

# Direct Approaches to Shelf Life Estimation

Michelle Quinlan<sup>1</sup>, James Schwenke<sup>2</sup>, Walt Stroup<sup>1</sup>

<sup>1</sup>University of Nebraska-Lincoln

<sup>2</sup>Boehringer Ingelheim Pharmaceuticals, Inc.



University of Nebraska  
Department of Statistics

## 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

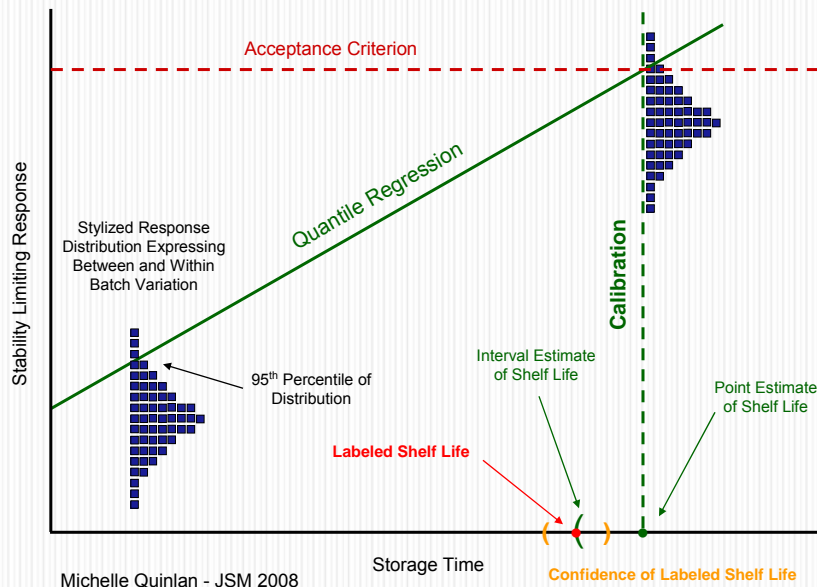
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## Indirect vs. Direct Methods

- ❑ 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

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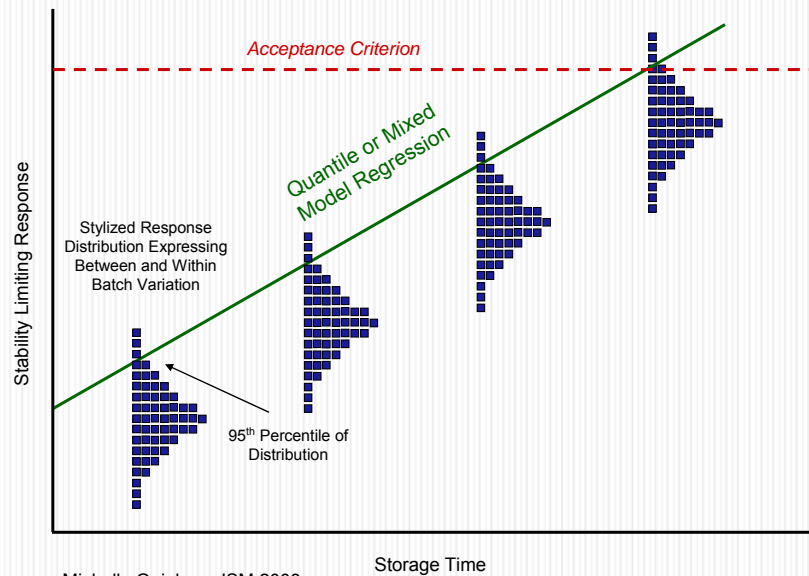
## Proposed Shelf Life Estimation Procedure



## 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

## Proposed Shelf Life Estimation Procedure



## 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

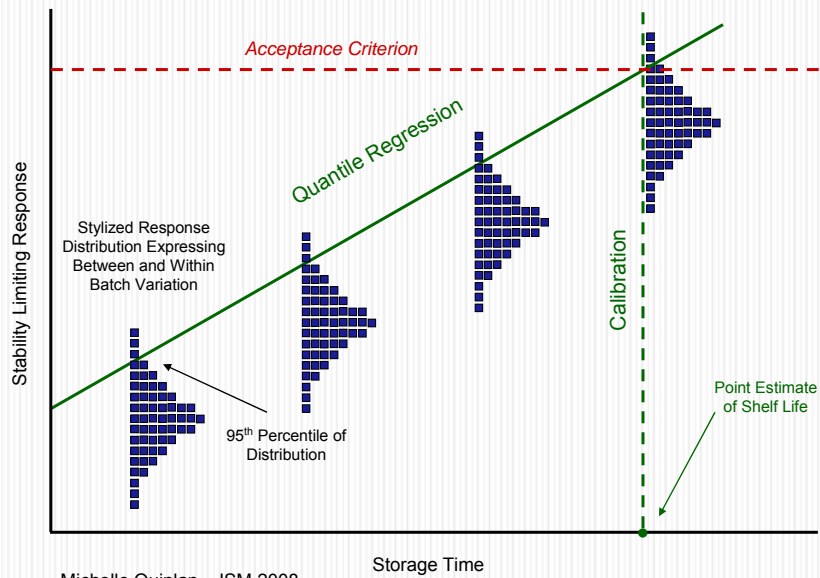
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## Quantile Regression

- ❑ Estimated shelf life is the time when estimated quantile intersects specification limit
- ❑ SAS<sup>®</sup> 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<sup>®</sup> Nlmixed to implement quantile regression are discussed later

