



Evaluating Current Practices in Shelf Life Estimation

PQRI Stability Shelf Life Working Group

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Midwest Biopharmaceutical
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Definition of Shelf Life

- From ICH Q1E

"An appropriate approach to retest period or shelf life estimation is to analyze a quantitative attribute (e.g., assay, degradation products) by determining the earliest time at which the 95 percent confidence limit for the mean intersects the proposed acceptance criterion."

- current ICH/FDA shelf life estimation procedure
- in practice, individual test results are often compared to the specification (FDA OOS Guidance)

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Background

- Since 1979, the Food and Drug Administration (FDA) has required that all prescription drugs have a shelf life (or expiration date) indicated directly on the container label.
- Similar requirements are in place in the European Union and around the world.

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Definition of Shelf Life

- From ICH Q1E

"An appropriate approach to retest period or shelf life estimation is to analyze a quantitative attribute (e.g., assay, degradation products) by determining the earliest time at which the 95 percent confidence limit for the mean intersects the proposed acceptance criterion."

- ICH Q1E gives no guidance concerning the individual test result (versus mean result)
- focus on the mean response limits assurance that individual test results will comply with specification

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Definition of Shelf Life

- From ICH Q1A

"The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label."

- definition of shelf life can apply to mean and individual units, current and future batches
- practical interpretation is if a batch is tested up to 'm' months without failing specification, the shelf life of that batch is at least 'm' months
- does not give understanding to how the shelf life is mathematically defined or how risk is assessed

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To What Does the Shelf Life on the Label Refer?

- The individual unit will remain within specification? (not likely, as the individual is tested under content uniformity rules)
- The mean of the units in a bottle will remain within specification?
- The mean of a batch will remain within specification?
- The mean of all batches will remain within specification?

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Shelf Life as Defined by ICH

- ICH guidance documents Q1A and Q1E provide recommendations for establishing testing requirements to evaluate stability data and estimate shelf life.
- A complete review of the ICH methods from the perspective of the product distribution is the focus of the proposed second PQRI paper (work still in progress) to be submitted for publication later this year.

A New Language for Shelf Life

- Five terms are presented here to enable a coherent discussion about shelf life in its various contexts.
 - some of these terms already exist in scientific discourse but are rarely, if ever, recognized as distinct and different entities, leading to misuse by industry, regulatory agencies and academia
 - in casual conversations, when little care is given to precise terminology and nomenclature, the same vague term "shelf life" is applied loosely to all these different concepts, creating confusion and preventing progress

Shelf Life as Defined by ICH

- A succinct description of these requirements is:
 - sample a minimum of three batches
 - measure the critical attribute(s) over the storage time periods recommended in ICH Q1A
 - perform a statistical analysis of the stability data as described in ICH Q1E, estimate the shelf life as the storage time when a 95% confidence limit crosses the acceptance boundary
 - set shelf life using ICH decision tree

Propose New Terms for Shelf Life

- true shelf life
- estimated shelf life
- supported shelf life
- maximum shelf life
- labeled shelf life

Intent of the ICH Q1E Strategy

- The estimate of shelf life, using ICH Q1E methodology, depends on sample size (in particular, the number of batches) as well as the level of confidence.
- While no explicit quality statement is provided, the intent of the ICH Q1E strategy is to establish the storage time during which the critical attribute(s) will be considered acceptable for all "future batches manufactured, packaged, and stored under similar circumstances.
- Unfortunately, as will be discussed in detail later, the statistical methodology recommended in this guidance document is incompatible with this intent.

