Direct Approach To Shelf Life Estimation

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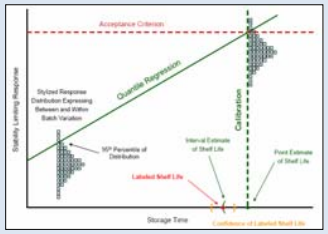
Shelf Life Estimation

- 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



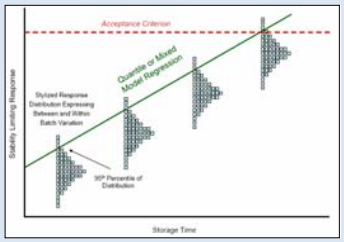
- Methodology addresses and allows for QbD philosophy
  - Utilizes all response data to directly estimate shelf life
    - Does not rely on worst batch scenario
    - Rewards for including additional batches
  - Provides more information about stability process
    - Models either mean or percentile 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
  - 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:
  - Can be used when distribution is skewed
  - Allows relationship between x and y to change depending on the quantile
  - Quantiles not as influenced by outliers
  - Quantiles are monotone equivarient, unlike ordinary linear regression
  - Can test for difference in slopes across quantiles
- Estimated shelf life is the time when estimated quantile intersects specification limit
- SAS® Proc Quantreg
  - Models response using weighted loss function dependent on the quantile
  - Does not allow for random batch effects (inference to entire population of batches)



Calibration

- 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
- 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

Quantile Regression in NLMIXED

- Methods involve specifying distribution function in NLMIXED (method's 1, 2, 3, 5 based on noncentral t-distribution of a percentile)
  - 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 probit(*p*)*se
  - Method #4: Distribution of sample quantile (*Hao* and *Naiman*)
    - Approximately normal with mean μ+probit(*p*)*σ and variance

$$\frac{p(1-p)}{n} * \frac{1}{f(Q^p)^2}$$

  - Method #5: NCT - use weights based on specific quantile
  - Method #6: MIXED using weight statement

Simulation Results

- Methods #2, 5, 6 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
  - Methods do not perform as well for extreme quantiles
- Results using NLMIXED will not match Quantreg due to differences in optimization algorithms
  - Quantreg uses linear programming methods (simplex, interior point, smoothing) to minimize weighted absolute sum of squares
  - NLMIXED uses convergence algorithms (such as Quasi-Newton) based on likelihood function

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

PQRI Stability Shelf Life Working Group

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