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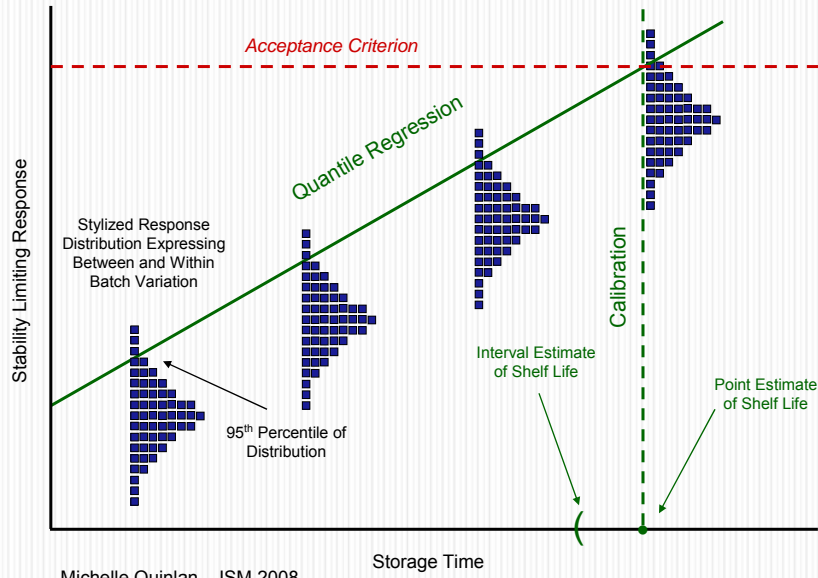
## Proposed Shelf Life Estimation Procedure



## Calibration

- Statistical calibration (inverse regression) techniques are used to directly estimate true shelf life where estimated quantile intersects specification limit

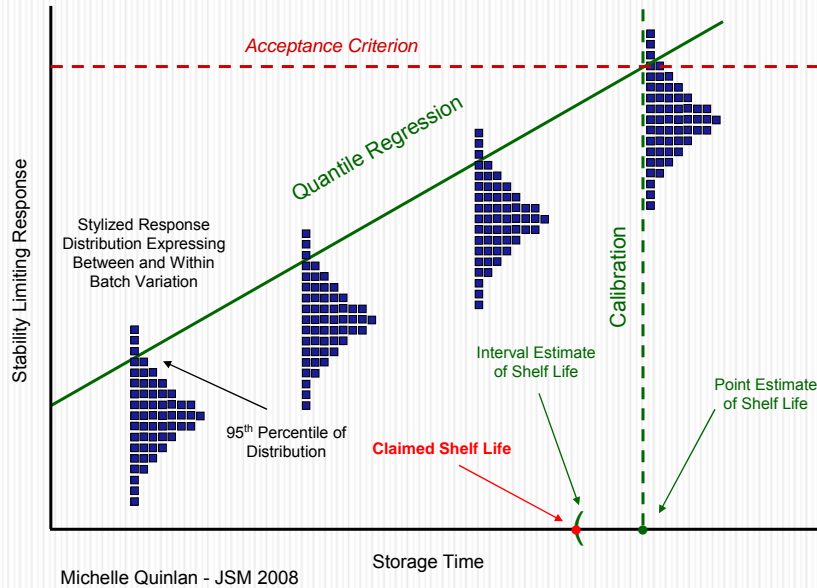
## Proposed Shelf Life Estimation Procedure



## 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

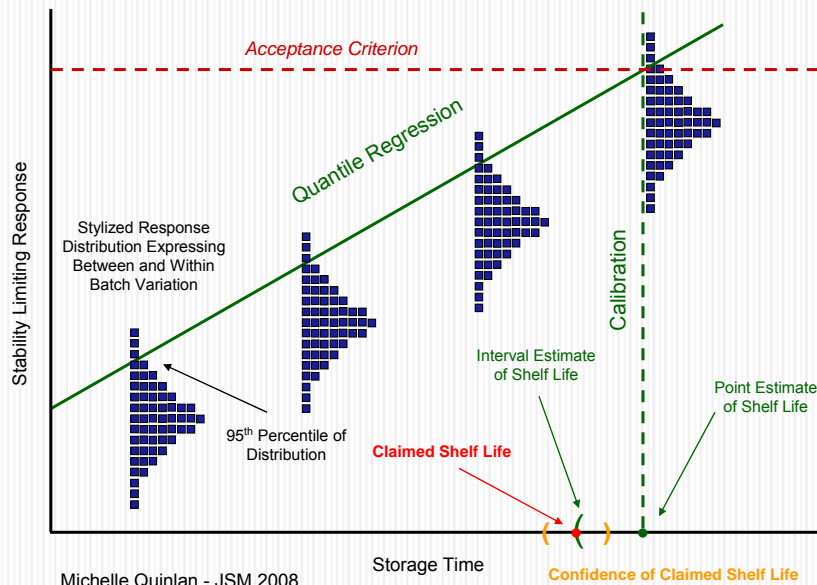
## Proposed Shelf Life Estimation Procedure



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## Proposed Shelf Life Estimation Procedure



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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
- ❑ 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 #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  $\text{probit}(p) * \text{se}$
  - Method #4: Distribution of sample quantile (*Hao and Naiman*)
    - Approximately normal with mean  $\mu + \text{probit}(p) * \sigma$  and variance

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

- Method #5: NCT - use weights based on specific quantile

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## 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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