True Shelf Life

- The *true shelf life* is the true but unknown limit on the period of storage time during which the pharmaceutical or drug product is considered fit for use and effective.
 - in this context, the *true shelf life* can also be referred to as the *true product shelf life*, to be most specific
 - it is this unknown storage time, the true product shelf life, which is to be estimated through a stability study
 - because the true product shelf life applies to current and future batches, it only has meaning when the manufacturing process is under statistical control
 - Otherwise, batches manufactured today may not be representative of batches manufactured in the future

Estimated Shelf Life

- A stability study is a designed experiment where the pharmaceutical product is stored in environmental chambers and followed for a prescribed amount of storage time.
 - periodically, the product is sampled to measure a series of stability limiting properties
 - from these data, an estimate of the true product shelf life is obtained. In general, this estimate of the true product shelf life is called the *estimated shelf life* or the *estimated product shelf life*

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Maximum Shelf Life

- The *maximum shelf life* is the maximum allowed extrapolated product shelf life estimate based on the decision tree provided in ICH Q1E.
 - the decision tree provided in ICH Q1E is a series of questions resulting in a limit to how far an estimated product shelf life can be extrapolated beyond the maximum storage time measured in a stability study

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Supported Shelf Life

- Any suitably conservative estimate of the true product shelf life, as supported by statistical calculations, is called the *supported shelf life*.
 - it is intended to be a conservative estimate of product shelf life to help assure that a high proportion of product remains fit for use up to that estimated storage time
 - for example, in the ICH Q1E guidance, the supported shelf life is the time point where the 95% confidence limits (one-sided or two-sided depending on the properties of the stability limiting characteristic being measured) intersect the acceptance limit(s)

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Maximum Shelf Life

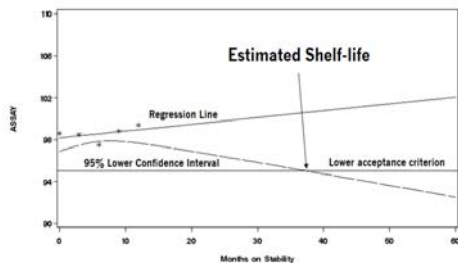
- For example, if a 12-month stability study was being considered, any shelf life estimate may be limited to a maximum of 24 months of storage time (2 times the length of storage time considered in the stability study) by following the ICH decision tree.
 - the maximum shelf life is dependent on the actual data only in that the statistically estimated shelf life must be longer than the decision tree shelf life, but the extent to which it exceeds the decision tree is not taken into account

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Example of Supported Shelf Life



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Supported Shelf Life and Maximum Shelf Life

- The following figure is a summary of the current industry practice for setting shelf life.
 - the data set has data through 12 months
 - the statistically estimated shelf life is > 60 months
- Scenario 1
 - the 40°C/75%RH data (accelerated condition) does not show a significant change
 - the maximum shelf life is 24 months
 - which is 2 times the available 12-month long term data

40°C/75%RH

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Supported Shelf Life and Maximum Shelf Life

- Scenario 2
 - The 40°C/75%RH data (accelerated condition) shows a significant change
 - the 30°C/65%RH (intermediate condition) meets specifications through 12 months
 - the maximum shelf life is 18 months
 - 1.5 times the available 12-month long term data

40°C/75%RH

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Labeled Shelf Life

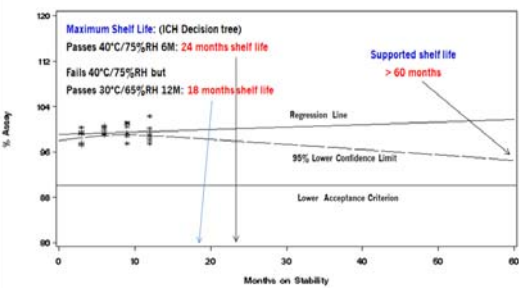
- Because the intention of the shelf life claim made by a manufacturer is that the true product shelf life is equal to or longer than the labeled *shelf life* (with high confidence), the labeled shelf life must be defined as the shorter of the supported shelf life and maximum shelf life.
- The labeled shelf life is what is printed on the drug product's label and is used to calculate the expiry date.

