ICH GUIDELINES FOR STABILITY

WHAT DOES ICH STAND FOR ?

The complete name of ICH is the “International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use”.

WHAT IS ICH ?

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.

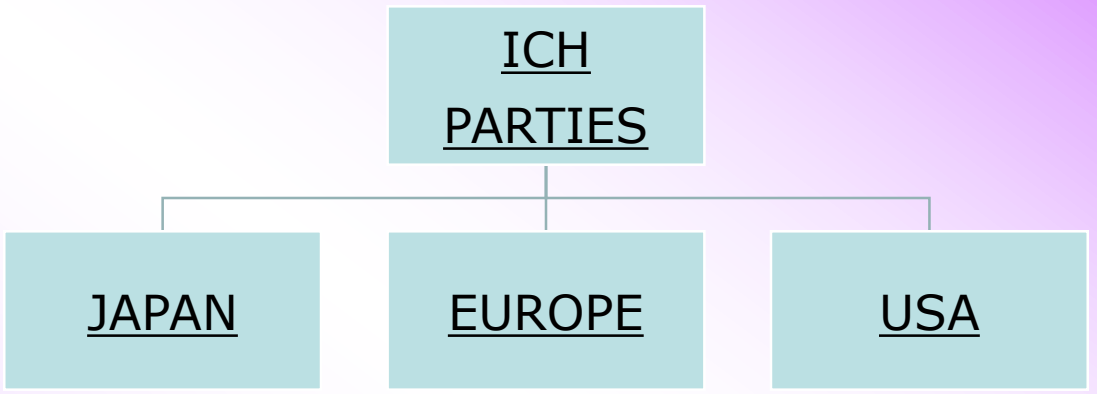
WHEN WAS ICH STARTED ?

The birth of ICH took place at a meeting in April 1990, hosted by the EFPIA in Brussels.

WHAT IS THE PURPOSE OF ICH ?

The objective of ICH is to increase international harmonization of technical requirements to ensure that safe, effective, and high quality medicines are developed and registered in the most efficient and cost effective manner.

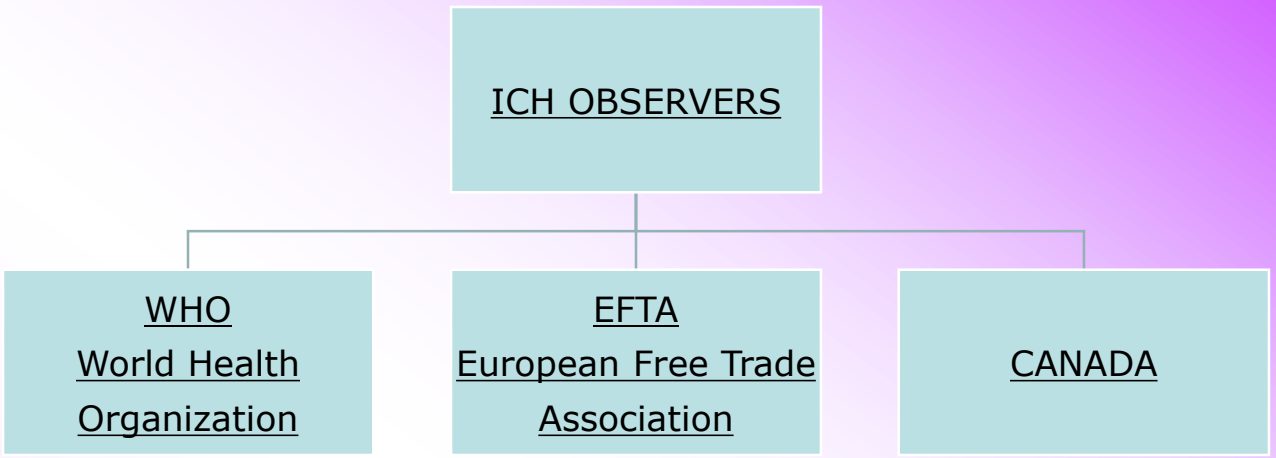
WHO ARE THE MEMBERS ?



