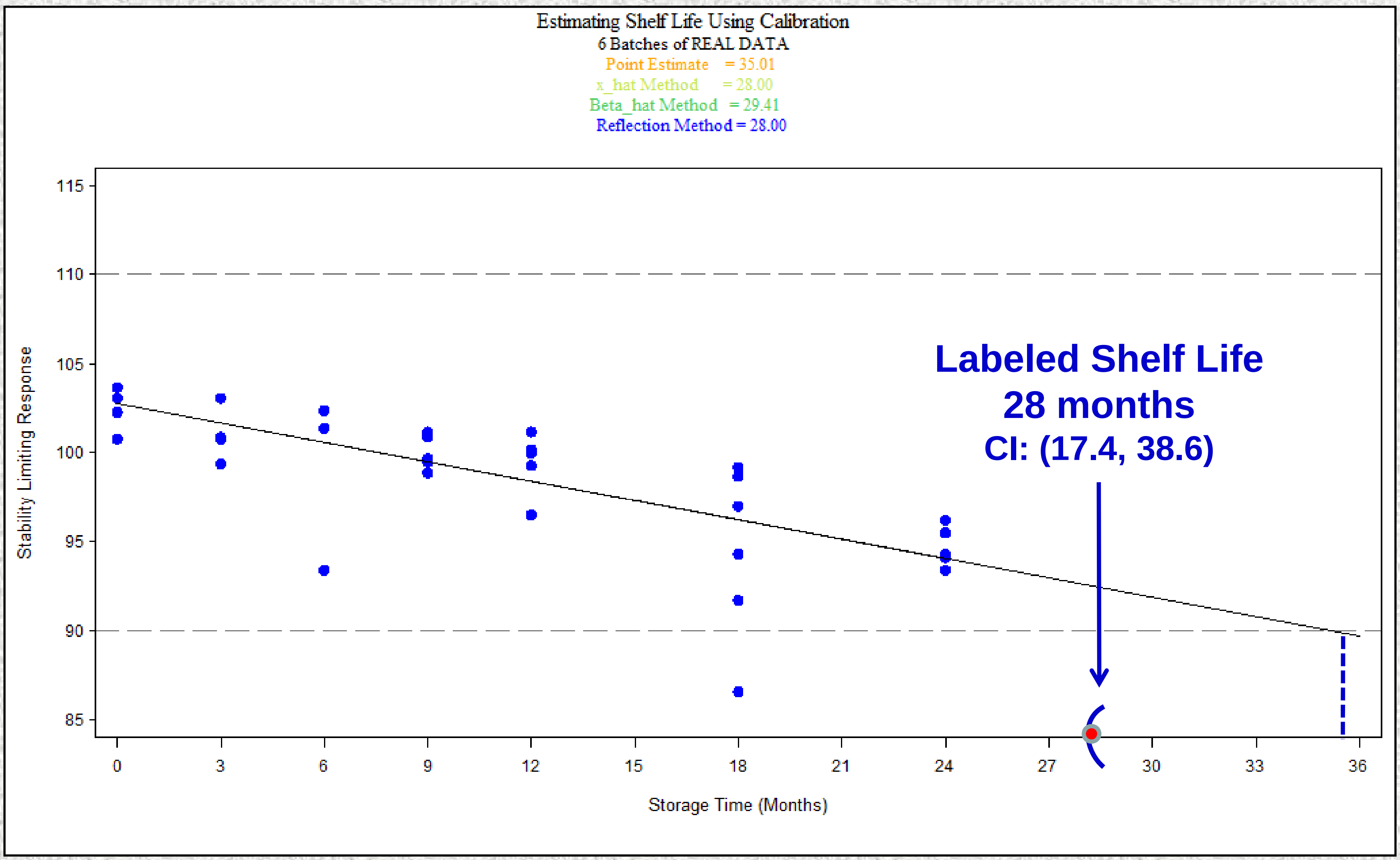
Example using ***real-life*** data

- Data:
  - Blinded
  - 24-month
  - assay response (% label claim)
  - specification limits 90-110%
  - 6 batches
- Shelf life estimate using ICH guidelines: 23.8 months
- Shelf life estimate using Mixed Model: 28 months

Example: real-life data (6 batches), ICH



Example: real-life data (6 batches), Mixed Model



PQRI Product Quality Research Institute

Future/Continued Research

- Develop theory/methodology for quantile regression with random batch effects to estimate shelf life
  - Model a quantile of response distribution instead of mean
- Determine robustness of proposed method to estimate shelf life using a limited number of months of real-life data
- Determine the optimal interval to construct around labeled shelf life
- Determine sampling distribution of shelf life estimates using ICH and proposed methodology

Acknowledgements

This research is funded through the

PQRI Stability Shelf Life Working Group

PQRI is the Product Quality Research Institute,
Arlington, Virginia

References

- Chow, S.C. (2007). Statistical Design and Analysis of Stability Studies. Chapman & Hall/CRC, Boca Raton, FL.
- Chow, S.C. and Shao, J. (1991). Estimating Drug Shelf-Life with Random Batches, *Biometrics*, 47: 1071-1079.
- ICH Q1E: www.ich.org
- Shao, J. and Chow, S.C. (1994). Statistical Inference in Stability Analysis, *Biometrics*, 50: 753-763.