Shelf Life Determination:

The PQRI Stability Shelf Life Working Group Initiative

Understanding Shelf Life

- What is the true (but unknown) shelf life of a product?
  - The period of time during which a pharmaceutical product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf life is used to establish the expiry date of a batch. (WHO)
  - The length of time all batches meet the approved specifications?
    - Is there a consensus understanding of what this says?
    - Do we agree that this is the ideal?
    - How to best quantify "... the length of time all batches meet ..." and estimate shelf life?

Understanding Shelf Life

- Statistical estimation of shelf life
  - stability studies are performed under both long term and accelerated storage conditions
    - measure response over storage time for stability limiting characteristics of the drug product
    - collect response data to statistically estimate the shelf life of a drug product
  - data is generally available based on individual measurements of composite samples (solid dosage forms) over storage time for 3 or more batches of drug product

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Understanding Shelf Life

- ICH methodology
  - minimum of 3 batches
  - ICH approach utilizes a fixed batch model
  - allows pooling of data from batches that are not significantly different (α=0.25)
  - ICH 95% CI on individual or pooled batch mean
  - ICH approach is based on estimating a minimum batch shelf life
    - leading to a lower product shelf life
  - prediction made by the analysis of the 3 batches is used to set the shelf life of all future batches

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PQRI SSL WG Initiative

- SSL WG working definition
  - true shelf life is the longest time such that a proportion of individual stability results complying with specifications is at least q, for a given q
  - q is set by sponsor in agreement with regulatory to define a limiting quality standard
    - accommodates shelf life based on either the mean (or median, q=0.50) batch response or individual stability results (q>0.50)
    - quantifies an acceptable risk and benefit
  - addresses both between and within batch variation
  - extends inference of shelf life to future batches

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- SSL WG working definition
  - an alternate random batch model may be more appropriate to predict future batch performance
  - batch to batch variability should be accounted for in the model
  - statistical methodology should produce a more accurate estimate of the true shelf life with the inclusion of more batches in the data set

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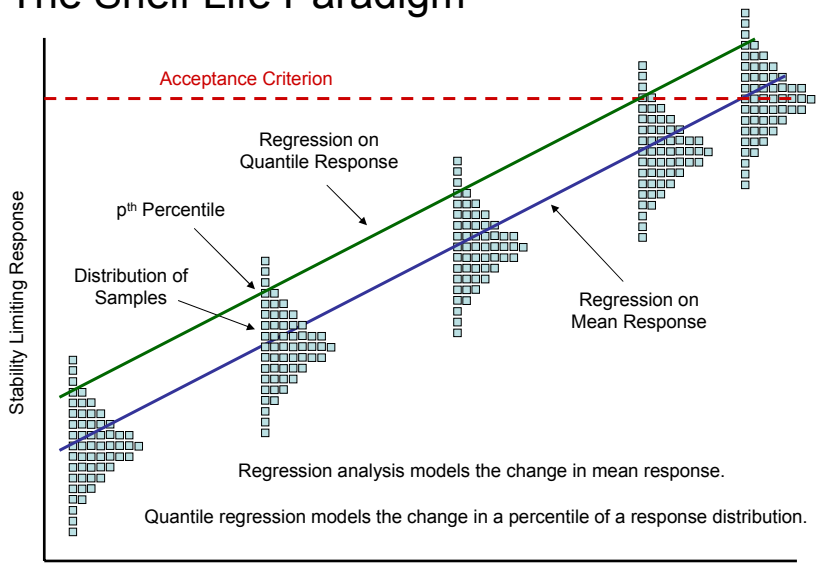
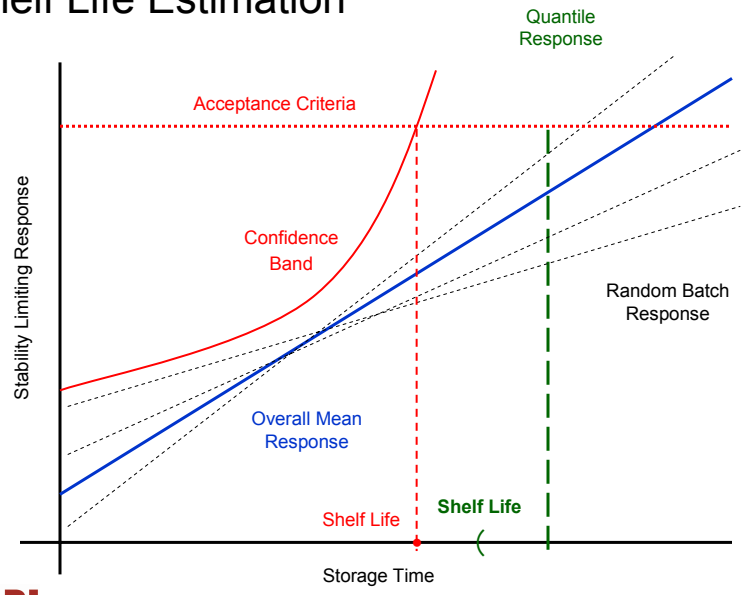
The Shelf Life Paradigm