- The Ministry of Health, Labour & Welfare (MHLW)
- Japan Pharmaceutical Manufacturers Association (JPMA)

- The European Commission (EC)
- European Federation of Pharmaceutical Industries and Associations (EFPIA)

- The Food & Drug Administration (FDA)
- The Pharmaceutical Research and Manufacturers of America (PhRMA)

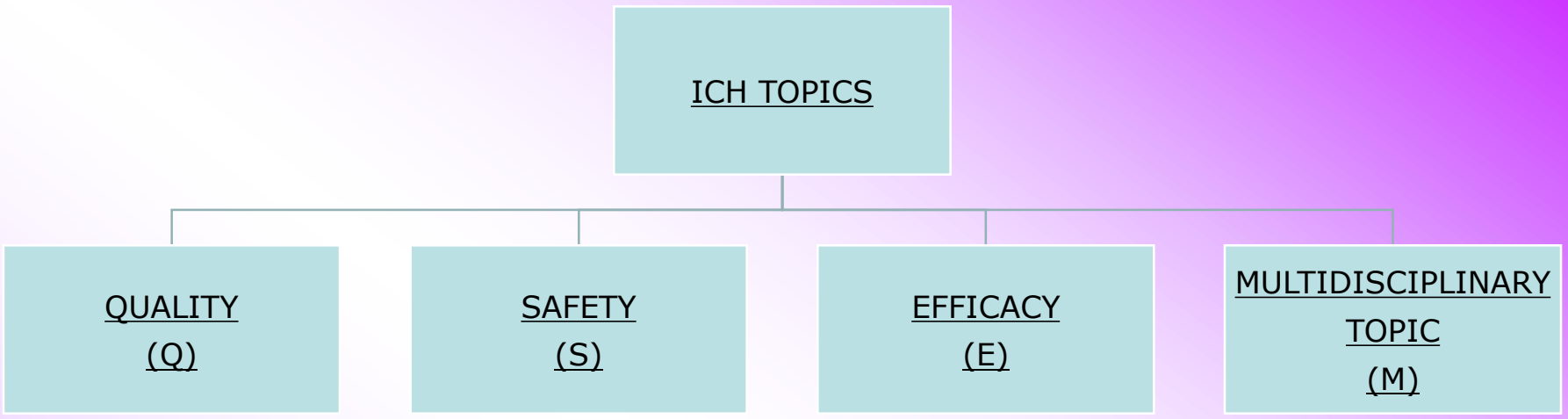


ICH STEERING COMMITTEE

- Determines the policies & procedures for ICH.
- Selects topics for harmonization.
- They meet twice a year.

ICH SECRETARIAT

- Concerned with preparation for, documentation of, meetings of the SC.



- Stability Testing
- Impurity Testing

- Carcinogenicity Testing
- Genotoxicity Testing

- Dose Response Studies
- Good Clinical Practice

- MedDRA
- ESTRI
- CTD

FORMAL ICH PROCEDURE

- *Step1 :* Consensus building
- *Step2 :* Confirmation of six party consensus
- *Step3 :* Regulatory Consultation and Discussion
- *Step4 :* Adoption of an ICH Harmonized Tripartite guideline
- *Step5 :* Implementation

STEP 1 : CONSENSUS BUILDING

- Steering committee (SC) adopts a concept paper.
- The EWG prepares an initial draft of the guideline.
- When the agreement is reached among all 6 party EWG members, then the EWG will sign the *step 2 expert signoff sheet*.
- This consensus is submitted to steering committee within a specified time period.
- If the EWG members are not able to submit within the given time period, a report has to be send to SC
- The SC may
  extend the time period (or)
  abandon the consensus.

STEP 2 : CONFIRMATION OF SIX PARTY CONSENSUS

- Step 2 is reached when the SC agrees, based on the report submitted by EWG.

- And the consensus is signed off by the SC as *step 2 final document*.

STEP 3 : REGULATORY CONSULTATION AND DISCUSSION

A. **<u>Regional regulatory consultation</u>**

- Regulatory consultation is carried on in 3 region:

1. In European union (EU) its published as draft Committee for Medical Product for Human Use (CHMP).

2. In Japan its translated & issued by Ministry of Health, Labour and Welfare (MHLW).

3. In USA its published as draft guidance in the Federal Register.

- The regulatory parties exchange information on the comment they have received to arrive at a single Harmonised Guideline.

B. Discussion of regional consultation comments

- EWG is resumed after obtaining the consultation result.
- The draft document generated as a result of step 3 phase is called *step 4 Experts Document*.
- The step 4 Experts Document signed by the EWG regulatory parties and the sign off is called as *step 4 Expert Signoff*.
- This document is submitted to SC.

STEP 4 : ADOPTION OF AN ICH HARMONISED TRIPARTITE GUIDELINE

- Step 4 is reached on when the SC agrees based on the reports from EWG.

- The *step 4 Final Document* is signed off by the SC.

STEP 5 : IMPLEMENTATION

- The Harmonised Tripartite Guideline immediately moves to the final step of process that is the regulatory implementation.

- The implementation dates are reported back to the SC and published by the ICH Secretariat on the ICH website.

