

An Update from the PQRI Stability Shelf Life Working Group

Presented by:

James Schwenke
Boehringer Ingelheim Pharmaceuticals, Inc., U.S.A.

Non-Clinical Statistics Conference
September 23-25, 2008
Leuven, Belgium

Stability Shelf Life Working Group

- PQRI SSL WG
 - Product Quality Research Institute (PQRI)
 - 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.

PQRI SSL WG Webinar

- presented July 8, 2008
 - by-invitation for PQRI membership
 - formal presentation with email questions and answers
- full handout of the presentation can be obtained at
 - http://www.pqri.org/commworking/minutes/pdfs/dptc/sslwg/Addl/PQRI_SSL_WG_Webinar_Presentation_-_08_July_2008.pdf
 - or simply Google “schwenke webinar”
- today’s presentation is a short version of the webinar

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.

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

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.

Stability and Shelf Life

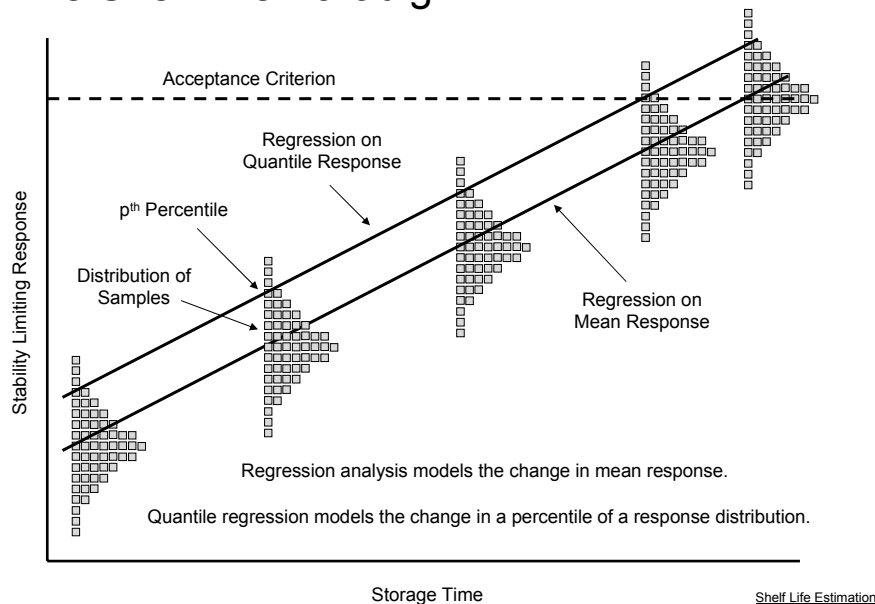
- Primary intention of a shelf life claim is to provide a storage time during which it is ensured that the drug product (stability limiting characteristics) remains within specification.
- Quality by Design (QbD) philosophy encourages the development of robust processes, methods and designs to enhance 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.

