Proposed Methodology for Shelf Life Estimation

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Outline

- Product Quality Research Institute (PQRI) Stability Shelf Life Working Group
- Shelf Life Estimation
- Simulation Results
- Example using real-life data
- Future/Continued Research

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

- Objectives
  - Investigate statistical methods for estimating shelf life which allow the sponsor to define and manage risk
  - Assess alternative methods for estimating shelf life
  - 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*"
  - 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 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
- 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

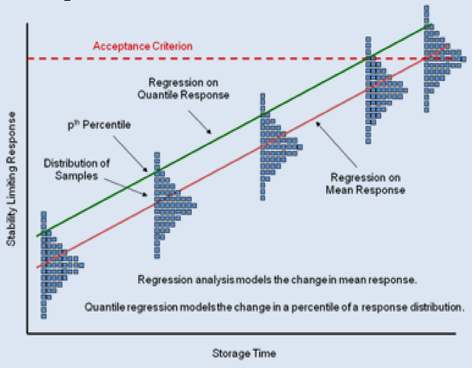
Random Batch Analysis

- Proposed statistical analysis takes into account batch-to-batch variation via random batch effects
- By appropriately accounting for batch-to-batch variation, the question of batch "poolability" is eliminated
- Including batch-to-batch variation allows for more straightforward estimation and interpretation of shelf life
- Inference can be made to future batches

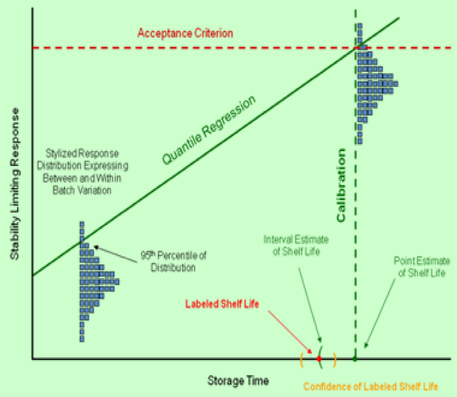
Proposed Methodology

- 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
- Use mixed model (random batch effects) on stability limiting response
  - Estimated shelf life is then "*applicable to all future batches*" (ICH Q1E)
  - Involves lower interval estimate on calibrated point

Proposed Shelf Life Estimation Procedure



Proposed Shelf Life Estimation Procedure



- 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
- 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
  - 2-sided interval estimate is a diagnostic tool
  - Analogous to Chow's (2007) *safety margin* which provides useful information regarding drug safety beyond labeled shelf life
  - 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
- Method 2 produces less conservative estimates (usually $\geq$ other methods in linear case)

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

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

  $\varepsilon_{ij} \sim N(0,\sigma_\varepsilon^2)$ $batch_{0i} \sim N(0,\sigma_b^2)$ $batch_{1i} \sim N(0,\sigma_{b*m}^2)$
- NLMIXED was used to analyze mean response and is compared with ICH approach

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

- Percentage of time true shelf life is captured (*labeled* $\leq$ *true*)
  - **ICH method:** 98%, 99%
  - **Mixed Model method:** 98%, 95%
- 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 – 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

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

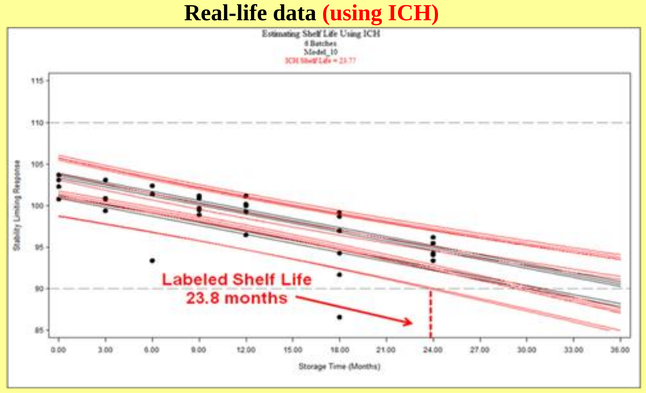
Simulation Results, True Shelf Life: 33.3 months

- 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**) ???

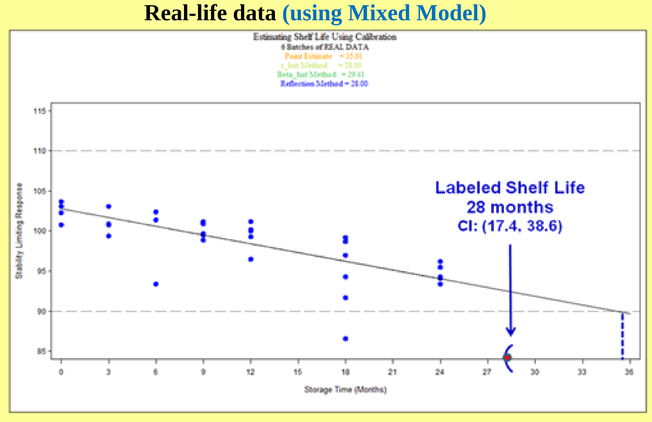
Example using 6 batches of *real-life* data

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

Real-life data (using ICH)



Real-life data (using Mixed Model)



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 estimates using ICH and proposed methodology

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