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Supported Shelf Life and Maximum Shelf Life



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Current Industry Procedure

- Current industry procedure for determining the labeled shelf life for a new drug product
 - assess “ICH Shelf Life” based on long term data, accelerated data and if applicable intermediate condition data against the ICH decision tree
 - perform statistics if applicable
 - test for poolability of slopes and intercepts
 - pool slopes and intercepts as applicable
 - use the pooled mean square error calculated from all batches

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Supported Shelf Life and Maximum Shelf Life

One side effect of the ICH method of setting shelf life using the decision tree is that the maximum shelf life set for 2 compounds that have vastly different statistically estimated shelf lives (one may be 25 months and the other may be 72 months) will be both given a 24 month shelf life by the ICH decision tree

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Current Industry Procedure

- The labeled shelf life is then the shorter of the ICH decision tree shelf life and the shelf life estimated by statistical analysis (supported shelf life).
- The labeled shelf life may also be set shorter than the maximum shelf life for business reasons.

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Citation

Capen, R.C., et.al., 2012. On the Shelf Life of Pharmaceutical Products. *AAPS PharmSciTech*, Vol. 13, Issue 3, 911-918.

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Current Practices in Shelf Life Estimation

- Exactly what should be modeled and how does it relate to the product shelf life?
 - individual tablet
 - composite sample of several tablets
 - often a need to acquire enough material to assay
 - package unit (bottle or blister pack)
 - stability batches or all future batches
 - fixed or random batch effects
- Assumes a consistency between the product unit (tablet) and the experimentation unit (aliquot of several tablets).

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Evaluating Current Practices in Shelf Life Estimation

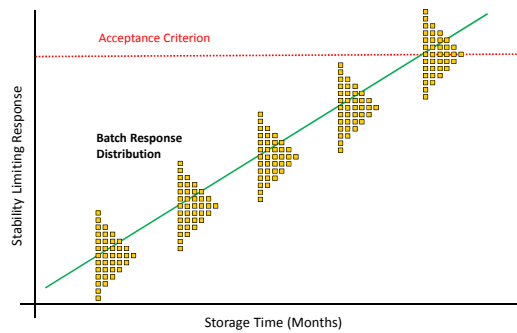
Highlights from
Proposed Second PQRI Paper

Work in Progress

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The Stability Study Paradigm



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Current Practices in Shelf Life Estimation

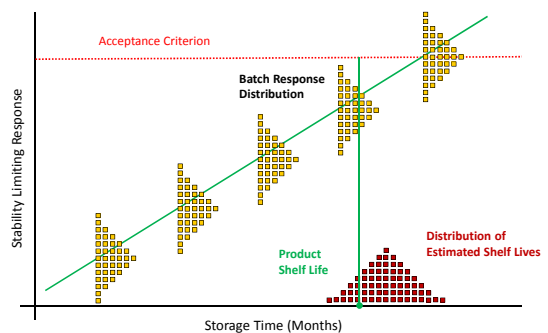
- ICH Guidance defines shelf life as
"The shelf life of a pharmaceutical product is the maximum time at which the true mean response of a stability limiting characteristic crosses the acceptance criterion."
- stated intent of ICH is to estimate a shelf life from
"... which the critical attributes of the drug product remain acceptable for all future batches".
- basis for the current ICH/FDA shelf life estimation procedure which we will be investigating

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The Shelf Life Paradigm



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Current Practices in Shelf Life Estimation

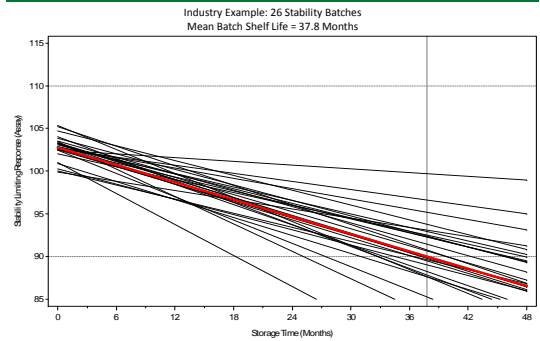
- Often a simple linear (straight line) regression model is assumed to characterize the response-time continuum.
- First-order nonlinear models are more appropriate for some stability limiting characteristics
 - quadratic models may be useful to approximate nonlinear models if sufficient data are not obtained to characterize the asymptote
- ICH guidelines allow for the “pooling” of batch data following a testing scenario
 - allows for a common regression model to describe the “pooled” batch data

