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Review Article

## Evaluation of stability data – An overview

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### ABSTRACT

The guidance on the evaluation and statistical analysis of stability data provided in the parent guideline is brief in nature and limited in scope. The parent guideline states that regression analysis is an appropriate approach to analyzing quantitative stability data for retest period or shelf life estimation and recommends that a statistical test for batch poolability be performed using a level of significance of 0.25. However, the parent guideline includes few details and does not cover situations where multiple factors are involved in a full- or reduced-design study. This review is intended to provide recommendations on how to use stability data generated in accordance with the principles detailed in the ICH guideline “Q1A(R) Stability Testing of New Drug Substances and Products” (hereafter referred to as the parent guideline) to propose a retest period or shelf life in a registration application. This guideline describes when and how extrapolation can be considered when proposing a retest period for a drug substance or a shelf life for a drug product that extends beyond the period covered by “available data from the stability study under the long-term storage condition” (hereafter referred to as long-term data). The scope of the guideline addresses the evaluation of stability data that should be submitted in registration applications for new molecular entities and associated drug products. The guideline provides recommendations on establishing retest periods and shelf lives for drug substances and drug products intended for storage at or below “room temperature”. It covers stability studies using single- or multi-factor designs and full or reduced designs.

**Keywords:** stability data; statistical analysis; ICH guideline; shelf life; single or multi factor design

### 1. INTRODUCTION

The design and execution of formal stability studies should follow the principles outlined in the parent guideline. The purpose of a stability study is to establish, based on testing a minimum of three batches of the drug substance or product, a retest period or shelf life and label storage instructions applicable to all future batches manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within acceptance criteria throughout its retest period or shelf life. Although normal manufacturing and analytical variations are to be expected, it is important that the drug product be formulated with the intent to provide 100 percent of the labeled amount of the drug substance at the time of batch release. If the assay values of the batches used to support the registration application are higher than 100 percent of label claim at the time of batch release, after taking into account manufacturing and analytical

variations, the shelf life proposed in the application can be overestimated. On the other hand, if the assay value of a batch is lower than 100 percent of label claim at the time of batch release, it might fall below the lower acceptance criterion before the end of the proposed shelf life. A systematic approach should be adopted in the presentation and evaluation of the stability information. The stability information should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including those related to particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms). The adequacy of the mass balance should be assessed. Factors that can cause an apparent lack of mass balance should be considered, including, for example, the mechanisms of degradation and the stability-indicating capability and inherent variability of the analytical procedures (Ruberg *et al.*, 1991). The basic concepts of stability data evaluation are the same for single- versus multi-factor studies and for full- versus reduced-design studies. Data from formal stability studies and, as appropriate, supporting data should be evaluated to determine the critical quality attributes likely to influence the quality and performance of the drug substance or product. Each attribute should be assessed separately, and an overall assessment should be made of the findings for the purpose of proposing a retest period or shelf life. The retest period or shelf life

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proposed should not exceed that predicted for any single attribute.

In general, certain quantitative chemical attributes (e.g., assay, degradation products, and preservative content) for a drug substance or product can be assumed to follow zero-order kinetics during long-term storage (Carstensen, 1977). Although the kinetics of other quantitative attributes (e.g., pH, dissolution) is generally not known, the same statistical analysis can be applied, if appropriate. Qualitative attributes and microbiological attributes are not amenable to this kind of statistical analysis. The recommendations on statistical approaches in this guideline are not intended to imply that use of statistical evaluation is preferred when it can be justified to be unnecessary. However, statistical analysis can be useful in supporting the extrapolation of retest periods or shelf lives in certain situations and can be called for to verify the proposed retest periods or shelf lives in other cases (Shao *et al.*, 1994).

## 2. Data presentation

Data for all attributes should be presented in an appropriate format (e.g., tabular, graphical, narrative) and an evaluation of such data should be included in the application. The values of quantitative attributes at all time points should be reported as measured (e.g., assay as percent of label claim). If a statistical analysis is performed, the procedure used and the assumptions underlying the model should be stated and justified. A tabulated summary of the outcome of statistical analysis and/or graphical presentation of the long-term data should be included.

## 3. Extrapolation

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. Whether extrapolation of stability data is appropriate depends on the extent of knowledge about the change pattern, the goodness of fit of any mathematical model, and the existence of relevant supporting data. Any extrapolation should be performed such that the extended retest period or shelf life will be valid for a future batch released with test results close to the release acceptance criteria (Murphy *et al.*, 1990).

