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

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

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-sided lower confidence bound for 5th quantile of true shelf life
  - As additional 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 (\( j \))
  - 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: \( y = \beta_0 + \beta_1 x + \epsilon \)
  - Linear/batch effect on intercept
  - Random batch effect on intercept
- 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%, 95%
  - 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

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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 0
- 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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