Estimating Shelf Life Using Quantile Regression with Random Batch Effects

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August 5, 2009

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

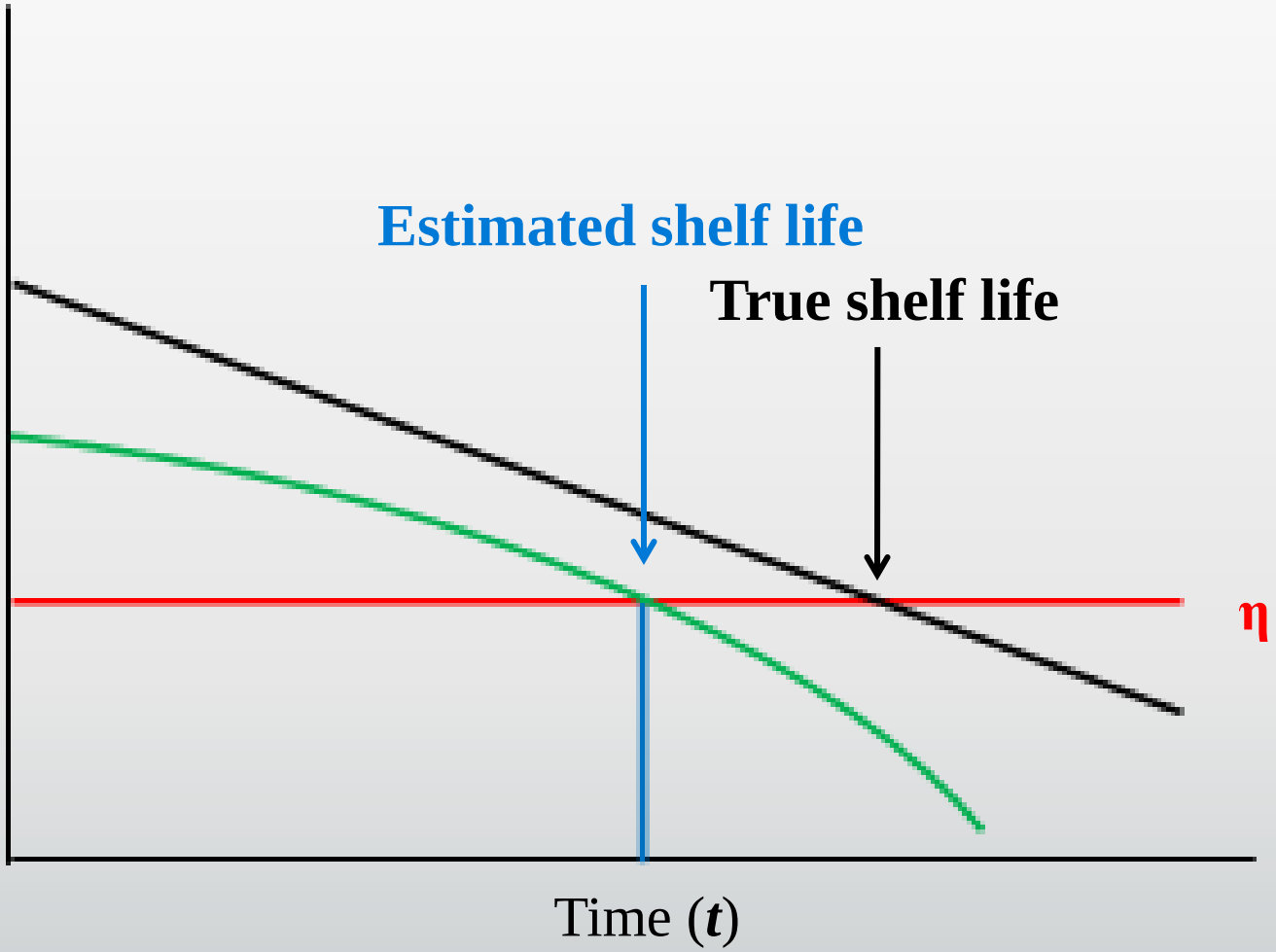
Shelf Life

- 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

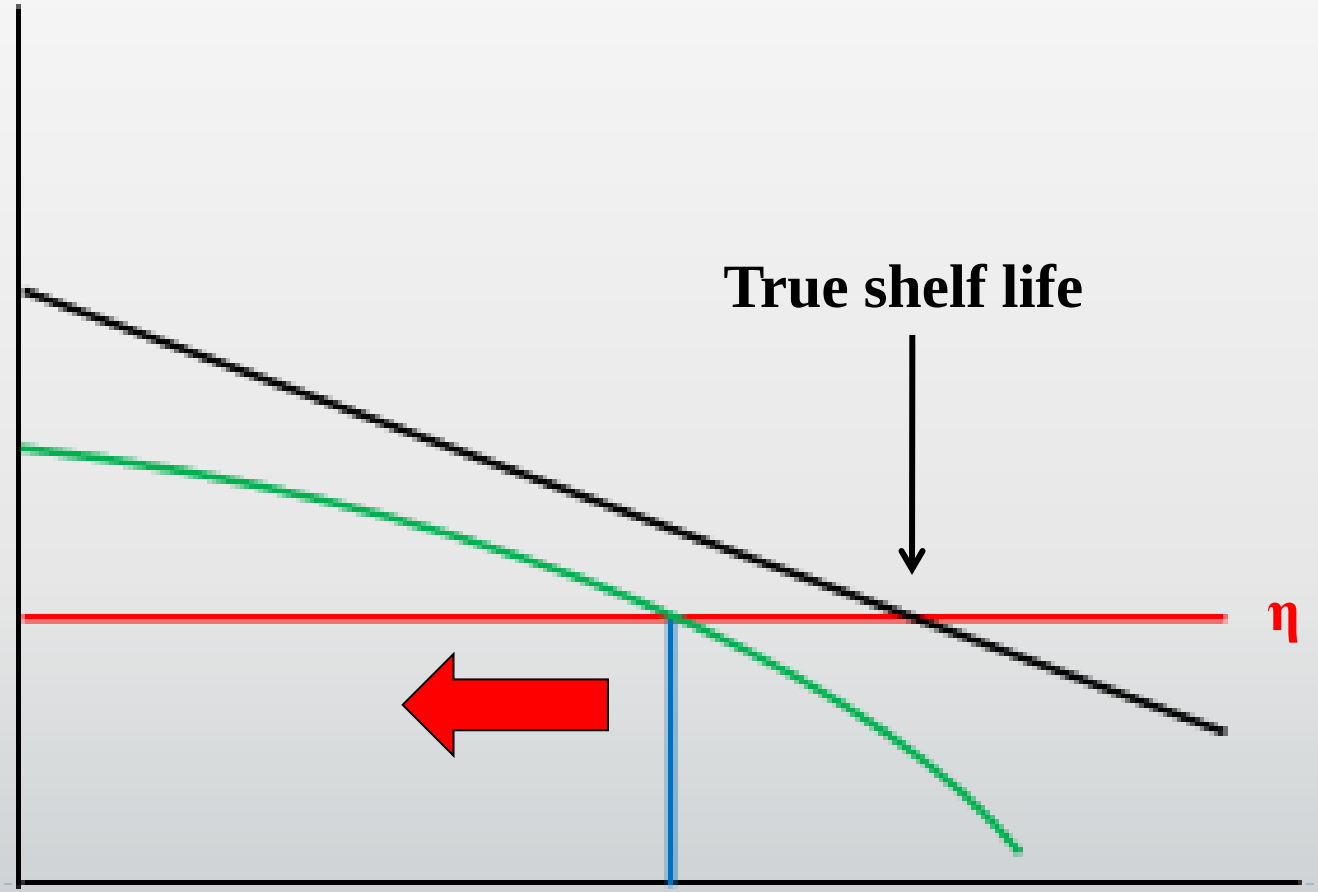
$$y_{ij} = \beta_{0i} + \beta_{1i} x_{ij} + e_{ij}$$