An extrapolation of stability data assumes that the same change pattern will continue to apply beyond the period covered by long-term data. The correctness of the assumed change pattern is critical when extrapolation is considered. 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 fit of the data to the assumed

line or curve. No such internal check is possible beyond the period covered by long-term data. Thus, a retest period or shelf life granted on the basis of extrapolation should always be verified by additional long-term stability data as soon as these data become available. Care should be taken to include in the protocol for commitment batches a time point that corresponds to the end of the extrapolated retest period or shelf life (Yoshioka *et al.*, 1997).

## 4. Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products Intended for Room Temperature Storage

A systematic evaluation of the data from formal stability studies should be performed as illustrated in this section. Stability data for each attribute should be assessed sequentially. For drug substances or products intended for storage at room temperature, the assessment should begin with any significant change at the accelerated condition and, if appropriate, at the intermediate condition, and progress through the trends and variability of the long-term data. The circumstances are delineated under which extrapolation of retest period or shelf life beyond the period covered by long-term data can be appropriate (Fairweather *et al.*, 1995).

### 4.1. No significant change at accelerated condition

Where no significant change occurs at the accelerated condition, the retest period or shelf life would depend on the nature of the long-term and accelerated data.

#### 4.1.1. Long-term and accelerated data showing little or no change over time and little or no variability

Where the long-term data and accelerated data for an attribute show little or no change over time and little or no variability, it might be apparent that the drug substance or product will remain well within the acceptance criteria for that attribute during the proposed retest period or shelf life. In these circumstances, a statistical analysis is normally considered unnecessary but justification for the omission should be provided. Justification can include a discussion of the change pattern or lack of change, relevance of the accelerated data, mass balance, and/or other supporting data as described in the parent guideline. Extrapolation of the retest period or shelf life beyond the period covered by long-term data can be proposed. The proposed retest period or shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data.

#### 4.1.2 Long-term or accelerated data showing change over time and/or variability

If the long-term or accelerated data for an attribute show change over time and/or variability within a factor or among factors, statistical analysis of the long-term data can be useful in establishing a retest period or shelf life. Where there are differences in stability

observed among batches or among other factors (e.g., strength, container size and/or fill) or factor combinations (e.g., strength-by-container size and/or fill) that preclude the combining of data, the proposed retest period or shelf life should not exceed the shortest period supported by any batch, other factor, or factor combination. Alternatively, where the differences are readily attributed to a particular factor (e.g., strength), different shelf lives can be assigned to different levels within the factor (e.g., different strengths). A discussion should be provided to address the cause for the differences and the overall significance of such differences on the product. Extrapolation beyond the period covered by long-term data can be proposed; however, the extent of extrapolation would depend on whether long-term data for the attribute are amenable to statistical analysis.

#### 4.1.2.1. Data not amenable to statistical analysis

Where long-term data are not amenable to statistical analysis, but relevant supporting data are provided, the proposed retest period or shelf life can be up to one-and-a-half times, but should not be more than 6 months beyond, the period covered by long-term data.

#### 4.1.2.2 Data amenable to statistical analysis

If long-term data are amenable to statistical analysis but no analysis is performed, the extent of extrapolation should be the same as when data are not amenable to statistical analysis. However, if a statistical analysis is performed, it can be appropriate to propose a retest period or shelf life of up to twice, but not more than 12 months beyond, the period covered by long-term data, when the proposal is backed by the result of the analysis and relevant supporting data.

### 4.2. Significant change at accelerated condition

Where significant change occurs at the accelerated condition, the retest period or shelf life would depend on the outcome of stability testing at the intermediate condition, as well as at the long-term condition.

#### 4.2.1 No significant change at intermediate condition

If there is no significant change at the intermediate condition, extrapolation beyond the period covered by long-term data can be proposed; however, the extent of extrapolation would depend on whether long-term data for the attribute are amenable to statistical analysis (Chen *et al.*, 1997).

##### 4.2.1.1 Data not amenable to statistical analysis

When the long-term data for an attribute are not amenable to statistical analysis, the proposed retest period or shelf life can be up to 3 months beyond the period covered by long-term data, if backed by relevant supporting data.

