Evaluation for Stability data Q1E

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Q1E provides recommendations on :

- How to use stability data generated according to Q1AR
- When and how a retest period or a shelf life can be extended beyond the period covered by long-term data

Q1E contains

examples of statistical approaches to stability data analysis

- **Extrapolation**

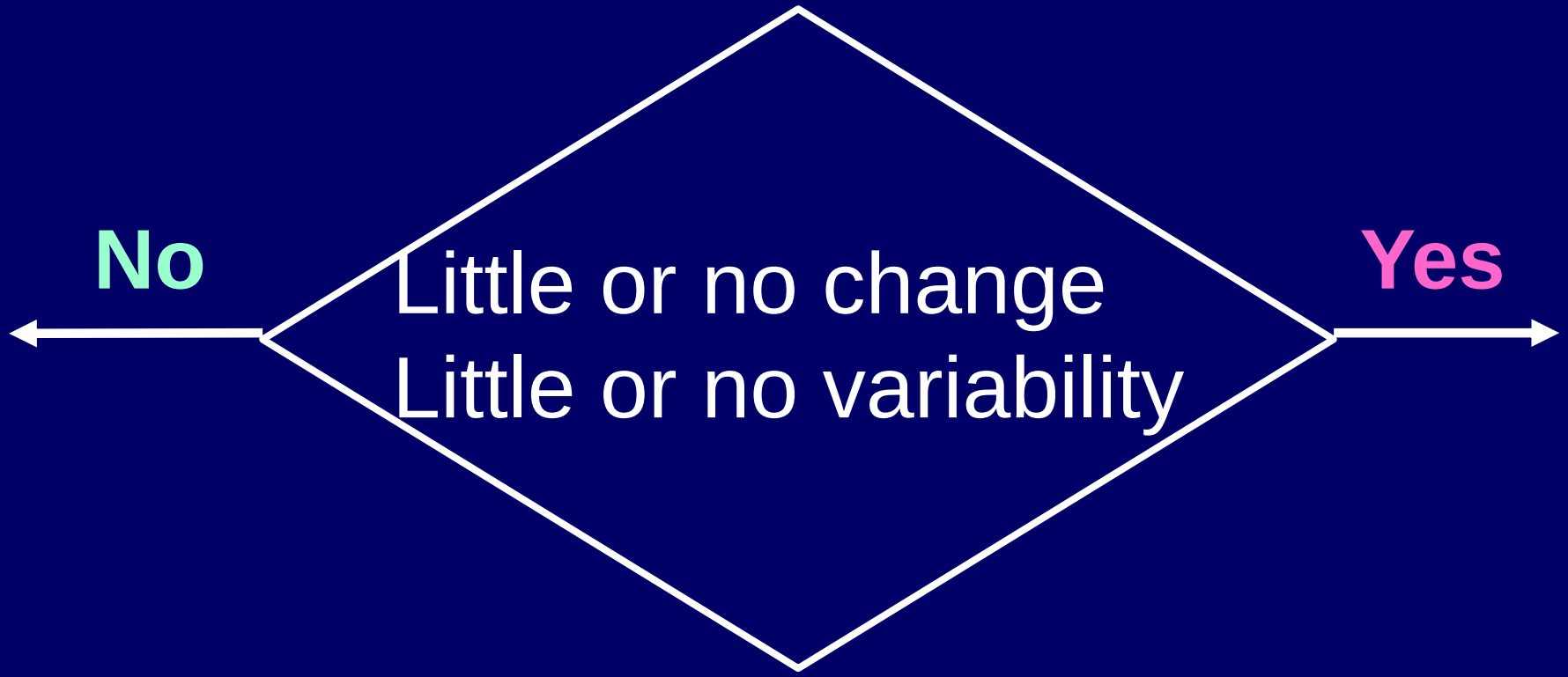
  to extend retest period/shelf life

- **Statistical approaches**

  recommended in the guideline

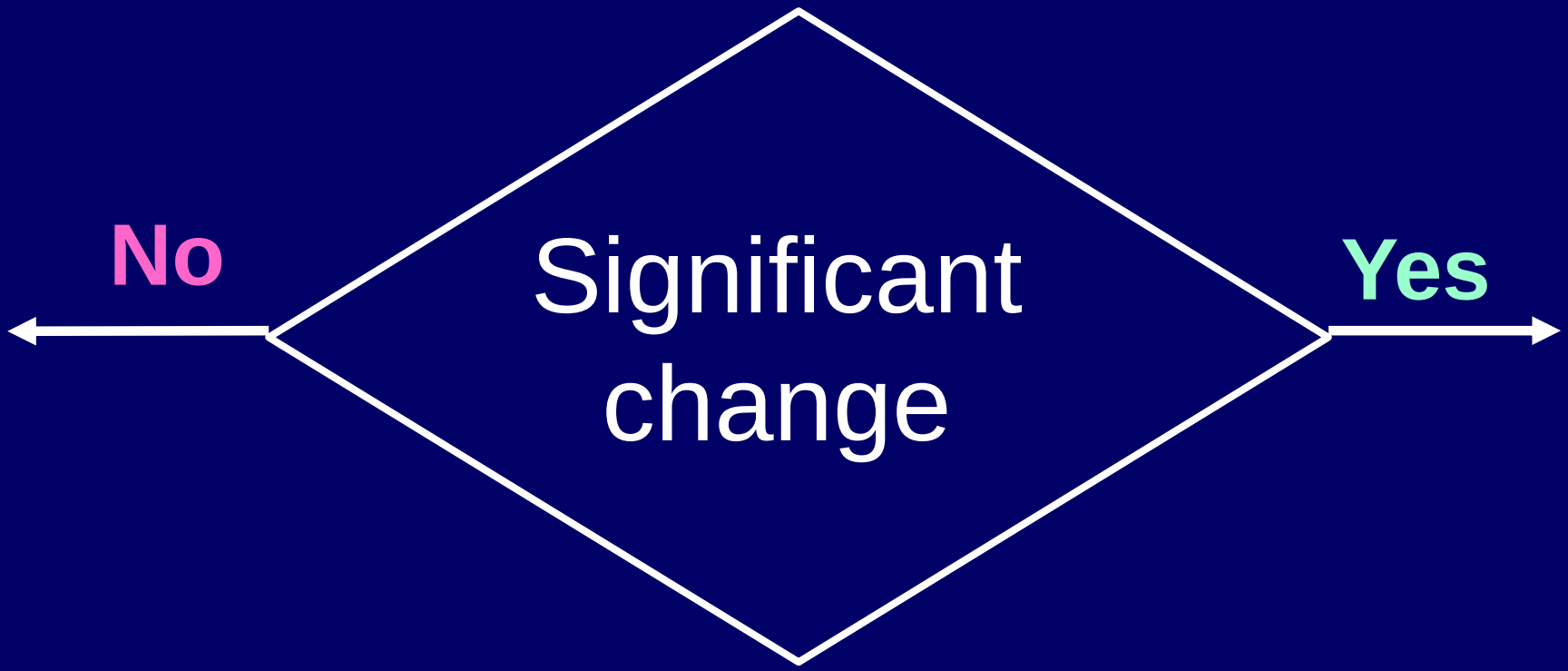
Accelerated condition

Where no significant change occurs at accelerated condition

