Current Practices in Shelf Life Estimation

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Shelf Life Estimation

- ICH estimation methods
- Typical stability study
- Shelf Life paradigm
- Regression methods for estimating shelf life
- Actual stability study results
- Summarize empirical distribution of estimated shelf life
- Extend to random batch analyses

- ICH Guideline Q1A defines "Shelf Life (also referred to as expiration dating period)" as

  "The shelf life for a pharmaceutical product is the maximum time at which a stability limiting characteristic stays within acceptance criteria."

- Also in Q1A, "Specification Shelf Life" is defined as

  "The combination of physical, chemical biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its re-test period, or that a drug product should meet throughout its shelf life."

Definitions of Shelf Life – ICH Q1E

- ICH Guideline Q1E defines shelf life as

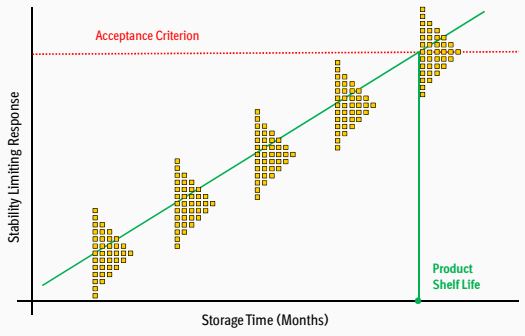
  "The shelf life of a pharmaceutical product is the maximum time at which the true mean response of a stability limiting characteristic crosses the acceptance criterion."

  - basis for the current ICH/FDA shelf life estimation procedure
  - limited assurance that individual test results will comply with the specification up to m months
  - focus on the mean response implies the risk to fail specification at shelf life will be 50%

Typical Stability Study

- Minimum of 3 stability batches
  - can be 6 or more batches included in study
  - can be several studies combined together
- Study duration can be 6-12-24-36-48 months
  - longer studies can have interim reports
  - length of study can depend on shelf life desired
- Various environmental conditions
  - more severe environmental condition can act as an accelerated testing for milder conditions

The Shelf Life Paradigm



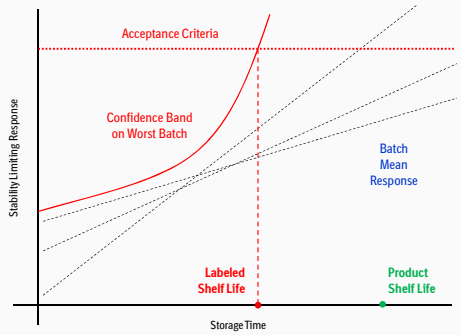
The Shelf Life Paradigm

- General concerns
  - Exactly what should be modeled and how does it relate to the product shelf life?
    - individual tablet
    - composite sample of several tablets
    - packaged unit (bottle or blister pack)
    - stability batches or all future batches
  - How does results of content uniformity studies affect the decision process?
  - If focused on the mean response, when the mean crosses the acceptance criteria, 50% of product out of specification.

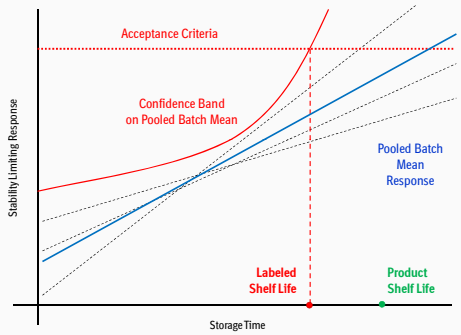
ICH Shelf Life Estimation Methods

- ICH methodology
  - minimum of three batches
  - batches are considered fixed effects for the analysis
  - batches can be pooled if no significant differences
    - 0.25 level of significance for tests involving batches
    - 0.05 level of significance for tests involving other factors
      - package type, storage orientation, coating, etc.
  - construct 95% confidence intervals on individual (or pooled) batch means
  - find minimal storage time where confidence interval crosses acceptance criteria