NCS: 25 September 2008

PQRI Stability Shelf Life Working Group

8

The Shelf Life Paradigm



NCS: 25 September 2008

PQRI Stability Shelf Life Working Group

9

The Shelf Life Paradigm

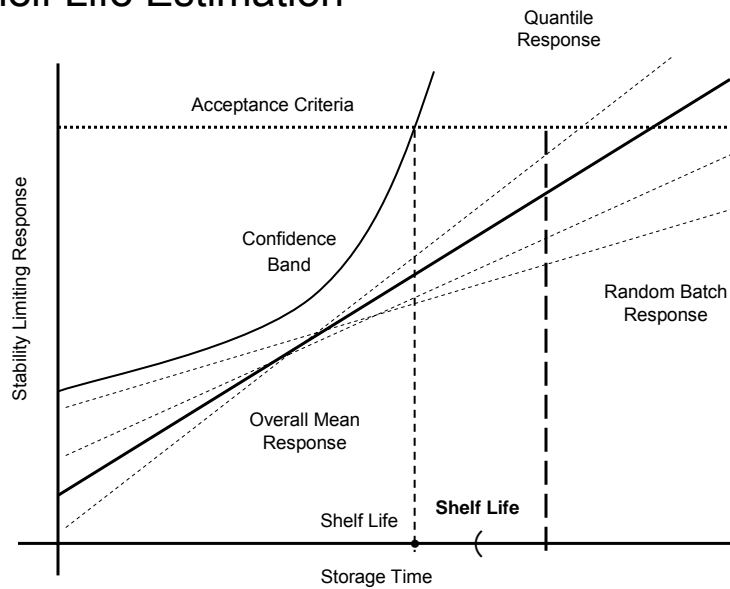
- We assume that the objective of the stability study is consistent with the definition of the acceptance criteria and with the data collected.
- The choice of the value of the percentile to be used for estimating a shelf life is left to the appropriate decision maker. For example:
 - If the objective 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 95th or 99th percentile might be more appropriate.

NCS: 25 September 2008

PQRI Stability Shelf Life Working Group

10

Shelf Life Estimation



Shelf Life Paradigm

NCS: 25 September 2008

PQRI Stability Shelf Life Working Group

11

Summary of Proposed Methodology

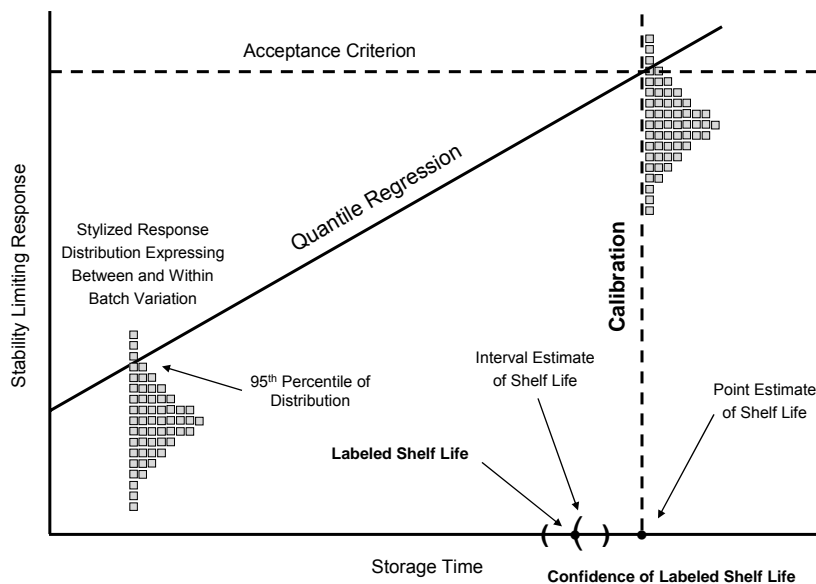
- The following slides are an overview of the current methodology being developed by the Working Group.
- this is ongoing research
 - the statistical philosophy has been defined
 - not all components of the statistical methodology have been developed
- provides a consistent and flexible methodology for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

