Establishing the Shelf Life of Pharmaceutical Products

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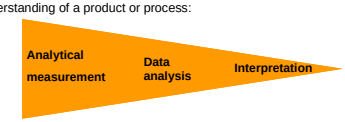
On behalf of the PQRI Stability Shelf Life Working Group

INTRODUCTION

At least three distinct steps are necessary to gain knowledge and understanding of a product or process:



The quality within each step influences the quality of the resulting knowledge. Therefore, developing and instituting best scientific methods at each step supports the ongoing Quality-by-Design (QbD) and the 21st Century Manufacturing initiatives by enabling the greatest understanding of a product or process.

Statistical analysis of stability data and the relationship of this process to the setting of product specifications has been a subject of discussion among those who conduct measurements, analyze data, and make decisions based on the information.

The PQRI Stability Shelf Life (SSL) Working Group was formed in late 2006 to investigate current and alternative statistical methods for estimating the shelf life of pharmaceutical products with stability data. The interest in alternative methods was stimulated by several factors: (1) the need to make statistical approaches more compatible with larger and larger amounts of data collected under QbD; (2) the desire to avoid a "circular argument" when product specifications and shelf life are determined from the same set of data rather than separately (specifications based on critical product attributes rather than capability); and, (3) the desire to make practices for setting shelf life compatible with the expectations of shelf life from regulatory bodies and the general public.

SHELF LIFE DEFINITIONS

General Concepts

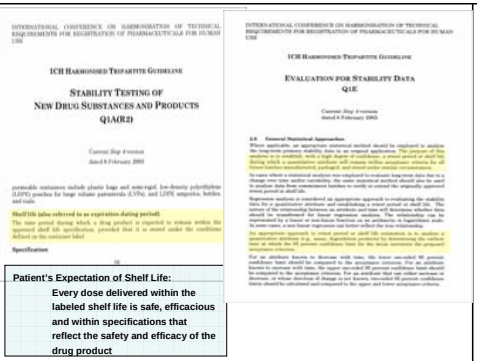
Despite the apparent simplicity of the term "shelf life", its precise definitions vary, and each has significant implications for the quality control of pharmaceutical products. In general, the term "shelf life" is used for three related, but fundamentally different, concepts which we propose to denote as "true", "estimated", and "claimed". The true shelf life is an unknown property of the pharmaceutical product in question. By collecting and analyzing stability data, we obtain information on changes of a product's quality attributes over time, and can estimate the true shelf life. However, due to the uncertainty associated with any estimate, and due to regulatory requirements and risk analysis, the claimed shelf life on a marketed product may be shorter than the estimated shelf life.

Dilemmas

The SSL Working Group is focusing on developing alternative methods for calculating estimated shelf life. Several competing definitions of true shelf life exist, with each corresponding to a specific statistical methodology that implements the philosophy underlying that definition.

The current ICH Q1E guideline approach for estimating shelf life focuses on the use of a 95% confidence band for the mean result based on a fitted regression that represents expected batch performance and is derived from the intersection of this confidence band with the acceptance criterion. The focus on mean batch performance is at odds with current compliance paradigms in which the same criteria are applied to individual results at individual time points throughout a stability study. In essence, different and conflicting interpretations of shelf life are being applied.

The underlying ICH Q1E definition of true shelf life is attractive (i.e., as the time that a batch mean stays within pre-set limits) since it focuses on a batch parameter. However, to bring data analysis methods in line with the current compliance paradigm's focus on individual doses, one of the alternatives being explored by the SSL Working Group is based on the time that a proportion of individual dosage units stays within acceptance criteria.


ICH HARMONISED TRIPARTITE GUIDELINE

STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS Q1A(R2)

ICH HARMONISED TRIPARTITE GUIDELINE

EVALUATION FOR STABILITY DATA Q1E

Patient's Expectation of Shelf Life:
Every dose delivered within the labeled shelf life is safe, efficacious and within specifications that reflect the safety and efficacy of the drug product

ICH Q1A	ICH Q1E	Patient Expectation
Relies on validity of specification criteria Lack clarity concerning the meaning of "drug product" and what it means "to remain within specification".	Claimed shelf life is defined by the mean performance of a small number of "registration" batches.	It is impossible to provide 100% assurance that all individual units are within specification limits throughout shelf life solely through QC testing.
Does it mean: Any individual dosage unit must be within specification throughout shelf life? Or Any testing unit of a batch (which might be a composite of multiple individual dosage units) must be within specification? Or Batch means of multiple drug product lots tested under an approved stability protocol must be within specification?	The focus on the Batch Mean: o Contradicts reality in the field in which FDA requires that Individual test results be compared to the specification (FDA OOS Guidance) o Lacks explicit control on the expected performance of individual dosage units (except for the dose content, USP <905>) Flawed poolability test which is based on significance test: o May result in a shelf life that is extrapolated from a single worst batch. o Disincentive for studying batches on stability as it may increase the likelihood the batches are not poolable.	Practical alternative is to base shelf life on period during which a high percentage of individual units remain within limits linked to safety and efficacy of the drug product (as opposed to based on process capability as still currently being enforced by regulatory authorities). Need to establish relationship between acceptance criteria in testing specifications and a quality statement (so-called "Quality Standard" or "Coverage")

