



A REVIEW ON STABILITY STUDIES OF PHARMACEUTICAL PRODUCTS

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ABSTRACT

Stability studies are a routine procedure for ensuring the maintenance of pharmaceutical product safety, quality and efficacy throughout the shelf life. These pharmaceutical products are followed by the guidelines issued by Regulatory bodies like ICH, WHO or other regulatory agencies. Stability testing provides evidence that the quality of a drug product under the influence of various environmental factors changes with time. Stability Studies of Pharmaceutical Product Capacity of a pharmaceutical product in a given packaging system to remain within established specifications to maintain its Quality and deliver the desired Performance throughout the retest or expiration period. This review article includes introduction about stability studies, types of stability studies, and guidelines issued for shelf life estimation of pharmaceutical products.

Key Words: Stability, Types of Stability Studies, Stability Guidelines, Stability Testing.

INTRODUCTION

Stability of pharmaceutical product expressed as the time period during which the drug product retain same properties and characteristics that it possessed at the time of manufacture. The stability of product is expressed as the expiry period or technically as shelf life. Expiration period is a valuable quality attribute for all pharmaceutical dosage forms. The expiration date should be preferably accompanied by detail of specific storage. Adequate stability data acquired stability data acquire by manufacture should be available to support the expiration period and storage condition specified. The stability of finished pharmaceutical products depends, on the one hand, on environmental Factors such as ambient temperature, humidity and light, and, on the other, on product-related Factors, e.g. the chemical and physical properties of the active substance (API) and of pharmaceutical excipients, the dosage form and its composition, the manufacturing process, The nature of the container-closure system and the properties of the packaging materials for established drug substances in conventional dosage forms, literature data on the decomposition process and degradability of the active substance are generally available together with adequate analytical methods. Thus, the stability studies may be restricted to the dosage forms.¹

Importance of Stability Studies

- Product instability of active drug may lead to under medication due to lowering concentration of the drug in dosage form.
- During decomposition of active drug toxic products may be formed.
- Instability may be due to changing in physical appearance though the principles of kinetics are used in predicting the stability of drug there different between kinetics and stability study.

- To protect the reputation of the manufacturer by assuring that the product will retain fitness for use with respect to all functionally relevant attributes for as long as they are on the market.^{1,2}

Table 1: Types of Stability Studies

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

Table 2: Codes and titles used in ICH Guidelines

ICH Code	Guideline title
Q1A	Stability testing of New Drug Substances and Products (Second Revision)
Q1B	Stability testing : Photo stability testing of New Drug Substances and Products
Q1C	Stability testing of New Dosage Forms
Q1D	Bracketing and Matrixing Designs for stability testing of Drug Substances and Products
Q1E	Evaluation of stability data
Q1F	Stability data package for Registration Applications in Climatic Zones III and IV
Q5C	Stability testing of Biotechnological/Biological Products

Type of Stability of drug substance ^{1,4}

Physical Stability:

The original physical properties, including appearance, palatability, uniformity, dissolution and suspend ability are retained. Physical stability affect to drug uniformity and release rate hence it is important from safety and efficiency point of view.

Chemical Stability:

Each active ingredient retains its chemical integrity and labelled potency within the specified limits. The Chemical stability of drug is of great importance since it becomes less effective as it undergoes degradation. Also drug decomposition may yield toxic by-products that are harmful to the patient.

Microbiological Stability:

Sterility or resistance to microbial growth is retained according to the Specified requirements. Antimicrobial agents retain effectiveness within specified limits. Microbiological instability of a sterile drug product could be hazardous.

Therapeutic Stability: The therapeutic effect remains unchanged.

Toxicological Stability: No significant increase in toxicity occurs.