WORLDWIDE ZONES AND THE TEMPERATURE AND HUMIDITY CONDITIONS

Zone	Mean kinetic temperature	Yearly average humidity (%RH)
Zone I (Moderate)	21 ℃	45
Zone II (Mediterranean)	25 ℃	60
Zone III (Hot, dry)	30 ℃	35
Zone IV (Very hot, moist)	30 ℃	70

COUNTRIES BELONGING TO VARIOUS ZONES

Regions	Zone I &II	Zone III&IV
EUROPE	All countries	
AMERICA	Argentina, Bolivia, Canada, Mexico, US	Brazil, Columbia, Cuba, Jamaica
ASIA	Afghanistan, china, Iran, Nepal, turkey	Bahrain , Hong Kong, India, Oman , Pakistan, Srilanka,UAE
AFRICA	Egypt, Algeria, south Africa, Libya	Angola, Benin, Congo, Uganda, Sudan, Somalia, Senegal

ICH GUIDELINES FOR STABILITY

ICH GUIDELINES FOR STABILITY

Q1A(R2)	***Stability Testing of New Drug Substances and Products***
Q1B	***Stability Testing : Photostability Testing of New Drug Substances and Products***
Q1C	***Stability Testing for New Dosage Forms***
Q1D	***Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products***
Q1E	***Evaluation of Stability Data***
Q1F	***Stability Data Package for Registration Applications in Climatic Zones III and IV***

STABILITY

- Stability of a Pharmaceutical preparation can be defined as “the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic & toxicological specification throughout its shelf life”.

PURPOSE OF STABILITY TESTING

- To ensure the efficacy, safety and quality of active drug substance and dosage forms.

- To establish shelf life or expiration period and to support label claims.

STABILITY TESTING OF NEW DRUG SUBSTANCES & PRODUCTS
Q1 A(R2)

- Principle

- To provide evidence how quality of drug substance or product varies
- To establish a retest period for drug substance or shelf life for drug product.

DRUG SUBSTANCE

Stress testing

- To identify degradation product
- To evaluate its susceptibility to hydrolysis

➢ Carried out on a single drug substance

➢ Photostability is an integral part of this testing

Selection of batches

➢ Studies carried on atleast 3 primary batches

➢ The primary batch should be of pilot scale

➢ Should be packed in same container closure system as proposed for storage and distribution

Testing frequency

To establish the stability profile of drug substance

For long-term storage

12 month study

– Testing frequency

0 3 6 9 12

For accelerated storage

6 month study

– Testing frequency

0 3 6

(initial) (final)

If significant change occur

– Increase the testing by adding sample at final time point

– Include 4th time point in study design

For intermediate storage

12 month study

- Testing frequency

0 6 12

If significant change occur

- A 4th time point can be included

Storage condition

- Drug substance is evaluated to test
  - Its thermal stability
  - Sensitivity to moisture

Table 1: **General case**

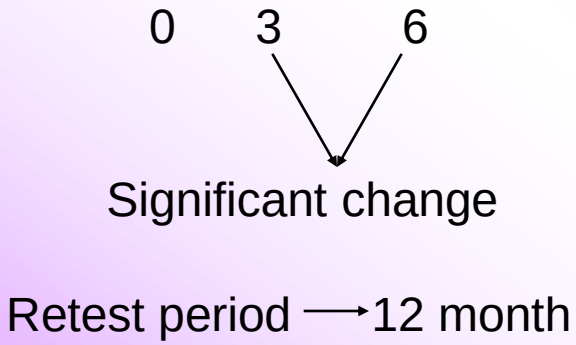
Study	Storage condition	Minimum time period for data submission
LONG TERM	25ºC±2ºC/60%RH±5%RH Or 30ºC±2ºC/65%RH±5%RH	12 MONTH
INTERMEDIATE	30°C±2°C/65%RH±5%RH	6 MONTH
ACCELERATED	40°C±2°C/75%RH±5%RH	6 MONTH

Long-term studies

0 6 12 ↓ Significant change	0 3 6 12 ↓ Additional testing at intermediate condition

Table 2: **Drug substance intended for storage in a refrigerator**

Study	Storage condition	Minimum time period for data submission
LONG TERM	5°C±3°C	12 MONTH
ACCELERATED	25°C±2°C/60%RH±5%RH	6 MONTH



DRUG PRODUCT

- Stability studies based on
  - Behavior & properties of drug substance
  - The stability study of drug substance

Selection of batches
Testing frequency
Storage condition

- General case
- Drug product stored under refrigerator
- Drug products packaged in impermeable containers
  - act as a barrier to moisture or solvents
  - conducted at controlled humidity condition

- Drug products packaged in semi-permeable containers
  - aqueous products should be evaluated for water loss
  - conducted at low relative humidity

Statements & labeling

- The statement should be based on the stability evaluation of drug substance.
- Specific instruction should be provided for drug substance that cannot tolerate freezing.
- Terms such as “ambient condition” or “room temperature” should be avoided.
- Retest period derived from stability information.
- Retest date should be displaced on container label.