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ICH Shelf Life Estimation – Pooled Batches



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Current Practices in Shelf Life Estimation

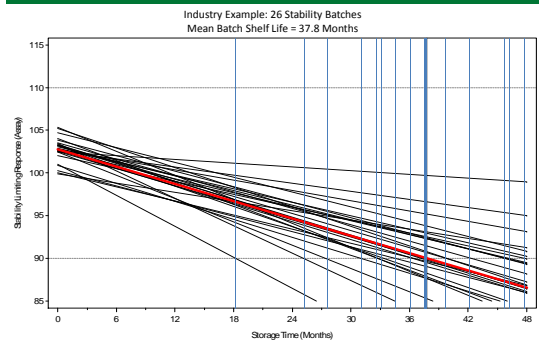
- Batch poolability
 - if batches cannot be pooled, shelf life is estimated on results of the worst batch
 - if batches can be pooled, between and within batch variation is combined
- Random batch effects
 - the 0.25 level of significance used to test hypotheses involving fixed batch effects is intended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

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Distribution of Shelf Life Estimates



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Current Practices in Shelf Life Estimation

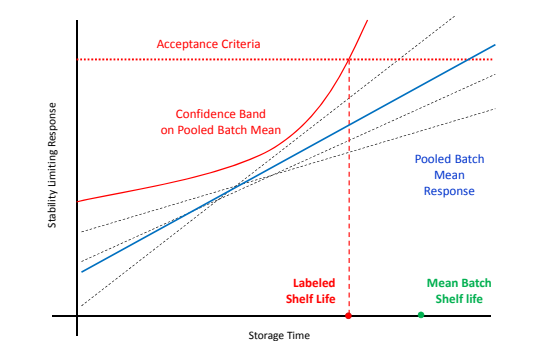
- Real-life example contributed by one of our PQRI members
 - 26 stability batches
 - all on same product
 - most kept on study for 24 months
 - product was assayed for the active ingredient
 - taken together as a “population”, the estimated shelf life is 37.8 months

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ICH Shelf Life Estimation – Pooled Batches

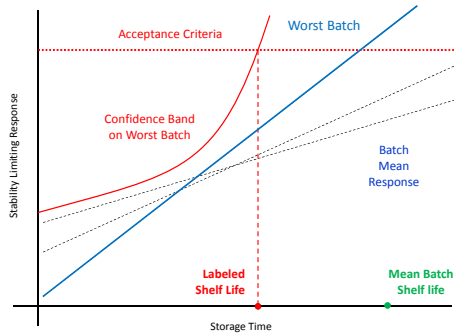


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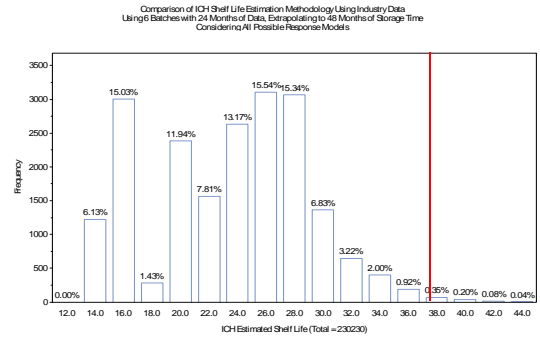
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ICH Shelf Life Estimation – No Pooling



6-Batch Estimate of Shelf Life



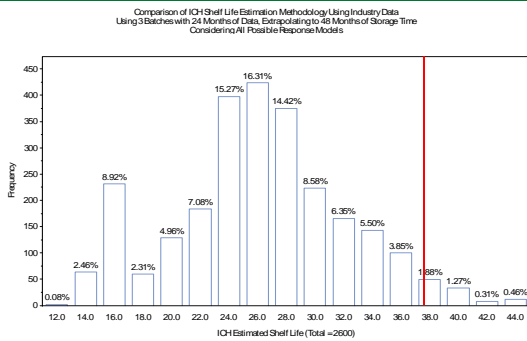
Current Practices in Shelf Life Estimation

