PQRI Stability Shelf Life Working Group

Michelle Quinlan[1], Walt Stroup[1], James Schwenke[2]
[1]University of Nebraska-Lincoln
[2]Boehringer Ingelheim Pharmaceuticals, Inc.

Product Quality Research Institute (PQRI)

http://www.pqri.org

❑ **Founded 1999 as a collaborative effort by Center for Drug Evaluation and Research (CDER)/FDA, AAPS, and several pharmaceutical industry associations**

❑ **Focuses on research projects whose results provide continuing scientific basis for regulatory policy**

❑ **Results of research are submitted to CDER to help ensure the quality, safety, performance of pharmaceutical products**

❑ **Member organizations cover a wide variety of scientific issues related to pharmaceutical products**

❑ **Mission: Conduct research/gather information through working groups and technical committees on regulatory pharmaceutical practices**

❑ **PQRI Structure:**

- Board of Directors
  - ❖ Authority over collection/disbursement of funds
  - ❖ Conduct administrative procedures required to ensure effective operation
- Steering Committee
  - ❖ Composed of members from sponsoring organizations
  - ❖ Sole authority over all scientific activities
  - ❖ Responsible for recommending all Institute funds spent for activities
- Technical Committees (4)
  - ❖ Provide technical and scientific guidance, direction, review for PQRI Working Groups
  - ❖ Consist of scientists/regulatory experts from industry and FDA
  - ❖ Make technical/scientific recommendations to Steering Committee
- Working Groups
  - ❖ Guided by technical committee
  - ❖ Consist of scientists from industry, academia, FDA
  - ❖ Generate, evaluate, discuss information
  - ❖ Develop PQRI recommendations, technical reports, scientific papers

❑ **Working Groups overseen by Technical Committees:**

- Drug Product Technical Committee (DPTC)
  - ❖ Includes Stability Shelf Life Working Group
- Drug Substance Technical Committee (DSTC)
- Manufacturing Technical Committee (MTC)
- Biopharmaceuticals Technical Committee (BTC)

Stability Shelf Life Working Group (SSL WG)

❑ **Formed in 2006**

❑ **Members of Working Group include Statistical and Pharmaceutical Scientists from industry and academia**

- James Schwenke (Co-Chair), *Boehringer Ingelheim*
- Pat Forenzo (Co-Chair), *Novartis*
- Suntara Cahya, *Eli Lilly*
- Dave Christopher, *Schering Plough*
- Michael Golden, *GlaxoSmithKline*
- Paula Hudson, *Eli Lilly*
- Nate Patterson, *Vertex*
- Michelle Quinlan, *University of Nebraska-Lincoln*
- Dennis Sandell, *Siegfried Pharma Development*
- Trace Searls, *Sandoz*
- Walt Stroup, *University of Nebraska-Lincoln*
- Dave Thomas, *Johnson&Johnson*
- Terry Tougas, *Boehringer Ingelheim*

❑ **Objective: Investigate and develop improved statistical approaches for setting shelf life based on stability data**

- Review current ICH guidelines and best practices in the estimation of shelf life or retest period for stability indicating quality attributes of pharmaceutical products
- Suggest improved or alternative statistical approaches for estimating shelf life or retest periods that are consistent with Quality by Design (QbD) philosophy

❑ **Potential impact of research:**

- Extend scientific knowledge with respect to evaluating pharmaceutical product stability data
- Improve understanding of new/existing pharmaceutical products
- Facilitate application of QbD principles
- Enhance safety and efficacy through a more accurate estimation of shelf life

❑ **Current work:**

- Develop relevant, consistent, appropriate philosophy and terminology suitable for shelf life estimation
- Provide required foundation for further theoretical work
- Discuss and clarify issues related to shelf life methodology
- Develop Data Warehouse
  - ❖ Advertise for contributed data sets
  - ❖ Compile industry data
  - ❖ Validate/test results with data

❑ **Preliminary topics to be addressed:**

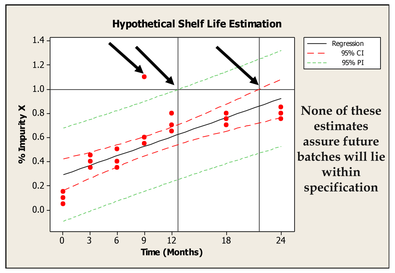
- Random batch analyses to address future batch release
- Regression (model based) versus ANOVA methods
- Quantifying future observations
- Quantifying future confidence/prediction intervals

