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# GUIDELINES FOR THE STABILITY TESTING OF PHARMACEUTICALS

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- Introduction
- Phases of testing
- Intended market
- Design of stability studies
- Guidelines for submitting documentation
- Content of stability reports
- Summary sheet
- Other conditions..



# Introduction

- » Definition and its importance
- » Preamble
- » Scope
- » Objective

## Definition and its importance

- The stability is defined as “the ability of a pharmaceutical product to retain its chemical, physical, and microbiological and biopharmaceutical products within specified limits throughout its shelf life.”
- The stability tests are “a series of tests designed to obtain information on the stability of a pharmaceutical product in order to define its shelf life and utilization period under specified package and storage conditions.”
- In general stability is important for industrially manufactured products to overcome the adverse climatic conditions etc.

- The stability and expiry date of products depend upon this formulation and conclusions from stability studies are to be drawn.
- The important factors that influence the stability of drugs are as follows;
  - Environmental factors
  - Product related factors.
    - » (Chemical and physical properties of drug substance, Dosage form and its composition, Manufacturing process used, Nature of container/ packaging etc)

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- Literature on decomposition process and degradability of active substances should be available with adequate analytical methods for drug.
  - Actual stability of dosage form largely depends on the formulations and packaging closure and also process development given high priority.
  - The stability studies should guarantee the maintenance of quality, safety and efficacy throughout shelf life of a product.
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# PREAMBLE

- The guidelines seek to exemplify the core stability data, package required for new drug substances and products.
- It is not always necessary to follow guidelines when there are scientifically justifiable reasons for using alternative approaches.
- The guidelines provide a general indication on requirements for stability testing but leaves flexibility to encompass the variety of different situations and are characteristics of material being evaluated.
- Details of specific requirements for sampling, test requirements for particular dosage form are not covered in these guidelines.

# OBJECTIVES

- The major objectives of stability testing are
  - ‡ To select adequate formulations
  - ‡ To determine shelf life and storage conditions
  - ‡ To substantiate the claimed shelf life
  - ‡ To verify that no changes have been introduced in formulation that adversely affects the stability.



## SCOPE



- The guidelines primarily address the information required in registration applications for new molecular entities and associated drug products.
- The guidelines do not primarily seeks to cover the information required for abbreviated or abridged applications, variations, and clinical trial applications.

# PHASES OF TESTING

- ◆ In development phase
- ◆ For registration dossier
- ◆ In post registration period.

- ❖ In general, the accelerated stability tests are carried in order to determine the alternative formulations, packaging materials and also in final formulations and manufacturing process.
- ❖ These tests are generally carried out to enable the stability, shelf life and storage conditions during the development of new formulation.
- ❖ The manufacturer will require submitting information on the stability of the product derived from various tests performed on final dosage forms and in its final container and packaging.

- The date to be submitted is obtained from both accelerated and real time studies.
- Recently published and obtained information regarding the tests should also be done and submitted during this phase.
- With the approval of regulatory authorities a tentative shelf life is established when manufacturer has undertaken by virtue of signed statement to continue and complete required studies and submit the results.

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- # The ongoing real time stability studies to substantiate the expiry date and the storage conditions previously projected.
  - # Data confirming a tentative shelf life should be submitted for registration body and ensures quality and safety of products with reference to degradation.
  - # Additional stability studies are required whenever major modifications are made to formulation, manufacturing process, packaging or method of preparation.
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## Ω INTENDED MARKET:

- The design of stability testing programme, the intended market and climatic conditions are taken, in which the drug products will be used.
- Four climatic zones are distinguished i.e.

(Zone)	(Open air)	(Storage room)
Zone 1: Temperate ~	10.9°C ± 75% RH	18.7°C ± 45% RH
Zone 2: Subtropical~	17 °c ± 70% RH	21.1°C ± 52%RH
Zone 3: Hot/Dry~	24.4°C ± 39%RH	26°C ± 54% RH
Zone 4: Hot/ Humid~	26.5°C ± 77% RH	28.4°C ± 70%RH

REGION	ZONE I AND II COUNTRIES	ZONE III AND IV COUNTRIES
Europe	All Countries	~~~~~
America	Argentina, Bolivia, Chile, Canada, Mexico, Peru, Uruguay, <i>USA</i>	Barbados, Belize, Brazil, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Guyana, Haiti, Honduras, Jamaica, Columbia, Cuba, Nicaragua, Dutch Antilles, Panama, Paraguay, Puerto Rico, Venezuela. All of these countries are assigned to CZ IV
Asia	Afghanistan, Armenia, Azerbaijan, China, Georgia, Iran, Israel, Japan, Kazakhstan, Kirghizia, Korea, Lebanon, Nepal, Syria, Tadjikistan, Turkey, Turkmenia, Uzbekistan	Bahrain, Bangladesh, Hong Kong, <i>INDIA</i> , <i>Indonesia</i> , Iraq (III), Jordan (III), Kampuchea, Qatar, Kuwait, Laos, Malaysia, Maldives Islands, Myanmar, Oman, Pakistan, Philippines, Saudi Arabia, Singapore, Sri Lanka, Taiwan, Thailand, United Arab Emirates, Vietnam, Yemen
Africa	Egypt, Algeria, Tunisia, Libya, Morocco, Namibia, Ruanda, South Africa, Zambia, Zimbabwe	Angola, Ethiopia, Benin, Botswana (III), Burkina Faso, Burundi, Djibouti, Ivory Coast, Gabon, Gambia, Ghana, Guinea, Cameroon, Kenya, Longo, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Niger, Nigeria, Senegal, Sierra Leone, Somalia, Sudan, Tanzania, Togo, Chad (III), Uganda, Zaire, Central African Republic
Australian/ Oceanic	Australia, New Zealand	Fiji. Society Islands, Marshall Islands, New Caledonia, Papua-New Guinea, Samoa, Tonga