NCS: 25 September 2008

PQRI Stability Shelf Life Working Group

12

Proposed Shelf Life Estimation Procedure



NCS: 25 September 2008

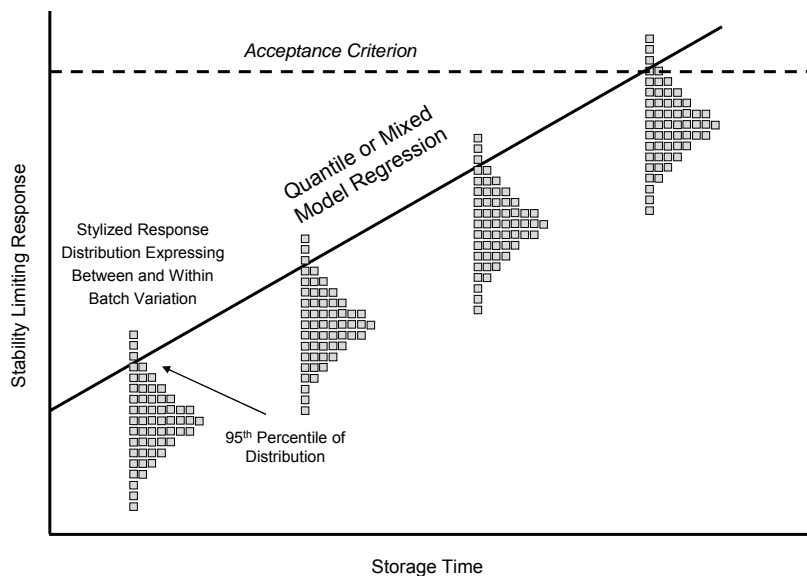
PQRI Stability Shelf Life Working Group

13

QbD as Part of Shelf Life Estimation

- the proposed shelf life estimation methodology, either based on quantiles or the mean, with random batch effects, is consistent with 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”

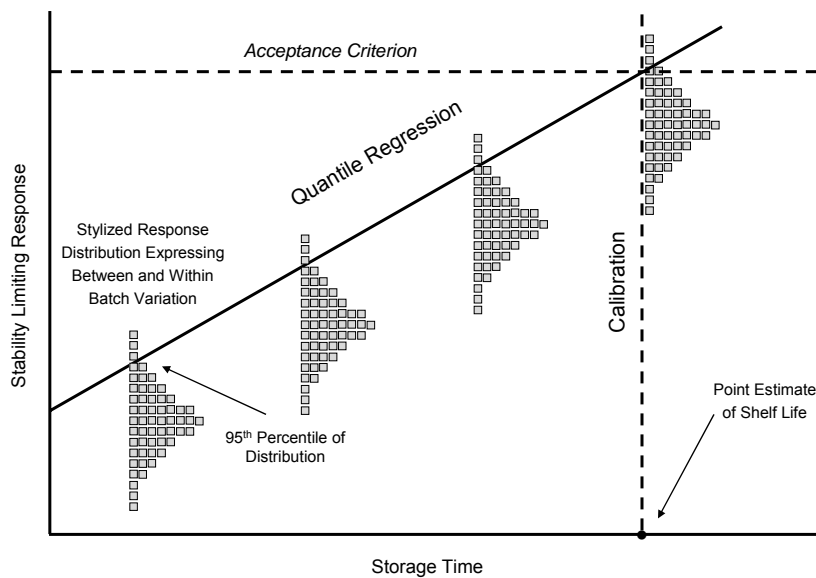
Proposed Shelf Life Estimation Procedure



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

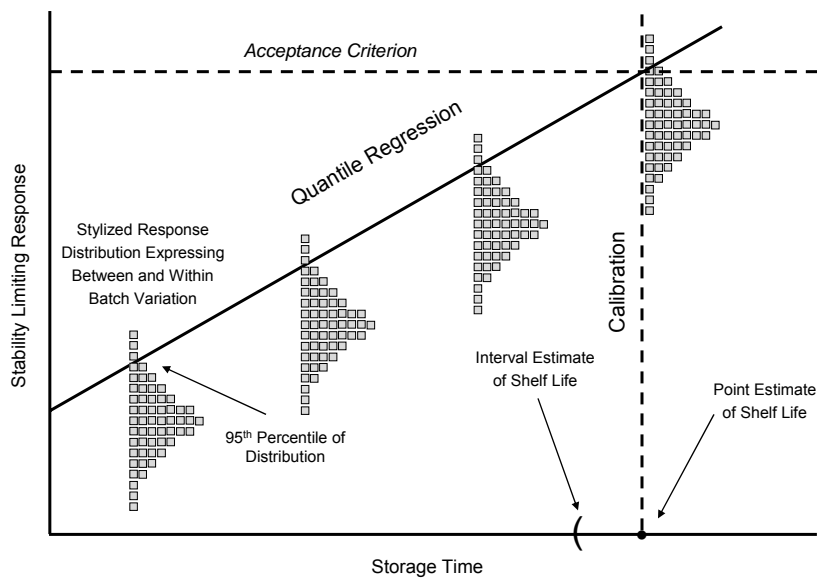
Proposed Shelf Life Estimation Procedure



