Direct Approaches to Shelf Life Estimation

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Outline

- Shelf Life Estimation
- Indirect vs. Direct Methods
- Proposed Shelf Life Estimation Procedure
  - Quantile Regression
  - Calibration
- Quantile Regression in Nlmixed
  - Simulation Results
- Conclusions
Shelf Life Estimation

- Intention is to provide a storage time during which it is ensured a drug product (stability limiting characteristic) remains within specification.
- Method for estimating shelf life should be consistent with Quality by Design (QbD) initiative.
- Current method proposed by ICH Q1E is to base shelf life estimate on 95% confidence interval for mean.
  - Gives no guidance regarding individual test results.
- Estimate should reflect future batch performance.

Indirect vs. Direct Methods

- ICH approach estimates shelf life indirectly by interval estimate on the mean.
- It is unclear if this approach captures the target probability.
  - Does a high proportion of product meet specification?
  - Future batch results are not addressed.
- Research is being conducted to determine a consistent, flexible methodology for directly estimating shelf life.
  - Consistent with how acceptance criteria is defined.
  - Appropriate for modeling percentile response and overall mean response.
  - Estimate of shelf life is where an acceptably high proportion of product meets specification.
Proposed Shelf Life Estimation Procedure

- Proposed methodology is not an example of QbD
- Methodology addresses and allows for QbD philosophy
  - Utilizes all response data to directly estimate shelf life
  - Does not rely on worst batch scenario
  - Rewards for including additional batches
  - Provides more information about stability process
    - Models either mean or percentile response
    - Directly models between batch variation
Quantile Regression

- Quantile regression changes the focus of model from expected value of mean to a percentile of response distribution
- Allows relationship between x and y to change depending on quantile
- Relaxes assumptions of Normality and homoscedasticity
- Seeks to minimize the mean weighted distance from observations to estimated quantile
- Confidence intervals are constructed based on asymptotic or bootstrap methods
Quantile Regression

- Benefits over regression on mean when distribution is skewed
- Quantiles not as influenced by outliers
- Quantiles are monotone equivariant, unlike ordinary linear regression
- Can test for difference in slopes across quantiles

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Quantile Regression

- Estimated shelf life is the time when estimated quantile intersects specification limit
- SAS® Proc Quantreg
  - Models response using weighted loss function dependent on quantile
  - Does not allow for random batch effects (inference to entire population of batches)
- Methods using SAS® Nlmixed to implement quantile regression are discussed later

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Calibration

- Statistical calibration (inverse regression) techniques are used to directly estimate true shelf life where estimated quantile intersects specification limit.
Proposed Shelf Life Estimation Procedure

- 95th Percentile of Distribution
- Acceptance Criterion
- Storage Time
- Stability Limiting Response
- Quantile Regression
- Calibration
- Point Estimate of Shelf Life
- Interval Estimate of Shelf Life
- Calibration

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- Statistical calibration (inverse regression) techniques are used to directly estimate true shelf life where estimated quantile intersects specification limit.
- Calibrated estimate of shelf life is an estimate with uncertainty, thus a lower interval estimate is obtained as a conservative estimate of shelf life.

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**Proposed Shelf Life Estimation Procedure**

- **95th Percentile of Distribution**
- **Acceptance Criterion**
- **Storage Time**
- **Stability Limiting Response**
- **Quantile Regression**
- **Calibration**
- **Point Estimate of Shelf Life**
- **Interval Estimate of Shelf Life**
- **Claimed Shelf Life**

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- Lower interval (confidence, prediction, or tolerance) estimate around calibrated point estimate is the claimed shelf life.

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**Proposed Shelf Life Estimation Procedure**

- **95th Percentile of Distribution**
- **Acceptance Criterion**
- **Stability Limiting Response**
- **Quantile Regression**
- **Calibration**
  - **Point Estimate of Shelf Life**
  - **Interval Estimate of Shelf Life**
  - **Confidence of Claimed Shelf Life**

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- Calibrated estimate of shelf life is an estimate with uncertainty, thus a lower interval estimate is obtained as a conservative estimate of shelf life.
- Lower interval (confidence, prediction, tolerance) estimate around calibrated point estimate is the claimed shelf life.
- As information on the quality of the claimed shelf life estimate, a two-sided interval estimate is obtained about the claimed shelf life.

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Quantile Regression in Nlmixed

- Methods involve specifying distribution function in Nlmixed
  - Method #1: Noncentral t-distribution (NCT) - noncentrality parameter is $p\%$ of expected mean
  - Method #2: NCT - first estimate quantile then perform linear regression on estimates
  - Method #3: NCT - noncentrality parameter is mean plus $\text{probit}(p) \ast \text{se}$
  - Method #4: Distribution of sample quantile (Hao and Naiman)
    * Approximately normal with mean $\mu + \text{probit}(p) \ast \sigma$ and variance
    $\frac{p(1-p)}{n} \frac{1}{f(Q')^2}$
  - Method #5: NCT - use weights based on specific quantile

Simulation Results

- Methods #2, 5 perform best overall for estimating intercept and slope closest to true parameters
- Results indicate methods are not sensitive to sample size, methods work well even for small $n$
- Results using Nlmixed will not match Quantreg due to differences in optimization algorithms
  - Quantreg uses linear programming methods (simplex, interior point, or smoothing)
  - Nlmixed uses convergence algorithms such as Quasi-Newton

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Conclusions

- Indirect methods focus on mean rather than individual test results meeting specification
- Methodology is being developed to directly estimate shelf life using proposed procedure
- Direct methods (quantile regression, calibration) focus on percentile of distribution and parameter of interest
  - Consistent with how acceptance criteria is defined
- Future research will be conducted to finalize a method for estimating shelf life using quantile regression with random batch effects together with calibration

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References