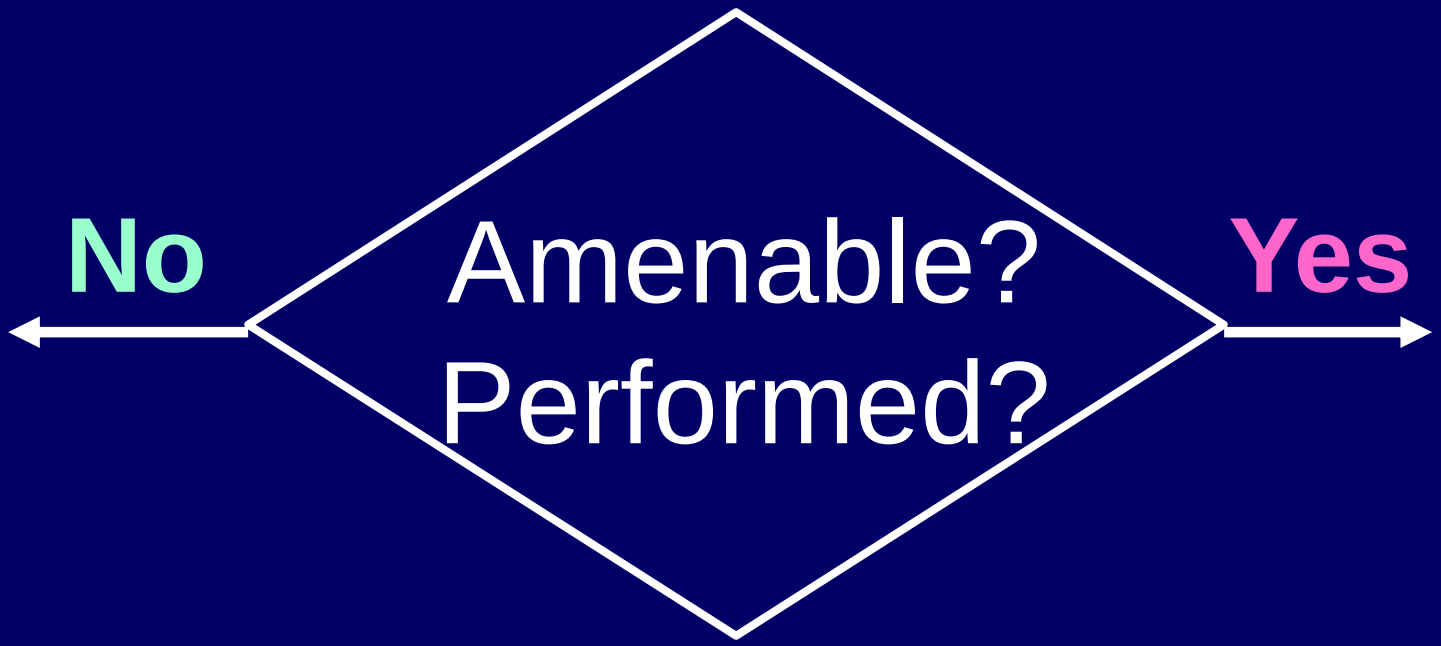


Accelerated data & Long-term data

Where accelerated data show significant change



Intermediate condition



Statistical analysis

Supporting data

Four outcomes passing through crossroads for Room Temperature Storage

Outcome 1　12 month extension

accelerated data show

