



## An Update from the PQRI Stability Shelf Life Working Group

Presented by:

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University of Nebraska – Lincoln

## Welcome to the Webinar

The purpose of today's webinar is to disseminate information on the current progress of the PQRI Stability Shelf Life Working Group.

Our objective is to describe our philosophy toward stability studies and shelf life estimation, in addition to presenting our current efforts toward developing a flexible statistical methodology that is consistent with our philosophy and consistent with the QbD (Quality by Design) initiatives.

We are offering this webinar as a means to elicit comments and questions about our efforts from the pharmaceutical community and to establish a communication link to our Working Group for the future.

## Admonition Statement Relative to Anti-Trust

“Our discussions today are subject to the anti-trust guidance applicable in the U.S. Nothing discussed at this meeting is intended to restrict the individual decision-making of any member company or to represent an agreement to coordinate marketing or sales conduct. Those participating in this meeting are instructed to avoid discussion of competitively sensitive subjects, including, confidential marketing, sales, and pricing information.”

**Questions?**



**Comments?**

Send us your questions and comments by e-mail at any time during this presentation. We are actively monitoring the Webinar Inbox.

**[shelf.life.rdg@boehringer-ingelheim.com](mailto:shelf.life.rdg@boehringer-ingelheim.com)**

This e-mail address will stay active and be monitored for as long as our Working Group stays active. It is another communication link for you to directly interact with us. Please feel comfortable to e-mail us at any time with your comments or questions.

## Discussion Outline

1. Introduction
2. The Shelf Life Paradigm
3. Definitions of Shelf Life  
eMail Questions (20 minutes)
4. Shelf Life Estimation
5. Common Perceived Concerns  
eMail Questions (20 minutes)
6. Example
7. Overview of Proposed Shelf Life Estimation  
Final eMail Questions (20 minutes + 1 hour optional)

## Stability Shelf Life Working Group

- PQRI SSL WG
  - Working Group established in late 2006
  - members include statistical and pharmaceutical scientists from industry and academia
- Objectives
  - to propose best practices with respect to stability quality attributes
  - investigate statistical methods for estimating shelf life consistent with FDA Quality by Design (QbD) initiative
  - enhance pharmaceutical products through accurate estimation of shelf life

## Stability Shelf Life Working Group

- Work Plan
  - review existing statistical stability literature
  - create a glossary of stability terminology
  - reconsider the definition of shelf life
  - develop alternative methodologies for estimating shelf life consistent with definition
    - conducted in collaboration with University of Nebraska-Lincoln for statistical support
  - evaluate proposed shelf life estimation methodology with existing stability data for blinded re-analysis

## Stability Shelf Life Working Group

- Subgroups
  - CMC Subgroup
    - monitor progress of Working Group from CMC Development perspective
  - Statistical Subgroup
    - monitor progress of Working Group from statistical perspective
  - Data Warehouse Subgroup
    - survey pharmaceutical companies within Working Group to create a data warehouse of stability data from a variety of products, stability limiting attributes and stability trials

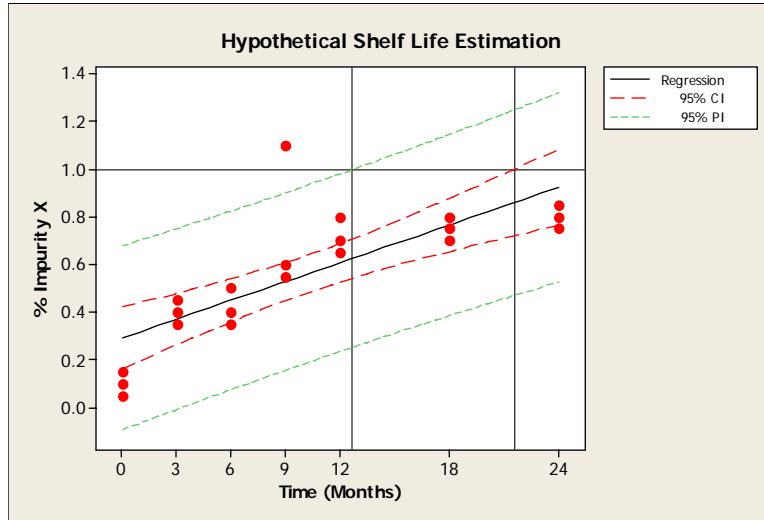
## PQRI Stability Shelf Life Working Group

Suntara Cahya	Eli Lilly and Company
David Christopher	Schering Plough Research Institute
Patrick Forenzo	Novartis Pharmaceuticals Corporation
Abhay Gupta	FDA / CDER
Paula Hudson	Eli Lilly and Company
Svetlana Lyapustina	Drinker Biddle & Reath LLP
Nate Patterson	Vertex Pharmaceuticals, Inc.
Michelle Quinlan	University of Nebraska-Lincoln
Dennis Sandell	Siegfried Pharma Development
James Schwenke	Boehringer Ingelheim Pharmaceuticals, Inc.
Walt Stroup	University of Nebraska-Lincoln
Dave Thomas	Johnson & Johnson
Terry Tougas	Boehringer Ingelheim Pharmaceuticals, Inc.

