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stab: An R package for drug stability data analysis

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ABSTRACT

In the pharmaceutical industry, drug stability studies are routinely performed to measure the degradation of an active pharmaceutical ingredient (API) within a drug product. The purpose of drug stability studies is to examine how the API in a drug product varies with time under influence of a variety of environmental factors. The most important study is to establish the expiration date (i.e., the shelf life) of the product. Thus, the aim of this study was to develop an **R** package to calculate the shelf life based on drug stability data according to the suggested algorithms by ICH Tripartite Guidelines for Q1E Evaluation.

1. Introduction

One major characteristic of a drug product is the stability profile of the active pharmaceutical ingredient (API) over time [1]. The pharmaceutical industry thus routinely performs drug stability studies to measure API degradation in drug products, the purpose of which is to examine how the API in a drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light. In order to determine the rates of chemical and physical reactions and their relationships with environmental factors, accelerated, intermediate and long-term studies are usually conducted: accelerated and intermediate studies are so-called short-term stability studies conducted under exaggerated conditions; long-term studies simulate the actual packaging and conditions used for storage.

One of the most important aims of drug stability studies is to establish the expiration date (shelf life) of the product. The expiration date printed on the package label of a drug product is determined by the shelf life, which is defined as the length of time under the specific conditions of storage that the API will remain within acceptance criteria defined to ensure its identity, strength, quality, and purity.

Shelf life is estimated based on the International Conference of Harmonization (ICH) Tripartite Guidelines for "Q1E Evaluation of Stability Data" [2]. These guidelines outline a stepwise approach for the evaluation of drug stability data in order to find when and how much extrapolation can be considered for a proposed shelf life. Extrapolation of shelf life needs to be performed at the start when there is any significant change under accelerated and intermediate conditions; then, extrapolation of the shelf life (i.e., the proposed shelf life) beyond the period covered by the long-term data can be proposed. Moreover, the guidelines also recommend that the proposed shelf life should be set according to the shelf life estimated by statistical analysis of long-term data from different batches of a drug product. The objective of statistical analysis is to determine whether the variation is the same

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among different batches in order to then estimate the shelf life.

In addition, the Guidelines [2] indicate that at least three batches of a drug product should be tested to allow for some estimation of batch-to-batch variability. Batch variation testing needs to be performed using appropriate statistical tests, and analysis of covariance (ANCOVA) is commonly employed in this situation, where time is treated as a covariate, to test the statistical differences of both the slopes and the intercepts of regression lines between batches [2]. A significance level of 0.25 [3–5] used in the pooling test is adopted for this program owing to the expected low power of the design and the limited sample size in formal stability studies. Thus, if batch-to-batch variation is small ($P > 0.25$), drug stability data from several batches should be pooled to obtain a unified estimated shelf life for all product batches. Then, the shelf life is calculated at the time point where the lower (i.e., 95%) or upper (i.e., 105%) confidence interval about the fitted regression line crosses the lowest or the highest acceptable limit, respectively.

At present, the Food and Drug Administration (FDA) provides a program called the "SAS Drug Formulation Stability Program" [6] to perform expiration date estimation based on linear regression analysis, in which users can change the default settings (i.e., the upper or lower acceptance criteria) by SAS scripting. In addition, the "Shelf life macro" is provided in SigmaPlot©, which can calculate shelf life but cannot assist users in the evaluation of batch-to-batch variation. However, these macros are not user-friendly and are not easy to utilize feasibly. Therefore, to overcome these difficulties, we have developed a package for analyzing drug stability data based on the **R** statistical program (**R** Development Core Team 2008), a freeware and open structure; this package is easy to install through the **R** interface and is available for a wide range of computer operating systems. Moreover, we followed the ICH Tripartite guidelines for the evaluation of drug stability data [2] in the designing of this tool. This paper describes the **stab** package for **R**, including the principles of statistical testing for the poolability of batches and the algorithm for calculating the shelf life, followed by the contents of the **stab** package. Finally, an example of the use of the **stab** package to calculate a shelf life is provided.

2. Method

2.1. Decision tree for drug stability data evaluation

The purpose of this step is to guide users in how to conduct extrapolation in order to obtain a proposed retest period and then to determine the proposed shelf life. This step involves the building of a "Decision Tree for Drug Stability Data Evaluation," based on Appendix A [2]. Drug stability data for each attribute should be assessed sequentially. For a drug product intended for storage at room temperature, stability data with any significant changes should be assessed under accelerated conditions and intermediate conditions, and then progression should be made through the trends and variability of the long-term data.

2.2. Statistical approaches to drug stability data analysis

The aim of this step is to test batch-to-batch variation based on ANCOVA and then to estimate the shelf life. There are two variations of this step depending on the situation, as described below.

2.2.1. A single batch

This approach enables estimation of the retest period or shelf life for a single batch of a drug product. The relationship between assay and time is assumed to be linear [7]; then, the degradation of potency over time for a batch can be described by the following simple linear regression model:

$$Y_j(t) = \alpha + \beta t_j + \varepsilon_j, \quad j = 1, \ \ldots, \ n \tag{1}$$

where $Y_j(t)$ is the assay result (percent of the label claim) at sampling time t_j; α is the intercept, which is the percent of the label claimed at the initial time point; β is the slope, which is the degradation rate per time unit; and ε_j are normal random variables with a mean of zero and a variance of σ^2.

Consequently, the standard error (SE) of the estimated mean degradation line and the 95% lower and upper confidence limits of the regression line can be calculated. Then, two-sided 95% confidence intervals of the regression line for assay values (% relative to the original amount) of a drug product intersect with the upper and lower acceptance criteria of the drug amount claimed on the label, and the shortest time point is considered to be the shelf life of the drug product.

$$P(x) = (\alpha + \beta x) \pm t(0.05, n-2) \times \mathrm{SE} \tag{2}$$

where $P(x)$ is the lower or upper acceptance criteria; t (0.05, $n-2$) is the 5% upper quartile of a central t distribution with ($n-2$) degrees of freedom; and x is the shelf life. This algorithm can also be applied to data analysis of impurities (drug degradation) with established acceptable limits.

2.2.2. Multiple batches

When there are multiple samples with multiple batches (i.e., more than 2 batches) available for testing, ANCOVA can be used to determine whether the regression lines obtained from different batches have a common slope and a common time-zero intercept, where `time` is considered the covariate. ANCOVA is also able to estimate the within-batch variances with larger `df` than analyzing separately when there is more than one batch or more than one packing. To model the linear regressions of multiple batches of the same drug product, the model for ANCOVA is

$$Y_i(t) = \alpha_0 + \alpha_i + (\beta_0 + \beta_i)t + \varepsilon_{it}, \quad i = 1, \ \ldots, \ n \tag{3}$$

where $Y_i(t)$ denotes the observed mean value of the ith batch at t month; α_0 and β_0 are the common intercept and slope of all batches, respectively; α_i and β_i are the deviation of the individual intercept and slope of the ith batch from α_0 and β_0, respectively; and ε_{it} is the model error term that follows $N(0,\sigma)$ distribution [8].