ICH Shelf Life Estimation – No Pooling



ICH Shelf Life Estimation – Pooled Batches



ICH Estimation Methodology

- usually a simple linear (straight line) regression model is assumed to characterize the response-time continuum
  - first-order nonlinear models are more appropriate for some stability limiting characteristics
  - we will focus on simple linear regression models
- simple linear model

$$y_{ij} = b_{0i} + b_{1i}\,(\text{month}_j) + \varepsilon_{ij}$$

  - y_{ij} = observation at j^{th} month for i^{th} batch
  - b_{0i} = batch intercept and b_{1i} = batch regression slope
  - ε_{ij} = residual error with Normal assumptions

ICH Estimation Methodology

- ICH methodology suggest to test for equal regression slopes among stability batches first
  - if batch slopes are nonsignificant ($\alpha = 0.25$)
    - common regression slope is assumed among batches
    - batch intercepts are tested
      - if batch intercepts are nonsignificant ($\alpha = 0.25$)
        - common intercept is assumed among batches
        - batches are pooled
  - if batch slopes are significant, no further testing is considered
  - ICH does not allow for a model with a common batch intercept and unequal slopes (which can be an important model)

ICH Estimation Issues

- Regression model selection
  - there are four possible linear regression models
    1) full model: unequal intercepts and slopes among batches
    2) common intercept with unequal slopes among batches
    3) unequal intercepts with common slope among batches
    4) common intercept and slope (pooled batches)
  - Model #2 is not allowed following ICH guidelines
    - still considered an important model to consider by colleagues
    - for stability limiting characteristics that should be at 0% or 100% at 0-months storage time

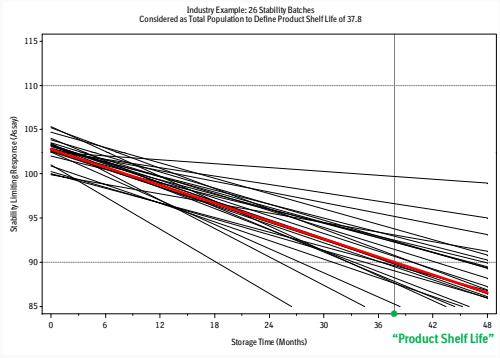
ICH Estimation Issues

- Batch poolability
  - if batches cannot be pooled, shelf life is estimated on results of the worst batch
  - if batches can be pooled, between and within batch variation is combined
- Random batch effects
  - the 0.25 level of significance used to test hypotheses involving fixed batch effects is intended to accommodate batch-to-batch variation
  - available software allows for random batch analysis
  - would avoid batch poolability issue

Real-Life Example Data Set

- Real-life example contributed by one of our PQRI members
  - 26 stability batches
  - all on same product
  - most kept on study for 24 months
  - assay was measured
- will use to study empirical distributional properties of estimated shelf life using 3- and 6-batch studies

Product Shelf Life



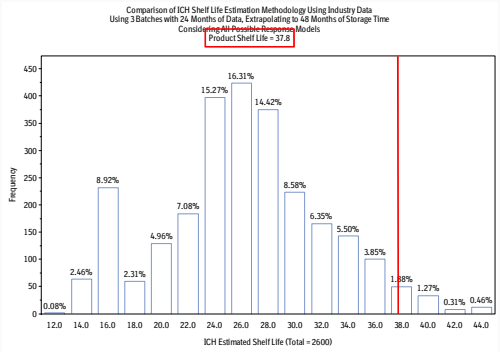
Empirical Study of Distributional Properties

- use real-life stability batch data set
  - consider entire 26-batch data set defines the product population of batches
  - use all batches to product shelf life
    - estimate regression line assuming batches are random
    - product shelf life is storage time where regression line crosses acceptance criteria
- consider all possible sets of 3 and 6 batches
  - conduct ICH estimation methods for shelf life
  - summarize results

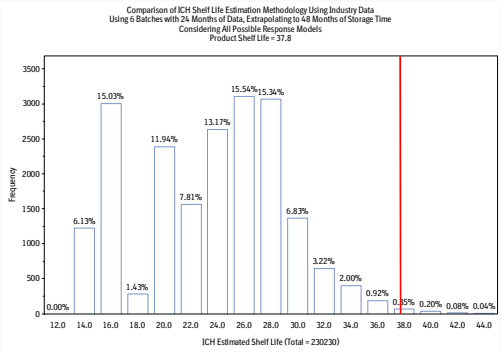
Empirical Study of Distributional Properties