## Stability and Shelf Life

- Primary intention of a shelf life claim is to provide a storage time during which it is ensured that the drug product (stability limiting characteristics) remains within specification.
- Quality by Design (QbD) philosophy encourages the development of robust processes, methods and designs to enhance pharmaceutical product development.
- The Working Group's efforts are directed toward providing an alternative methodology for estimating shelf life which is predictive of future batch performance, consistent with the common (mis)understanding of shelf life, and based in QbD philosophy.

## Stability Issues Example Plot



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## Stability Issues Example Plot

Possible estimates of shelf life:

- 22-months
  - based on ICH confidence interval approach
- 13-months
  - based on prediction interval
- 9-months
  - dependent on the out-of-specification (OOS) observation
- 24-months
  - ignoring OOS observation, all other observations are within specification

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## Shelf Life Estimation Considerations

- ICH Guidelines do not provide a methodology for estimating the “time period during which a drug product is expected to remain within the approved shelf life specification”
  - the concept of random batches is approached through an ad hoc setting of the level of significance (alpha level) when testing among batches
  - shelf life can be estimated by the worst batch results
  - shelf life is estimated based on a confidence interval justification
  - future batch results do not seem to be addressed
  - shelf life estimate is not directly related to overall results of stability limiting response

## Definition of Shelf Life

1. 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 the 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

## Definition of Shelf Life

2. 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)
- 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

## Alternative Definition of Shelf Life

An alternative definition the Working Group is using to inspire discussion is “*The shelf life of a pharmaceutical product is the maximum time at which the response of a stability limiting characteristic for a batch does not exceed the acceptance criteria.*”

- guaranteeing that every individual unit of a batch meets specification is not statistically possible or feasible from a manufacturing perspective
- instead of showing all tablets meet specification, discussions focus on an estimate of shelf life where an acceptably high proportion of product meets specification
- conducting research to develop an appropriate statistical methodology

## Alternative Definition of Shelf Life

- It is recognized that shelf life may need to be estimated under different testing scenarios, such as determining a shelf life appropriate for product used in a clinical trial.
- With the “working definition”, it is assumed that the acceptance criteria has been defined with respect to a specific unit of measurement, for example, a tablet or the mean of several tablets.
- It is also assumed that the acceptance criteria is consistent with the data collected and the purpose of the stability trial.
- Our mandate is not to consider setting specification limits or acceptance criteria.

## Alternative Definition of Shelf Life

- Our contribution as a Working Group comes through the development of an alternative statistical methodology appropriate for estimating shelf life under a variety of stability testing scenarios.
- We are building flexibility into the estimation procedure to allow the estimation of shelf life to be consistent with the definition of the acceptance criteria, data collected, and the objective of the stability study.
- We are developing statistical methodology that will allow the benefits of a development plan based on QbD principles to be realized through the estimation of shelf life.

Questions?



Comments?

Send us your questions and comments by e-mail to:

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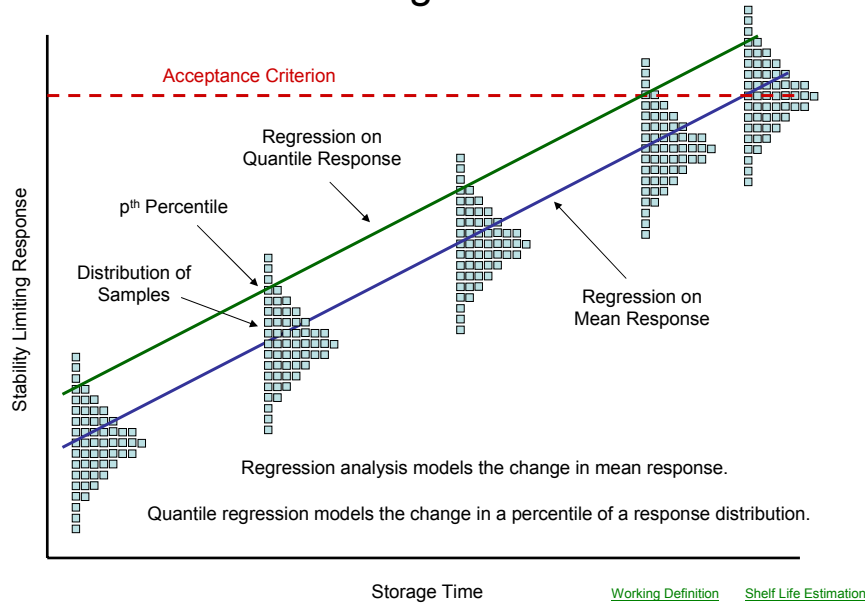
We will take about 20 minutes to answer as many questions as we can, then continue with the presentation.

