Stability:-
Basic Concepts and Objectives

ESSENTIAL DEFINITIONS ACCORDING TO ICH

STABILITY

STABILITY is officially defined as the time lapse(period) during which drug substance (API) or drug product (FPP) to retains the same properties and characteristics(i.e. Physical, Chemical, Microbiological, Therapeutic and Toxicological specifications to maintain its identity, strength, quality, and purity) that it possessed at the time of manufacture.

ACCELERATED STABILITY TESTING

These are the studies designed to increase the rate of chemical degradation and physical change of a drug by using exaggerated storage conditions as part of the formal stability testing programmes. The data thus obtained, in addition to those derived from real – time stability studies, may be used to assess longer – term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes.

LONG-TERM STABILITY STUDIES

Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of an API or FPP, during and beyond the expected shelf-life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the re-test period or the shelf-life, to confirm the projected re-test period and shelf-life, and to recommend storage conditions.

ONGOING STABILITY STUDY

The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected re-test period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP.

STRESS TESTING–FORCED DEGRADATION (API)

Studies undertaken to elucidate the intrinsic stability of the API. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

To identify potential degradants (degradation pathways) of the API and assess if they can be formed during mfg. or storage of the FPP (Finished Pharmaceutical Product)

STRESS TESTING–FORCED DEGRADATION (FPP)

Studies undertaken to assess the effect of severe conditions on the FPP. Such studies include photo stability testing (see ICH Q1B) and compatibility testing on APIs with each other in FDCs and API(s) with excipients during formulation development.

MEAN KINETIC TEMPERATURE (MKT):

MKT, as defined by the USP, is a “single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures”

RE-TEST PERIOD

The period of time during which the API 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 FPP,when stored under the defined conditions.

SHELF LIFE (Expiration dating period, conformance period):

The time period during which an API or a FPP is expected to remain within the approved shelf-life specification, if stored under recommended conditions.

SPECIFICATION - RELEASE

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

SPECIFICATION - SHELF LIFE

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of an API throughout its re-test period, or that an FPP should meet throughout its shelf life.

PRIMARY BATCH (called also exhibit batch)

A batch of an API or FPP used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf life, respectively. A primary batch of an API should be at least a pilot scale batch. For a FPP, two of the three batches should be at least pilot scale batch, and the third batch a production batch.

PRODUCTION (SCALE) BATCH

A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application.

SUPPORTING DATA

Data, other than those from formal stability studies, that support the analytical procedures, the proposed re-test period or shelf life, and the label storage statements. Such data include (1) stability data on early synthetic route batches of API, small-scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing; (2) information regarding test results on containers; and (3) other scientific rationales.

➔ TYPES OF STABILITY

- Mainly Five types of Stability are generally recognized

Type of Stability	Condition Maintained throughout the shelf life of drug product
Chemical	Each active ingredient retains its chemical integrity and labeled potency within the specified limit
Physical	The original Physical properties including appearance palatability, uniformity, dissolution and suspendability are retained.
Microbiological	Sterility or resistance to microbial growth is retained according to specified requirement.
Therapeutic	Therapeutic effect remains unchanged
Toxicological	No significant increase in toxicity occurs

➔ What happens due to Instability ?

1) Increase in the concentration of API :-

For some products, loss of vehicle can result in an increase in the concentration of active drug.

For example, some lidocaine gels exhibit this behaviour, perfusion bags sometimes allow solvent to escape and evaporate so that the product within the bags show an increase in the concentration.

2) Loss of content uniformity :-

Suspensions are the drug delivery system most likely to show a loss of content uniformity as a function of time. For such systems, determination of ease of redispersion or sedimentation volume may be included in a stability protocol.

3) Decline of microbiological status :-

The microbiological status of a pharmaceutical product can change significantly with time . First, micro – organisms present in the product at the time of manufacture may reproduce and thus increase the number of viable micro-organisms.

Drug assayed for the bioburden at the time of manufacture, is within limits, and when tested after say 6 months storage, exceed the maximum permitted limits.

4) Formation of toxic degradation products :-

If a drug degrades to a molecular species that is toxic, there must be a special attention given to the quantity of such products. E.g. Conversion of p-amino salicylic acid to p-amino phenol (Toxic).