- 3-batch analysis
  - consider all possible combinations of 3 batches from the 26
  - there are 2,600 combinations
  - conduct regression analysis allowing for all four models
    - does not follow ICH
    - allows for common intercept / unequal slope model
    - model is included by my analytical scientists
  - estimate shelf life from best fitted model
- 6-batch analysis
  - there are 230,230 possible combinations (7.5 days to run)
  - randomly chose 20,000 (15.5 hours to run)

3-Batch Estimate of Shelf Life



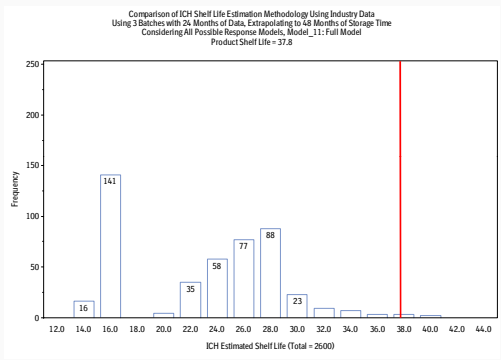
6-Batch Estimate of Shelf Life



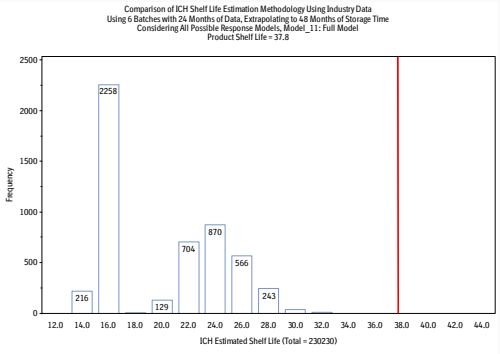
ICH Estimation Methodology

- Comparing the two empirical distributions
  - there is a shifting toward shorter estimated shelf lives with an increase in the number of batches included in the analysis
    - counterintuitive
    - increase in the number of batches should reflect an increase in the amount of information about the product
    - increase in the amount of information about the product should reflect a better estimate of shelf life
      - should see a shift in distribution toward longer shelf lives
      - better estimates of product shelf life (37.8 months)
  - disincentive for industry to include more stability batches

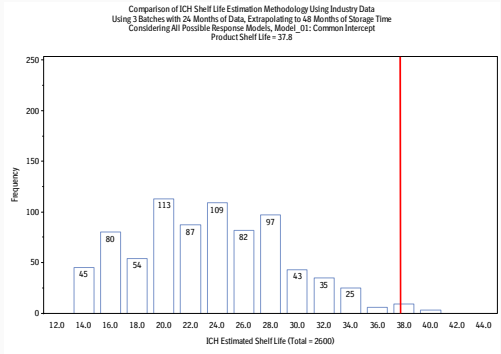
3-Batch Estimate of Shelf Life
n = 466 (18%) mean = 22.9 months SD = 5.86



