Stability Testing

Learning objectives

Students will be able to:

- Explain the purpose of stability testing and its importance in pharmaceutical development.
- Differentiate between the types of stability testing and their applications.
- Demonstrate how stability studies establish re-test periods and shelf life.

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1. Introduction

Stability testing is the process of evaluating how the quality of a drug substance or drug product varies with time under environmental factors such as temperature, humidity, and light.

The testing is conducted to establish:

- Re-test period for the drug substance
- Shelf life for the drug product.
- Recommended storage conditions

Re-test date: The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given drug product.

Shelf life (also referred to as expiration dating period): The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

ICHQ1 Guidelines Overview

The ICH Q1 guidelines are a set of guidelines that provide guidance on stability testing of new drug substances and drug products. The guidelines are harmonized by regulatory authorities in most countries around the world, which means that the regulatory requirements for stability testing are generally similar in most countries.

The ICH Q1 guidelines consist of the following five parts:

- ICH Q1A(R2): Stability testing of new drug substances and drug products
- ICH Q1B: Photostability testing of new drug substances and drug products
- ICH Q1C: Stability testing of new dosage forms
- ICH Q1D: Bracketing and matrixing designs for stability testing of new drug substances and drug products
- ICH Q1E: Evaluation of stability data

The ICH Q1 guidelines are an important resource for anyone involved in the development, manufacture, or testing of drug substances and drug products. They provide comprehensive guidance on all aspects of stability testing, which is essential for ensuring that drug products are safe and effective for patients.

In this document, a drug substance refers to the API, while drug product means the finished product.

2. Types of stability studies

2.1. Stability studies based on conditions

◊ **Long-term stability testing** is conducted at the intended storage conditions of the drug substance or drug product for over 12 months

◊ **Accelerated stability testing** is conducted at elevated temperatures and/or humidity conditions for 6 months

◊ **Intermediate stability testing** is conducted at intermediate temperatures and humidity conditions for 12 months if the product fails to meet its specifications during accelerated stability testing

◊ **Stress stability testing** is performed on drug substances and drug products during the drug development process. It is conducted at extreme temperatures, humidity, and/or light conditions. Stress stability testing is typically conducted over a period of 1 to 2 months

Stress testing helps identify degradation products and degradation pathways.

- Typically, it's done on a single batch of the drug substance/product.
- It involves raising temperatures in 10°C increments, for example, 50°C and 60°C, above the levels used in accelerated testing.
- Humidity of 75% RH or higher, when necessary, is part of the assessment.
- Hydrolysis across different pH values is assessed when in solution or suspension.
- Photostability testing is essential and follows ICH Q1B standards.
    - **Brief overview of ICHQ1B: Photostability Testing**

Photostability testing must be carried out on at least one batch of product. the test protocol should specify:

- The type and intensity of lighting (imitate outdour or indoor lights)
- The exposure distance from the source,
- Exposure conditions (duration, frequency, etc.).

2.2. Stability studies based on material to be tested

Stability studies on the drug substance

The aim is to:

- Define the intrinsic stability of the molecule,
- Identify degradation products,
- Establish the kinetics of appearance of degradation products,
- Implementation of analytical techniques for identification and dosing,
- Determine the re-test period and define the storage conditions,
- Guide the choice of control methods on the Drug product,
- Guide the conditions for stability studies of the Drug product.

Conditions for which stability studies on drug substances are required:

. Monographed drug substance but for which no shelf life has been established,
. Non-monographed drug substance,
. Known drug substance, obtained by a new synthesis process.

Stability studies on the drug product

The aim is to:

. Identify the degradation products coming from the interaction of the different components of the formula,

. Establish the kinetics of appearance of degradation products,
. Implementation of analytical techniques for the identification and dosage of degradation products,
. Determine the shelf life of the product,
. Define conservation conditions during storage and in use.

Conditions for which stability studies on drug product are required:

. New drug,
. Qualitative or quantitative changes in composition;
. Changes in primary packaging;
. Change of manufacturing site;
. Confirmation of the announced shelf life and storage conditions;
. Extension of the product shelf life.

In-use stability studies

The objective of in-use stability studies is to establish the shelf life and storage conditions of a multidose pharmaceutical product after opening and/or reconstitution.

The test is carried out in order to simulate the use of the product (opening, reconstitution, samples, etc.).

Stability studies on intermediate and bulk products

These products must be included in the stability program, when they are stored or transported from one site to another before undergoing the rest of the manufacturing steps in order to assess the impact of their packaging on the stability of the product.

3. Selection of batches and specifications

Drug Substance:

- Minimum 3 primary batches of the drug substance
- Minimum size of a pilot scale,
- Synthesis route and manufacturing identical to that of the marketing batches,
- Packaging identical to that intended for its marketing.

Drug product:

- Minimum 3 primary batches,
- Two of the three batches should be at least pilot scale batches and the third one can be smaller, if justified.
- Same manufacturing process as that used for the marketing batches,
- Batches of product should be prepared from different batches of drug substance.
- Packaging identical to that intended for its marketing.