➔ <u>OBJECTIVES OF STABILITY TESTING</u>G:-

(1) Our concerns for patients' welfare:-

- Obviously, our primary reason for stability testing should be our concern for the well-being of the patients who will use our products. Sometimes in the mad rush to comply with other requirements, this important fundamental may be discounted or forgotten. Indeed, sometimes one gains the impression that is some quarter's stability is regarded as having clinical relevance.
- Certainly, if a product that does not degrade to toxic decomposition products and that is characterized by a narrow therapeutic ratio is present on the market at only 85% of label claim; one would not expect patients to be dropping dead in the streets because of this deficiency instability.
- However, this is not to say that stability problems can never have serious clinical consequences. For example, in the early 1980s a packaging stability problem with nitroglycerine tablets unfortunately resulted in some tablets have 10% of label claim. Since nitroglycerine is used for the emergency treatment of a most serious cardiac conditions, angina, there is unfortunately strong cause for concern that some patients may have died as a result of this stability problem.

(2) To protect the reputation of the producer.

We should be jealous for the reputation that the stability of our pharmaceutical products – compounded or manufactured – enjoys. Thus a most important reason for conducting a stability testing program is to assure ourselves the our products will indeed retain fitness for the use with respect to all functionally relevant attributes for as long as they are on the market.

(3) Requirements of regulatory agencies

In many parts of the world, there are legal requirements that certain types of stability tests, as required by regulatory agencies, must be performed. Obviously, the law must be obeyed. However, it is wrong to abdicate from all scientific judgements and only conduct those stability tests that a regulatory agency is perceived as requiring. Indeed, there are occasions when any manufacturer with a true dedication to quality will perform stability tests that are over and above those required by regulation.

(4) To provide a database that may be of value in the formulation of other products.

Data obtained in the stability evaluation of product X in 1999 may prove to be of value when, in 2003, we start developing product Y. There may be occasions, although they are probably rare, when it will worthwhile to continue stability testing on an R&D formulation that we know will never be marketed just because we are interested in the stability of a new excipient that we have included in the formulation.

(5) Shelf-life & storage condition and labeling specification:-

By carrying out stability testing we can find out the shelf –life and expiry date can be calculated. We ca have information about best storage condition at which drug will contain its characteristic for long time. And if there is any specification that we can write it on the label.

(6) Adequate formulation & container closer systems.

We can have idea about the formulation which will be more stable. And if during stability testing we find any specification of container. e.g. Menadione injection is packed in amber color ampoule to protect from photo degradation.

(7) How quality of drug substance or product varies with the time under the influence of various factors.

(8) Degradation product & possible degradation pathway

(9) Development & validation of stability indicating methodology

(10) Prevent great loss by recalling the batch due to stability.

If any difficulty is found during storage and in marketed product, than industry has to recall all the drugs of that batch which is not economical . But if stability studies are carried out than we may over come those problems.

(11) To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product

(12) Providing evidence on how quality of drug substance or product varies with the time under the influence of various factors like temp, humidity and light.

(13) Loss/increase in concentration of API

(14) Modification of any attribute of functional relevance, e.g., aalteration of dissolution time/profile or bioavailability

(15) Loss of pharmaceutical elegance and patient acceptability

➔ Stability study requirement and guidance regarding this is covered in

1. **I**nternational **C**onference on **H**armonization (ICH) of technical requirements or registration of pharmaceutical for humane use.
2. ASEAN(Association of South-East Asian Nations) guideline for stability of drug products.
3. WHO guideline for stability of pharmaceutical products.
4. USFDA guideline
5. SUPAC guideline

TYPE OF STABILITY STUDIES:-

1. Accelerated stability testing
2. intermediate testing
3. Long term testing
4. Stress testing
5. forced degradation testing
6. Photo stability testing
7. Thermal analytical techniques for stability testing (DSC,microcalorimetry)

Overview of ICH guideline for stability testing

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

STRESS TESTING

Stress testing of the drug substance can help identify the likely degradation products, which can in turn help to establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.