## Alternative Definition of Shelf Life

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## The Shelf Life Paradigm



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## The Shelf Life Paradigm

- We assume that the objective of the stability study is consistent with the definition of the acceptance criteria and with the data collected.
- The choice of the value of the percentile to be used for estimating a shelf life is left to the appropriate decision maker. For example:
  - If the objective of the stability study is to estimate a shelf life appropriate for a clinical trial, the mean response might be modeled through standard regression techniques.
  - If the objective of the stability study is for product labeling for market, the 95<sup>th</sup> or 99<sup>th</sup> percentile might be more appropriate.

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## Statistical Terminology

### Fixed versus Random Batch Effects

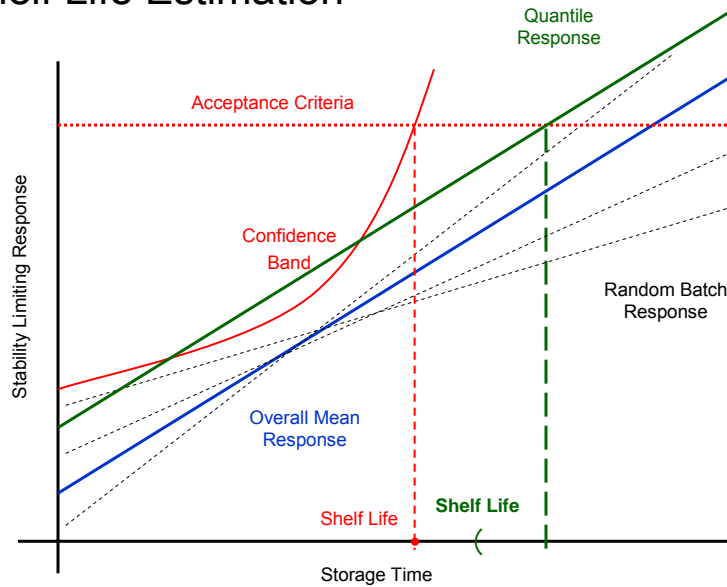
- Fixed versus random effects, in statistical terminology, refers to how sources of difference or sources of variation are interpreted in a statistical analysis.
  - Fixed effects refer to the difference in mean response among various repeatable applied treatments.
  - Random effects refer to an explainable source of variation that contributes to the experimentation variation in a defined way.
  - Acknowledging random effects in a statistical analysis allows better inference and interpretation of study results.

## Statistical Terminology

### Fixed versus Random Batch Effects

- The terminology “random batch effects” (or simply “random batches”) does not imply any untoward statement about the quality of a stability batch.
  - You might not be able to tell, but, statisticians do understand that batch production is a well-designed, controlled process.
  - Batches are not produced at random with whatever materials happen to be laying around at the time.
  - In a statistical analysis, “random batch effects” refer to the variation observed in response among batches, the overall batch-to-batch variation in response.

## Shelf Life Estimation



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## Common Perceived Concerns

- The current ICH methods provide acceptable estimates for shelf life, what are the benefits for proposing new methods?
  - providing an alternative approach that is more in line with current practices that every test result needs to meet specification (FDA OOS Guidance)
  - better alignment with QbD initiatives providing a more robust estimation methodology
    - more consistent estimate of shelf life with regard to future batch performance
    - does not penalize inclusion of additional batches or replicate data in estimation process

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## Common Perceived Concerns

- Why does the definition of shelf life need to be re-evaluated?
  - there are multiple potential definitions of shelf life, depending on how one interprets the guidances (ICH Q1A, Q1E, FDA OOS Guidance)
  - compromise is needed between these definitions for better public understanding
    - need for a scientific foundation for the statistical methodology
    - need for providing a reasonable quality standard
    - not to specify what level of quality is appropriate, only how to define quality

- ICH guideline Q1A defines “Shelf life (also referred to as expiration dating period)” as

*“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.”*

- The “Specification-Shelf Life” is defined in the same document as

*“The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its retest period, or that a drug product should meet throughout its shelf life.”*

- 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 criteria.”*

- FDA OOS Guidance

*“The term OOS results includes all test results that fall outside the specifications or acceptance criteria established in drug applications, ..., or by the manufacturer. The term also applies to all in-process laboratory tests that are outside of established specifications.”*

## Common Perceived Concerns

- An alternative methodology for estimating shelf life has the risk of resulting in a shorter shelf life, compared to existing methods.
  - likely not true
  - concern does not take into consideration the current process for pooling response stability data
  - current ICH methods are based on a worst-batch extrapolation
  - methodology will allow flexibility for quality choice of risk level
    - the methodologies will make the risk / benefit decisions transparent

## Common Perceived Concerns

- Would more data (batches, time points, replicates at time points) be required for estimation of shelf life?
  - probably not,
    - would depend on the amount of between and within batch variation in response
    - well-controlled process would require less data
    - additional data would be rewarded by a better understanding of the products characteristics
  - estimation of shelf life would use current statistical methods and software
    - methods would use response data more efficiently
    - provide more realistic results

**Questions?**



**Comments?**

Send us your questions and comments by e-mail to:

**[shelf.life.rdg@boehringer-ingelheim.com](mailto:shelf.life.rdg@boehringer-ingelheim.com)**

We will take about 20 minutes to answer as many questions as we can, then continue with the presentation.

