ICH
harmonisation for better health

ICH STABILITY TESTING GUIDELINES

Q1A-Q1F => STABILITY GUDELINES

❖ Ms. DURGADEVI G,
DEPARTMENT OF PHARMACEUTICAL ANALYSIS,
COIMBATORE.

ICH

- **“International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use”.**
- ICH is a joint initiative involving both regulators and research-based industry representatives of the **EU**, **Japan** and the **US** in scientific and technical discussions of the testing procedures required to assess and ensure the **safety, quality and efficacy** of medicines.

DRUG STABILITY

- "A measure of how pharmaceutical products **maintains its quality** attribute over a time."

ICH STABILITY TESTING GUIDELINES

STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS	PHOTOSTABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS	STABILITY TESTING FOR NEW DOSAGE FORMS
Q1A(R2)	Q1B	Q1C
BRACKETING AND MATRIXING DESIGNS FOR STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS	EVALUATION OF STABILITY DATA	STABILITY DATA PACKAGE FOR REGISTRATION APPLICATIONS IN CLIMATIC ZONES III & IV
Q1D	Q1E	Q1F

Q1A(R2)
STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS

- 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 drug substance or a shelf life for the drug product and recommended storage conditions.**

- General
- Stress testing
- Selection of batches
- Container closure system
- Specification
- Testing frequency
- Storage conditions
- Stability commitment
- Evaluation
- Statements/ Labelling
- Photostability testing

- **General**

The design of the formal stability studies for the drug substance/ product should be based on knowledge of the behavior and properties of the drug substance and from **stability studies on the drug substance and on experience gained from clinical formulation studies.**

- **Stress Testing**

Stress testing of the drug substance can help identify the likely **degradation products**

It should include the **effect of temperatures** (in 10°C increments (e.g., 50°C, 60°C, etc.) above that for accelerated testing), **humidity** (e.g., 75% RH or greater) where appropriate, **oxidation, and photolysis** on the drug substance.

The testing should also evaluate the susceptibility of the drug substance to **hydrolysis** across a wide range of pH values when in solution or suspension.

- **Photostability Testing**

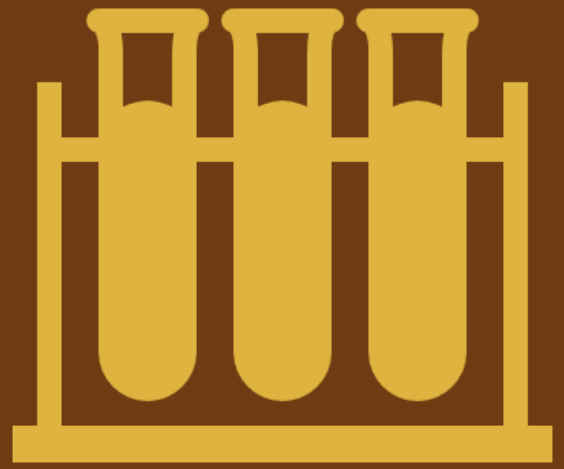
Photostability testing should be conducted on **at least one primary batch** of the drug product if appropriate.

- **Selection of Batches**

Data from formal stability studies should be provided on **at least three primary batches** of the drug substance/ product.

The batches should be manufactured to a minimum of **pilot scale** by the same synthetic route as, and using a method of manufacture and procedure that simulates the final process to be used for, production batches.

The overall quality of the batches of drug substance placed on formal stability studies should be **representative** of the quality of the material to be made on a production scale.



- **Container Closure System**

The stability studies should be conducted on the drug substance/ product packaged in a container closure system that is the same as or **simulates the packaging proposed for storage and distribution and marketing** (including, as appropriate, any secondary packaging and container label).

- **Specification**

Specification, which is a **list of tests, reference to analytical procedures, and proposed acceptance criteria and shelf life specifications** is addressed in ICH Q6A and Q6B.

In addition, specification for **degradation products in a drug substance is discussed in Q3A and drug product is addressed in Q3B.**

The testing should cover, as appropriate, the **physical, chemical, biological, and microbiological attributes.** Validated stability-indicating analytical procedures should be applied.

- **Testing Frequency**

For drug substances 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 **(e.g., 0, 3, and 6 months),** from a **6-month study** is recommended.

When testing at the **intermediate storage condition** is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points **(e.g., 0, 6, 9, 12 months), from a 12- month study** is recommended.