PHOTOSTABILITY TESTING OF NEW DRUG SUBSTANCES & PRODUCTS Q1 B

Photostability testing studies include:

- Test on drug substance.
- Test on exposed drug product outside the immediate pack.
- Test on drug product in the immediate pack.
- Test on drug product in the marketing pack.

Light source

Option 1: Artificial daylight lamp combining both visible & UV output

Option 2: Cool white fluorescent & near UV lamp

output max. energy emitted

Procedure

- Sample exposed to light source/actinometric system

Eg: Quinine chemical actinometry

2%w/v aq.solution of quinine monohydrochloride dihydrate

- *Option 1:*

  In 20ml colourless ampoule

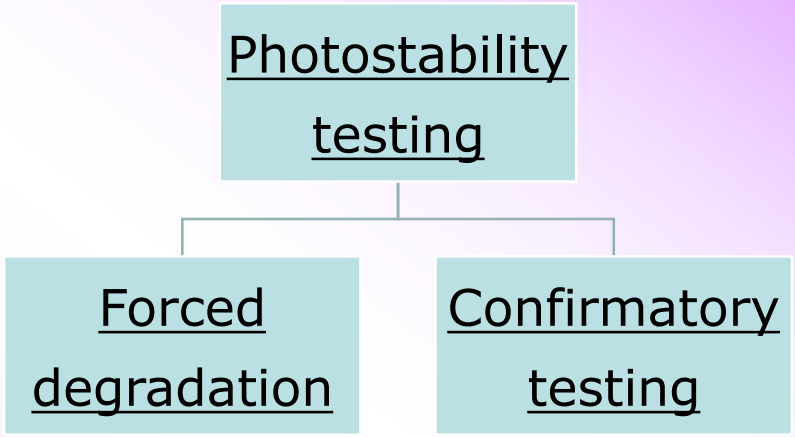
- *Option 2:*

  In 1cm quartz cell

Change in absorbance calculated by

$\triangle A = AT - A0$

DRUG SUBSTANCE



- Evaluate the photosensitivity
- Its used alone or in solution
- Placed in chemically inert & transparent containers.
- Variety of exposure condition

