



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

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## PQRI

- Product Quality Research Institute
  - Purpose
    - “... serve as a forum for academia, industry and FDA to work cooperatively to conduct pharmaceutical product quality research and to support development of public standards ...”
  - Mission
    - To advance science-based pharmaceutical product quality regulation.

## PQRI Function

- PQRI advances science-based regulation, within the framework of risk management principles by:
  - conducting research and testing
  - collecting, analyzing and interpreting data
  - communicating results of its work to the public
- PQRI develops scientific consensus among regulatory authorities, industry and academia by:
  - providing a forum and process to discuss data and best practices, and to introduce important regulatory questions
  - sharing its research and recommendations through public presentations and publications

## PQRI Strategic Direction

- shift from reacting to Regulatory Guidelines to trying to establish best practices for consideration by regulatory authorities
- embracing the FDA and ICH (Q8, 9 and 10) initiatives and aligning our scientific efforts to support
- extensive use of publications and workshops to stimulate more widespread discussion on important issues related to the quality of pharmaceuticals
- presents consensus recommendations to regulators and standard-setting bodies

## 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
  - creation of a glossary of stability terminology
  - reconsideration of 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

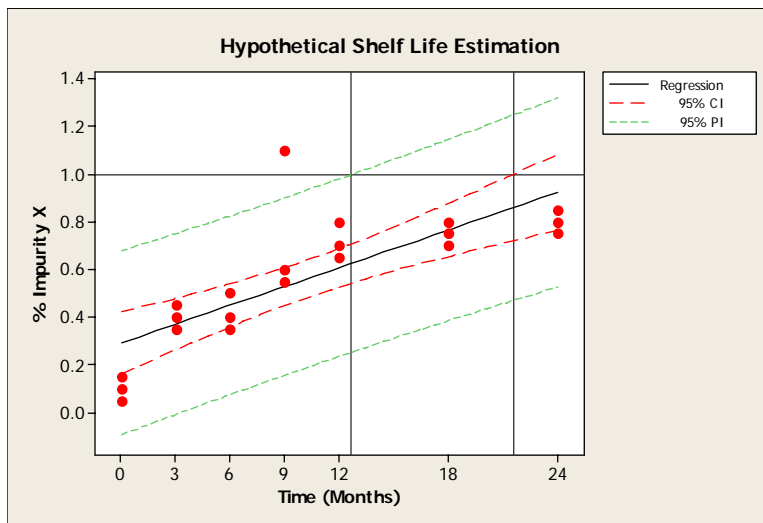
## Stability Shelf Life Working Group

- 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 results

## SSL WG Effort to Date

- began discussions by reviewing ICH Q1E Guideline
  - current issues
    - fixed versus random batches
    - means versus individual response
  - definition of shelf life
  - methods
    - regression model construction
    - strategies for pooling response data

## Stability Issues Example Plot



MBSW: May 19-21, 2008

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## Stability Example Plot

Possible estimates of shelf life:

- 22-months
  - based on ICH confidence interval approach
- 13-months
  - based on prediction intervals
- 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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## 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 and consistent with the common (mis)understanding of shelf life.

## 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 is estimated through 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

## Definitions of Shelf Life

1. The shelf life for a pharmaceutical product is the maximum time at which a stability limiting characteristic stays within acceptance criterion.
  - 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
  - approach which gives little understanding to how the shelf life is mathematically defined

## Definitions of Shelf Life

2. 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 m months will be 50%

## Definitions of Shelf Life

3. The shelf life of a pharmaceutical product is the maximum time at which the response of a stability limiting characteristic for all tablets (or other unit) in the batch does not exceed the specification limit.
  - we assume this is what everyone wants, what many think we ensure, and something we will never be able to guarantee
  - instead of showing all tablets meet specification, current discussions focus on a more appropriate estimate of shelf life when an acceptably high proportion of tablets (or other unit) meet specification
  - beginning research to develop statistical methodology

[Quantile Regression](#)

## Reconsideration of Shelf Life

- reconsideration of the definition of shelf life
  - focus on estimating shelf life as the parameter of interest
    - shelf life of the product
    - based on overall response of product
    - based on a percentage of units within specification
    - need to address question of multiple stability limiting characteristics

## Reconsideration of Shelf Life

- considering several options for estimating shelf life
  - “standard” approaches
    - random and fixed batches
    - confidence and prediction intervals on (overall) batch response
  - alternative approaches
    - quantile regression
    - calibration methods
    - tolerance interval estimates
    - interval estimates based on the distribution of interval estimates