- Data set was used to study the empirical distributional properties of the estimated shelf life following ICH methodology using 3-batch and 6-batch “studies”.
 - shelf life was estimated for each “study” and recorded
 - using 3 batches, there are 2,600 combinations
 - using 6 batches, there are 230,230 combinations
 - which would take 7.5 days to run with my old computer
 - I didn’t do that ... sorry!
 - randomly choose 20,000 sets of 6 batches
 - the run was finished when I woke up

Current Practices in Shelf Life Estimation

- 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 amount of information about the product should reflect a better (longer) estimate of shelf life
 - disincentive for industry to include more registration batches in their stability studies

3-Batch Estimate of Shelf Life

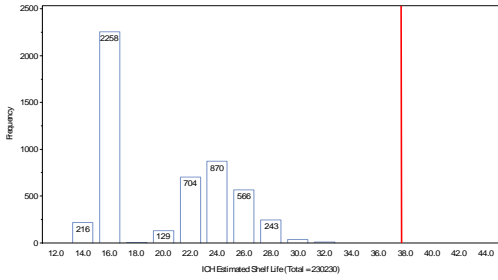


Current Practices in Shelf Life Estimation

- Results look worse when they are partitioned into the three (four) possible models associated with the simple linear regression model.
 - unequal intercepts and slopes among batches
 - common intercept with unequal slopes among batches
 - unequal intercepts with common slope among batches
 - common intercept and slope (pooled batches)
- Model #2 is not specifically allowed under the ICH “slopes first” methodology.
 - important model for researchers
- “Slopes first” philosophy cannot be applied to nonlinear and quadratic models

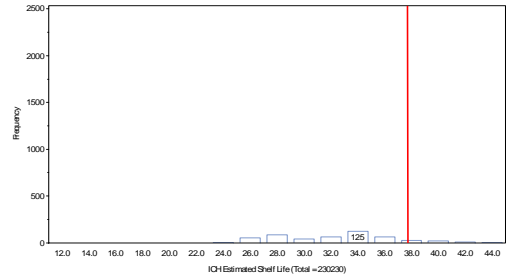
Current Practices in Shelf Life Estimation

Comparison of ICH Shelf Life Estimation Methodology Using Industry Data
Using 6 Batches with 24 Months of Data, Extrapolating to 48 Months of Storage Time
Considering All Possible Response Models, Model_11: Full Model



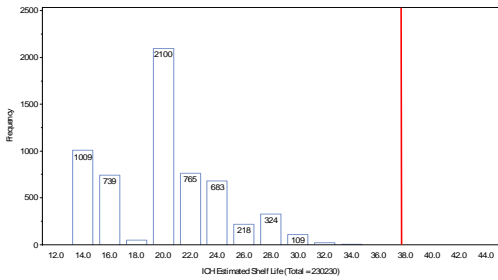
Current Practices in Shelf Life Estimation

Comparison of ICH Shelf Life Estimation Methodology Using Industry Data
Using 6 Batches with 24 Months of Data, Extrapolating to 48 Months of Storage Time
Considering All Possible Response Models, Model_02: Common Intercepts and Slopes



Current Practices in Shelf Life Estimation

Comparison of ICH Shelf Life Estimation Methodology Using Industry Data
Using 6 Batches with 24 Months of Data, Extrapolating to 48 Months of Storage Time
Considering All Possible Response Models, Model_01: Common Intercept



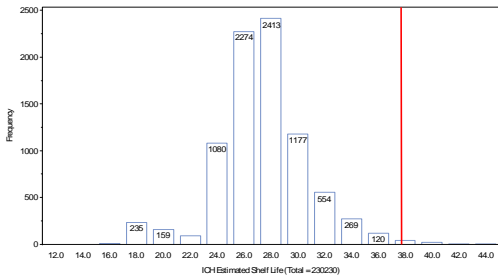
Current Practices in Shelf Life Estimation