no significant change

accelerated data & long-term data

little or no change

little or no variability

Outcome 4　no extension

significant change

at accelerated condition

at intermediate condition

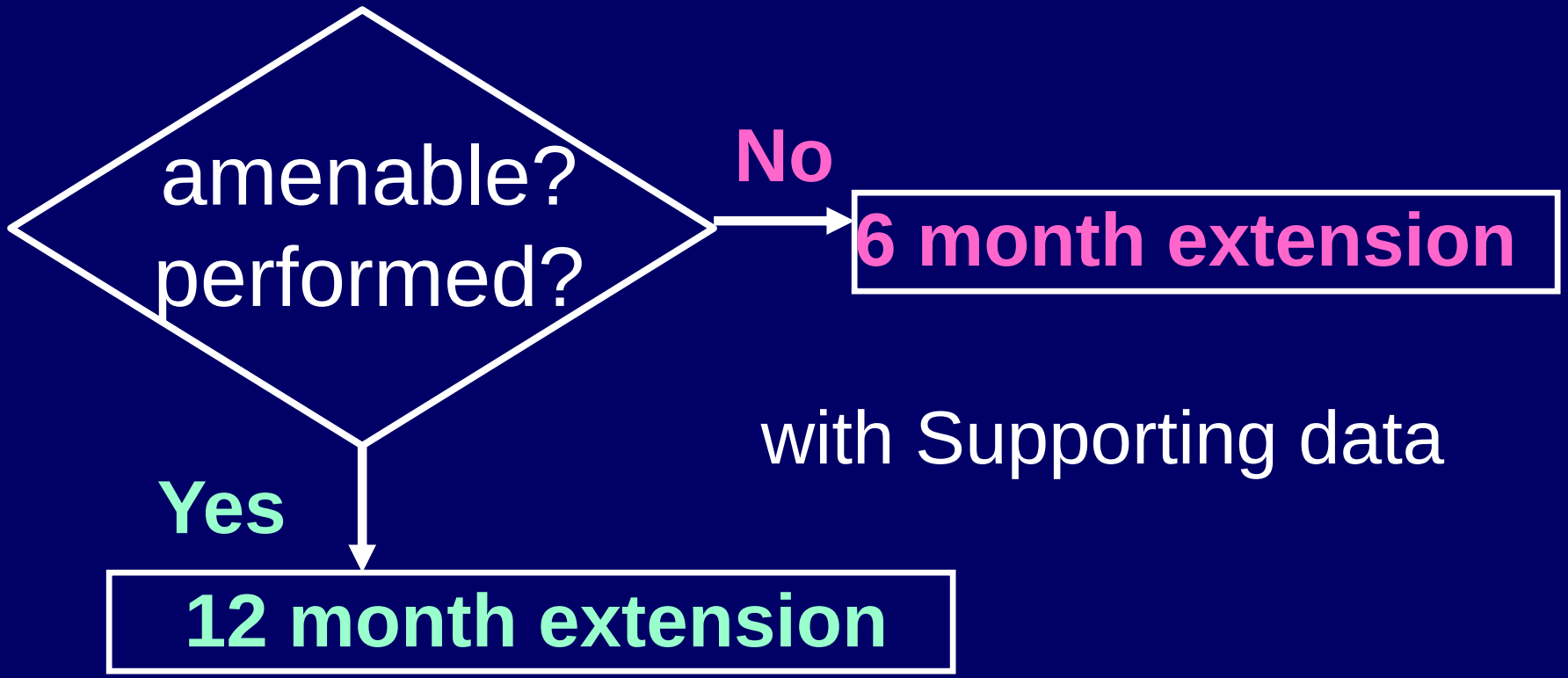
Statistical analysis

longer retest period/shelf life

(not necessarily required)