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

- **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

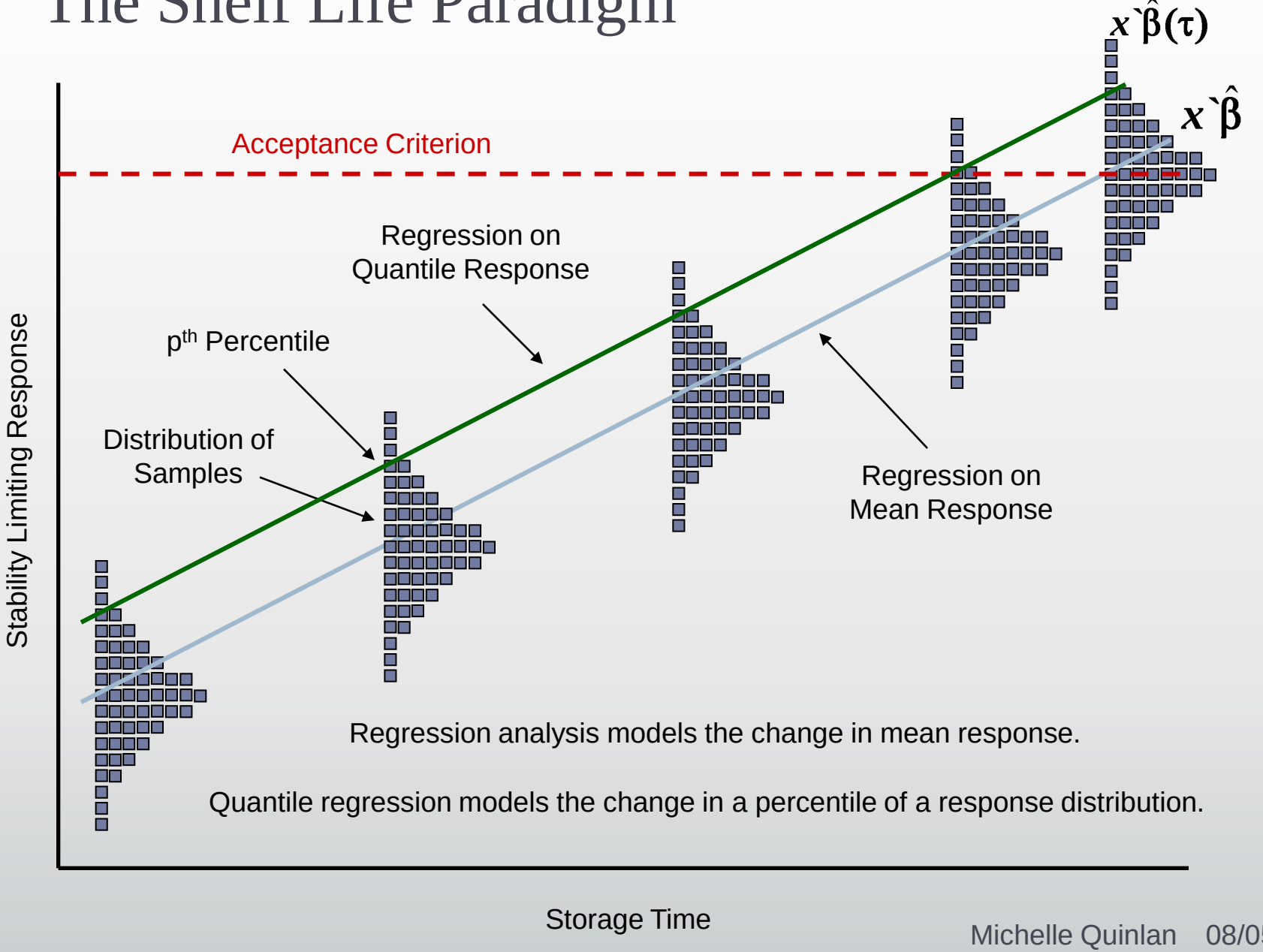
	Not Poolable	Poolable
***3 batches*:**		
% of runs:	**94.2%**	**5.8%**
Average Estimate:	**28.5 (24.8, 32.1)**	**31.7 (28.5, 34.5)**
	27.6 (23.0, 31.8)	**30.7 (27.8, 33.5)**
Underestimate:	**99%**	**80%**
	99%	**94%**
***6 batches*:**		
% of runs:	**99.5%**	**0.5%**
Average Estimate:	**27.5 (24.5, 30.5)**	**32.1 (30.4, 33.9)**
	30.6 (28.2, 33.0)	**32.0 (30.3, 33.5)**
Underestimate:	**99%**	**82%**
	97%	**82%**

PQRI Product Quality Research Institute

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

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

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

$$\sum_i \sum_j \rho_\tau \left(y_{ij} - x_{ij}\beta - \alpha_i \right) + \lambda \sum_i |\alpha_i|$$

- Questions to address
  - How to determine λ?
  - What is the relationship between λ 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

Acknowledgements

This research is funded through the

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PQRI is the Product Quality Research Institute, Arlington, Virginia