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 Finrence (Co-Chair), Novartis
  - Sunanta 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 Saaria, Sandzoe
  - Walt Stroup, University of Nebraska-Lincoln
  - Dave Thomas, Johnson and Johnson
  - Terry Toupas, 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
- 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
  - Conduct "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
  - Conduct analysis of variance models as a "model-free" approach
  - 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
  - Conduct 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 Confidence Intervals?
- 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)
- Characteristics of future confidence/prediction intervals:
  - Coverage of Tls does not depend on percentile, only on a level
  - Changing µ1 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