Product Shelf Life Extension Based on Statistical Analysis of the Collected Stability Data

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1. Introduction:

The Food and Drug Administration requires pharmaceutical companies to establish a shelf life for all new drug products through a stability analysis. This is done to ensure the quality of the drug taken by an individual is within established levels. Stability testing is a routine procedure performed on drug substances and products. In early stages, accelerated stability can be used as a “worst case” evaluation to determine what types of degradation products may be found after long-term storage. Testing under more gentle conditions (those recommended for long-term shelf storage), and slightly elevated temperatures, can be used to determine a product’s shelf life and expiration dates. According to FDA guidelines, ICH Q1A (R2) - Stability Testing of New Drug Substances and Product, a suitable statistical method should be used for the stability data evaluation in order to establish product shelf life: shelf life will be determined based on the time at which the 95% confidence limit for the mean curve (CI) of the stability response intersects the acceptance criteria. Using JMP software, collected data can be easily analyzed and shelf life can be determined. Shelf life extension may be recommended, with the support of the statistical analysis, which can potentially save companies a lot of money and resources, having the product on the shelves for several years longer.

2. Pooling all the data into one data set:

If the batch to batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by applying appropriate statistical test, like regression line slope and intercept comparison: if Y1=μ1*X1+ß1 and Y2=μ2*X2+ß2 are linear equations, μ1=μ2 indicates slope similarity, B1=B2 indicates intercepts similarity, which means the trend is similar for both lines. Stability time points function as x-axes and stability test results function as y-axes. The null hypothesis is that the slopes and intercepts are equal; the alternative hypothesis is that the slopes and intercepts are not equal. If the p-value of time*lot interaction is equal to or larger than 0.25, there is insufficient evidence to reject the null hypothesis and conclude that the slopes are different. If the p-value of lot effect is equal to or larger than 0.25, there is insufficient evidence to reject the null hypothesis and conclude that the intercepts are different. All the data can be pooled into one data set if the p-value of the slope and intercept equivalence test is equal to or larger than 0.25.

3. Regression Fit:

Once the data is collected, a regression line should be fitted to the data. Stability timer points function as x-axes and stability test results function as y-axes. The goodness of fit of the linear regression must be verified: the fit is good if the p-value in lack of fit analysis is larger or equals to 0.1. Trend of the regression fit should be tested for significance: if p-value in ANOVA table is smaller than 0.1, trend is proven as significant. The null hypothesis in this case is whether the slope of the regression equation equals to zero: if Y=μ*x+B, the null hypothesis is μ=0, which means that there is no trend since the line is parallel to the x-axes and there is no change in stability test results through the time.

4. Shelf Life Predication:

Shelf life will be determined based on the time at which the 95% confidence limit for the mean curve (CI) intersects the acceptance criteria. Confidence limits for the mean are an interval estimate for the mean. A confidence interval generates a lower and upper limit for the mean. The interval estimate gives an indication of how much uncertainty there is in the estimate of the true mean.

After performing regression line slope and intercept comparison for all the lots, p-value of time*lot interaction is 0.819 and p-value of lot effect is 0.7257, which means the data can be pooled into one data set in order to predict the shelf life, since the slopes and intercepts are similar.

5. Conclusion:

Based on the statistical analysis described above, recommended shelf life for this drug is 27 months.

There is a good fit of the regression line and ANOVA p-value is < 0.0001* which means regression line fit is good and stability trend is proven as significant.

Based on JMP statistical analysis it was possible to increase the product shelf life from 18 months to 27 months.

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