# Estimating Shelf Life Using Quantile Regression with Random Batch Effects

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# Outline

- PQRI Stability Shelf Life Working Group
- Shelf Life Estimation
- Mean: Fixed vs. Random Batches
- Quantile Regression: Fixed vs. Random Batches
- Ad hoc methods for MMQR (Mixed Model Quantile Regression)
- Example: Shelf Life Estimation Methods
- Future/Continued Research

# PQRI SSL Working Group

- Late 2006 Product Quality Research Institute (PQRI) Stability Shelf Life (SSL) Working Group was established
  - Address issues related to current shelf life estimation procedures
  - Assess alternative methods
  - Enhance safety, efficacy of pharmaceutical products
  - Investigate statistical methods for estimating shelf life which allow individual companies to define/manage risk

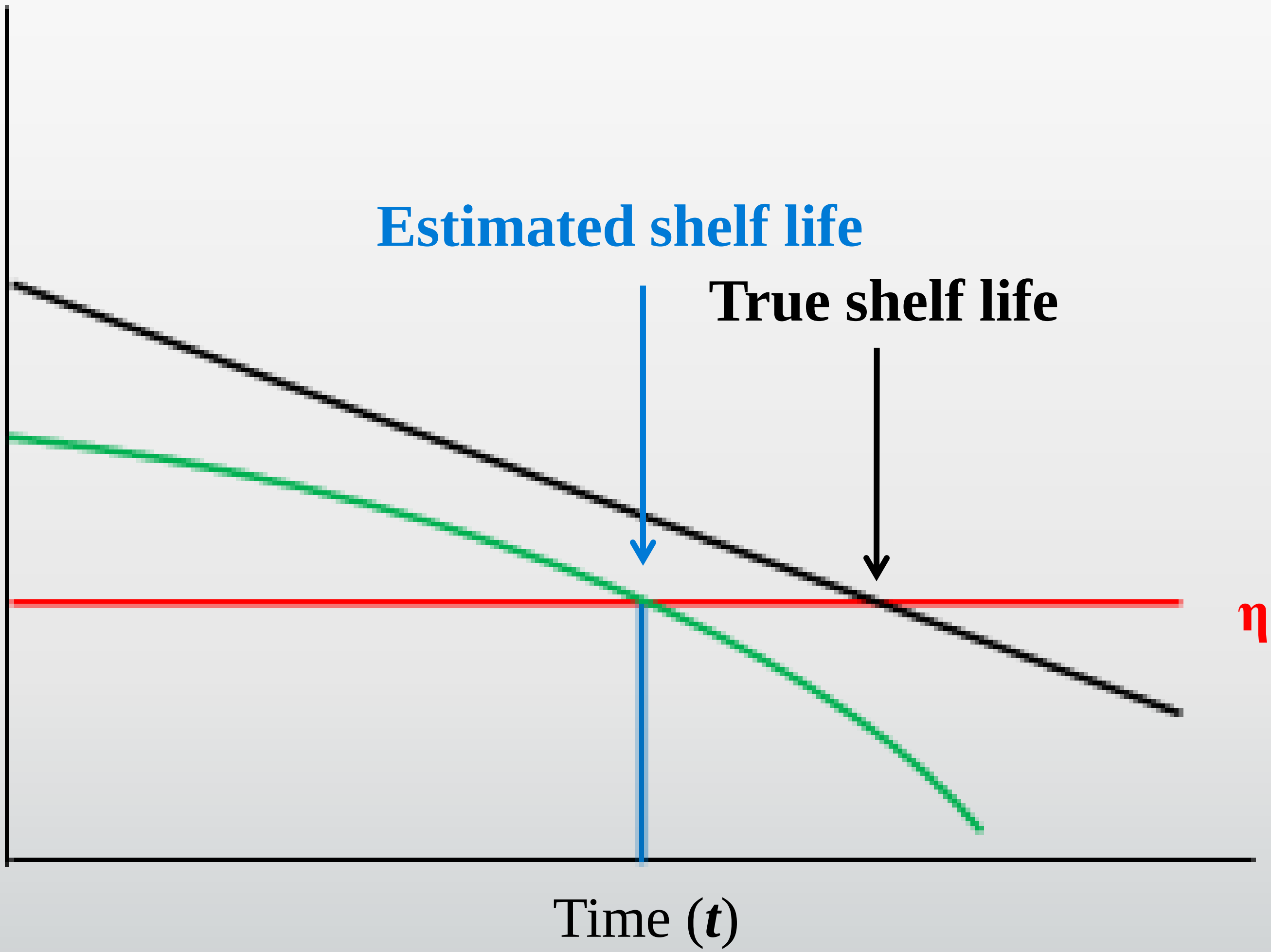
# Shelf Life

- 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*"