Where

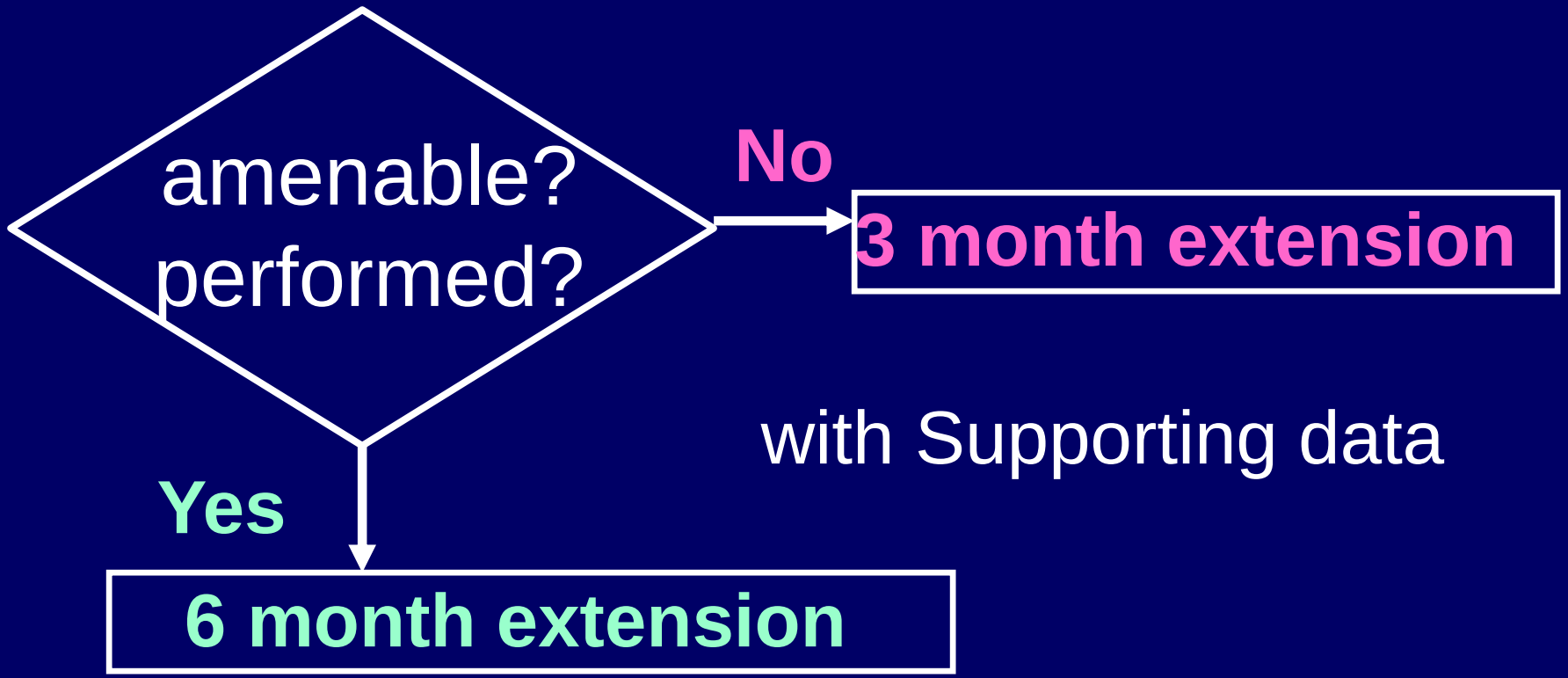
- **Accelerated data show no significant change**
- **Changes and variations in accelerated data**
  long-term data



Where

Significant change at accelerated condition

but not at intermediate condition



Statistical analysis

longer retest period/shelf life

not always required

Where

- **significant change**
  at accelerated & intermediate conditions
- **variability in long-term data**