- Information necessary for handling, packaging and labeling

Presentation of the samples

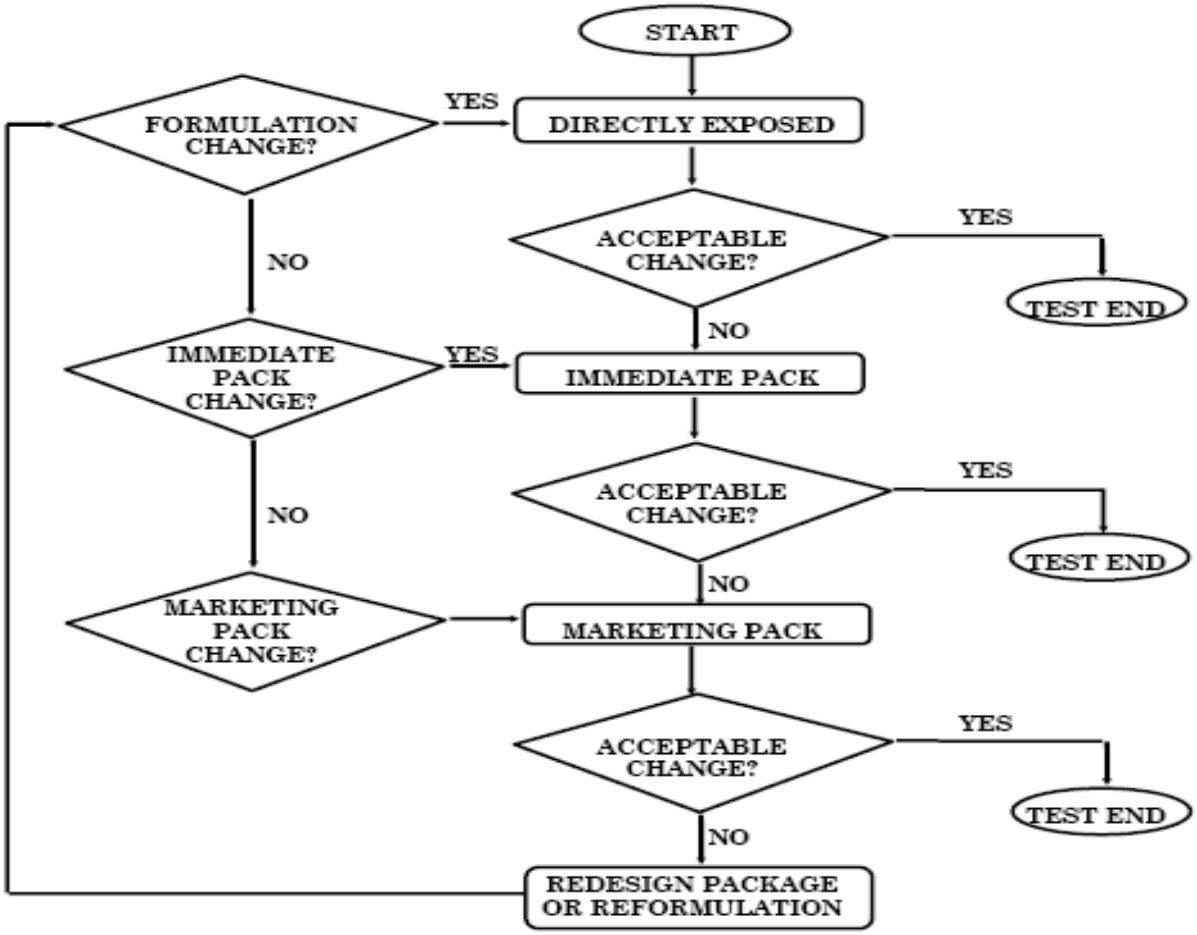
- Physical characteristic of the sample should be taken care
- Interaction between the sample and any material should be eliminated
- Small amount of solid sample placed in glass or plastic dish
- If its liquid sample its exposed in chemically inert and transparent container

Analysis of samples

- Should be performed with the control
- Sample examined for change
  - in physical property
  - in assay and degradants

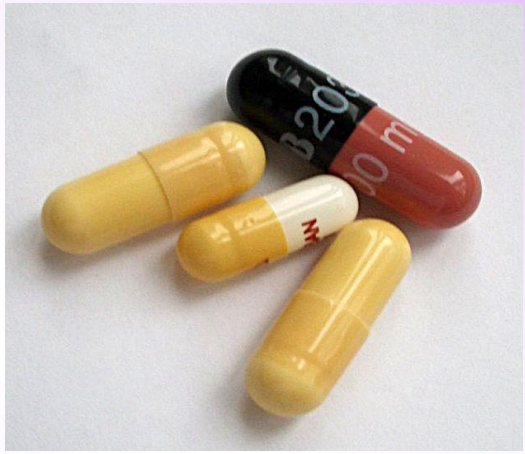
DRUG PRODUCT

DECISION FLOW CHART FOR PHOTOSTABILITY TESTING OF DRUG PRODUCTS



STABILITY TESTING FOR NEW DOSAGE FORMS Q1 C

A new dosage form is defined as a drug product which is a different pharmaceutical product type, but contain the same active substance as included in the existing drug product.



Eg: Different administration route (oral to parenteral)

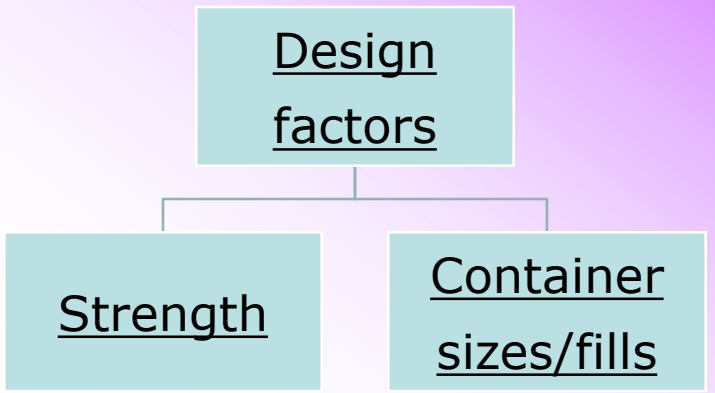
Specific delivery systems (immediate release tablet to modified release tablet)

BRACKETING & MATRIXING DESIGN FOR STABILITY TESTING OF NEW DRUG SUBSTANCE & PRODUCT Q1 D

- A ***full study*** design is one in which samples of every combination of all design factors are tested at all time points.
- A ***reduced design*** one in which sample for every factor combination are not tested at all time points.