## Shelf Life Example

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

Assay was one of the stability limiting characteristics to be statistically analyzed.

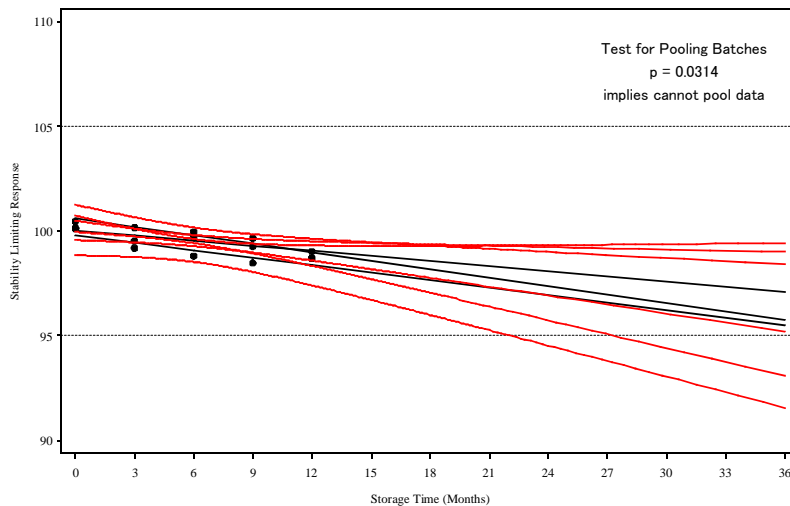
The acceptance criteria were set at 95% to 105% of the claimed dosage.

Assay followed a simple linear model (straight line) response decay.

Three batches were included in the stability study.

## Shelf Life Example using ICH

Results of Stability Trial with 3 Batches  
By Batch Analysis



## Shelf Life Example – By-Batch Analysis

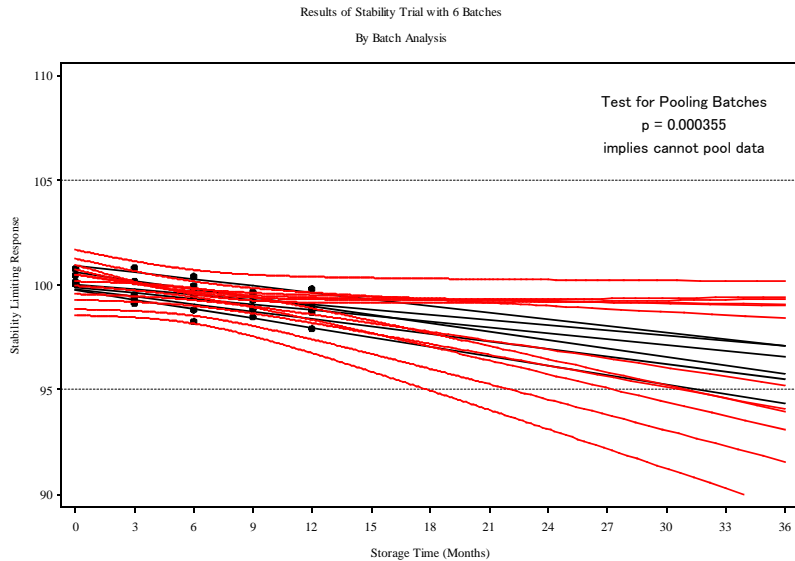
- Using current ICH statistical methodology, the batch data could not be pooled ( $p=0.0314$ , testing directly to common model).
- The result of not being able to pool the batch data is to use the most limiting (worst) batch results to estimate shelf life.
  - based on confidence bounds about each batch's mean response
  - batch with most rapid decline (or first to exceed acceptance criteria – shortest shelf life)
  - gave estimated shelf life of about 22 months
    - short of desired 24-month claim

## Shelf Life Example – By-Batch Analysis

(to continue with a somewhat contrived story line)

- In an attempt to achieve the desired 24-month shelf life claim, three more batches were added to the stability analysis.

## Shelf Life Example using ICH



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## Shelf Life Example – By-Batch Analysis

(to continue with a somewhat contrived story line)

- In an attempt to achieve the desired 24-month shelf life claim, three more batches were added to the stability analysis.
- Again, batch results could not be pooled ( $p=0.000355$ )
  - based on confidence bounds about each batch's mean response
  - batch with most rapid decline (or first to exceed acceptance criteria – shortest shelf life)
  - gave estimated shelf life of about 18 months!!
    - shorter than 3-batch analysis!!