- *Shelf life*
  - Length of time defined quality of the product is expected to remain within approved specifications, provided it is stored under specified conditions (ICH Q1A (R2))

# Shelf Life Estimation



# Shelf Life Estimation: ICH Guidelines

- ICH guidelines suggest testing for batch poolability using $\alpha = 0.25$
  - "Poolability" means can we simplify

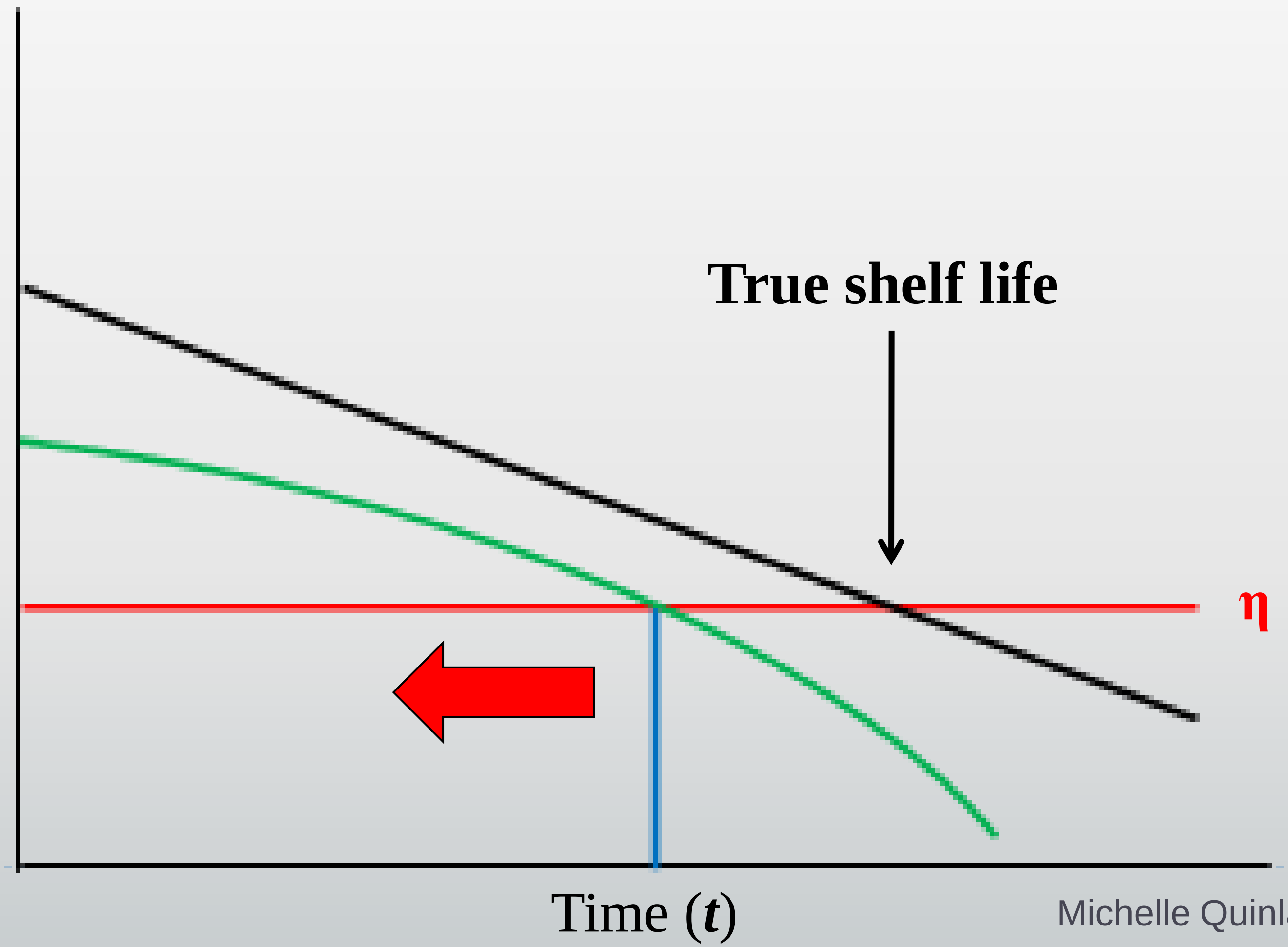
$$y_{ij} = \beta_{0i} + \beta_{1i} x_{ij} + e_{ij}$$

$$\text{to} \quad y_{ij} = \beta_0 + \beta_1 x_{ij} + e_{ij} \ ?$$

- **YES** → Use all data to compute CI for mean
- **NO** → Use worst batch to estimate shelf life

