

# Evaluation of ongoing stability data for Zolpidem film coated tablets using statistical methods for trending analysis

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## Introduction

Pharmaceutical manufacturers must carry out ongoing real-time stability studies in order to substantiate the expiry date and the storage conditions previously projected. Therefore, high-quality stability data is crucial to justify the set specification limits (Huynh-Ba, 2008). The stability data, together with the specification limits, is pivotal for the setting and/or extending of the product shelf-life, as well as its storage conditions. Ongoing stability studies are intended to prove that during the labelled shelf-life period and under “real life conditions”, the product retains the quality defined in the authorization/registration process. Stability studies are initiated annually and may be used to support product or process modifications, being vital to certify the continuous quality of production batches (ICH, 2003). In order to identify potential issues and ensure data quality, it is preferable to use objective and statistical methods for analysis of possible stability data trends.

According to the ICH Q1E guideline, evaluation of the stability data, after shelf life assessment, should progress through the trends and variability of the long-term stability data (ICH, 2003). The trending in stability studies i.e., the evaluation of stability data (not necessarily statistical) is performed in order to identify stability data trends, as well as their impact on product stability (Yoshioka and Stella, 2000). This article presents an overview of a statistical approach for trending analysis of stability data for Zolpidem film coated tablets (5 mg and 10 mg). An assessment was made to determine whether obtained data shows increasing/decreasing trends over time and whether it indicates discernible change or not.

## Materials and methods

In order to evaluate the stability data and to identify the pattern of data that indicates change over time, data from stability studies for Zolpidem 5mg and 10mg film coated tablets was subjected to trend analysis. In order to evaluate the trends and variability of the long-term stability data, three stability indicating parameters were analyzed: assay, dissolution rate and related and degradation products. In order to assess the trend of the parameters: assay of Zolpidem, dissolution rate of Zolpidem and related and degradation products, all the stability data obtained for these parameters was collected throughout the years. Data was assorted using tables and graphically, according to the stability study frequency at which they were obtained. The results were graphically presented versus the interval of  $\pm 3SD$  (3 times the standard deviation), and with a prediction fitting of 99% as well. A regression analysis was made in order to make predictions about future stability data values. The Six Sigma statistical approach was used for detecting the trend outliers.

## Results and discussion

Zolpidem film coated tablets 5mg and 10mg are pharmaceutical products with long manufacturing history, following the same manufacturing route, on the same manufacturing site, according to the prescribed manufacturing procedure in Alkaloid AD, Skopje. This product has a well-established stability. Ongoing stability studies in Alkaloid AD, Skopje are performed on one batch annually for long-term stability testing, including batches from 2009, 2010, 2011, 2012, 2013, 2014, 2015 and 2016.

The analysis of all collected data for assay of Zolpidem, indicates no discernible change. All results within a batch remained almost constant around the initial value (excluding the possible analytical error during the analysis). The 99% prediction fitting equation indicated that the trend is mildly decreasing (approximately 1.0% from the initial time-point to the 36 months frequency). One outlier was statistically detected, but it did not exceed the shelf-life specification limits. Results for this investigated parameter remained within the shelf-life requirements.

The evaluation of data obtained from the analysis of dissolution rate of Zolpidem, indicated no discernible change. All results within a batch remained almost constant around the initial result value (excluding the possible analytical error during the analysis). The 99% prediction fitting equation indicated that the trend is mildly decreasing (approximately 2.0-2.5% from the initial time-point to the 36 months frequency). No outliers were detected. Results for this investigated parameter remained within the shelf-life requirements.

For all collected data for the parameter single impurity content, no discernible change was detected. All the results within a batch remained almost constant around the initial result value (excluding the possible analytical error during the analysis). The 99% prediction fitting equation indicated that the trend is mildly increasing (approximately 0.0004% from the initial time-point to the 36 months frequency, which is discernible). One outlier was detected, but it did not exceed the shelf-life specification limits. The total impurities content data, within all batches, showed no discernible change. All the results within a batch remained almost constant around the initial value (excluding the possible analytical error during the analysis). The 99% prediction fitting equation indicated that the trend is mildly decreasing (approximately 0.003% from the initial time-point to the 36 months frequency, which is discernible). There was one outlier detected, but it did not exceed the shelf-life specification limits. Results for the single impurity content, as well as for the total impurity content parameter remained within the requirements of the shelf-life specification.

## Conclusion

The presented results indicate that the parameters assay and dissolution rate, as well as the parameter related and degradation products, considered as critical quality attributes, reveal very similar profiles for all tested batches at the same conditions and settings. The results for all batches follow defined trends, suggesting that there is no statistically significant difference in these parameter trends. The absence, or the presence of only one statistically detected outlier that is within the set

specification limits, ensures that the tested product retains its quality over the course of its predetermined shelf-life.

## References

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