In-use:

- Minimum 2 batches, at least pilot scale batches.
- At least one of the batches should be chosen toward the end of its shelf life.

Specifications, as discussed in ICH Q6A, Q6B, and Q3A, encompass tests, analytical procedures, and acceptance criteria. Testing should cover the following:

- Physical aspects: colour, clarity, closure integrity, particulate matter, particle size distribution,…
- Chemical aspects: active substance assay(s), pH, …
- Biological/microbiological aspects: Total viable count, sterility, …
- Preservative content and functionality in the drug product.

4. Testing Frequency and Stability Commitment

Frequency of testing should be sufficient to establish the stability profile of the drug product.

Storage condition	Proposed re-test/shelf life period	Frequency of testing for drug substances/drug product
Long-term	≥12 months	Every 3 months over the first year, Every 6 months over the second year, Annually thereafter
Accelerated	6 months	At least three time points, including the initial and final time points (e.g., 0, 3, and 6 months)
Intermediate	12 months	At least four time points, including the initial and final time points (e.g., 0, 6, 9, and 12 months)

If primary batch data does not cover the proposed re-test period or shelf life, post-approval stability studies commitment is required. Commitment options depend on data availability:

1. Data on at least three batches covering the shelf life: no commitment
2. Data on at least three batches: Continue long-term and accelerated studies
3. Data on fewer than three batches: Continue long-term and accelerated studies and add more batches.
4. No production batch data: Commit to testing the first three batches.

5. Storage conditions

In general, a drug product should be evaluated under storage conditions that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

The World Health Organization (WHO) defines four climatic zones for the purpose of pharmaceutical stability:

Zone	Name	Climate	Example countries
I	Temperate	21°C±2°C 45%RH±5%	Canada, France, Germany, Japan, United Kingdom, United States
II	Subtropical and Mediterranean	25°C±2°C 60%RH±5%	Algeria, Argentina, Australia, Brazil, China,
III	Hot and dry	30°C±2°C 35%RH±5%	Egypt, Iran, Iraq, Jordan, Kuwait,
IV	Hot and humid	30°C±2°C 65%RH±5%	Colombia, Indonesia, Malaysia,

- General case

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

- *Drug substances/drug products intended for storage in a refrigerator*

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

- Drug substances/drug products intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	- 20°C ± 5°C	12 months
Accelerated	A single batch at 5°C ± 3°C or 25°C ± 2°C	Appropriate time period

- *Drug substances/drug products intended for storage below -20°C*

They should be treated on a case-by-case basis.

- *Drug products packaged in impermeable containers*

- Moisture sensitivity and solvent loss are not concerns.
- Stability studies can be conducted under controlled or ambient humidity conditions.

- *Drug products packaged in semi-permeable containers*

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss. Proceed as in General case.

6. Evaluation

Stability studies aim to set re-test periods for drug substances and shelf life for drug products.

- If data show little degradation and variability, you might not need complex statistical analysis.
- Analyzing data involves figuring out when a mean value crosses an acceptance limit.
- If batches are quite consistent, it's helpful to combine their data.
- The way data change over time can be linear, quadratic, or cubic.
- You can sometimes extend re-test periods or shelf life beyond observed data, considering degradation reasons, accelerated tests, models, batch size, and supporting data.
- Evaluation should cover the main content, degradation products, and other relevant attributes.

What is a "Significant change"?

It is defined as failure to meet the specifications in case of drug substance.

The following changes are considered significant for a drug product:

- A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
- A 5% loss in water from its initial value
- Any degradation product's exceeding its acceptance criterion;

- Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, re-suspendibility, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions;

and, as appropriate for the dosage form:

- Failure to meet the acceptance criterion for pH; or
- Failure to meet the acceptance criteria for dissolution for 12 dosage units..

The decision tree in Appendix A 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.

Important definitions

Variability refers to the observed differences in the stability of a drug substance or drug product between different batches or within a batch.

Change refers to the changes in the stability of a drug substance or drug product over time.

Regression analysis is considered an appropriate approach to evaluating the stability data for a quantitative attribute and establishing a retest period or shelf life.

Special instructions

- The shelf life of the Drug product must in no case exceed that of the materials which constitute it.
- The shelf life of a generic medicine must in no case exceed that of the original product

7. Statements/Labeling

A storage statement should be established for the labeling in accordance with relevant national/regional requirements.

- The statement should be based on the stability evaluation of the drug product.
- Where applicable, specific instruction should be provided, particularly for drug products that cannot tolerate freezing.
- Terms such as “ambient conditions” or “room temperature” should be avoided.
- There should be a direct link between the label storage statement and the demonstrated stability of the drug product.
- An expiration date should be displayed on the container label.