##### 4.2.1.2 Data amenable to statistical analysis

When the long-term data for an attribute are amenable to statistical analysis but no analysis is performed, the extent of extrapolation should be the same as when data are not amenable to statistical analysis. However, if a statistical analysis is performed, the proposed retest period or shelf life can be up to one-and-a-half times, but should not be more than 6 months beyond, the period covered by long-term data, when backed by statistical analysis and relevant supporting data.

### 4.3 Significant change at intermediate condition

Where significant change occurs at the intermediate condition, the proposed retest period or shelf life should not exceed the period covered by long-term data. In addition, a retest period or shelf life shorter than the period covered by long-term data could be called for.

## 5. Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products Intended for Storage Below Room Temperature

### 5.1. Drug substances or products intended for storage in a refrigerator

Data from drug substances or products intended to be stored in a refrigerator should be assessed according to the same principles as described in Section 4 for drug substances or products intended for room temperature storage.

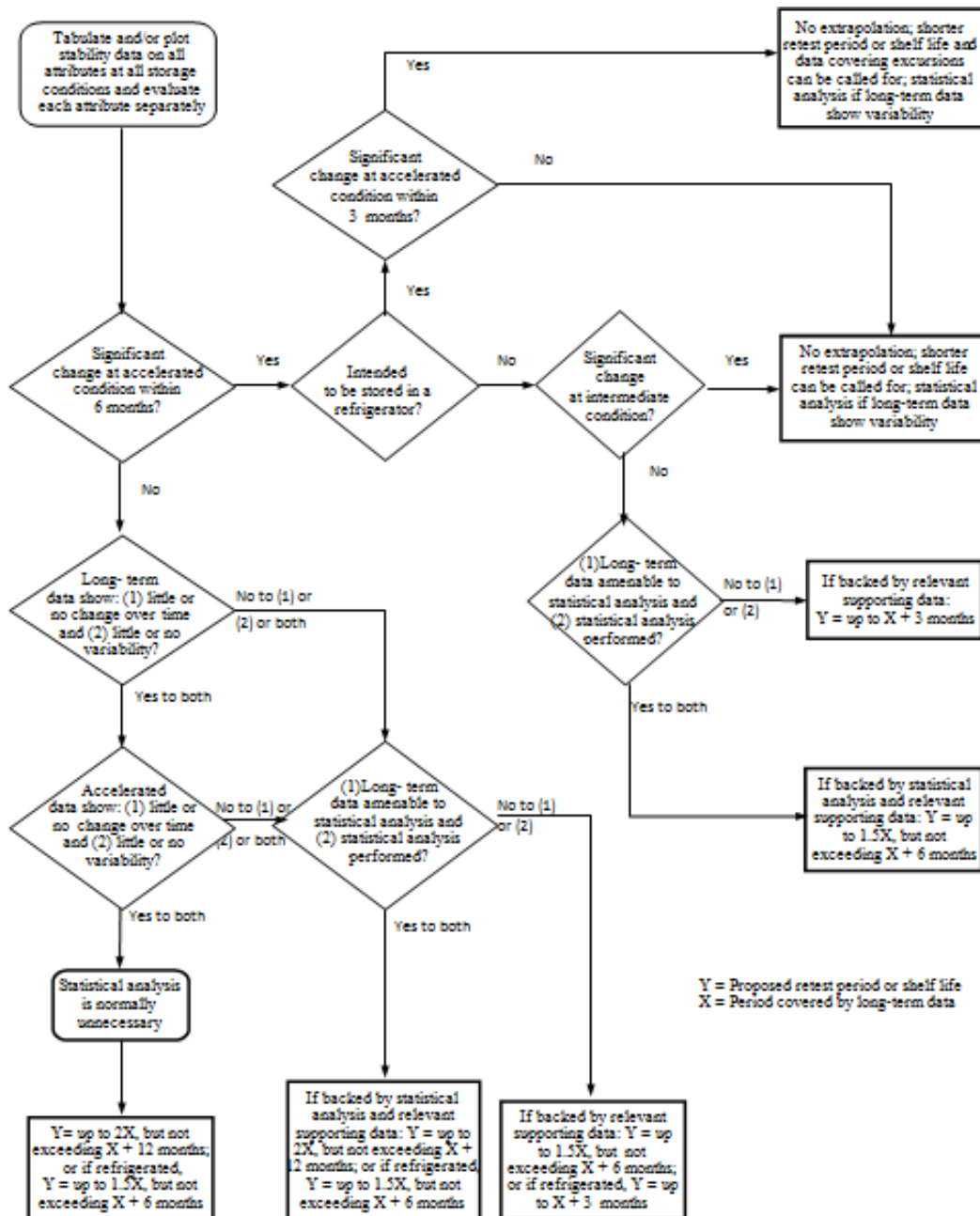
#### 5.1.1. No significant change at accelerated condition