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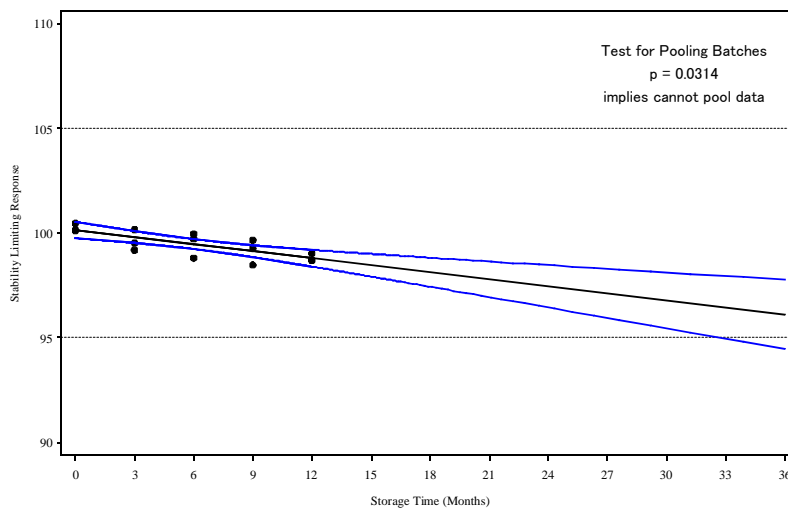
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## Shelf Life Example – Pooled Analysis

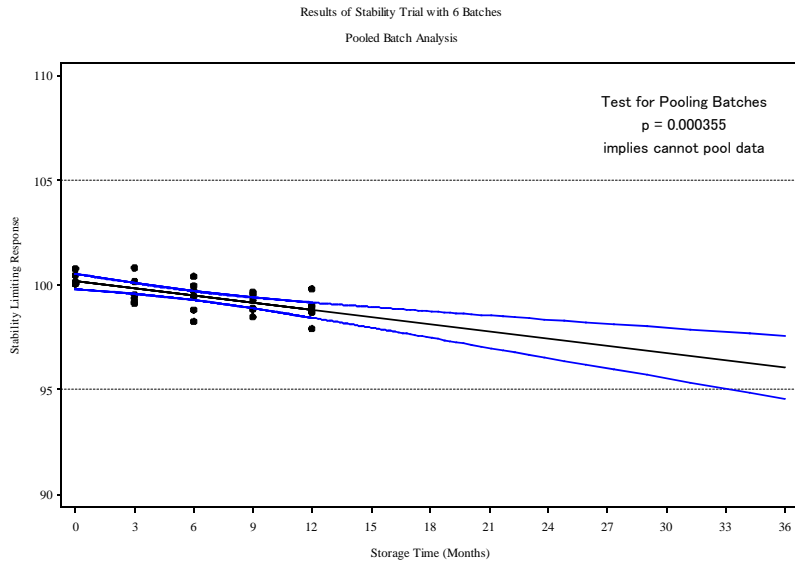
- To see what would have been the resulting shelf life estimate if the batch responses could have been pooled, consider the following 3 and 6-batch analyses.

## Shelf Life Example – Pooled Analysis

Results of Stability Trial with 3 Batches  
Pooled Batch Analysis



## Shelf Life Example – Pooled Analysis



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## Shelf Life Example – Pooled Analysis

- To see what would have been the resulting shelf life estimate if the batch responses could have been pooled, consider the following 3 and 6-batch analyses.
- Both analyses, although unachievable because of the test (abbreviated results presented here) for poolability, would have resulted in acceptable estimates of shelf life.

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## Shelf Life Example – Random Batch Analysis

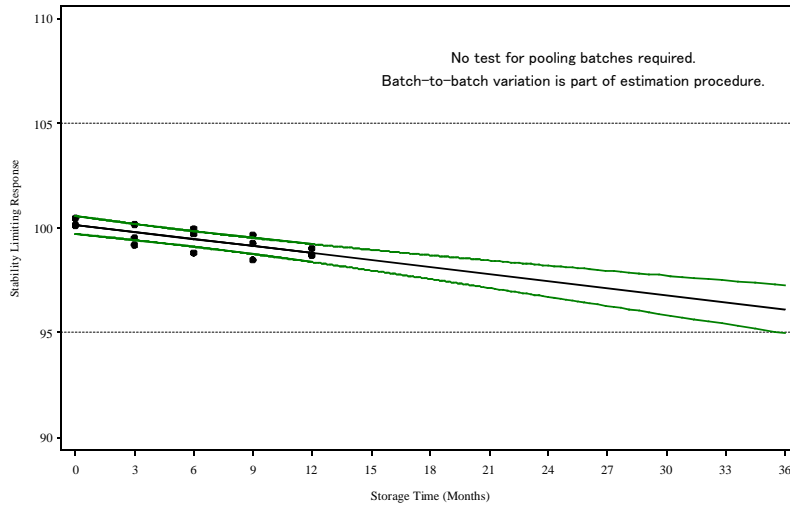
- The Working Group’s proposed statistical analysis takes in to account batch-to-batch variation (random batch effects).
- By appropriately accounting for batch-to-batch variation in the estimation of shelf life, the question and restriction if batches are “poolable” is eliminated.
- Including batch-to-batch variation in the estimation of shelf life, allows for a more straightforward estimation and interpretation of shelf life.