GUIDELINES FOR STABILITY TESTING

To assure that optimally stable molecules and products are manufactured, distributed and given to the patients, the regulatory authorities in several countries have made provisions in the drug regulations for the submission of stability data by the manufacturers. Its basic purpose was to bring in uniformity in testing from manufacturer to manufacturer. These guidelines include basic issues related to stability, the stability data requirements for application dossier and the steps for their execution. Such guidelines were initially issued in 1980s.²

These were later harmonized (made uniform) in the International Council for Harmonization (ICH) in order to overcome the bottleneck to market and register the products in other countries. The ICH was established in 1991, it was a consortium formed with inputs from both regulatory and industry from European commission, Japan and USA and various guidelines for drug substance and drug product came into existence regarding their quality, safety and efficacy. These guidelines are called as quality, safety, efficacy and multi- disciplinary (also called as Q, S, E and M) guidelines.⁴ The World Health Organization (WHO), in 1996, modified the guidelines because the ICH guidelines did not address the extreme climatic conditions found in many countries and it only covered new drug substances and products and not the already established products that were in circulation in the WHO umbrella countries. In June 1997, United States Food and Drug Administration (US FDA) also issued a guidance document entitled

Expiration dating of solid oral dosage form containing Iron. WHO, in 2004, also released guidelines for stability studies in global environment.⁷ ICH guidelines were also extended later for veterinary products. A technical monograph on stability testing of drug substances and products existing in India has also been released by India Drug Manufacturers Association.⁸ Further, different test condition and requirements have been given in the guidance documents for active pharmaceutical ingredients, drug products or formulations and excipients. The codes and titles covered under ICH guidance have been outlined in the (Table 2) & (Table 3).

Series of guidelines related to stability testing have also been issued by the Committee for Proprietary Medicinal Products (CPMP) under the European Agency for the Evaluation of Medicinal Products (EMEA) to assist those seeking marketing authorization for medicinal products in European Union.² These are listed in (Table 4).

Table 3: ICH Q1A Summary of Stability Parameters

Study Type & Condition		Storage Condition	Time Period (Months)	Comments
General Case:	Long-term	25 °C±2°C/60% RH±5% RH or 30°C±2°C/65% RH±5% RH	12	Must cover retest or shelf life period at a minimum and includes storage, shipment and subsequent use.
	Intermediate	30°C±2°C/65% RH±5% RH	6	
	Accelerated	40°C±2°C/75% RH±5% RH	6	
Refrigeration:	Long-term	5°C±3°C	12	Must cover retest or shelf life period at a minimum and includes storage, shipment and subsequent use.
	Accelerated	25°C±2°C/60% RH±5% RH	6	
Freezer:	Long term	-20°C±5°C	12	Must cover shelf life period at a minimum and includes storage, shipment and subsequent use.

Table 4: CPMP Guidelines for Stability

CPMP code	Guideline title
CPMP/QWP/576/96 Rev. 1	Guideline on Stability Testing for Applications for Variations to a Marketing Authorization
CPMP/QWP/6142/03	Guideline on Stability Testing for Active Substances and Medicinal Products Manufactured in Climatic Zones III and IV to be marketed in the EU
CPMP/QWP/609/96 Rev. 1	Note for guidance on Declaration of Storage Conditions for Medicinal Products Particulars and Active Substances
CPMP/QWP/122/02 Rev. 1	Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products
CPMP/QWP/072/96	Note for Guidance on Start of Shelf Life of the Finished Dosage Form
CPMP/QWP/2934/99	Note for Guidance for In-Use Stability Testing of Human Medicinal Products
CPMP/QWP/576/96	Note for Guidance on Stability Testing for a Type 2 variation to a Marketing Authorization
CPMP/QWP/ 159/96	Note for Guidance on Maximum Shelf-Life for Sterile Products after First Opening or Following Reconstitution

CLIMATIC ZONES FOR STABILITY TESTING

For the purpose of stability testing, the whole world has been divided into four zones (I - IV) depending upon the environmental conditions the pharmaceutical products are likely to be subjected to during their storage. These conditions have been derived on the basis of the mean annual temperature and relative humidity data in these regions. Based upon this data, long-term or real-time stability testing conditions and accelerated stability testing conditions have been derived. The standard climatic zones for use in pharmaceutical product stability studies have been presented in the (Table 5).⁹ The break-up of the environmental conditions in each zone and also the derived long-term stability test storage conditions, as given by WHO have also been presented. The stability conditions have also been harmonized and adjusted to make them more practical for industry application and rugged for generalized application.^{3,8}