Stress testing is likely to be carried out on a single batch of the drug substance. 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. Photo stability testing should be an integral part of stress testing. Perform essentially during Preformulation study. Done on single batch same composition & quality as marketing batch including packaging. Conducted for period of **6 months**.

Stress testing of FPPs in solid state

Storage conditions	Testing period*
40°C, 75 % RH; open storage**	3 months
50-60 °C, ambient RH; open storage	3 months
Photostability; according to ICH	according to ICH

* 3 months or 5-15% degradation, whatever comes first
** For API1-API2, or API-excipient, or FPP without packing material, typically a thin layer of material is spread in a Petri dish. Open storage is recommended, if possible.

Stress testing of API in solution

Storage conditions	Testing period*
pH ± 2, room temperature	2 weeks
pH ± 7, room temperature	2 weeks
pH ± 10-12, room temperature	2 weeks
H_2O_2, 0.1-2% at neutral pH, room temperature	24 hours

* Storage times given or 5-15% degradation, whatever comes first

STABILITY PROGRAMME

If a manufacturer wants to apply for the registration of a new drug, i.e. if he is applying for a

(1) **Investigative New Drug Application (IND)** or

(2) **New Drug Application (NDA**) or**(ANDA)** then he has to assure the FDA regarding the drug's/drug product's safety, quality and efficacy.

For this he has to carry out stability tests and submit stability data specified by **Q1A (R2).**

An API is considered as stable if it is within the defined/regulatory specifications when stored at **30±2°C** and **65±5% RH** for 2 years and at **40±2°C and 75±5%RH** for 6 months.

These guidelines divide the world into four zones and specify the temperature and relative humidity conditions to be maintained by each zone for stability studies.

✉ **CLIMATIC ZONE**

The zones into which the world is divided based on the prevailing annual climatic conditions

International Climatic Zones and Climatic Conditions

Climatic Condition	Zone I Temperate	Zone II Mediterranean (sub-tropical)	Zone III Hot/dry or Hot/moderate RH	Zone IV Very hot/humid
Mean Annual Temperature	< 20°C	20.5-24°C	>24°C	>24°C
Kinetic Mean Temperature (Virtual temperature)	21°C	26°C	31°C	31°C
Mean Annual Relative Humidity	45%	60%	40%	70%

Few countries of various zones

Zone I : Britain, North Europe, Russia, Canada
Zone II : U.S.A, Japan , South Europe
Zone III : Iran, Iraq, Sudan
Zone IV : Brazil, Ghana, Indonesia, Phillipines
INDIA COMES IN III AND IV ZONE

DESIGNING STEPS

1) SELECTION OF BATCHES
2) TEST PROCEDURES AND TEST CRITERIA
3) SPECIFICATIONS
4) STORAGE TEST CONDITIONS
5) TESTING FREQUENCY
6) PACKAGING MATERIAL
7) EVALUATION
8) STATEMENTS AND LABELLING.

⏩ Selection of batches

♣ Stability information from accelerated & long term testing should be provided on batches of same formulation & dosage form in the container & closure proposed for marketing.

♣ Stability data on **three** primary batches are to be provided.

- ♣ The composition, batch size, batch number and manufacturing date of each of the stability batches should be documented and the certificate of analysis at batch release should be attached.
- ♣ Expected that atleast 1st two batches manufactured should be tested for long term stability studies.

⏩ Testing frequency

According to ICH

STABILITY TESTING	TESTING INTERVALS
Real time testing (Q1 & CPMP-QWP/556/96)	0,3,6,9,12,15,24 months
Accelerated testing (Q1A(R)	0, 3 & 6 months
I**ntermediate** (Q1A (R))	0,6,9 & 12 months

➔ For accelerated testing , FDA guidelines suggest 0,2,4 & 6 months
WHO guidelines 0,1,2,3**, & 6** months

➔ **FDA, CPMP & WHO** guidelines don't suggest for intermediate testing

⏩ Storage test conditions

ACCORDING WITH ICH Q1A AND Q1F

Zone I AND II	***TEMPERATURE***	***RELATIVE HUMIDITY***
Long term study	25^0C ± 2	60% ± 5 RH
Intermediate study	30^0C ± 2	65% ± 5 RH
Accelerated study	40^0C ± 2	75% ± 5 RH
Zone III AND IV	***TEMPERATURE***	***RELATIVE HUMIDITY***
Long term study	30^0C ± 2	65% ± 5 RH
Accelerated study	40^0C ± 2	75% ± 5 RH

