Stability Shelf Life
Working Group

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on behalf of the Working Group

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Outline

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• ICH Guidelines for Shelf Life Estimation
• Distributions
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  – Batch Shelf Lives
• Research Efforts of Working Group
  – Fixed vs. Random Batches
  – Simulation Example of Shelf Life Estimation Procedures
  – Quantile Regression with Random Effects
• Accomplishments of Working Group
• Summary
Background: PQRI Stability Shelf Life Working Group

• Established in late 2006
• Purpose
  “investigate and develop improved statistical approaches for setting shelf life based on stability data…put forth for consideration with respect to existing regulatory guidances”
• Objective
  “consider current regulatory guidances and scientific literature to propose enhancements, consistent with QbD principles, regarding CMC/statistical issues in shelf life estimation”
• Members include statistical and pharmaceutical scientists from industry, regulatory agencies, and academia
Working Group Members

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

• Shelf life (expiration dating period): “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.”

(ICH Q1A (R2))
ICH Guidelines for Shelf Life Estimation

• Q1E states the purpose of a stability study is to establish

“with a high degree of confidence, a retest period or shelf life during which a quantitative attribute will remain within acceptance criteria for all future batches [emphasis added] manufactured, packaged, and stored under similar circumstances.”

• Q1A: shelf life should be determined based on a minimum of three batches
ICH Guidelines for Shelf Life Estimation

• Shelf life estimate is determined by the earliest time at which the 95% confidence interval for mean response of a stability limiting characteristic intersects the acceptance limit, treating batches as fixed effects.
ICH Guidelines for Shelf Life Estimation

• Implicit in ICH are the definitions of
  o *Batch* shelf life: time the batch mean response over time (i.e. batch-specific regression line) crosses the acceptance limit
  o *Product* shelf life: the minimum batch shelf life
  o These are not explicitly defined but are inferred from the prescribed methodology

• ICH objective
  → Estimate the **minimum** batch shelf life
Batch Response Over Time

One Batch

Batch shelf life

True batch response

Storage Time
Batch Response Over Time

Three Batches

Batch shelf lives

worst case (three batches)
Adding More Batches

Six Batches

Batch shelf lives

worst case (three batches)

worst case (six batches)
Distribution of Batch Responses Over Time
Depiction of Two Distributions

Y = Stability-Limiting Resp

Distribution of batch responses over time (y-axis)

Product shelf life

Distribution of batch shelf lives (x-axis)
ICH Guidelines for Shelf Life Estimation

• Data from individual batches can be pooled together as if observed from one batch
• ICH guideline suggests a statistical testing procedure for batch poolability using $\alpha = 0.25$
• Poolable?
  YES $\Rightarrow$ Use all data and compute CI for mean
  NO $\Rightarrow$ Use worst batch and compute CI for mean

Either way the objective is to estimate the minimum batch shelf life
ICH Guidelines

- Product Shelf Life
  - Allowable shelf life of worst batch
- Adding more batches:
  - Less likely to pool
  - Shelf life is more often based on a single, worst case batch
ICH Methodology

- ICH addresses objective of estimating the minimum shelf life, but with important limitations
  - Estimate obtained applies only to batches used in analysis, but goal of inference is supposed to be *future batches*
  - Increasing the number of batches tends to lead to a decreased estimate of shelf life regardless of the true minimum shelf life
    - Ex: Weigh same stone daily on same balance, smallest recording becomes lower as years pass - not because stone or balance are changing, but because measurement variability makes a new “record low” inevitable
- Stability Shelf Life Working Group established to
  - Investigate ICH methodology/current regulatory guidance
  - Address the ICH limitations
PQRI Stability Shelf Life Working Group

• Research efforts include developing alternative statistical methodology based on a transparent relationship between ICH methodology and product shelf life

• Outcomes of our discussions and efforts:
  o Treating batches as random effects
  o Advancements to the methodology allowing estimation of quantiles of the distribution of batch shelf lives in addition to the mean
Fixed vs. Random Batches

- ICH methodology treats batches as **fixed** effects
  - Result: shelf life estimate is only applicable to those batches observed
- Mixed model analysis treats batches as **random** effects
  - Accounts for batch-to-batch variation
    - Allows variation among batches to be part of estimation process
  - Batches are viewed as a sample from the *population* of batches in order to characterize the distribution of batch shelf lives
  - Result: shelf life estimate is applicable to future batches
- Mixed model is an alternative approach to tests for poolability
Example: Fixed vs. Random Using Real Data
ICH (six batches) = 15.2 months

Mixed Model = 26.8 months
Benefits of Random Batch Analysis

- Mixed Model appropriately accounts for batch-to-batch variation
- Eliminates the issue of batch poolability by allowing the sources of variation to be a part of the estimation process
- Inference can be made to future batches; estimated shelf life is applicable to all future batches (ICH Q1E)
- Appropriate modeling of batch-to-batch variation allows for more straightforward estimation and interpretation of shelf life
Desirable Characteristics of the “Ideal” Shelf Life Estimation Procedure

• Estimate a suitably small quantile of batch shelf lives (consistent with ICH objective of estimating the minimum)
  o Batch shelf life is the time the batch-specific regression line intersects the acceptance limit (consistent with ICH)
  o Distribution of responses in a random batch analysis is used to estimate a quantile of the distribution of batch shelf lives (on x-axis)
    o Methods are being investigated to accomplish this

• Allow a more transparent connection between the estimation of shelf life and the management of risk
Recall: Depiction of Two Distributions

Distribution of batch responses over time (y-axis)

Product shelf life

Distribution of batch shelf lives (x-axis)
Simulation Example: Actual, ICH, LMM, & W.I.P.