## STABILITY STUDY STORAGE CONDITIONS

STABILITY STUDY	STORAGE CONDITIONS	TESTING FREQUENCY (MONTHS)
Accelerated	$40 \pm 2^{\circ}\text{C}$ & $75 \pm 5\% \text{ RH}$	0,1,2,3 & 6
Intermediate	$30 \pm 2^{\circ}\text{C}$ & $65 \pm 5\% \text{ RH}$	0,3,6,9,12,18,24 & 36
Long term	$25 \pm 2^{\circ}\text{C}$ & $60 \pm 5\% \text{ RH}$	0,3,6,9,12,18,22,24,26,36,48 & 60





☑ DESIGN OF STABILITY STUDIES

☑ Drug substance

☑ Drug product.

# DRUG SUBSTANCE

- ▶ Introduction
- ▶ Selection of batches
- ▶ Test procedures and criteria
- ▶ Specification
- ▶ Storage conditions
- ▶ Testing frequency
- ▶ Packaging materials
- ▶ Evaluation
- ▶ Statements

## INTRODUCTION

- Information on the stability of the pure drug substance is an integral part of systematic approach to stability evaluation.
- Stress test helps to determine the intrinsic stability of molecule by degradation pathways in order to identify the degradation products.
- Primary stability studies are intended to show that drug substance will remain within specifications during re-test period if stores under recommended storage conditions.

## SELECTION OF BATCHES

- The stability information from accelerated and long term testing is provided on at least 3 batches.
- Long term testing should cover a minimum of 12 months on 3 batches at the time of submission.
- The batches should be manufactured by pilot plant scale and should be provided with the same manufacture procedures.
- Overall quality of batches placed for stability testing should be represented of both quality of material during manufacturing and testing.

## SPECIFICATIONS

- Limits of acceptability should be derived from profile of material used during pre-clinical and clinical stage.
- This includes individual and total upper limits for impurities and degradation products.

## STORAGE CONDITIONS

- The storage conditions should be sufficient to cover the storage, transport and subsequent use and the application of same conditions as applied for drug product are used.
- The temperature sensitive substances should be stored under an alternative lower temperature conditions.

- **Commonly used conditions are:**

- Long term testing ~  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  &  $60\%RH \pm 5\%$  12months
- Accelerated testing ~  $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$  &  $75\%RH \pm 5\%$  6months
- Intermediate conditions~  $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$  &  $60\%RH \pm 5\%$  6months
- (for drug substances used in manufacture of dosage forms tested long term at  $25^{\circ}\text{C}/60\%RH$  included in registration application)

- Significant change at  $40^{\circ}\text{C}/75\%RH$  on  $30^{\circ}\text{C}/60\%RH$  defined as failure to meet specification.
- Long term testing covered beyond 12months to cover appropriate re-test periods and submitted.

## PACKAGING

- The containers to be used in long term, real time stability evaluation should be the same as actual packaging.



## EVALUATION

- The design of stability study, is to establish, a testing on the minimum of 3 batches of drug substance and evaluating the stability information.
- An acceptable approach to quantitative characteristics that are expected by decrease with the time is to determine the time at which 95% of confidence limit for mean degradation curve intersects the acceptable lower specification limit.
- If the batch to batch variability is small then it is advantageous to combine the data into one overall estimate and this is done by applying statistical tests to the slopes of regression lines and zero time intercepts for individual batches.
- The nature of any degradation relationships will determine the need for transformation of data for linear regression analysis.

- Usually the relationship can be represented by a linear, quadratic (or) cubic function on an arithmetic (or) logarithmic scale.
- In general statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches to assure degradation line.
- The data shows little degradation and little variation and hence it is not necessary to do formal analysis, but it provides a full justification for the commission.
- Limited extrapolation of real time data beyond the observed range extends the expiration dating at approval time, when AST is done; and therefore the extrapolation should be done in each application.
- In general the evaluation method should cover not only the assay but the levels of degradation products and other appropriate attributes.

# STATEMENTS

- It should contain the following information.
  - Storage temperature range.
  - National/regional requirements.
  - Stability evaluation procedures.
  - Specific requirements etc.
- The terms such as “ambient conditions” or “room temperature” are unacceptable and retest is derived from stability information.