6-Batch Estimate of Shelf Life
n = 5035 (25%) mean = 19.9 months SD = 4.60

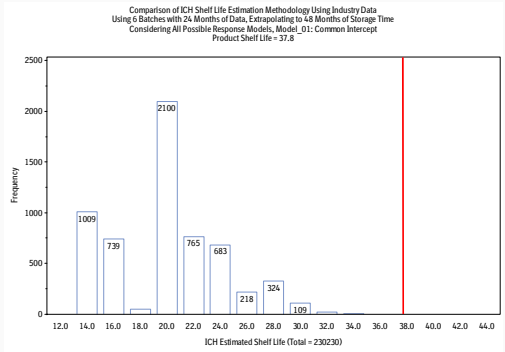


3-Batch Estimate of Shelf Life
n = 788 (30%) mean = 23.3 months SD = 5.71



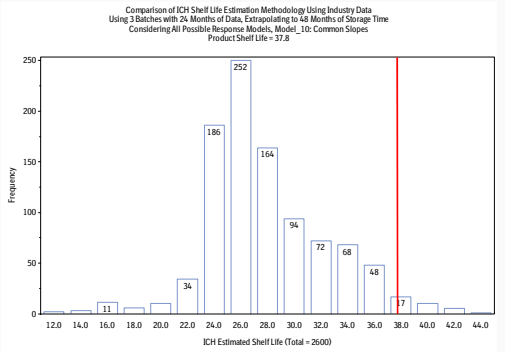
6-Batch Estimate of Shelf Life

n = 6015 (30%) mean = 20.1 months SD = 4.13



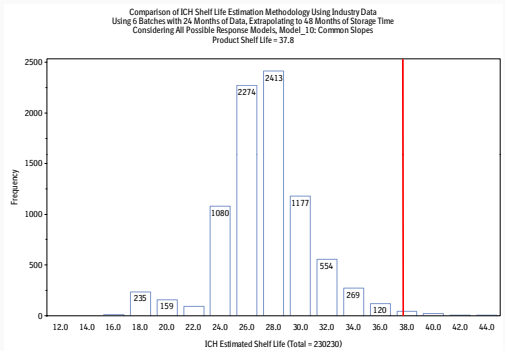
3-Batch Estimate of Shelf Life

n = 983 (38%) mean = 27.8 months SD = 4.61



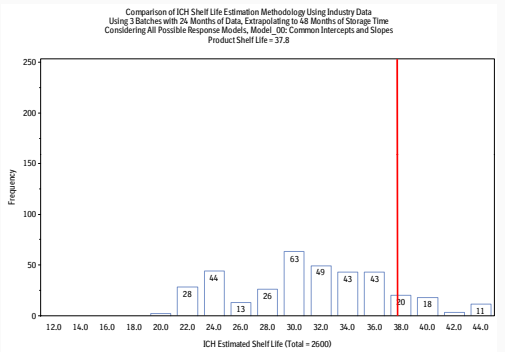
6-Batch Estimate of Shelf Life

n = 8451 (42%) mean = 27.3 months SD = 3.425



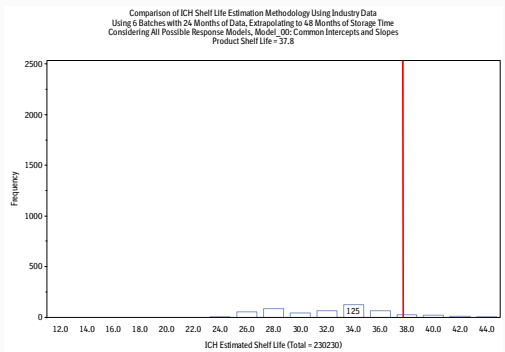
3-Batch Estimate of Shelf Life

n = 363 (14%) mean = 31.2 months SD = 5.70



6-Batch Estimate of Shelf Life

n = 499 (3%) mean = 32.5 months SD = 4.23



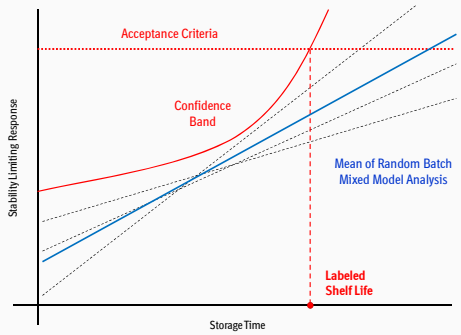
ICH Estimation Methodology

- Poolability
  - concept is to estimate shelf life on the best fitted regression
  - accommodate random variation among batches by allowing pooling of batch data through regression parameter estimates
    - allow for common slope and intercept models to characterize batch response
    - use $\alpha = 0.25$ level of significance
  - estimate of shelf life too heavily dependent on best model
  - assuming unequal slopes forces the shelf life estimate to be based on worst batch
    - tends to minimize shelf life estimate