→ **Statistical analysis can be appropriate to verify retest period/shelf life**

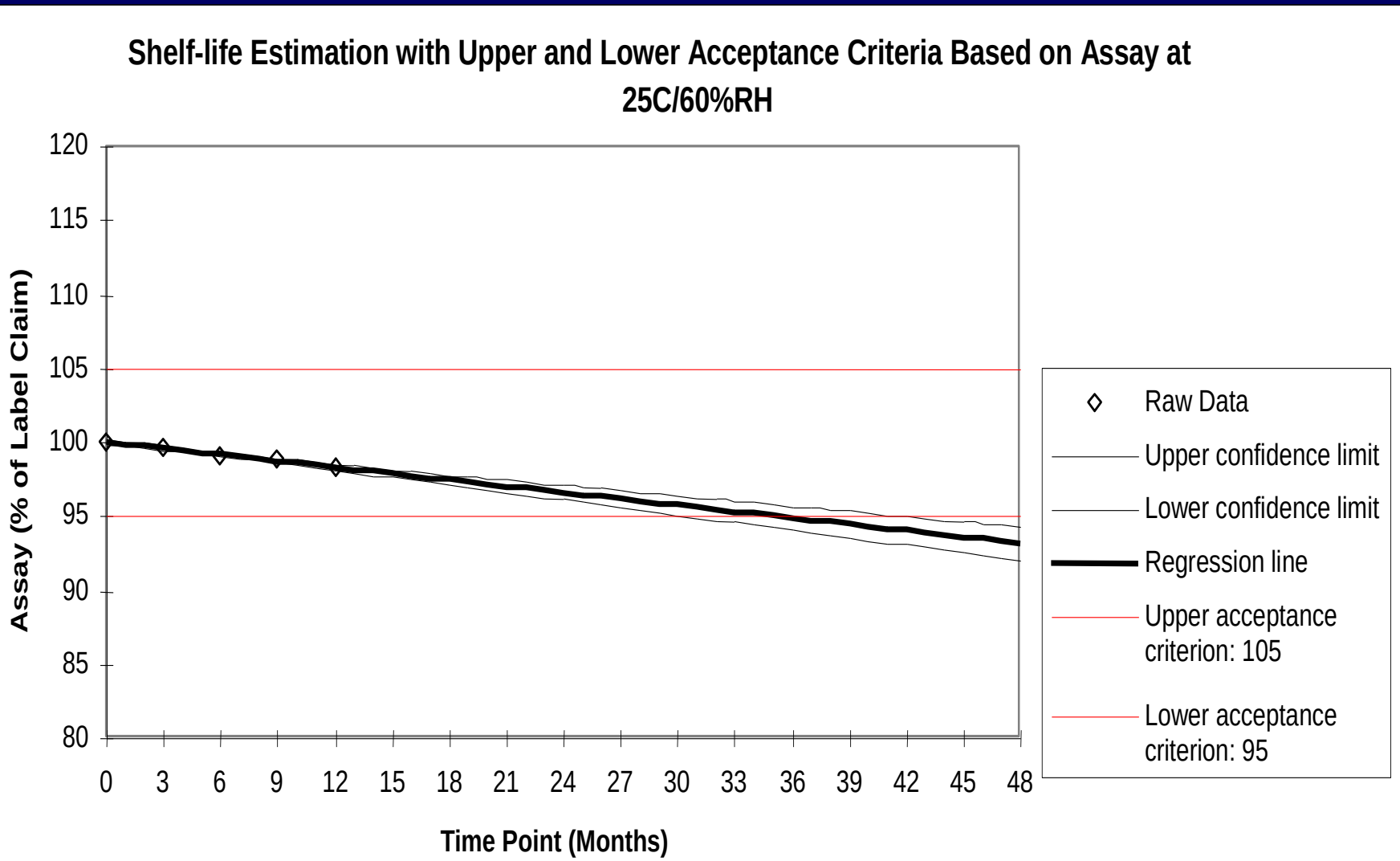
Statistical approaches recommended in the Appendix

- How to analyze long-term data for appropriate quantitative attributes
- How to use regression analysis for retest period/shelf life estimation
- Examples of statistical procedures to determine poolability of data from different batches or factor combinations

Regression analysis

Establish retest period/shelf life
with a high degree of confidence

Quantitative attribute will remain
within acceptance criteria
for all future batches


Shelf-life Estimation with Upper and Lower Acceptance Criteria Based on Assay at 25C/60%RH
Assay (% of Label Claim)
120
115
110
105
100
95
90
85
80
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
48
Time Point (Months)
Raw Data
Upper confidence limit
Lower confidence limit
Regression line
Upper acceptance criterion: 105
Lower acceptance criterion: 95

Statistical approaches

for determining whether data from different batches/factor combinations can be pooled

- (Approach #1)　Whether data from　all batches/factor combinations support the proposed period
- (Approach #2 “Poolability test”)
  Whether data from all batches/factor combinations can be combined for overall estimate of a single period
- (Alternative approaches)

Approaches #1 and #2 can also be applied to data analysis for multi-factor studies including Bracketing & Matrixing Designs

Basic Principles

- A shelf life is set based on long-term data
- The extent of extrapolation will depend on accelerated (and if applicable, intermediate) data, as well as long-term data
- Supporting data are useful in predicting long-term stability in primary batches

Basic Principles (cont'd)

- Statistical analysis is not always necessary for setting a shelf life
- A shelf life beyond the period covered by available long-term data can be proposed with supporting data, with or without statistical analysis
- Where a statistical analysis is performed, longer extrapolation can be justified

MHLW Perspective - Q1E

Before Q1E

EU---12 month extrapolation with or without statistical analysis;

US--- max 6 month extrapolation with statistical analysis;

Japan--- no practical extrapolation

- Q1E provides guidance on the extent of shelf life extrapolation in a variety of situations
- Q1E clearly describes the role of accelerated data and of supporting data in shelf life estimation