Where the long-term or accelerated data show change over time and/or variability, the proposed retest period or shelf life can be up to 3 months beyond the period covered by long-term data if (1) the long-term data are amenable to statistical analysis but a statistical analysis is not performed, or (2) the long-term data are not amenable to statistical analysis but relevant supporting data are provided.

Where the long-term or accelerated data show change over time and/or variability, the proposed retest period or shelf life can be up to one-and-a-half times, but should not be more than 6 months beyond, the period covered by long-term data if (1) the long-term data are amenable to statistical analysis and a statistical analysis is performed, and (2) the proposal is backed by the result of the analysis and relevant supporting data.

#### 5.1.2. Significant change at accelerated condition

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed retest period or shelf life should be based on the long-term data. Extrapolation is not considered appropriate. In addition, a retest period or shelf life shorter than the period covered by long-term data could be called for. If the long-term data show variability, verifi-



**Figure 1: Decision Tree for Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products (excluding Frozen Products)**

evaluation of the proposed retest period or shelf life by statistical analysis can be appropriate.

**5.2. Drug substances or products intended for storage in a freezer**

For drug substances or products intended for storage in a freezer, the retest period or shelf life should be based on long-term data. In the absence of an accelerated storage condition for drug substances or products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition (e.g., during shipping or handling).

**5.3 Drug substances or products intended for storage below -20°C**

For drug substances or products intended for storage below -20°C, the retest period or shelf life should be based on long-term data and should be assessed on a case-by-case basis.

**6. General Statistical Approaches**

Where applicable, an appropriate statistical method should be employed to analyze the long-term primary stability data in an original application. The purpose of this analysis is to establish, with a high degree of confidence, a retest period or shelf life during which a quantitative attribute will remain within acceptance criteria

for all future batches manufactured, packaged, and stored under similar circumstances.

In cases where a statistical analysis was employed to evaluate long-term data due to a change over time and/or variability, the same statistical method should also be used to analyse data from commitment batches to verify or extend the originally approved retest period or shelf life.

Regression analysis is considered an appropriate approach to evaluating the stability data for a quantitative attribute and establishing a retest period or shelf life. The nature of the relationship between an attribute and time will determine whether data should be transformed for linear regression analysis. The relationship can be represented by a linear or non-linear function on an arithmetic or logarithmic scale. In some cases, a non-linear regression can better reflect the true relationship.

An appropriate approach to retest period or shelf life estimation is to analyze a quantitative attribute (e.g., assay, degradation products) by determining the earliest time at which the 95 percent confidence limit for the mean intersects the proposed acceptance criterion.

For an attribute known to decrease with time, the lower one-sided 95 percent confidence limit should be compared to the acceptance criterion. For an attribute known to increase with time, the upper one-sided 95 percent confidence limit should be compared to the acceptance criterion. For an attribute that can either increase or decrease, or whose direction of change is not known, two-sided 95 percent confidence limits should be calculated and compared to the upper and lower acceptance criteria.

The statistical method used for data analysis should take into account the stability study design to provide a valid statistical inference for the estimated retest period or shelf life. The approach described above can be used to estimate the retest period or shelf life for a single batch or for multiple batches when the data are combined after an appropriate statistical test (Ruberg *et al.*, 1992).

## CONCLUSION

The basic concepts of stability data evaluation are the same for single- versus multi-factor studies and for full-versus reduced-design studies. Data from formal stability studies and, as appropriate, supporting data should be evaluated to determine the critical quality attributes likely to influence the quality and performance of the drug substance or product. Each attribute should be assessed separately, and an overall assessment should be made of the findings for the purpose of proposing a retest period or shelf life. The retest period or shelf life proposed should not exceed that predicted for any single attribute. However, statistical analysis can be useful in supporting the extrapolation of retest periods or shelf lives in certain situations and

can be called for to verify the proposed retest periods or shelf lives in other cases.

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