❑ **Future research:**

- Review strengths/weaknesses of current guidelines and common industry practices for establishing shelf life
- Investigate statistical pooling of batch response data or other stability study design factors (i.e. storage orientation, package type, etc.)
- Extend statistical approaches to tests on multiple stability limiting product characteristics in determining shelf life

SSL WG Work Plan

❑ **Shelf Life Estimation/Definition of Problem**



- This figure represents four potentially different estimates of shelf life stemming from different interpretations:
  - ❖ 22-month shelf life based on confidence interval (direct interpretation of ICH guidelines)
  - ❖ 13-month shelf life could be supported by prediction interval
  - ❖ 9-month shelf life could be defined dependent on out-of-spec observation at 9-months
  - ❖ Disregarding out-of-spec observation at 9-months, a 24-month shelf life could potentially be judged reasonable
- However, none of the hypothetical shelf life estimates obtained without statistical support assure the avoidance of out-of-spec results up to the claimed shelf life
- Primary intention of shelf life is to provide a storage time during which it is ensured the drug product remains within specification
- Current approaches to specifications, acceptance criteria and shelf life determination do not provide this guarantee

❑ **One-Sample Distribution**

- Complete tolerance interval simulations
- Develop “prediction bounds” for future confidence/prediction intervals
- Conduct simulation study to investigate bootstrap coverage for future confidence/prediction intervals

❑ **Extension to Regression Analysis (Fixed Batch Effects)**

- Extend one-sample distribution development to linear/nonlinear models
- Incorporate simultaneous adjustments
- Conduct simulation study to determine the meaning of simultaneous interval estimates

❑ **Extension to Mixed Models (Random Batch Effects)**

- Extend regression development to random batch problem
- Consider linear/nonlinear regression models
- Consider analysis of variance models as a “model-free” approach
- Consider time-dependent sequential “prediction” bounds
- Conduct simulation study to characterize properties

❑ **Application to Shelf Life**

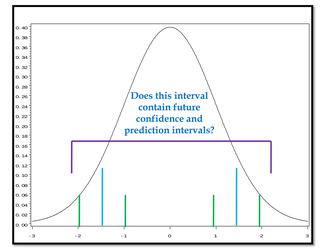
- Apply statistical methods for fixed/random batch effects
- Discuss time-dependent alert limits for trend analyses
- Characterize effectiveness to bound future confidence/ prediction intervals and out-of-spec observations
- Consider time-dependent sequential approach through analysis of variance techniques for fixed/random batches

Work Plan Preliminary Results

❑ **Validating simulation procedures**

- Run simulations to investigate coverage of confidence, prediction, tolerance, simultaneous tolerance intervals
  - ❖ Validate simulation strategy for future complex simulations
  - ❖ Become confident procedure produces accurate, reliable results
- Confidence Intervals (CI): mean response
- Prediction Intervals (PI): future response
- Tolerance Intervals (TI): percentile of a distribution
- Simultaneous Tolerance Interval: % of the data

❑ **What are Simultaneous Tolerance Intervals?**



❑ **SAS® PROC CAPABILITIES** (method 3) may be used to create a 2-sided simultaneous tolerance interval

- Protects at least *p%* of the data (common definition of tolerance interval)

❑ **Protecting future confidence/prediction intervals**

- TIs protect all simulated CIs, but not desired % of PIs
- Using Bonferroni’s method (α/m) to correct for multiple comparisons:
  - ❖ Simultaneous TIs protect future PIs with expected coverage
  - ❖ Expected vs. actual coverage varies slightly depending on α level

❑ **Characteristics of future confidence/prediction intervals:**

- Coverage of TIs does not depend on percentile, only on α level
- Changing μ/σ does not affect coverage of future CI/PIs
- Results based on simulations using 1,000 iterations (n = 30 for each iteration)

❑ **Bootstrap simulations**

- Bounds using empirical distribution of CI/PIs do not protect future CI/PIs
- Bootstrap method:
  - ❖ Too narrow for protecting future CI/PIs
  - ❖ Too wide for protecting future observations
- Large variation in coverage rates between simulations (each consisting of 1,000 iterations)

❑ **Preliminary results will be used to:**

- Propose statistical methodology for stability analysis
  - ❖ Estimate/confirm shelf life
- Consider time-dependent alert limits for trend analyses
- Conduct simulation study to compare different stability analysis scenarios
  - ❖ Consider fixed vs. random batch analyses for estimating shelf life
- Use industry data to demonstrate appropriateness of methodology