BRACKETING

Bracketing is the design of a stability schedule such that samples on the extremes of certain design factors are tested at all time points.



- Capsules of different strengths made with different fill plug sizes from same powder blend,
- Tablets of different strengths manufactured by compressing varying amounts of same granulation, and
- Oral solution of different strengths with formulations that differ only in minor excipients (eg: colourant, flavourings).

➢ Bracketing cannot be applied when different excipients are used among strengths.

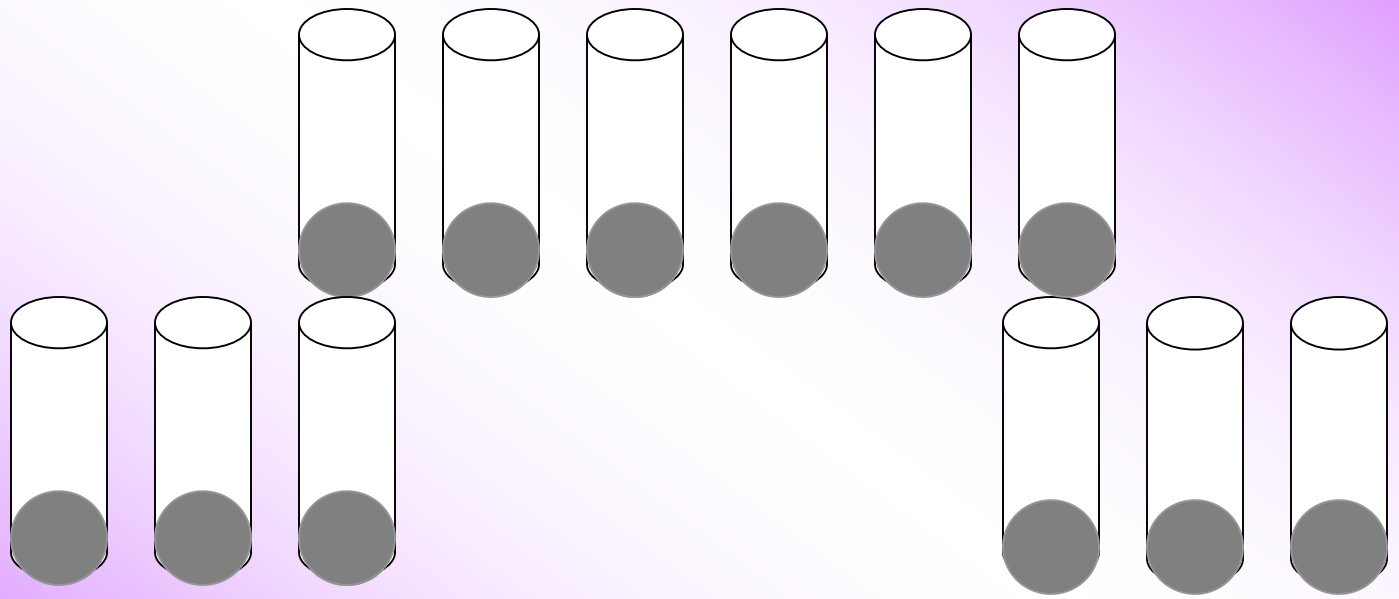
➢ Bracketing can be applied to study of container closure system.

➢ Characteristics of the container closure system include:

- container wall thickness,
- closure geometry,
- surface area to volume ratio,
- headspace to volume ratio,
- water vapour permeation rate.

MATRIXING

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



3rd month

6th month

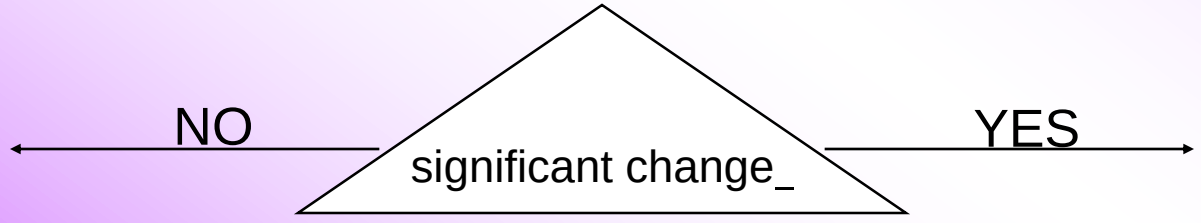
EVALUATION OF STABILITY DATA Q1E

- *Q1E provides recommendations on* :

- *How* to use stability data generated according to Q1A(R2).

- *When* and *how* a retest period or a shelf life can be extended beyond the period covered by long-term data.