Shelf Life Estimation



Summary

Proposed estimation methodology provides a consistent and flexible methodology for directly estimating shelf life

- allows estimation on mean or percentile response
- quantifies an acceptable risk and benefit
- provides more information about stability process
- consistent with how acceptance criteria is defined
- uses between and within batch variation
- extends inference to future batches
- does not penalize for additional data

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Simulated Data Example

The following example is based on the results of a 12-month stability trial for a pharmaceutical product.

assay as stability limiting characteristics

acceptance criteria: 95% to 105%

simple linear (straight line) response model

three batches included in study

24-month shelf life was desired

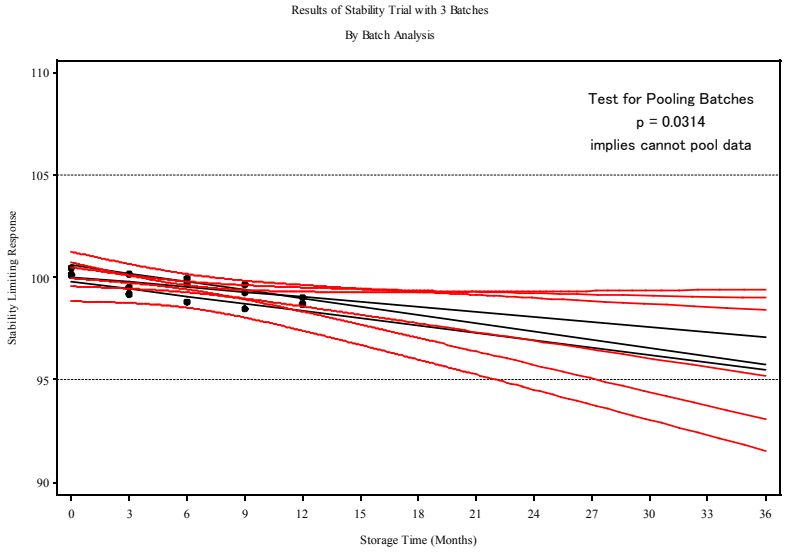
Simulated Data Example

Using current ICH statistical methodology, the batch data could not be pooled (p=0.0314 testing directly to common model).

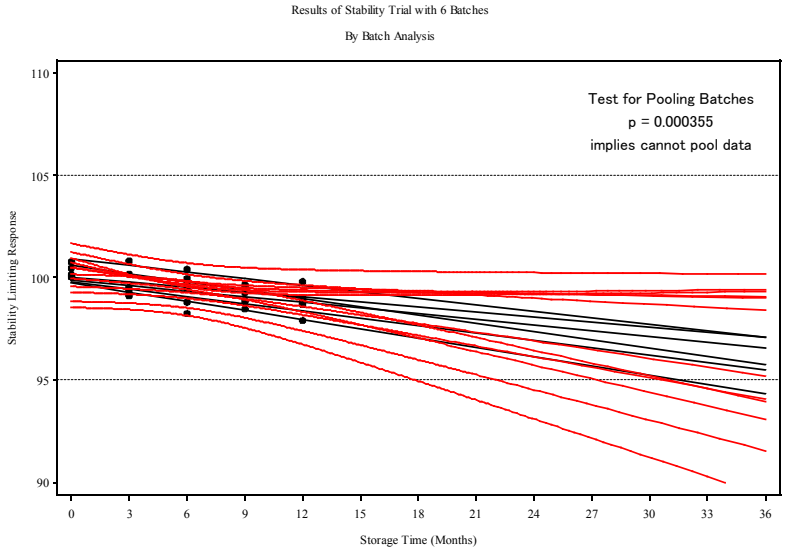
The results of not being able to pool the batch data is to use the most limiting (worst case) batch results to estimate shelf life.