Table 5: ICH Climatic zones and long term stability conditions^{3,8,9}

Climatic Zone	Climate Definition	Major Countries /Region	MAT*/Mean annual partial water vapour pressure	Long-term testing conditions
I	Temperate	United Kingdom, Northern Europe, Russia, United states	<15C/<11hPa	21°C/45%RH
II	Subtropical and Mediterranean	Japan, Southern Europe	>15-22°C />11-18 hPa	25°C/60%RH
III	Hot and Dry	Iraq, India	>22°C/<15 hPa	30°C/35%RH
IVa	Hot and humid	Iran, Egypt	>22°C/>15-27 hPa	30°C/65%RH
IVb	Hot and very humid	Brazil, Singapore	>22°C/>27 hPa	30vC/75%RH

*MAT - Mean annual temperature measured in open air.

STABILITY TESTING PROTOCOL

Stability testing is the systematic approach towards drug development process. Stability data for the drug substance are used to determine optimal storage and packaging conditions for bulk lots of the material. The stability studies for the drug product are designed to determine the expiry date or shelf life.

The protocol for stability testing is a pre-requisite for starting stability testing and is necessarily a written document that describes the key components of a regulated and well-controlled stability study. Because the testing condition is based on inherent stability of the compound, the type of dosage form and the proposed container-closure system, the protocol depends on the type of drug substance or the product. In addition, the protocol can depend on whether the drug is new or is already in the market.^{10,11} The protocol should also reflect the regions where the product is proposed to be marketed e.g. if the product is planned to be used in climatic zones I-III, IVa and IVb, the stability program must include all these zones.¹¹

A well designed stability protocol should contain the following information:

- Number of Batches
- Containers and closures
- Orientation of storage of containers
- Sampling time points
- Test storage conditions
- Test parameters
- Test methodology
- Acceptance criteria

1 Numbers of Batches: Stability studies at developmental stages are generally carried out on a single batch while studies intended for registration of new product or unstable established product are done on first three production batches, while for stable and well-established batches, even two are allowed. If the initial data is not on a full scale production batch, first three batches of drug product manufactured post-approval should be placed on long-term studies using the same protocol as in approved drug application. Data on laboratory scale batches obtained during development of pharmaceuticals are not accepted as primary stability data but constitute supportive information. In general, the selection of batches should constitute a random sample from the population of pilot or production batches.⁸

2 Containers and Closures: The testing is done on the product in immediate containers and closures proposed for marketing. The packaging materials include aluminium strip packs, blister packs, Alu-Alu packs, HDPE bottles etc. This may also include secondary packs, but not shippers. Products in all different types of containers/closures, whether meant for distribution or for physician and promotional samples, are to be tested separately. However, for bulk containers, testing in prototype containers is allowed, if it simulates the actual packaging.⁸

3 Orientation of Storage of Containers: Samples of the solutions, dispersed systems and semi-solid drug products for stability studies must be kept upright and positioned either inverted or on the side to allow for full interaction of the product with the container-closure. This orientation helps to determine whether the contact between the drug product or solvent and the closure results in the extraction of chemical substances from the closure components or adsorption of product components in to the container-closure.¹⁰

4 Sampling time points: Frequency of testing should be such that it is sufficient to establish the stability profile of the new drug substance. For products with a proposed shelf life of at least 12 months, the testing frequency at the long-term storage condition should be every 3 months over the first year, every 6 months over the second year and annually thereafter throughout the proposed shelf life expiration date. In the case of accelerated storage conditions, a minimum of three time points, including the initial and end points, for example, 0, 3, and 6 months is recommended. When testing at the intermediate storage condition is necessary as a result of significant change at the accelerated storage condition, a minimum of four test points, including the initial and final time points, is recommended, for example, 0, 6, 9 and 12 months.