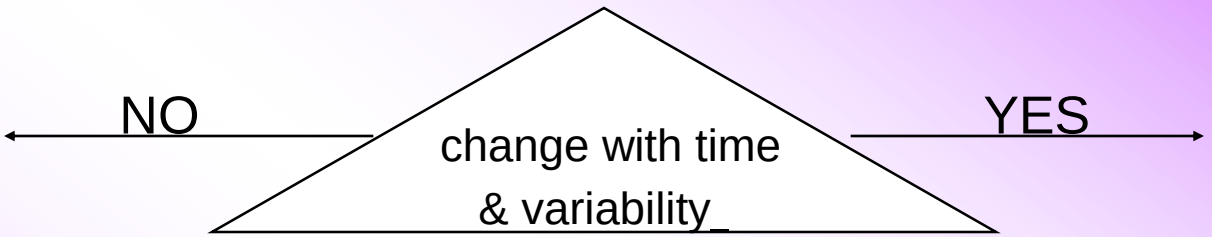
- *Data evaluation for retest period or shelf life estimation for drug substance or product intended for room temperature storage*



Accelerated condition

If No

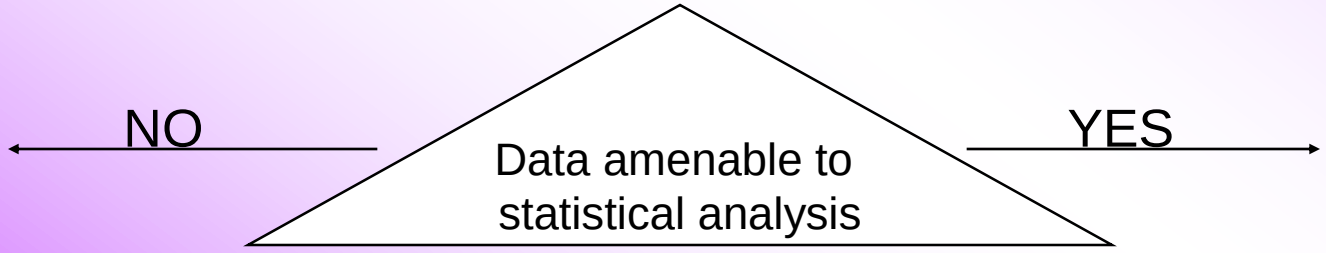
The retest period or shelf life depend upon the long-term data and accelerated data.



Long-term and accelerated data

If no : The product remains within the proposed retest period.

if yes: Statistical analysis used in establishing a retest period

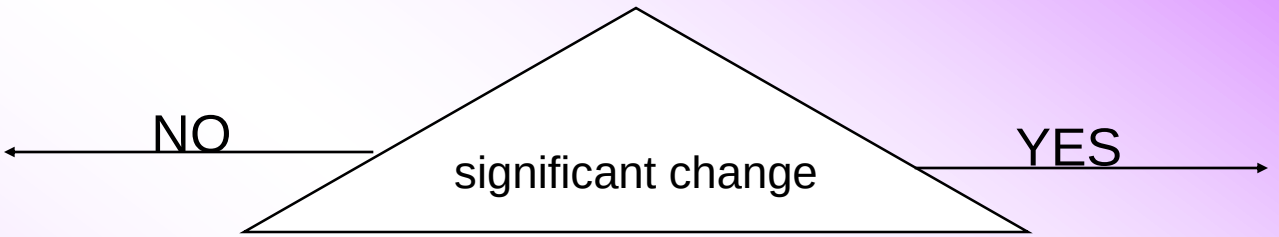


If no: Should not be more than 6 month beyond the period covered by long-term data.
i.e. 12 + 6

if yes: Should not be more than 12 month beyond the period covered by long-term data.
i.e. 12 + 12

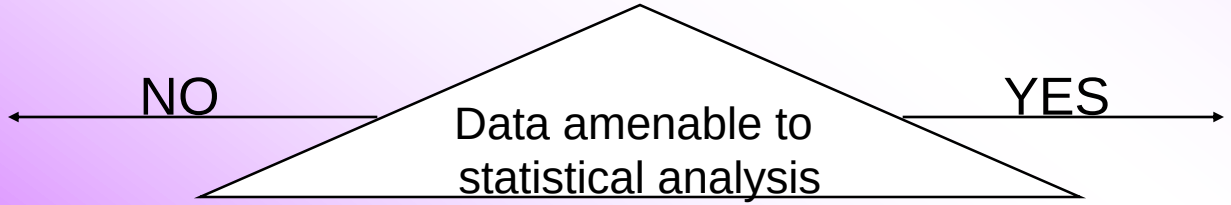
If YES

The retest period or shelf life depend on intermediate condition and long-term condition.



if yes: Should not exceed the period covered by long-term data.