## Shelf Life Example – Random Batch Analysis

- Our work to develop our proposed shelf life estimation methodology is not complete.
- To demonstrate the principles of the methods, the following are plots of the confidence band about the overall response mean, assuming random batch effects.

# Shelf Life Example – Random Batch Analysis

Results of Stability Trial with 3 Batches  
Random Batch Analysis



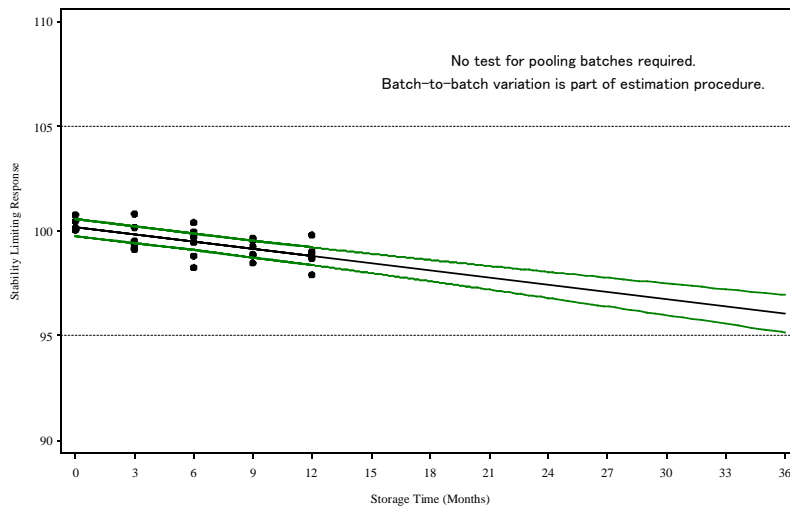
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# Shelf Life Example – Random Batch Analysis

Results of Stability Trial with 6 Batches  
Random Batch Analysis



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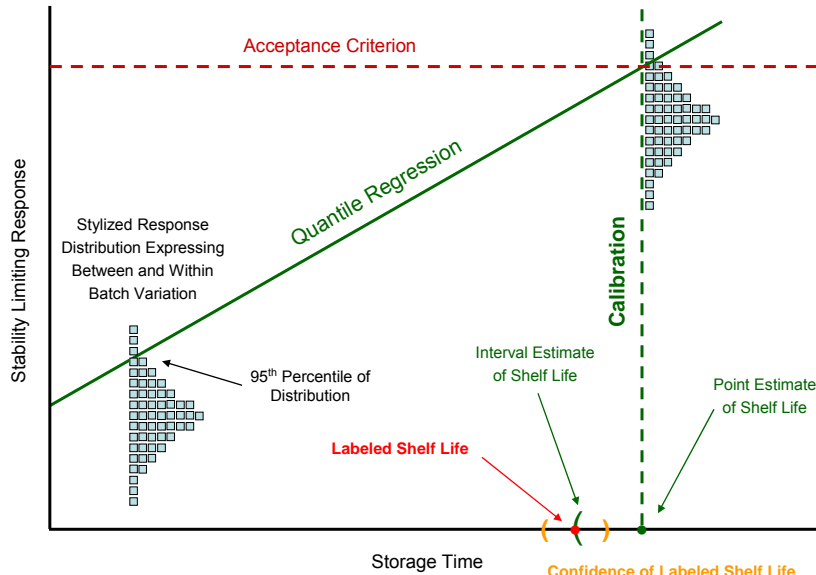
## Shelf Life Example – Random Batch Analysis

- The estimation of shelf life acknowledging batch-to-batch variation as a random effect is an appropriate methodology.
- It avoids the problems of testing the “poolability” of batches, which may result in using the “worst case” batch to estimate shelf life.
- It does not penalize, as in the “worst case” batch scenario, by using all response data to directly estimate shelf life.
- It rewards the shelf life estimate when additional batches are included in a stability study.

## Summary of Proposed Methodology

- The following slides are an overview of the current methodology being developed by the Working Group.
- this is ongoing research
  - the statistical philosophy has been defined
  - not all components of the statistical methodology have been developed
- provides a consistent and flexible methodology for directly estimating shelf life
  - consistent with how acceptance criteria is defined
  - appropriate for modeling percentile response, as well as the overall mean response

## Proposed Shelf Life Estimation Procedure



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## QbD as Part of Shelf Life Estimation