- based on confidence bounds about each batch's mean response
- batch with most rapid decline provides shortest shelf life (worst case)
- gave estimated shelf life of about 22 months

Shelf Life Estimation using ICH



Shelf Life Estimation using ICH



Simulated Data Example

Using WG proposed methodology,

- modeling overall mean response
- accommodating both between and within batch variation
- based on confidence bounds about overall mean batch response
- using reflection method (not most optimal, but easiest for today) to calibrate shelf life estimate
- batch with most rapid decline (worst case) provides a better understanding of batch-to-batch variation
- gave estimated shelf life of about 35 months

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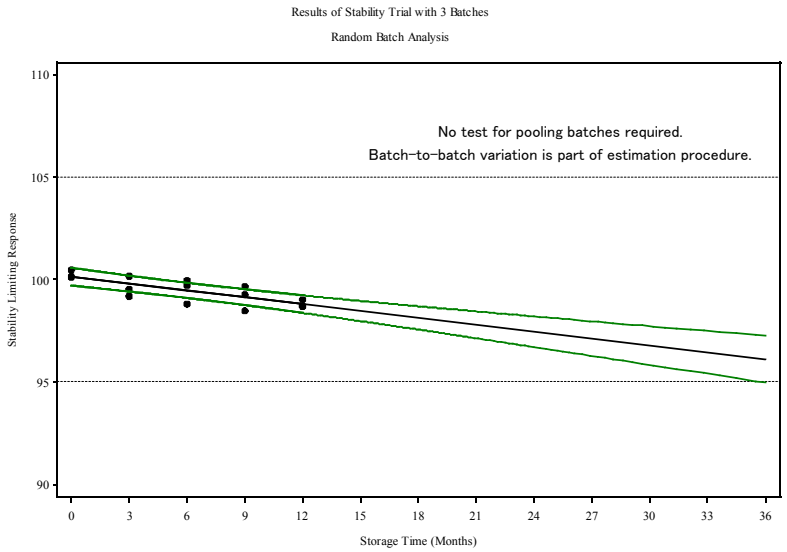

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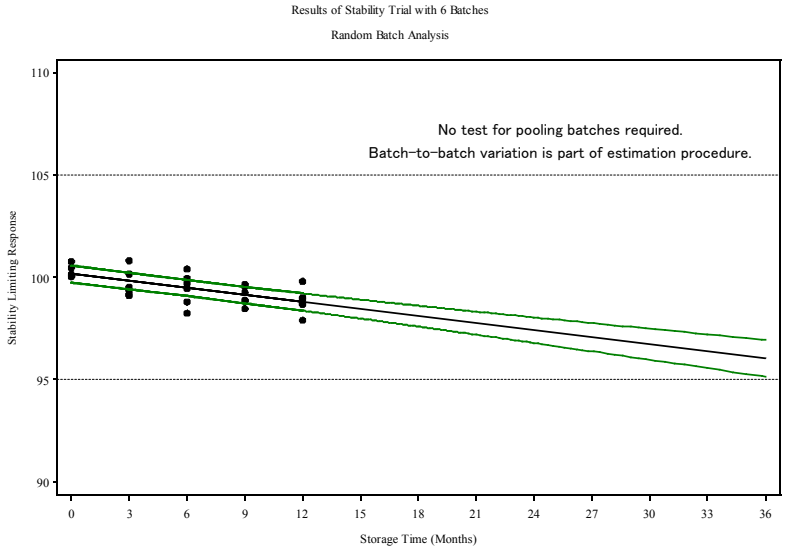

Summary

The Working Groups comes to the end of it's charter at the end of the year.

- currently working on draft paper discussing the definition of shelf life
- concluding development of SAS program to estimate shelf assuming fixed and random batches, and based on mean or proportion response