- **Storage Conditions:** In general, a drug substance should be evaluated under storage conditions that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be **sufficient to cover storage, shipment, and subsequent use.**

- **General case: Drug substance/ product**

Study	Storage condition	Minimum time period
• 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

- **General case: Drug products packaged in impermeable containers**

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be **conducted under any controlled or ambient humidity condition.**

- **General case: Drug products packaged in semi-permeable containers**

Study	Storage condition	Minimum time period
• Long term	• **25°C** ± 2°C/**40% RH** ± 5% RH or **30°C** ± 2°C/**35% RH** ± 5% RH	• 12 months
• Intermediate	• **30°C** ± 2°C/**65% RH** ± 5% RH	• 6 months
• Accelerated	• **40°C** ± 2°C/ **NMT 25% RH**	• 6 months

- **Drug substances intended for storage in a refrigerator**

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

- **Drug substances 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

- **Stability Commitment**

When available long term stability data on primary batches do not cover the proposed re-test period/ shelf life period granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the re-test period.

1. If the submission includes data from stability studies on **at least three production batches**, a commitment should be made to continue these studies through the **proposed re-test period/ shelf life (Accelerated studies for 6 months).**
2. If the submission includes data from stability studies on **fewer than three production batches**, a commitment should be made to continue these studies through the **proposed re-test period / shelf life (Accelerated studies for 6 months)** and to place additional production batches, to a total of **at least three, on long term stability studies through the proposed retest period / shelf life (Accelerated studies for 6 months).**
3. If the **submission does not include stability data** on production batches, a commitment should be made to place the **first three production batches** on long term stability studies through the **proposed re-test period / shelf life (Accelerated studies for 6 months).**

- **Evaluation**

The purpose of the stability study is to establish, based on **testing a minimum of three batches of the drug substance and evaluating the stability information** (including, as appropriate, results of the physical, chemical, biological, and microbiological tests), a re-test period applicable to all future batches of the drug substance/ dosage form manufactured under similar circumstances.

- **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 substance/ product. **Where applicable, specific instructions should be provided, particularly for drug substances / products that cannot tolerate freezing.** Terms such as "ambient conditions" or "room temperature" should be avoided.

Accelerated testing:

Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies.

Long term testing:

Stability studies under the recommended storage condition for the re-test period or shelf life proposed (or approved) for labeling

Bracketing:

The design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all time points as in a full design.

Matrixing:

The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point.

Q1B
STABILITY TESTING: PHOTOSTABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS

- This document is an annex to the main stability Guideline, and gives guidance on the basic testing protocol required **to evaluate the light sensitivity and stability of new drugs and products.**

GENERAL	• Preamble • Light Sources • Procedure
DRUG SUBSTANCE	• Presentation of Samples • Analysis of Samples • Judgement of Results
DRUG PRODUCT	• Presentation of Samples • Analysis of Samples • Judgement of Results

- **GENERAL**

The ICH Harmonized Tripartite Guideline covering the Stability Testing of New Drug Substances and Products (hereafter referred to as the Parent Guideline) notes that **light testing should be an integral part of stress testing.**

- **Preamble**

The intrinsic photostability characteristics of new drug substances and products should be **evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable change.**

A systematic approach to photostability testing is recommended covering, as appropriate, studies such as:

i) Tests on **the drug substance**;

ii) Tests on the **exposed drug product outside of the immediate pack**; and if necessary ;

iii) Tests on the **drug product in the immediate pack**; and if necessary

iv) Tests on the **drug product in the marketing pack.**

- **Light Sources**

The applicant should either maintain an appropriate **control of temperature** to minimize the effect of localized temperature changes or include a **dark control** in the same environment unless otherwise justified.

- **Procedure**

For confirmatory studies, samples should be exposed to light providing an overall **illumination of not less than 1.2 million lux hours** and an integrated near **ultraviolet energy of not less than 200 watt hours/square meter** to allow direct comparisons to be made between the drug substance and drug product.

- **DRUG SUBSTANCE**

For drug substances, photostability testing should consist of two parts: **forced degradation testing and confirmatory testing.**

The purpose of **forced degradation testing studies** is **to evaluate the overall photosensitivity of the material** for method development purposes and/or degradation pathway elucidation.

Confirmatory studies should then be undertaken **to provide the information necessary for handling, packaging, and labeling**

- **DRUG PRODUCT**

Normally, the studies on drug products should be carried out in a sequential manner starting with **testing the fully exposed product then progressing as necessary to the product in the immediate pack and then in the marketing pack.** Testing should progress **until the results demonstrate that the drug product is adequately protected from exposure to light.**

- **Presentation of Samples**

For samples of **solid drug substances**, an appropriate amount of sample should be taken and placed in a suitable **glass or plastic dish** and protected with a suitable **transparent cover** if considered necessary. Drug substances that are **liquids** should be exposed in **chemically inert and transparent containers**.