In case the same product of different strengths, multiple sizes, etc is required to be tested, reduced stability testing plans can be worked out, which involves less number of test points. The reduced testing plans are based on bracketing and matrixing statistical designs. Bracketing is 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. On the other hand, matrixing involves testing of a subset of the total number of possible samples for all combinations at a specific time point. Subsequently, another subset of samples for all factor combinations is tested. The factors that can be matrixes include batches, strengths with identical formulation, container sizes, fill sizes, and intermediate time points.^{8,11}

5 Sampling Plan: Sampling plan for stability testing involves, planning for the number of samples to be charged to the stability chambers and sampling out of the charged batch so as to cover the entire study. The first step should be the development of the sampling time points followed by the number of samples needed to be drawn at each pull point for complete evaluation of all test parameters and finally adding up to get the total number of samples. For example there would be a requirement of about 100 tablets per pull out in a long term or accelerated stability studies including 10 each for assay, hardness and moisture determination, 6 each for dissolution and disintegration and 50 for friability. This multiplied by the total number of pull outs will give the total number of tablets required for a study. This is followed by the development of a sampling plan, which includes the selection of the containers representing the batch as a whole but in an unbiased manner. A stratification plan has been suggested whereby from a random starting point every n^{th} container is taken from the filling or packaging line (n is chosen such that the sample is spread over the whole batch).⁸

6 Test Storage Conditions: The storage conditions to be selected are based upon the climatic zone in which the product is intended to be marketed or for which the product is proposed to be filed for regulatory approval. General recommendations on the storage conditions have been given by ICH, CPMP and WHO. The abridged/indicative ICH and WHO storage conditions for drug products have been given in (Table 7).

7 Test Parameters: The stability test protocol should define the test parameters that would be used for evaluation of the stability samples. The tests that monitor the quality, purity, potency, and identity which could be expected to change upon storage are chosen as stability tests. Therefore appearance, assay, degradation products, microbiological testing, dissolution, and moisture are standard tests performed on stability test samples. Microbiological tests include sterility, preservative efficacy and microbial count as applicable e.g. for liquid injectable preparations. The batches used for stability study must meet all the testing requirements including heavy metals, residue on ignition, residual solvents etc. Some of these are required at the time of product release but not required to be repeated during stability testing. Other tests like enantiomer purity, particle size and polymorphic form etc have also been discussed in ICH guidance Q6A.¹¹

8 Test methodology: It is always recommended to follow the procedures given in the official compendia, as the results obtained using the official tests, in general find better acceptance. If alternate methods are used, they are required to be duly validated. However, the assay of the drug should be carried out using a stability-indicating method, established by carrying out stress tests on the drug under forced decomposition conditions. This method should be validated for specificity, accuracy, precision and linearity, in the range to which the drug is expected to fall during stability studies. For the assay of degradation products, the validated method should also include the limits of detection/quantification. The methods reported in literature should be used after confirming reproducibility and carrying out minimal validation, say of linearity, range, etc. It is always recommended to prepare a standard test protocol (STP) for each test.^{8,10}

9 Acceptance criteria: All analytical methods are required to be validated before initiating the stability studies. Similarly, the acceptance criteria for the analytical results as well as that for the presence of degradation products should also be fixed beforehand. The acceptance criteria for each test in the stability study is fixed in the form of numerical limits for the results expressed in quantitative terms e.g., moisture pick-up, viscosity, particle size, assay, degradation products, etc. and pass or fail for qualitative tests e.g., odour, colour, appearance, cracking, microbial growth, etc. These acceptance criteria should also include individual and total upper limits for degradation products. ICH guideline Q3B(R2) related to impurities in new drug products addresses degradation products in new drug formulations. The degradation products of the active or interaction products from the active ingredients and excipients and/or active and container component should be reported, identified, and/or qualified when the proposed thresholds are exceeded. The reporting threshold of impurities is based upon the intended dose. If the maximum daily dose is less than or equal to 1gm, the limit is 0.1% and if greater than 1, the limit is 0.05%. The identification threshold of impurities is between 1.0-0.1% for the maximum daily dose ranging between 1mg and 2gm.^{8,11}

