Establishing the Shelf Life of Pharmaceutical Products

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On behalf of the PQRI Stability Shelf Life Working Group

INTRODUCTION

At least these three distinct steps are necessary to gain knowledge and understanding of a product or process:
- Analytical measurement
- Data analysis
- Interpretation

The quality within each step influences the quality of the resulting knowledge. Therefore, developing and instituting best scientific methods at each step supports ingredients 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 2005 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 “circle argument” regarding how 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 procedures 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 attempt to estimate this true shelf life. However, due to the uncertainty involved with any estimate derived from regulatory requirements and risk analysis, the claimed shelf life on a marketed product may be shorter than the true 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 the 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 fixed regression that represents model performance and is derived from the intersection of this confidence band with the acceptance criterion. The fixed regression is a fixed relationship that is calculated for each shelf life point and is determined throughout the 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 at which 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 stability paradigm, a focus on individual dosage units within each batch would be beneficial.

Quality Standard vs Acceptance Criteria

Example Quality Standard

The current practice in the pharmaceutical industry is to specify a test acceptance criteria without defining an underlying “quality standard”, or worse - to consider the acceptance criteria to be the quality standard. In an ideal Quality by Design environment one should specify a quality standard suitable for each parameter in question, and based on this determine a test structure (sample size, acceptance criteria and confidence interval). Only then should the batch meet all of the desired quality levels. Operating characteristics curves are a useful means of judging the appropriateness of a given test structure.

Evaluating Quantile Regression

Quantile regression would be performed using all representative stability results. 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.

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