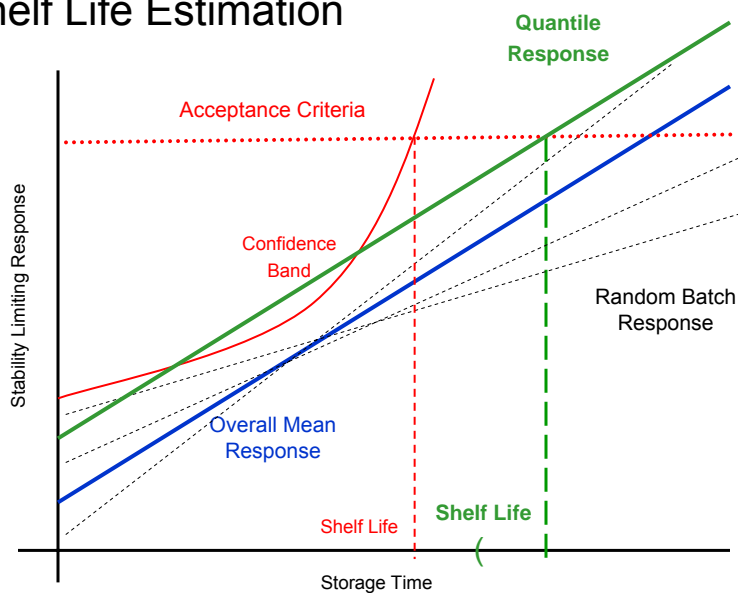
## Quantile Regression

- similar to traditional regression analysis
- estimates the trend in a specified percentile of the response distribution
  - moves focus of regression analysis away from mean
  - characterizes a percentile of the response distribution
    - corresponding to a proportion of observations below (or above) that percentile
  - consistent with Working Group’s [Definition #3](#) for shelf life
- available software is limited
  - SAS® and R routines
  - want to extend to include random batch effects

## Calibration

- based on an estimated regression model characterizing trend in stability data
- allows estimation of the storage time associated with the time the regression model crosses the specification limit
  - classical calibration problem where the value of the specification limit is of interest
- directly estimates shelf life
  - interval estimate about estimated storage time provides estimate of shelf life

## Shelf Life Estimation



## Common Perceived Concerns

- The current ICH methods provide acceptable estimates for shelf life, what are the benefits for proposing new methods?
  - better alignment with common understanding of shelf life of a pharmaceutical product
  - 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

## Common Perceived Concerns

- Why does the definition of shelf life need to be changed?
  - there are two incompatible, yet reasonable, definitions of shelf life in the ICH Q1A guideline
  - compromise is needed between these definitions for better public understanding
    - compromise must satisfy both the
      - need for a scientific foundation for the statistical methodology
      - need for providing a reasonable quality standard
    - will not specifying what level of quality is appropriate, only how to define quality

## Common Perceived Concerns

- Shelf life estimation methods should protect the overall mean response across storage time.
  - public perception is that each individual table (or other unit) is within shelf life limits
  - shelf life should reflect an acceptably high proportion of tablets (or other unit) meeting specification
  - shelf life estimate should address within batch and between batch variation

## 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

## Shelf Life Estimation

- based on calibrated point avoids many problems
  - the issue of using confidence or prediction interval estimates about batch response is avoided
    - shelf life is estimated directly as the parameter of interest
  - discussion is now on what interval estimate to use to estimate shelf life
    - confidence interval
    - prediction interval
    - some tolerance interval
    - distribution of interval estimate

## Tolerance Intervals for Calibration

- an ever-expanding topic with a variety of definitions
  - tolerance intervals are being discussed in both method transfer and stability contexts
- does not seem to be a consistent statement on tolerance intervals that can be easily demonstrated
- making progress on writing a definitive SAS® program on interval estimates
  - for complete understanding to make informed recommendations
  - compare among interval estimates
  - understand predictive capabilities of interval estimates

## Presentations

- presentation at Biometrics and poster at MBSW
  - to investigate
    - confidence and prediction intervals
    - tolerance intervals
      - one and two-sided
      - simultaneous
      - $\beta$ -expectation and  $\beta$ -content tolerance intervals
    - intervals based on distribution of confidence and prediction intervals
  - results should provide us with the necessary tools to recommend an estimate of shelf life

## PQRI Stability Shelf Life Working Group

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