# DRUG PRODUCT



- ▶ Introduction
- ▶ Selection of batches
- ▶ Test procedures and criteria
- ▶ Specification
- ▶ Storage conditions
- ▶ Testing frequency
- ▶ Packaging materials
- ▶ Evaluation
- ▶ Statements

# INTRODUCTION

- The stability studies design for finished product should be based on the following conditions i.e.
  - Knowledge of behavior of drug
  - Properties of drug
  - Experienced data from clinical formulation studies.
  - Stability studies of drug substance
- The likely changes on storage and rationale for selection of product should be stated.

## SELECTION OF BATCHES

- In the stability determinations around 3 batches of same formulation and dosage form for marketing.
- Two of the three batches should be prepared by pilot scale and the 3rd batch maybe smaller.
- The long term testing should cover at least 12 months duration at the time of submission.

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- Process should provide product of the same quality intended for marketing and meeting the same quality specification as to be applied for release of material.
  - The data on laboratory scale batches is not acceptable as primary stability information and data on associated formulations submitted as supportive information.
  - If the first 3 production batches manufactured post approval then stability is done by protocols as in approved drug application.
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## TEST PROCEDURES AND CRITERIA

- ❑ The testing should cover features susceptible to change during storage and the analytical test procedures should be fully validated and the assay should be stability indicating.
- ❑ The range of testing should cover not only chemical and biological stability but also loss of preservative, physical properties, characteristics etc.



# SPECIFICATIONS

- Limits of acceptance are related to release limits from the available stability information.
- The shelf life specification should allow acceptable and justifiable derivatives from release specifications based on stability evaluation and changes observed on storage.
- The various upper limits of degradation included justify the various levels observed in material used in pre-clinical and clinical studies.

## STORAGE TEST CONDITION

- The storage condition should be sufficient to cover storage, shipment and subsequent use.
- The various storage conditions indicated are:

- Long term testing	25°C +/- 2°C / 60%RH +/- 5%	12months
● Accelerated testing	40°C +/- 2°C / 75%RH +/- 5%	6months

- Significant change occurs due to accelerated stability testing at an intermediate condition [ $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$  /  $60\% \text{RH} \pm 5\%$ ] is defined as:
  - A 5% potency loss from the initial assay value of a batch.
  - Any specified degradant exceeding its specification limit.
  - The product exceeding its pH limits.
  - Dissolution exceeding the specification limit for 12 capsules/tablets.
  - Failure to meet specifications for appearance and physical properties.

- Specified changes for various drug products are:
  - Heat sensitive drug products~ alternative lower temperature condition
  - Solid dosage forms~ high relative humidities.
- The long term testing will be continued for a sufficient time beyond 12 months to cover shelf-life at appropriate test periods.

## TESTING FREQUENCY

- The frequency of testing should be sufficient to establish the stability characteristics of drug product.
- It is carried out for every three months over the first year, every six months over the second year and then annually.

## PACKAGING MATERIAL

- The testing should also be carried out in final packaging proposed for marketing.
- Additional testing of unprotected drug product form a useful part of stress testing and pack evaluation.

## EVALUATION

- A systematic approach should be adopted in the presentation and evaluation of the stability information and should cover physical, chemical, biological, microbiological quality characteristics.
- The design of the stability studies is to establish, based on testing a minimum of 3 batches of drug product, a shelf- life and label storage instructions applicable to all future batches.
- An acceptable approach for the qualitative characteristics decreases with time is to determine the time at which 95% one sided confidence limit intersects the acceptable lower limit.

- The nature of degradation relationship will determine the need for transformation of data for linear regression analysis ( linear, quadratic (or) cubic)
- An evaluation should contain not only assay, but the levels of the degradation products and appropriate attributes.
- The stability of drug products after reconstituting according to labeling should be addressed to provide appropriate and supportive information

## STATEMENT/LABELING

- A storage temperature range maybe used in accordance with the relevant national/regional requirements.
- The range should be based on the stability evaluation of drug product.
- Specific requirements should be stated for drug product that cannot tolerate freezing.
- The use of terms such as “ambient conditions” or “room temperature” is unacceptable.



# CONTENT OF STABILITY REPORT

## 1. General product information

- Name of drug substance and drug product
- Dosage form and strength including formulation
- Labeling
- Composition, type and size of container-closure.

## 2. Specifications and test methodology information

- Physical, chemical and microbiological characteristics and prior submission specifications.
- Test methodology used for each sample.
- Information on accuracy, precision and suitability of the methodology.
- Description of potency tests for measuring biological activity for biological products.

### 3. Study design and study calculation:

- Description of sampling plan:
  - » Batches and number selected
  - » Container~ closure and number selected.
  - » Number of dosage units selected.
  - » Sampling times
  - » Testing of drug for reconstitution of time of dispensing.
- Expected duration of study.
- Conditions for storage of products.

### 4. Stability data/ information

- Lot number and associated manufacturing data.
- The age of bulk active drug used in manufacturing (antibiotic)
- Analytical data and source of each data point.
- Summary of information on previous formulations obtained during product development.

## 5. Data analysis and conclusions

- Documentation of appropriate statistical methods.
- Evaluation of data including calculations, statistical analysis, plots or graphs.
- Results of statistical tests.
- Proposed expiration dating period and its justification.
- Release specifications.