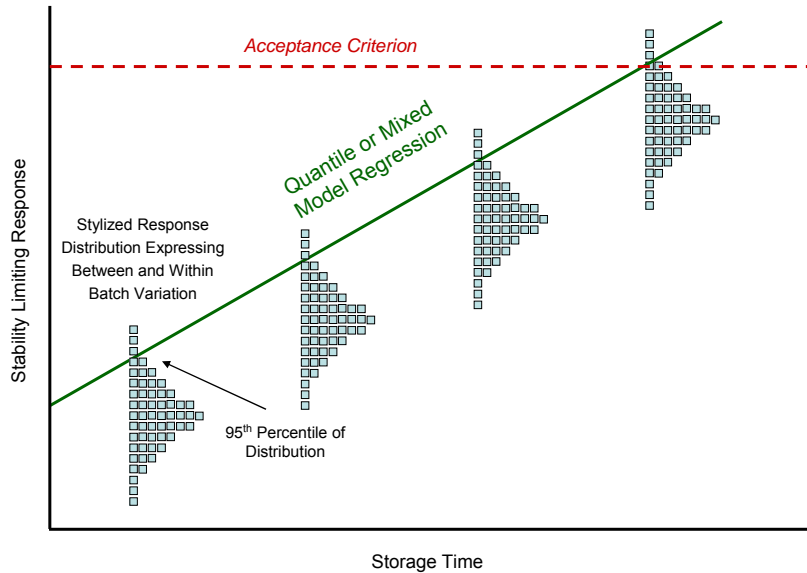
- proposed methodology is not an example of QbD
- however, the methodology does allow for, and addresses, QbD philosophy
  - utilizes all response data to directly estimate shelf life
    - does not rely on a worst batch scenario
    - rewards for including additional batches
  - provides more information about the stability process
    - through flexible modeling of either mean or percentile response
    - directly models between batch variation
    - allows user to define “quality”

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## Proposed Shelf Life Estimation Procedure



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## Proposed Shelf Life Estimation Procedure

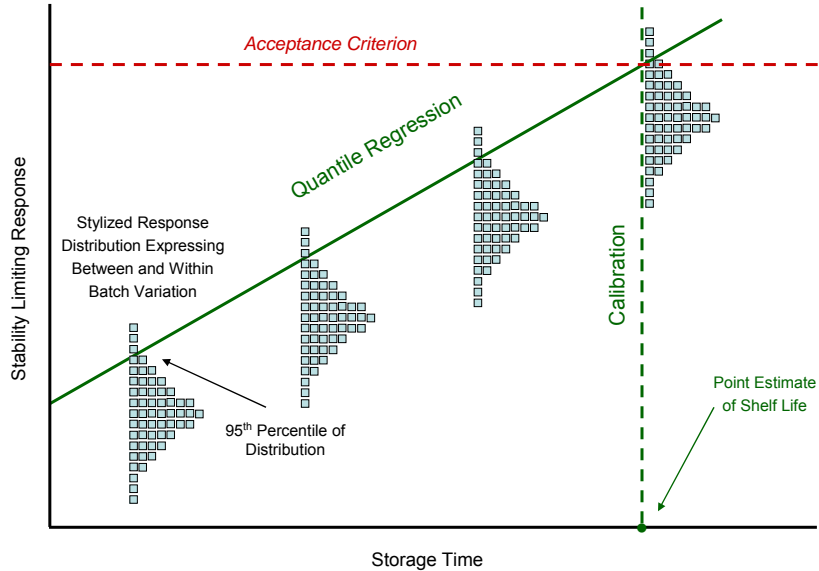
- assumes that the acceptance criteria is defined with respect to the data to be analyzed
- assumes that the acceptance criteria is consistent with the objectives of the stability study
- “quality” is then defined to be consistent with both the acceptance criteria and objectives of the stability study
  - model mean response
  - model percentile response

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## Proposed Shelf Life Estimation Procedure



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## Proposed Shelf Life Estimation Procedure

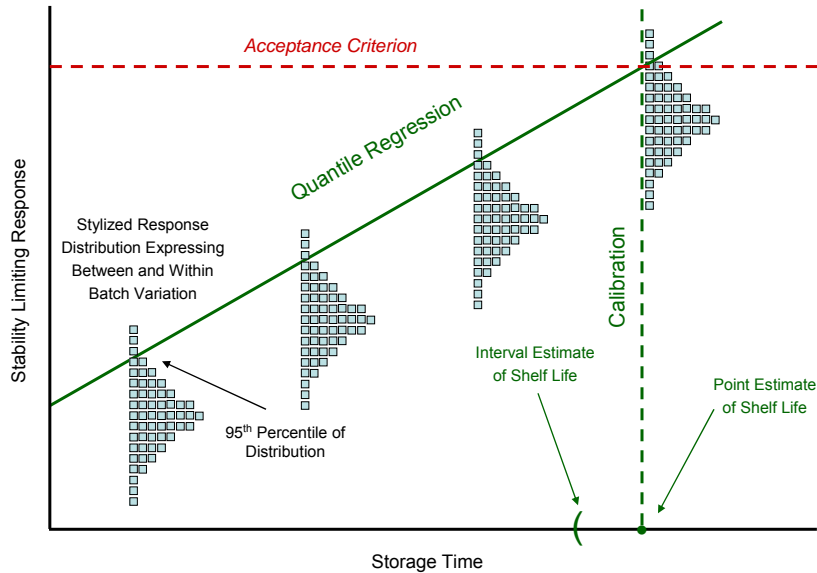
- statistical calibration (inverse regression) techniques are used to obtain a direct estimate of the true shelf life

