Proposed Stability Guideline
- Evaluation and Statistical Analysis of Stability Data

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The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and to establish a re-test period for the substance or shelf life for the drug product and recommended storage conditions. Stability studies should include testing of those attributes of the drug substance and drug product that are likely to influence quality, safety and efficacy. In this review, proposals of stability guideline for evaluation and statistical analysis of stability data in relation to the KFDA notification , ICH guidelines and FDA draft guidance are presented.

For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance and drug product with a proposed re-test period of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period. At the accelerated storage condition, a minimum of three time points, including the initial and final time points(ex., 0, 3, and 6 months), from a 6- month study is recommended.

Proposed guideline is intended to provided recommendations on how to use stability data generated and describes when and how extrapolation can be considered when proposing a re-test period for drug substance or a shelf life for a drug product that extends beyond the period covered by available data from the stability study under long term data. Extrapolation is the practice of using a known data set to infer information about future data. Extrapolation to extend the retest period or shelf life beyond the period covered by long term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition. An extrapolation of stability data assumes that the same change pattern will continue to apply beyond the period covered by long term data. When estimating a regression line or curve to fit the long term data, the data themselves provide a check on the correctness of the assumed change pattern, and statistical methods can be applied to test the goodness of the fit of the data to the assumed line or curve. Limited extrapolation of the real time data from the long term storage condition beyond the observed range to extend the re-test period can be undertaken at approval time if justified.

This justification should be based on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, existence of supporting stability data, etc. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data. Any evaluation should cover not only assay, but also the levels of degradation products and other appropriate attributes. The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Statistical methods - Linear regression, Poolability test, Reduced design(Bracketing and Matrixing), Full design - should be employed to test the goodness of fit of the data on all batches and combined batches to the assumed degradation line or curve. This guideline defines the stability data package for drug substance and drug product that is sufficient for a registration application.