# Adding More Batches…

- Harder to pool using **ICH** (batches fixed, model mean)
  → shelf life based on worst batch



# Fixed vs. Random Batches

- ICH guidelines address batch-to-batch variability via tests for poolability treating batches as fixed
  - Inference applies only to batches in analysis
- Random batches → more appropriate
  - Eliminates question of batch poolability
  - Straightforward estimation and interpretation of shelf life
  - Inference can be made to future batches

# Simulation Results for Mean: ICH vs. LMM

True Shelf Life: 33.33 months

- ***3 batches*:**

| | Not Poolable | Poolable |
|---|---|---|
| **% of runs:** | **94.2%** | **5.8%** |
| **Average Estimate:** | **28.5 (24.8, 32.1)** | **31.7 (28.5, 34.5)** |
| | **27.6 (23.0, 31.8)** | **30.7 (27.8, 33.5)** |
| **Underestimate:** | **99%** | **80%** |
| | **99%** | **94%** |

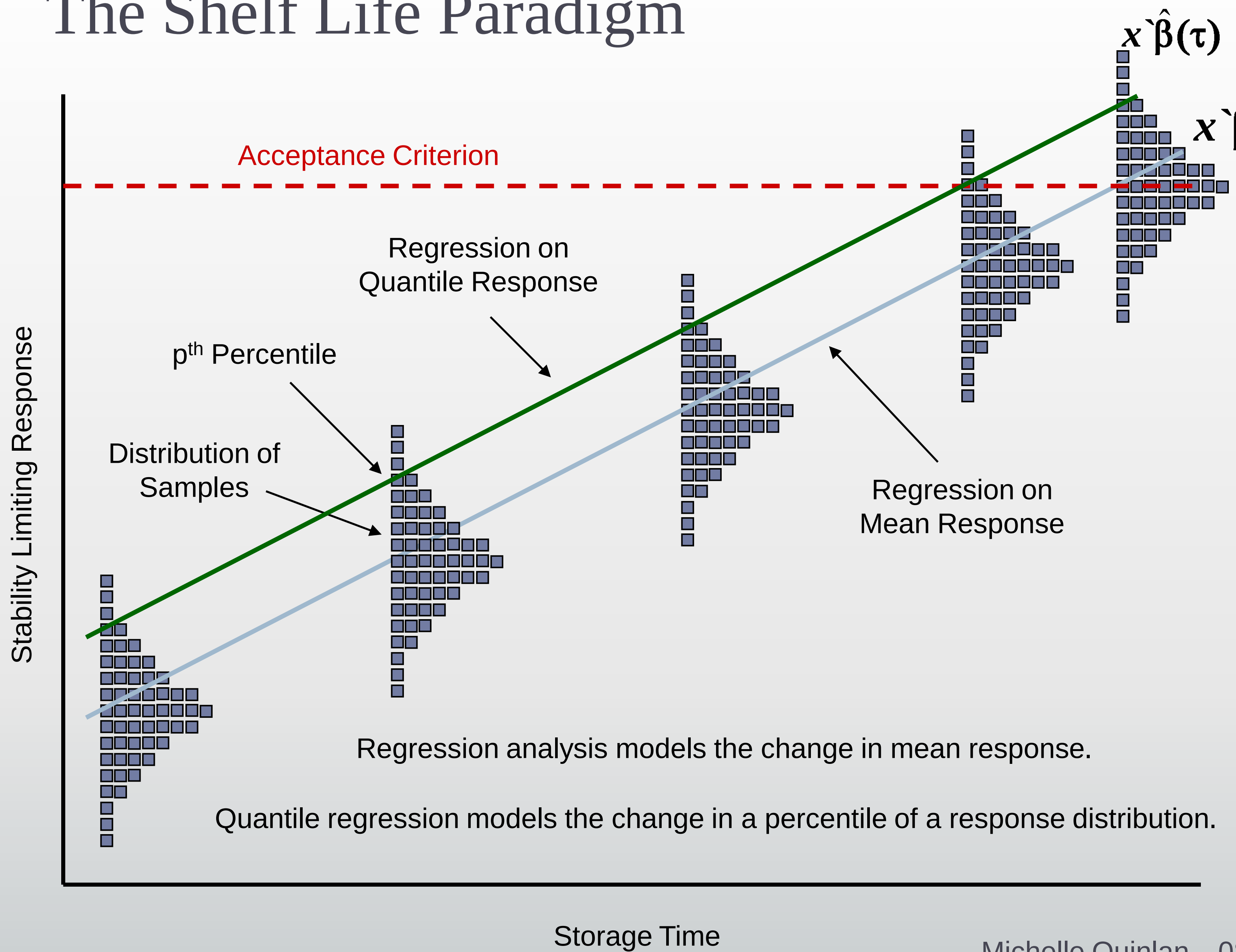
- ***6 batches*:**

| | Not Poolable | Poolable |
|---|---|---|
| **% of runs:** | **99.5%** | **0.5%** |
| **Average Estimate:** | **27.5 (24.5, 30.5)** | **32.1 (30.4, 33.9)** |
| | **30.6 (28.2, 33.0)** | **32.0 (30.3, 33.5)** |
| **Underestimate:** | **99%** | **82%** |
| | **97%** | **82%** |

# Mean or Quantile?

- Labeled Shelf Life using ICH guidelines:
  - "*provides the consumer the confidence that the drug product will retain its identity, strength, quality, and purity…*" (Chow, 2007)
    - Does modeling the mean provide this confidence?
  - No indication whether individual dose will stay within acceptance criteria
  - Under normality, implies only 50% remains within specification
  - Target may be quantile instead of mean

# The Shelf Life Paradigm




Regression analysis models the change in mean response.

Quantile regression models the change in a percentile of a response distribution.

# Estimating a Quantile: Quantile Regression

- Extends regression on mean to regression on a quantile of response distribution