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## Proposed Shelf Life Estimation Procedure



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## Proposed Shelf Life Estimation Procedure

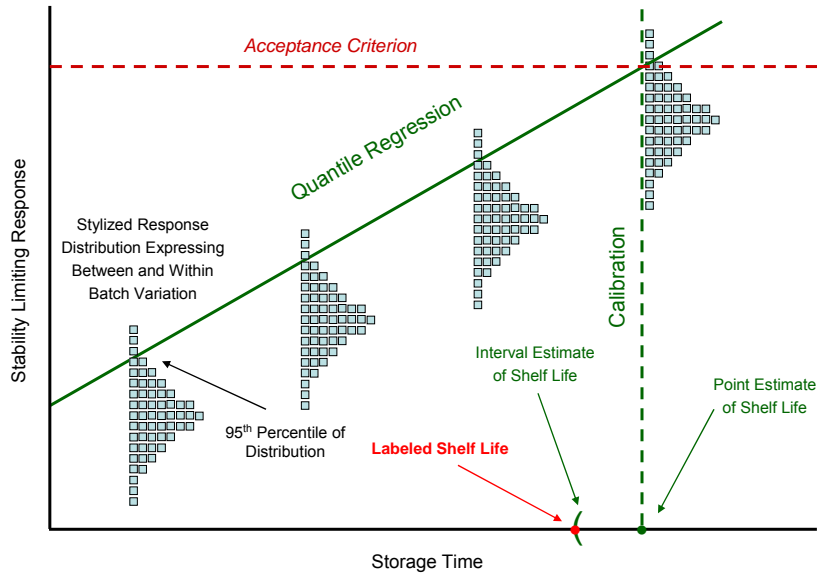
- statistical calibration (inverse regression) techniques are used to obtain a direct estimate of the true shelf life
- recognizing the calibrated estimate of shelf life is an estimate with uncertainty, a lower interval estimate is obtain as a conservative estimate of shelf life

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## Proposed Shelf Life Estimation Procedure



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## Proposed Shelf Life Estimation Procedure

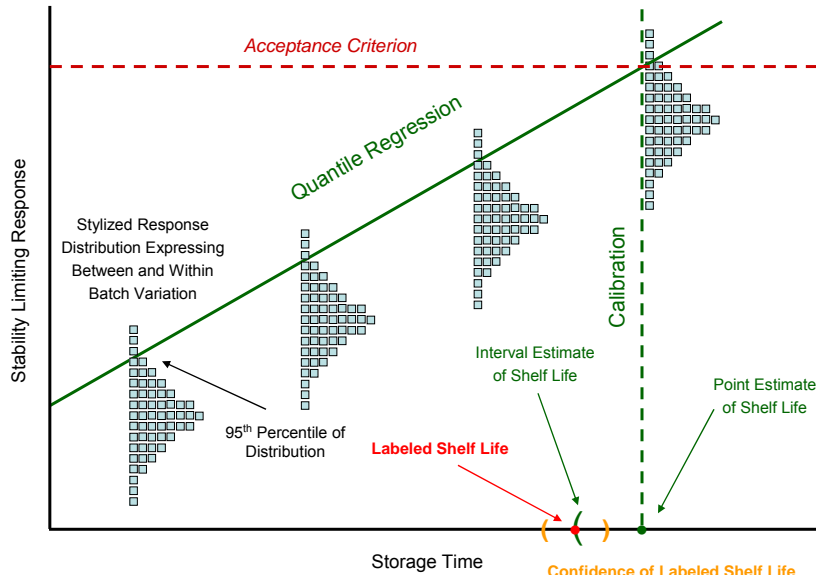
- statistical calibration (inverse regression) techniques are used to obtain a direct estimate of the true shelf life
- recognizing the calibrated estimate of shelf life is an estimate with uncertainty, a lower interval estimate is obtain as a conservative estimate of shelf life
- the lower bound of the interval estimate gives the labeled shelf life

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## Proposed Shelf Life Estimation Procedure



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## Proposed Shelf Life Estimation Procedure

- statistical calibration (inverse regression) techniques are used to obtain a direct estimate of the true shelf life
- recognizing the calibrated estimate of shelf life is an estimate with uncertainty, a lower interval estimate is obtained as a conservative estimate of shelf life
- the lower bound of the interval estimate gives the labeled shelf life
- as added information on the quality of the labeled shelf life estimate, a two-sided interval estimate is obtained about the labeled shelf life

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**Questions?**



**Comments?**

Send us your questions and comments by e-mail to:

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We will end this webinar with our last Q&A period. We are scheduled for another 20 minutes, with the option of going another hour, to answer as many questions as we can. If we still cannot get to all the questions in our Inbox, we will answer each individually as soon as possible.

Again, this e-mail address will remain active as long as the Working Group stays active. E-mail your questions and comments to us at any time. .... Thank you!