1.5

ICH Q1E Guideline

Evaluation of Stability Data

Step 4 in the ICH process

Comments for its application

1. Introduction

1.1 Objectives of the Guideline

The guideline provides recommendation on how to use stability data generated according Q1AR2
It is described:

- How to propose a retest period for drug substances and a shelf life for drug products in the registration application,
- When and how a extrapolation beyond available data can be considered.

2. Guidelines

2.1 General Principals

- A systematic approach should be adopted in the presentation and evaluation of the stability information.
- The stability information should include as appropriate the results from the physical, chemical, biological and microbiological tests.
  Mass balance should be considered.
- The basic concepts of stability evaluation are the same for single-versus multi-factor designs and for full versus reduced design studies.
- Data from formal stability studies and supporting data should be evaluated to determine the critical quality attributes.
- Each attribute should be assessed separately and an overall assessment should be evaluated to propose a retest period or a shelf life.
- In the appendix A a decision tree outlines a stepwise approach to stability data evaluation and when and how much extrapolation can be considered for a proposed retest period or shelf life.
- Appendix B provides information on
  - How to analyze long-term data for appropriate quantitative test attributes from a study with a multi-factor, full or reduced design
  - How to use regression analysis
  - Examples of statistical procedure to determine poolability of data from different batches
- Certain quantitative chemical attributes (assay, degradation products, preservative content) can follow zero order kinetics, therefore evaluation according appendix B
- Qualitative attributes are not amenable to statistical analysis.
- Statistical analysis is not intended to imply when it can be justified to be unnecessary.

2.2 Data presentation

Data of all attributes should be presented in an appropriate format:

- tabular
- graphical

- narrative

If a statistical analysis is performed, the procedure and the assumption underlying the model should be stated and justified.

2.3 Extrapolation

Extrapolation is the practice of using dataset to infer information about future data.

- Extrapolation to extend retest period or shelf life beyond period covered by long-term data an be proposed in the application
  - Particularly if no significant change is observed at the accelerated condition.
- An extrapolation assumes that the same change pattern will continue to apply beyond the period covered by long-term data.
- 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.

2.4 Data Evaluation for Retest Period of Shelf Life Estimation for Drug Substances or Products intended for Room Temperature Storage.

- Stability data for each attribute should be assessed sequentially
- Assessment starts with
- With any significant change at accelerated condition or
- or intermediate condition and
- and progress through the trends and variability of the long term data.
- See decision tree in appendix A

Data of Stability Testing			**Requirement**	**Extrapolation Beyond covered by long term data**
Accelerated	Intermediate	Long-term		
Drug substances and products intended for room temperature storage				
Little or no change, little or no variability	-	Little or no change, little or no variability	No statistical analysis required	≤ 12 months
Change over time and or variability		Change over time and or variability	• Long-term data amenable to statistical analysis, relevant supporting data • Not amenable to statistical analysis but relevant supportive data	• ≤ 12 months • ≤ 6 months
Significant change within 6 months	No significant change	Change over time and or variability	• Long-term data amenable to statistical analysis, relevant supporting data	• ≤ 6 months

			• Not amenable to statistical analysis but relevant supportive data	• ≤ 3 months
Significant change within 6 months	Significant change			No extrapolation
Drug substances and drug products intended for storage below room temperature				
No significant change at 25°C		Little or no change, little or no variability		≤ 6 months
No significant change at 25°C		Change over time and or variability	• Long-term data amenable to statistical analysis, relevant supporting data • Not amenable to statistical analysis but relevant supportive data	• ≤ 6 months • ≤ 3 months
Significant change within 6 months				No extrapolation
Significant change within 3 months				No extrapolation Address short time excursion of label storage
Drug substances or products intended for storage in a freezer				
				No extrapolation Address short time excursion by storing at 5°C

Appendix B: Examples of Statistical Approaches to Stability Data Analysis

- Linear regression analysis
- Poolability tests
- Statistical modeling

These procedures an be used in the analysis of stability data that are amenable to statistical analysis for a quantitative attribute for which there is a proposed criterion.
Significant change
within 6 months