- Minimize asymmetrically weighted sum of absolute errors

$$\min_{\beta} \sum_{i=1}^{n} \rho_{\tau} \; y_i - x_i`\beta(\tau)$$

where $\rho_{\tau}(u) = u(\tau - I(u < 0)), \tau \in (0,1)$

- Implemented using linear programming algorithms
  - Simplex
  - Interior point
  - Smoothing

# Quantile Regression with Fixed Effects
## ICH poolability criterion + SAS® Proc Quantreg

(True Shelf Life: 29.97 months, Quantile = 0.20)

| | Not Poolable | Poolable |
|---|---|---|
| ***3 batches*:** | | |
| **% of runs:** | **91.9%** | **8.1%** |
| **Average Estimate:** | **21.7 (14.5, 27.5)** | **28.1 (24.7, 31.6)** |
| **Underestimate:** | **99%** | **80%** |
| ***6 batches*:** | | |
| **% of runs:** | **99.6%** | **0.4%** |
| **Average Estimate:** | **20.7 (15.6, 25.8)** | **30.3 (28.4, 31.8)** |
| **Underestimate:** | **100%** | **35%** |

# Quantile Regression with Random Effects

- Reasonable to suspect fixed vs. random issues exist with QR
- Theory and methodology have been developed for
  - Modeling mean with random effects (PROC MIXED)
  - Modeling quantile with fixed effects (PROC QUANTREG)
- To complete the picture, method is needed to model a quantile with random batch effects
- Main objective:
  - Determine how $Zu$ in $y = X\beta + Zu + e$ can be integrated into quantile regression asymmetrically weighted loss function

# Theory/Methodology for MMQR

- Koenker (2005) views random effects model as penalized least squares model
  - Random effects "estimators" viewed as modifications of fixed effects shrunk toward zero according to penalty term
- Given the model $y = X\beta + Z\alpha + u,$ quantile regression estimators using penalized least squares minimize

$$\sum_{i} \sum_{j} \rho_{\tau} \quad y_{ij} - x_{ij}\beta - \alpha_{i} \quad + \lambda \sum_{i} | \alpha_{i} |$$

- Questions to address
  - How to determine $\lambda$?
  - What is the relationship between $\lambda$ and variance components?