Acceptance Criteria:

Significant change for a drug substance is defined as failure to meet its specification

1. A 5% potency loss from the initial assay value of a batch.
2. Any specified degradants exceeding its specified limit.
3. The product exceeding its pH limits.
4. Dissolution exceeding the specified limits for 12 capsules or tablets.
5. Failure to meet specifications for appearance and physical properties (e.g., color, phase separation, resuspendability, delivery per actuation, caking, hardness).

6. 5% loss in water from its initial value ,from packaged in a semi-permeable container

⏩ Specification - Release

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the **suitability of a drug product at the time of its release**

- ♣ It may be appropriate to **have justifiable differences** between the shelf life and release acceptance criteria based on the stability evaluation and the changes observed on storage.
- ♣ Shelf-life acceptance criteria should be derived from consideration of **all available stability information.**
- ♣ E.g. :Release and shelf-life dissolution acceptance criteria (Q and t) must be the same

⏩ Stability Commitment

- ♣ For confirmation of provisional (tentative) shelf-life, real-time data are required
- ♣ When available long term stability data on the primary batches donot cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish shelf life
- ♣ First 3 production batches on stability
- ♣ Follow up stability testing (FUST) – one batch per year

⏩ Evaluation

1. **Tabulate and plot** stability data on all attributes at all storage conditions and evaluate each attribute separately.
2. No significant change at accelerated conditions within six (6) months.
3. Long-term data show little or no variability and little or no change over time.

⏩ labeling

- ♣ The use of terms such as “ambient temperature “or “room temperature “ is unacceptable.
- ♣ Where applicable, specific requirement should be stated eg “protect from light “,”protect from freezing “. The use of precautionary statements should not be a substituted
- ♣ After the stability of the product has been evaluated,
- ♣ - store under normal storage conditions;
- ♣ - store between 2 and 8^{o}C (under refrigeration, no freezing);
- ♣ - store below 8 ^{o}C (under refrigeration);
- ♣ - store between -5 and -20^{o}C(in a freezer);
- ♣ - Store below -18^{o}C(in a deep freezer).
- ♣ Normal storage conditions have been defined by WHO as: “storage in dry, well-ventilated premises at temperatures of 15-25 ^{o}C or, depending on climatic conditions, up to 30^{o}C. Extraneous odours, contamination, and intense light have to be excluded.

STABILITY PROTOCOL AND REPORT

1. Batches tested
2. General information
3. Container/closure system
4. Literature and supporting data
5. Stability-indicating analytical methods

6. Testing plan
7. Test parameters
8. Test results
9. Other requirements (post-approval commitments)
10. Conclusions

Result sheets must bear date and responsible person signature / QA approval

REQUIREMENT OF TEMPERATURE DEPEND ON TYPE OF TESTING

TYPE OF STUDY	TEMPERATURE	RELATIVE HUMIDITY	TIME DURATION
Long term	25°C ± 2°C	/60% 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

DIFFERENT TEMPERATURE REQUIREMENT DEPEND UPON TYPE OF DOSAGE FORMS

FOR DISTINCT PRODUCTS	TYPE OF STUDY		
	AST	IST	LST
Solid oral DF, solids for reconstitution, dry &lyophilized powders in glass vials	40°C ± 2°C 75 % ± 5%RH	40°C±2°C 75 % ± 5% RH	40°C±2°C 75 % ± 5% RH
Liquids in glass bottles ,vials, sealed glass ampoules which provide an impermeable barrier to water loss	40°C ± 2°C Ambient Humidity	30°C±2°C Ambient humidity	25°C±2°C Ambient Humidity
Drug products in semipermeable containers	40°C ± 2°C NMT 25 % RH	30°C±2°C 65 % ± 5% RH	25°C±2°C 40 % ± 5% RH Or 30°C±2°C 35 % ± 5% RH

Stages where stability studies carried out

Stability testing is done in five different occasions when an NDA is being contemplated.