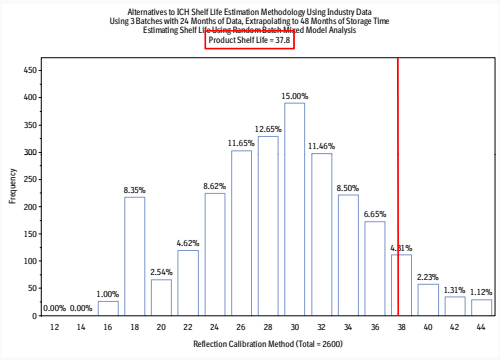
Random Batch Mixed Model Analysis

- Two rationale to suggest an alternative random batch analysis
  - can extend inference of estimated shelf life to future batches
  - avoids dependence of shelf life estimate on “best” model fit
- mixed model analysis would
  - model between-batch variation as a random effect
  - quantify both between and within-batch variation separately
  - allows broad and narrow inferences
  - allows estimation of shelf life through calibration techniques
    - defined by a one-sided (lower) interval estimate on calibration storage time point

Random Batch Mixed Models - Reflection



3-Batch Estimate of Shelf Life – Confidence Interval



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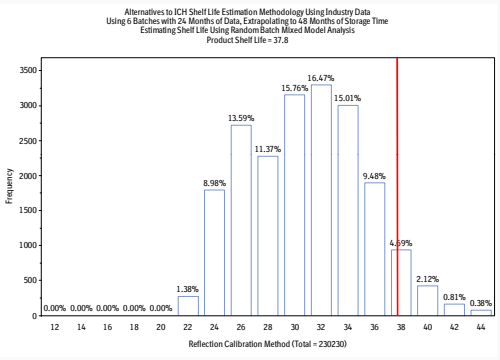
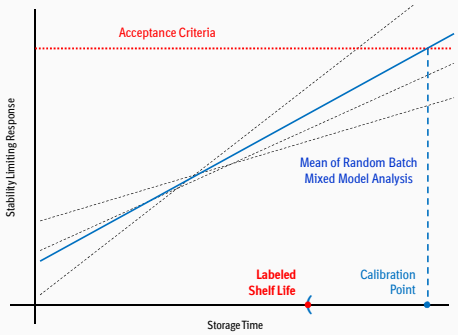


Random Batch Mixed Models – Distribution of β-hat



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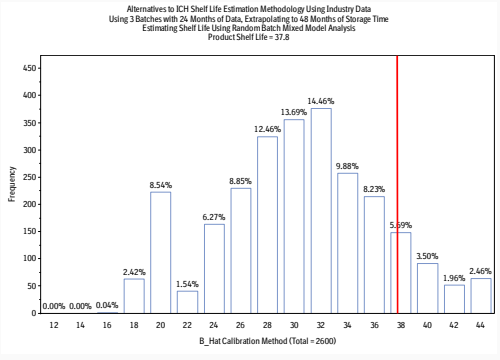

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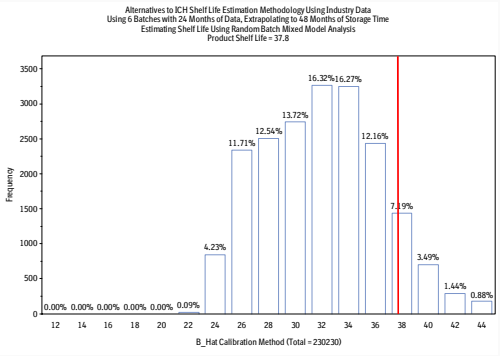

Conclusions

- Moving from a fixed-batch to a random-batch analysis has several advantages
  - can be used to extend the inference of a shelf life statement to future batches
    - depending on how well the stability data represent the manufacturing process
  - avoids the batch poolability issue
    - breaks the dependence of the estimate of shelf life on which reduced or pooled regression model is selected
    - avoids the issue of a common intercept / different slope regression model being appropriate or not

Conclusions

- better quantifies between and within-batch variation by using an appropriate statistical model
- allows additional stability batches to benefit the estimate of shelf life
  - for fixed-batch analysis, additional stability batches increases chance that shelf life is estimated by worst-batch
  - for random-batch analysis, additional stability batches adds to the information on between-batch variation
- better distributional characteristics of shelf life estimate

Conclusions

- Random-batch analysis
  - as presented, is still estimating an “average” batch shelf life
    - confidence interval approach was discussed which is consistent with ICH
    - still have conceptual problem that at shelf life, half of product unit is above specification limit
    - does not reflect desired quality statement
  - alternatives methods for shelf life estimation
    - tolerance intervals
    - quantile regression