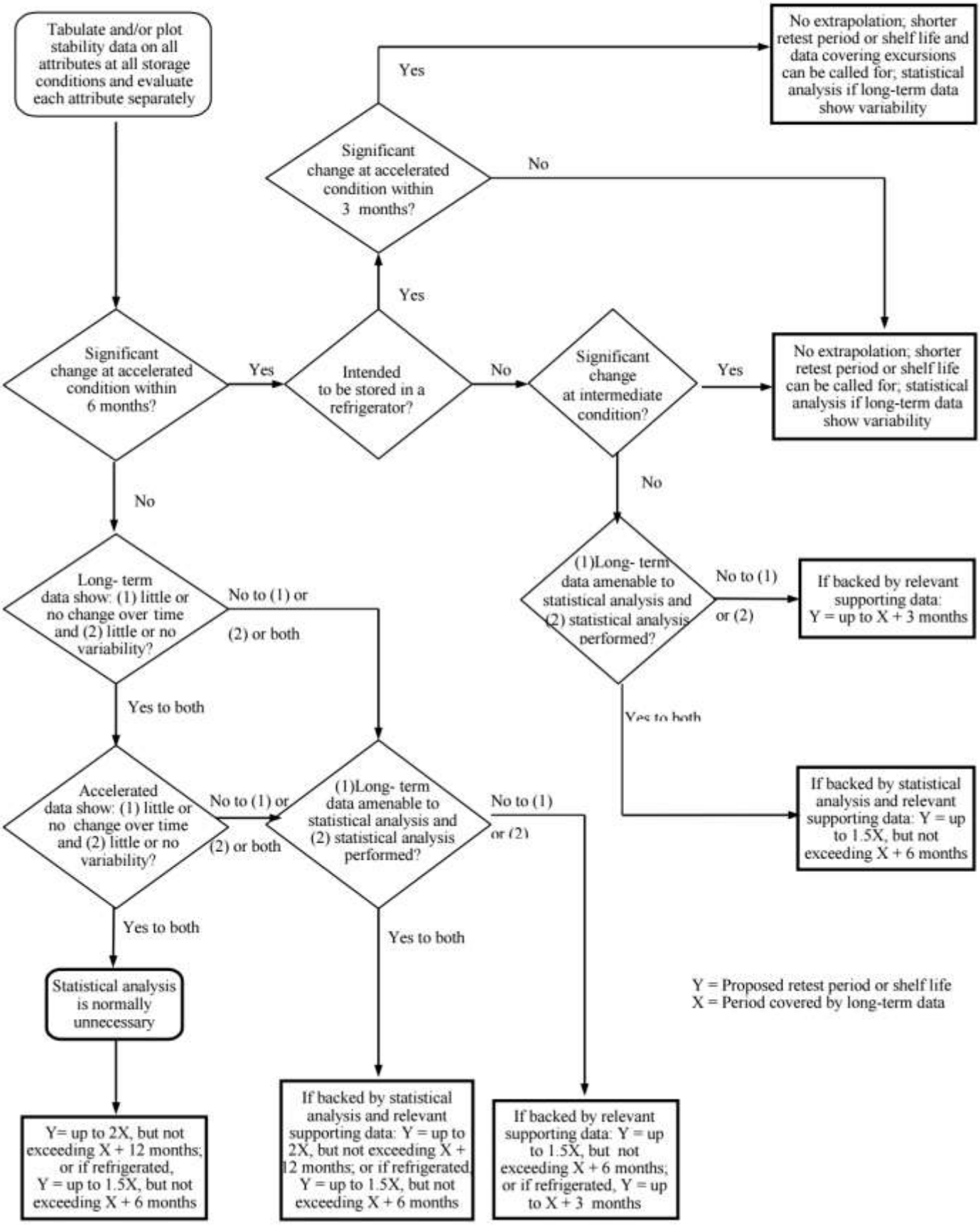
According to EMA, the following are required labeling statements depending on testing conditions where the product is stable:

- ☑ None
- ☑ Do not store above 30°C or Store below 30°C
- ☑ Do not store above 25°C or Store below 25°C
- ☑ Store in a refrigerator or Store and transport refrigerated
- ☑ Store in a freezer or Store and transport frozen

Conclusion

In conclusion, stability testing is a critical process for ensuring the quality and safety of pharmaceutical products. It helps determine how long a drug substance or product remains effective under various conditions. By conducting long-term, accelerated, and stress testing, we can establish re-test periods and shelf lives. These measures are essential for compliance with regulatory standards and ensuring that patients receive safe and effective medications. Properly designed stability studies, in line with international guidelines, provide the foundation for reliable and consistent pharmaceutical products.

Appendix A: Decision Tree for Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products (excluding Frozen Products)



References

- ICH Q1A(R2): Stability testing of new drug substances and products.
- ICH Q1B: Stability testing: Photostability testing of new drug substances and products.
- ICH Q1E: Evaluation for stability data.
- WHO TRS – 953: Annex 2- Stability testing of DRUG SUBSTANCE and finished pharmaceutical products.
- EMA Guideline: Guideline on declaration of storage conditions.
- EMA Guideline: Note For Guidance On In-Use Stability Testing Of Human Medicinal Products
- General Notices of USP 37 – NF 32.