If no : Statistical analysis used in establishing a retest period



If no: Can be up to 3month beyond the period covered by long-term data.
i.e. 12 + 3

if yes: Should not be more than 6 month beyond the period covered by long-term data.
i.e. 12 + 6

STABILITY DATA PACKAGE FOR REGISTRATION APPLICATIONS IN CLIMATIC ZONE III AND IV
Q1F

- This guideline defined the storage conditions for stability testing in countries located in Climatic Zone III (hot and dry) and IV (hot and humid).

Stability storage conditions for Zone- III & IV countries

Product	Types of study	
	Accelerated	Long term
Solid oral dosage forms , solids for reconstitution , dry and lyophilized powders in glass vials	40 ℃ /75% RH	30 ℃ and 35/70%RH (Zone- III & IV)
Liquid in glass bottles, vials, sealed, glass ampoules, which provide an impermeable barrier to water loss	40 ℃/ambient humidity	30 ℃/ ambient humidity
Drug products in the semi permeable containers	40 ℃/15%RH	30 ℃/40%RH
Drug products to be indented to be stored at refrigerator temperature	30 ℃ and 35/75%RH (Zone-III & IV) or 30 ℃ ambient humidity for liquid products	5±3 ˚C with monitoring but not control of humidity
Drug products intended to be stored at freezer temperature	5±3 ℃/ ambient humidity	-15±5 ˚C

Long term stability of rh-Cu/Zn-superoxide dismutase (SOD)-liposomes prepared by the cross-flow injection technique following International Conference on Harmonisation (ICH)-guidelines

- Liposomal stability and protein stability were tested under appropriate conditions.
- The size alterations of the vesicles, protein release and protein activity were also evaluated.
- Significant alterations of the liposomes nor any protein degradation was detected.

Eur J Pharm Biopharm. May 2002

Design and evaluation of self-emulsifying drug delivery systems (SEDDS) of nimodipine.

- The ability of self-emulsifying drug delivery systems (SEDDS) to improve solubility, dissolution rate and bioavailability of a poorly water-soluble calcium channel blocker, nimodipine (NM) was evaluated.
- In vitro dissolution studies indicated that NM loaded SEDDS could release complete amount of NM irrespective of the pH of the dissolution media.
- NM loaded SEDDS were subjected to various conditions of storage as per ICH guideline for 3 months.

AAPS PharmSciTech. Feb 2008.

Modified polysaccharides as fast disintegrating excipients for orodispersible tablets of roxithromycin

- Modified polysaccharides co grinded treated agar (C-TAG) and co grinded treated guar gum (C-TGG) were prepared by subjecting pure polysaccharides namely agar and guar gum respectively to sequential processes of wetting, drying and co grinding with mannitol (1:1).
- Evaluated for particle size distribution, derived properties, swelling index & biodegradability.
- Friability and Disintegration time as response parameters were used to formulate orodispersible tablets of roxithromycin and were evaluated for wetting time, water absorption ratio and in vitro drug release at salivary pH 6.4 and physiological pH 7.4.
- In vitro release both at salivary pH and physiological pH was found to be more than 90% within 30 min.
- Stability studies carried out as per ICH Q1A guidelines suggested the formulations to be stable for a period of 6 months.

AAPS PharmSciTech. Jan 2008

Effect of unconventional curing conditions and storage on pellets coated with Aquacoat ECD

- Purpose of this study was to develop storage stable pellets coated with the aqueous ethylcellulose dispersion Aquacoat ECD.
- The influences of accelerated storage conditions on the release behavior of Aquacoat/HPMC-coated drug pellets were investigated.
- Unconventionally harsh curing conditions (60 degrees C/75% RH or 80 degrees C) improved the storage stability of Aquacoat-coated pellets at accelerated conditions.

Drug Development and Industrial Pharmacy May 2009

REFERENCES

- Physical Pharmacy by *Alfred Martin*, B.I. Publications, 4th Edition, Pg no: 313-316.

- Stability of drugs & dosage forms by *Sumie Yoshika* & *Valentine J.Stella,* Springer Publications, Pg no: 205-224.

- Handbook of Isolation &Characterization of Impurities in Pharmaceuticals by *Ahuja & Alsante*, Elsevier Publications, Pg no: 103-105.

- www.ich.org
- www.ijpsonline.com (Oct-Dec 2004).
- www.pubmed.com

THANK YOU