3 Batch Analysis Results (2,600 Total)

Reduced Model	N	Percent	Mean Shelf Life	SD	Overall
1	466	18%	22.9	5.86	48% 23.2
2	788	30%	23.3	5.71	
3	983	38%	27.8	4.61	52% 28.7
4	363	14%	31.2	5.70	

Current Practices in Shelf Life Estimation

Comparison of ICH Shelf Life Estimation Methodology Using Industry Data
Using 6 Batches with 24 Months of Data, Extrapolating to 48 Months of Storage Time
Considering All Possible Response Models, Model_10: Common Slopes



Current Practices in Shelf Life Estimation

6 Batch Analysis Results (20,000 out of 230,230 Total)

Reduced Model	N	Percent	Mean Shelf Life	SD	Overall
1	5035	25%	19.9	4.60	55% 20.0
2	6015	30%	20.1	4.13	
3	8451	42%	27.3	3.43	45% 27.6
4	499	3%	32.5	4.23	

Current Practices in Shelf Life Estimation

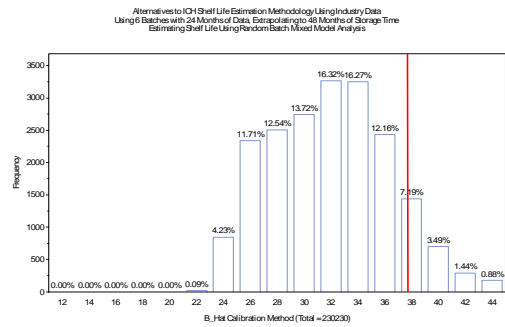
- An alternative random batch analysis will
 - extend inference of estimated shelf life to future batches
 - avoid dependence of shelf life estimate on “best” model fit (pooling)
- Mixed model analysis will
 - model between and within-batch variation as random effects
 - allow estimation of shelf life through calibration techniques
 - defined by a one-sided (lower) interval estimate on calibration storage time point

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6-Batch Estimate of Shelf Life – Confidence Interval

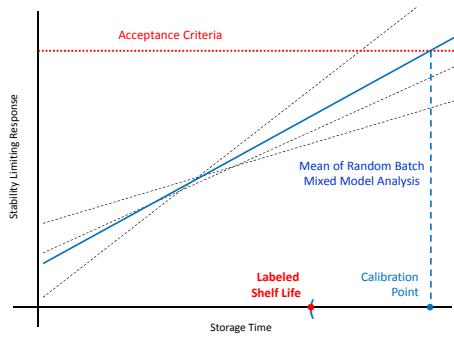


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Random Batch Mixed Models – Distribution of $\hat{\beta}$ -hat



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Current Practices in Shelf Life Estimation

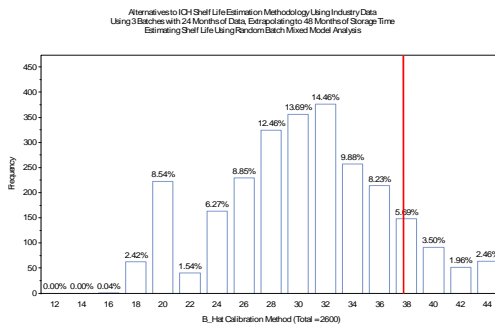
- Concerns remain
 - appears too great a percentage of shelf life estimates exceeds “population” shelf life
 - still have the conceptual problem that the mean of the batch response distribution is the basis for ICH methods
 - at ICH shelf life, half of product can be above specification limit
 - still based on a confidence interval for mean response
 - does not reflect desired quality statement

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3-Batch Estimate of Shelf Life – Confidence Interval



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Current Practices in Shelf Life Estimation

- Alternative methods being investigated
 - initial work being submitted by Quinlan, et.al., from her dissertation
 - random batch (mixed model) analysis
 - recognizing between-batch and within-batch variation
 - prediction intervals
 - extending estimated shelf life to the “next” batch
 - tolerance intervals
 - quantifying a proportion of the batch response distribution remaining within specification
 - extending quantile regression to random batch analysis

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