Proposed Shelf Life Estimation Procedure

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

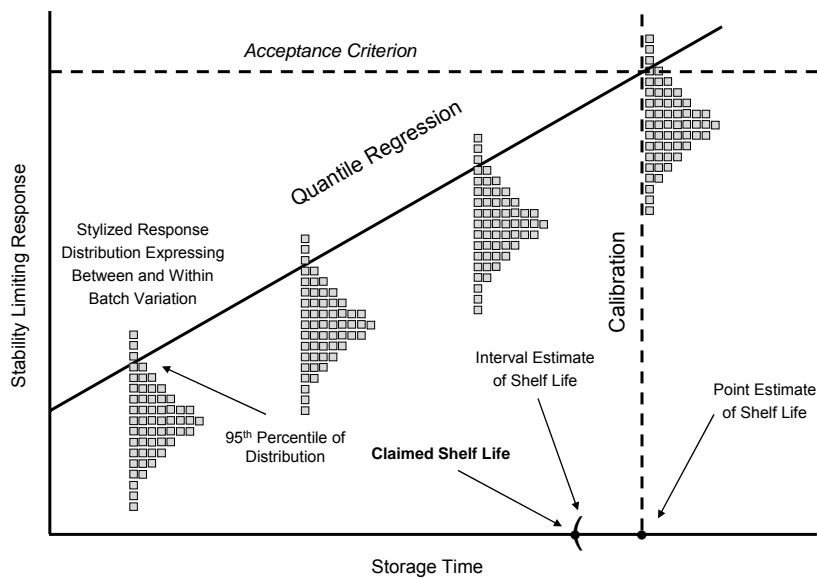
Proposed Shelf Life Estimation Procedure



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

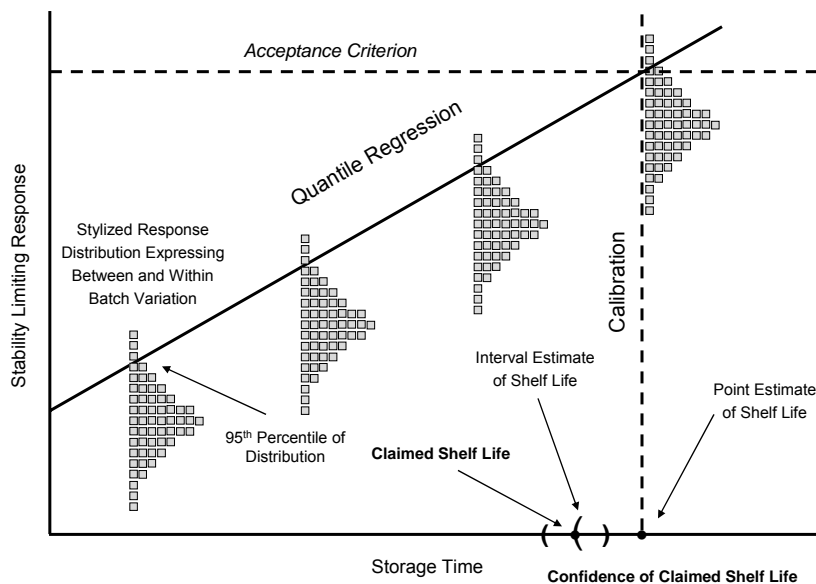
Proposed Shelf Life Estimation Procedure



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 claimed shelf life

Proposed Shelf Life Estimation Procedure



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 claimed shelf life
- as added information on the quality of the claimed shelf life estimate, a two-sided interval estimate is obtained about the claimed shelf life

Questions?



Comments?

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

shelf.life.rdg@boehringer-ingelheim.com

We will answer each question 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!