

**Topic Contributed Paper Session Proposal
JSM 2010, Vancouver, BC**

Session Title	<u>Pharmaceutical Stability Shelf Life: Philosophy, Intent and Estimation</u>
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Session Description	<p>The estimation of a pharmaceutical's shelf life is an important part of the NDA (new drug application) process toward obtaining FDA approval for marketing. Guidance is provided by FDA on the estimation of shelf life through the ICH (International Conference on Harmonization) documents Q1A (R2) – Stability Testing of New Drug Substances and Products and Q1E – Evaluation for Stability Data, both published in 2003. Several pharmaceutical industry organizations currently have working groups that are giving critical review of these guidances. The organizer and invited speakers of this proposed paper session are members of the Product Quality Research Institute (PQRI) Stability Shelf Life Working Group. At the end of 2009, we conclude a 3-year effort to provide a critical review of the current practices and suggest alternative statistical methodology for shelf life estimation. These speakers will provide an overview of the efforts of the Working Group from expanding upon the definition and intention of shelf life, a comparison of current and alternative estimation practices, and presentation of current advances in mixed model and quantile regression methods incorporating random batch effects for estimating shelf life. The organizer and invited speakers represent leaders in the area of shelf life methodology and estimation from FDA, the pharmaceutical industry and academia.</p> <p>This paper session is of interest to members of regulatory agencies governing pharmaceutical products, both nonclinical and clinical statisticians involved with the estimation of shelf life, and statisticians interested in current applications and advancements in mixed model and quantile regression theory and practices.</p>
Session Format	5 Speakers (20 minutes each) Q&A (10 minutes)

An Industry Perspective on Shelf Life and the PQRI Initiative**Abstract #307028**

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For pharmaceutical products, shelf life is the period of time during which a product, if stored correctly, is expected to comply with specifications as determined by stability studies. Regulatory guidance is provided in the ICH Q1A (R2) and Q1E documents which help to define current practices in the estimation of the shelf life of a pharmaceutical product. The Product Quality Research Institute Stability Shelf Life Working Group (PQRI SSL WG) was established in 2006 to provide a review of the philosophy, intent and statistical methods for estimating shelf life. This session provides an overview that effort, presented by members of the Working Group.

keywords: shelf life, PQRI, ICH

Some Reflections About Shelf Life**Abstract #306970**

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The shelf life of a pharmaceutical product is a key concept. The intention with this is to provide the user with guidance on how long the product can be used. ICH guidances describes shelf life as the time during which a pharmaceutical product consistently meets certain requirements that are needed to fulfill safety and efficacy claims, and also recommends a procedure how to determine the shelf life. When the PQRI SSL Working Group started its effort to study alternative shelf life estimation procedures it soon became apparent that published information concerning the formal “mathematical” definition of shelf life was unclear or even contradictory. A clarified language and alternative definitions were developed. Understanding the meaning and intention of a shelf life claim provides the framework for developing and comparing statistical methodologies consistent with the WG’s discussions.

keywords: shelf life

Current Practices in Shelf Life Estimation**Abstract #307026**

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Current practices as suggested by the ICH guidelines for the estimation of shelf life are based on the results of a stability study involving a minimum of three batches of the pharmaceutical

product. The suggested statistical methodology considers batch as a fixed effect, allowing for the pooling of the data from the batches if there are no significant batch effects, using $\alpha=0.25$. Typically, 95% confidence intervals are constructed for the individual or pooled batch mean response which is used to determine the allowable shelf life claim. Using a real-life data set, the current shelf life estimation methodology will be demonstrated, highlighting some of the controversial aspects of the methodology that inspired the PQRI Stability Shelf Life Working Group.

keywords: shelf life, estimation, pooling

The Philosophy and Intent of Stability Shelf Life

Abstract #306934

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To expand discussion on the current definition of shelf life, a key problem had to be addressed in that, for clinical research and development, a pharmaceutical product is generally judged on the basis of mean response, while commercial batches are essentially judged by individual results. In addition, perceived expectations of the consumer were also considered. Development of a statistical methodology for estimating shelf life must be done in consideration of the issues and challenges of assessing and managing risk relative to different quality standards.

keywords: shelf life, risk assessment, quality standard

Alternative Shelf Life Estimation Methodologies

Abstract #307030

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PQRI Stability Shelf Life Working Group has worked to advance statistical methodology to estimate shelf life consistent with considerations articulated elsewhere in this session. Methodology and inference implicit in fixed and random batch approaches are examined. In some cases standard mixed model procedures suffice. Other cases require consideration of a quantile of the relevant distribution to assess whether a product meets pre-specified acceptance limits. We consider fixed and random batch quantile regression. For fixed batches, standard quantile regression is useful for estimating shelf life. Random batches require new quantile techniques. Methods using existing statistical software and extension of quantile regression to random batch effects are presented. Comparison of shelf life estimation results from the various methods is made via simulation and using a real-life data set.

keywords: shelf life, random batch effects, quantile regression