# Ad Hoc Methods for MMQR

- Many ways to address MMQR
  - Some methods do not converge or produce unrealistic estimates
- Reasonable methods:
  - Estimate quantile then perform linear regression
  - Specify mean as *predicted value* + $\Phi(p)$**se*
  - Distribution of sample quantile (*Hao & Naiman*)
  - Specify weights based on quantile
  - Use only parts of the data based on quantile
  - Model the mean and estimate quantile (TI approach)

# Example SAS® Code for Ad Hoc Methods

- Using NLMIXED:

```
data data; set data;
    check=&int+&slope*month+probit(&q)*sqrt(&var_int+&var_slope+&var_error);
    if result ge check then weight=&q; else weight=1-&q; run;
proc nlmixed data=data tech=newrap;
    parms beta0=&int beta1=&slope s_b0=&std_int s_b1=&std_slope se=&std_error;
    mu=beta0+beta1*month+random_b0*weight+random_b1*weight*month;
    model result ~ normal(mu, se*se);
    random random_b0 random_b1 ~ normal([0, 0], [s_b0*s_b0, 0, s_b1*s_b1])
    subject=batch;
    mean = beta0 + beta1*month;
    predict mean out=means5 alpha=0.05;
    ods output ParameterEstimates=parms5; run;
```

# Example SAS® Code for Ad Hoc Methods

- Using MIXED:

```
data data;  set data;
    check=&int+&slope*month+probit(&q)*sqrt(&var_int+&var_slope+&var_error);
    if result ge check then w=&q; else w=1-&q; run;
proc mixed data=data;
    class batch;
    model result=month/solution;
    random batch batch*month/solution;
    weight w;
    ods output covparms=parms7 solutionF=fixed;  run;
```

# Performance of Ad Hoc Methods

- How well to they estimate the true quantile?
  - Estimate quantile & perform linear regression; Distribution of sample quantile (*Hao & Naiman*)
    - Only meaningful for multiple obs. for batch*month
  - Specify mean (NLMIXED) as *predicted value* + $\Phi(p)$**se*
    - Trouble distinguishing between quantiles
  - Specify weights based on quantile
    - Accurate for quantiles around 0.50
    - MIXED more accurate than NLMIXED

# Performance of Ad Hoc Methods (cont.)

- Using only parts of the data
  - Severely underestimates; performance increases away from 0.50
- Model mean; estimate quantile (TI approach)
  - Accurate for most quantiles, slightly better for 0.50
  - MIXED underestimates for quantiles not around 0.50 and only 3 batches; MIXED closer than NLMIXED to true value for 6 batches

# Example: Estimation Methods (3, 6 batches)

- Model 0.20 quantile (*true = 29.97*)
  - ICH & Quantreg: **23.8, 17.6 months**
  - Ad hoc MMQR: **16.5-26.7, 25.9-30.0 months**
- Model 0.50 quantile (*true = 33.33*)
  - ICH & Quantreg: **26.7, 25.7 months**
  - Ad hoc MMQR: **23.3-29.0, 27.4-31.4 months**
- Model mean (*true = 33.33*)
  - ICH: **29.4, 28.7 months**
  - Mixed Model: **28.1, 31.2 months**

# Conclusions: Methods to Estimate Shelf Life

- Mean, batches fixed (ICH Q1E)
  - Not a consistent estimator; bias increases as *n* increases
  - Not *"applicable to all future batches"*
  - Relies on poolability
- Mean, batches random (Mixed Model)
  - Consistent estimator
  - *"applicable to all future batches"*
  - Accounts for batch-to-batch variability via random batches

# Conclusions: Methods to Estimate Shelf Life

- Quantile, batches fixed (ICH Q1E with Quantreg)
  - Targets quantile (“…*confidence that the drug product will retain its identity, strength, quality, and purity*…”)
  - Not applicable to future batches
  - Breaks down for q < 0.15, q > 0.85
- Quantile, batches random (Mixed Model Quantile Regression)
  - Targets quantile
  - Applicable to future batches
  - Ad hoc MMQR: no clear break down point, better than fixed batch QR
  - Theoretical MMQR methodology TBD

# Future/Continued Research

- Finish developing theory and methodology for MMQR
  - Start from penalized QR method discussed by Koenker
  - Incorporate estimation for variance components using $\hat{\beta}(\tau)$
  - Compare to ICH with QUANTREG
- Determine robustness of methodology using a limited number of months real-life data
- Determine sampling distribution of shelf life estimates using proposed methodology

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