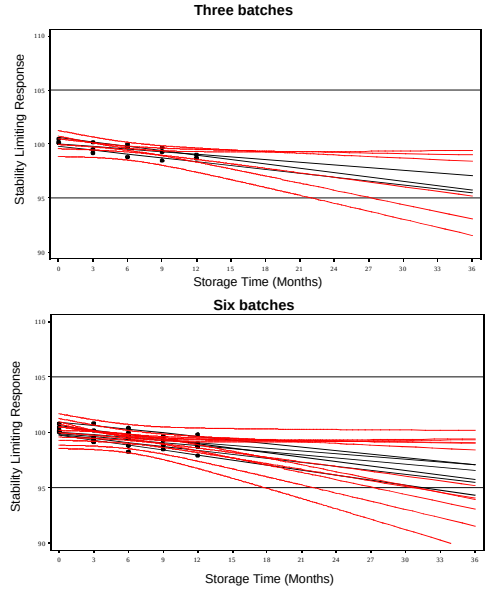
Quality Standard vs Acceptance Criteria

EXAMPLE **QUALITY STANDARD**: X% of all units (X is a high percentage) must have assay between 95-105%

EXAMPLE **TEST ACCEPTANCE CRITERIA**: Assay of 2 of 2 samples must be between 98-102% (usually is not linked to underlying quality standard)

The current practice in the pharmaceutical industry is to specify test acceptance criteria without defining an underlying "quality standard"; or worse - to consider the acceptance criteria to be the quality standard. In a true "Quality by Design" environment one should first specify a quality standard suitable for the characteristics in question, and based on this determine a test structure (sample size, acceptance criteria and tiers) appropriate to confirm whether the batch complies with the desired quality level or not. Operating characteristics curves are a useful means of judging the suitability of a given test structure."

Issues with ICH Q1E Poolability Testing



In this example, the three batches (top figure) are not poolable per ICH Q1E (i.e. poolability p-value < 0.25). The red lines indicate the 95% confidence bounds for the mean response of each batch. Per ICH Q1E, the times when these confidence bounds intersect the specification limits are the claimed shelf lives for the batches and the shortest claim, related to the response of one batch, should be chosen as the claimed shelf life for the product.

Work to date based on simulations and real stability data indicate it is more common that one is not able to pool batches based on the Q1E criteria. As shown in the figures above, stability data from three additional batches resulted in a shorter claimed shelf-life than that determined from the initial three batches. Due to the pooling criteria and the assumed fixed effect model of Q1E, additional stability data penalizes the producer, since only the data from a single batch (worst case) are used to determine the claimed shelf life. This phenomenon is counterintuitive to the QbD spirit, in which obtaining more data should result in a better understanding of the true quality of the product.

The Q1E process and model for pooling of stability slopes is also counter intuitive with the fact that the goal of pharmaceutical manufacture is to produce consistent batches by a consistent controlled manufacturing process. This is better represented by a random effect model versus the fixed effect model assumed in the Q1E guideline. There has been work in the literature exploring these concepts and modeling the stability slopes as a random entity. The SSL working group is exploring the "Random Batch" model concept as a better approach to determine the claimed shelf-life.

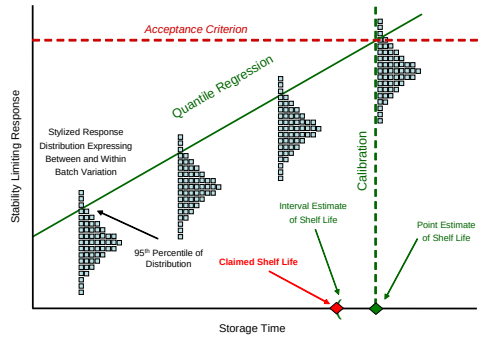
Shelf Life Estimation under Quality Standard Paradigm

The current practice in the pharmaceutical industry is to specify test acceptance criteria without defining an underlying Quality Standard; or worse - to consider the acceptance criteria to be the quality standard. It is impossible in a practical sense to provide 100% assurance that all individual dosage units will be within some specification limits throughout their shelf life. (This would require 100% inspection at the end of shelf life). This is aggravated by the current common approach to establishing specifications based on manufacturing process capability and limited data available from development and early manufacturing batches.

An alternative approach is to define a Quality Standard, i.e. a statement that a certain high percentage of individual units remain within the limits corresponding to known safety and efficacy of the product. Consequently, the shelf life can then be defined as the period where this high percentage of the dosage units remains within these limits. Separately, a test structure including sampling plans and acceptance criteria can be established to give a high assurance that the above limits are met. The SSL WG is evaluating Quantile Regression as one alternative approach for shelf life estimation under this Quality Standard paradigm. This approach requires a different derivation of acceptance limits as a Quality Standard should be based on safety and efficacy profile of the drug product.

QUANTILE REGRESSION & CALIBRATION

New Shelf Life Estimation Procedure Under Study



Quantile regression would be performed using all representative stability results. Statistical calibration (inverse regression) techniques are then used to obtain a direct estimate of the true shelf life.

Recognizing that calibrated estimate of shelf life is an estimate with uncertainty, a lower interval estimate is obtained as a conservative estimate of shelf life.

By using quantile approach, shelf life can be directly related to a Quality Standard. Note that using the 50% quantile (i.e., mean) is also possible but in contrast to current practice, in this approach it would be meaningfully linked to a Quality Standard.

NEXT STEPS

The Working Group continues development of the methodology to estimate shelf life using quantile regression together with calibration while incorporating random batch effects.

In addition, methodology is being developed to estimate shelf life using the mean response and modeling the between batch variation with random batch effects.

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