1. Preformulation and compatibility
2. Preclinical formulation
3. Clinical and NDA formulation
4. Commitment and product monitoring
5. Post NDA change of formulation

Preformulation and compatibility

In the early stage of drug designing, studies are done to find out what sort of decomposition is possible, what is the mechanism, sensitivity to moisture and oxygen interaction

probabilities (compatibilities) optimum pH and polymorphic information. Drug excipient interactions physical as well as chemical are extensively studied.

Preclinical formulation

Keeping the data from the Preformulation studies in mind formulations are designed and manufactured for use in Phase-I trials. More than the one or two formulations being used in Phase-I studies are manufactured and started on stability studies. This is because even a supposedly stable formulation may while in Phase-I use fail with respect to some stability issue, then you must have something to fall back upon.

Clinical and NDA formulation

When a product has passed Phase-I, its dosage level, interactions and stability profile are known to some degree and armed with this knowledge the "Clinical manufacturing group" of the company manufactures several batches of the product and keeps some products from every batch for stability. The required stability aspects of clinical are simply to ascertain that each batch is within specifications during the length of the trail.

Late Clinical and First Pilot Batch

The ICH stability guidelines require that three substantial batches, made in the same type production equipment intended for the final product, be made and that at least 12 months stability be in place at the time of NDA submittal.

Marketed product stability

At the time the NDA is filed, the large clinical and scate-up batches are only about a year old, and the stability data on them is not yet complete. So at this time, the company asks for an expiry date based on extrapolation of the existing stability data. The FDI will take all facts into consideration and grant an expiry date based on a commitment form the company that the company will continue to do stability studies on different batches.

The storage requirements and the sampling times are very clearly specified by the ICH guidelines.

RECENT ADVANCES IN STABILITY TESTING

1) Stability Testing of Herbal Products

Abstract:-

Since last one decade India has seen tremendous growth in herbal drug market, which has resulted in development of numerous proprietary herbal drug formulations by various manufacturers, majority of them comprising of polyherbal formulations. With the advancement of knowledge in the field of phytochemistry it has now been observed that many of these constituents present in the drug may react with each other raising the serious concern about the stability of such formulations. This is the area, which needs to be addressed in order to determine the efficacy of the formulation. This article is aimed to give some guidelines for undertaking stability studies for herbal products.

Stability testing of herbal products is a challenging task, because the entire herb or herbal product is regarded as the active substance, regardless of whether constituents with defined therapeutic activity are known. The objective of a stability testing

is to provide evidence on how the quality of the herbal products varies with the time under the influence of environmental factors such as temperature, light, oxygen, moisture, other ingredient or excipient in the dosage form, particle size of drug, microbial contamination, trace metal contamination, leaching from the container, *etc. and to establish a recommended storage condition, retest period and shelf-life. Therefore evaluation of the parameters* based upon chemical, physical, microbiological, therapeutic and toxicological studies can serve as an important tool in stability studies .

2) Recent Developments on Long-Term Stability Test Conditions

Abstract:
Stability testing is the only way to demonstrate that the pharmaceutical product would meet the laid-down specifications within acceptance criteria throughout its lifetime. It is also required to gain the regulatory approval. The birth of International Conference on Harmonization (ICH) in 1991 and finalization of the guideline Q1A in 1993 led to harmonization of the stability test requirements for new drug applications, and was instrumental in development of a series of ICH and other National and regional stability guidelines, both for the new and existing drugs. There have been some recent developments, especially with respect to defining of storage condition for long-term stability testing. This note traces the new developments.

REFERENCES:-

1) Drug Stability: Principles and Practices, 3rd Edition, edited by Jens T. Carstensen and C. T. Rhodes (Marcel Dekker, Inc., New York, 2000)

2) Modern Pharmaceutics.- Drugs and the Pharmaceutical Science by *G S. Banker and C T. Rhodes*.

3) I.C.H. guidelines.

4) THE PHARMA REVIEW (APRIL - MAY, 2008)

5) THE PHARMA REVIEW (DECEMBER, 2006)

6)JPS ,VOL 51,1962-"solid state stability",100

7)JPS,VOL 51,1962,"prediction of stability of drugs &pharmaceutical preparation ",811

8)www.pharmainfotech.com