3 batches

Some ICH results are extreme under- and over-estimates

95th percentile of distribution matches 5th percentile of actual distribution of batch shelf lives
Simulation Example: Actual, ICH, LMM, & W.I.P.

6 batches

As the number of batches increase, LMM is less variable than ICH.

95th percentile matches 5th percentile of actual distribution of batch shelf lives.
Modeling a Quantile Instead of the Mean

• No change to ICH definition
  o *Batch* shelf life: time the batch mean response over time (i.e. batch-specific regression line) crosses the acceptance limit
  o *Product* shelf life: the minimum batch shelf life

• ICH objective: establish a shelf life that provides consumers confidence the drug product will retain its strength and quality throughout the expiration dating period
  o Modeling a quantile of the distribution of batch means over time (i.e. regression lines) can be more appropriate than modeling the mean of that distribution
  o Quantiles can be modeled using quantile regression
Quantile Regression

- Quantile Regression models a quantile of the response distribution over time
  - Behavior of response distribution may change depending on the quantile of interest
  - Quantile regression minimizes an asymmetrically weighted sum of absolute errors (not squared error loss)
Quantile Regression with Random Effects

- Quantile regression with random effects models a quantile of the distribution while making inference to entire population of batches.
- No fully developed methodology
  - SAS® Proc Quantreg can be used only if batches are fixed.
- Ad hoc approaches have been considered.
- Goal is to develop new method and theory for Mixed Model Quantile Regression
  - Estimate variance components and predict random effects.
Accomplishments

• Based on ICH prescribed methodology, Working Group has proposed a quality standard for shelf life estimation based on two distributions:
  
  1) Distribution of changes in batch means over time (i.e. regression lines)
  
  2) Distribution of batch shelf lives

• Working Group has provided an enhanced understanding of
  
  o Shelf life estimation
  
  o Tolerance intervals
  
  o Random Batch Effects
  
  o Quantile Regression
Accomplishments

• Working Group has developed statistical approaches using a linear mixed model to
  1) Characterize the distribution of batch shelf lives
  2) Use this distribution to address the ICH objective
• Our research, together with an enriched interpretation of ICH objectives, has informed and directed the efforts of the Working Group
• Working Group has made various presentations/papers on its research…
Accomplishments - 2007

- Jackie Wroughton’s PhD dissertation (UNL Department of Statistics)
  - Research preceded establishment of the Working Group

- Midwest Biopharmaceutical Statistics Workshop (MBSW)
  - Poster presentation

- American Statistical Association Joint Statistical Meetings (JSM)
  - Oral presentation and paper for proceedings
Accomplishments - 2008

• Eastern North American Region (ENAR) International Biometrics Society Meetings - *Oral presentation*
• Midwest Biopharmaceutical Statistics Workshop (MBSW)
  - *Oral and poster presentation*
• Hosted Webinar highlighting our purpose and research efforts
• Joint Statistical Meetings (JSM)
  - *Oral presentation and paper for proceedings*
• Presentation given at USDA
• Nonclinical Statistics Conference in Leuven, Belgium
  - *Poster and two oral presentations*
• Presentation given to University of Connecticut Department of Statistics
• AAPS Annual Meeting - *Poster presentation*
Accomplishments - 2009

• PhRMA Leaders Meeting
  - Co-chairs invited as Stability Break-Out session speakers
• Eastern North American Region (ENAR) International Biometrics Society Meetings - Oral presentation
• Midwest Biopharmaceutical Statistics Workshop (MBSW) - Poster presentation, won 1st place Charlie Sampson Poster Award
• Joint Statistical Meetings (JSM) - Oral presentation
• FDA/Industry Statistics Workshop Panel discussion - Working Group Co-chair served as principal panelist, three other members served on the panel
• Non-Clinical Biostatistics Conference - Poster presentation
• Michelle’s Ph.D. dissertation (UNL Department of Statistics) - Expected date of completion May 2010
Future Publications

• Paper being written to clarify the operating definition of shelf life implicit in ICH guidance
  o True shelf life
  o Estimated shelf life
  o Claimed shelf life

• Subsequent paper(s) will focus on
  o ICH methods
  o Mixed model on the mean with random batches
  o Quantile Regression with fixed and random batches
  o Connection between distribution of batch mean responses over time and distribution of batch shelf lives
Summary

• ICH objective: estimate the minimum batch shelf life
  o Methodology treats batches as fixed effects
    □ Estimate is not directly applicable to future batches
  o Accounts for batch-to-batch variation via tests for poolability

• Linear Mixed Model
  o Accounts for batch-to-batch variation by treating batches as random effects
    □ Estimate is directly applicable to future batches
  o Alternative approach to tests for poolability

• Quantile Regression with random effects estimates a quantile of the distribution of batch responses, treating batch effects as random
  o Combines ICH objective with Linear Mixed Model to focus on characterizing distribution of batch shelf lives
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