- **Analysis of Samples**

At the end of the exposure period, the samples should be examined for **any changes in physical properties (e.g., appearance, clarity, or color of solution, dissolution/disintegration for dosage forms such as capsules, etc.).**

- **Judgement of Results**

The forced degradation studies should be designed **to provide suitable information to develop and validate test methods for the confirmatory studies.** These test methods should be capable of **resolving and detecting photolytic degradants** that appear during the confirmatory studies.

The confirmatory studies should **identify precautionary measures needed in manufacturing** or in formulation of the drug product, and if light resistant packaging is needed.

Depending on the extent of change **special labeling or packaging may be needed to mitigate exposure to light.** When evaluating the results of photostability studies to determine whether change due to exposure to light is acceptable, it is important to consider the results obtained from other formal stability studies in order **to assure that the product will be within proposed specifications during the shelf life.**

Q1C
STABILITY TESTING FOR NEW DOSAGE FORMS

- This addresses the recommendations on **what should be submitted regarding stability of new dosage forms** by the owner of the original application, after the original submission for new drug substances and products.

- **NEW DOSAGE FORMS**

A new dosage form is defined as a drug product which is a **different pharmaceutical product type, but contains the same active substance** as included in the existing drug product approved by the pertinent regulatory authority.

Such pharmaceutical product types include products of **different administration route** (e.g., oral to parenteral), **new specific functionality/delivery systems** (e.g., immediate release tablet to modified release tablet) and **different dosage forms of the same administration route** (e.g., capsule to tablet, solution to suspension).

Stability protocols for new dosage forms **should follow the guidance in the parent stability guideline** in principle. However, a reduced stability database at submission time (e.g., **6 months accelerated and 6 months long term data from ongoing studies) may be acceptable** in certain justified cases.

Q1D BRACKETING AND MATRIXING DESIGNS FOR STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS

- This guideline is intended to address recommendations on the **application of bracketing and matrixing to stability studies conducted in accordance with principles outlined in the ICH Q1A(R)** Harmonised Tripartite guideline on Stability Testing of New Drug Substances and Products

- **Bracketing**

Bracketing is the design of a stability schedule such that only **samples on the extremes of certain design factors** (e.g., strength, container size and/or fill) **are tested at all time points as in a full design**. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

Design Factors: Design factors are variables (e.g., **strength, container size and/or fill**) to be evaluated in a study design for their effect on product stability.

Strength: Bracketing can be applied to studies with **multiple strengths** of identical or closely related formulations.

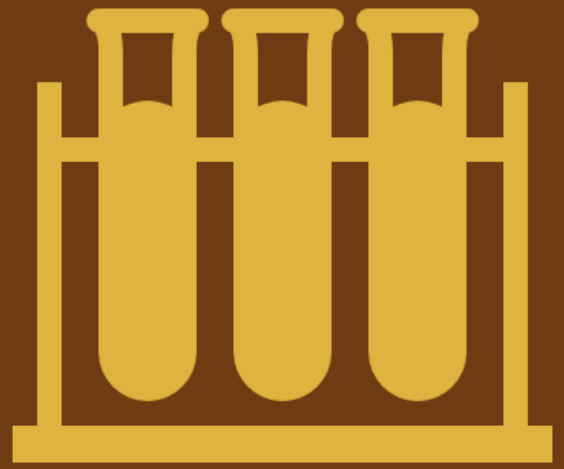
Container Closure Sizes and/or Fills: Bracketing can be applied to studies of the **same container closure system where either container size or fill varies while the other remains constant.**

- **Matrixing**

  - Matrixing is the design of a stability schedule such that a **selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point.** The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point.

  - The differences in the samples for the same drug product should be identified as, for example, **covering different batches, different strengths, different sizes of the same container closure system, and possibly, in some cases, different container closure systems.** When a **secondary packaging system** contributes to the stability of the drug product, matrixing can be **performed across the packaging systems**. **Each storage condition should be treated separately** under its own matrixing design.

  - **Design Factors:** Matrixing designs can be applied to strengths with identical or closely related formulations. Examples include **(1) capsules of different strengths made with different fill plug sizes from the same powder blend, (2) tablets of different strengths manufactured by compressing varying amounts of the same granulation, and (3) oral solutions of different strengths with formulations that differ only in minor excipients (e.g., colourants or flavourings).**



Q1E Evaluation for Stability data

- This document extends the main stability Guideline by explaining possible situations where **extrapolation of retest periods or shelf-lives beyond the real-time data** may be appropriate. Furthermore, it provides examples of statistical approaches to stability data analysis.

- **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).

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.**

- **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.

Q1F: Stability Data Package for Registration Applications in Climatic Zones III and IV

- Describes harmonized global stability testing requirements in order to facilitate access to medicines **by reducing the number of different storage conditions.**
- WHO conducted a survey amongst their member states to find consensus on **30°C/ 65% RH as the long term storage conditions** for hot-dry and hot-humid regions.

THANK YOU!