10. STABILITY TEST EQUIPMENT

The equipment used for stability testing is called stability chamber. These are specialized environmental chambers that can simulate the storage condition and enable evaluation of product stability based on real-time, accelerated and long-term protocols. They are available in both walk-in and reach-in styles. Smaller chambers are preferred for accelerated testing, as the retention time of products is much less in these cabinets, while the walk-in chambers are preferred for long-term testing. Such chambers or rooms are engineered and qualified to ensure uniform exposure of the set conditions to all the samples in the chamber. These chambers are expected to be dependable and rugged because of the requirement of uninterrupted use for years. They are fitted with appropriate recording, safety and alarm devices. In addition, photo stability chambers are also available and utilized both with and without temperature and humidity control. Two types of light sources are usually employed in photo stability chambers, one is the combination of cool white and near UV fluorescent tubes, while second are the artificial daylight lamps, e.g., xenon or metal halide. It is required to obtain a total exposure of 1.2 million lux h (h refers to hour). The visible light intensity is estimated using a lux meter. The calculation is made on how many hours of exposure are needed.^{2,8}

11. STABILITY TESTING METHODS²

Stability testing is a routine procedure performed on drug substances and products and is employed at various stages of the product development. In early stages, accelerated stability testing (at relatively high temperatures and/or humidity) is used in order to determine the type of degradation products which may be found after long-term storage. Testing under less rigorous conditions i.e. those recommended for long-term shelf storage, at slightly elevated temperatures are used to determine a product's shelf life and expiration dates. The major aim of pharmaceutical stability testing is to provide reasonable assurance that the products will remain at an acceptable level of fitness/quality throughout the period during which they are in market place available for supply to the patients and will be fit for their consumption until the patient uses the last unit of the product.¹²

Depending upon the aim and steps followed, stability testing procedures have been categorized into the following four types.

- Real-Time Stability Testing
- Accelerated Stability Testing
- Retained Sample Stability Testing

- Cyclic Temperature Stress Testing

The major aim of pharmaceutical stability testing is to provide reasonable assurance that the products will remain at an acceptable level of fitness/quality throughout the period during which they are in market place available for supply to the patients and will be fit for their consumption until the patient uses the last unit of the product.

Real-Time Stability Testing: Real-time stability testing is normally performed for longer duration of the test period in order to allow significant product degradation under recommended storage conditions. The period of the test depends upon the stability of the product which should be long enough to indicate clearly that no measurable degradation occurs and must permit one to distinguish degradation from inter-assay variation. During the testing, data is collected at an appropriate frequency such that a trend analysis is able to distinguish instability from day-to-day ambiguity. The reliability of data interpretation can be increased by including a single batch of reference material for which stability characteristics have already been established. Stability of the reference material also includes the stability of reagents as well as consistency of the performance of the instrument to be used throughout the period of stability testing. However, system performance and control for drift and discontinuity resulting from changes in both reagents and instrumentation must be monitored.^{2,13}

Accelerated Stability Testing: In accelerated stability testing, a product is stressed at several high (warmer than ambient) temperatures and the amount of heat input required to cause product failure is determined. This is done to subject the product to a condition that accelerates degradation. This information is then projected to predict shelf life or used to compare the relative stability of alternative formulations. This usually provides an early indication of the product shelf life and thus shortening the development schedule. In addition to temperature, stress conditions applied during accelerated stability testing are moisture, light, agitation, gravity, pH and package. In accelerated stability testing the samples are subjected to stress, refrigerated after stressing, and then assayed simultaneously. Because the duration of the analysis is short, the likelihood of instability in the measurement system is reduced in comparison to the real-time stability testing. Further, in accelerated stability testing, comparison of the unstressed product with stressed material is made within the same assay and the stressed sample recovery is expressed as percent of unstressed sample recovery. For statistical reasons, the treatment in accelerated stability projections is recommended to be conducted at four different stress temperatures. However, for thermolabile and proteinaceous components, relatively accurate stability projections are obtained when denaturing stress temperatures are avoided.¹³

The concept of accelerated stability testing is based upon the Arrhenius equation (1) and modified Arrhenius equation (2):^{13,14}

$$\ln K = \ln A + \Delta E/RT \quad \dots\dots\dots(1)$$

where K = degradation rate/s,

A = frequency factor/s,

ΔE = activation energy (kJ/mol),

R = universal gas constant (0.00831 kJ/mol),

T = absolute temperature (K)

$$\log \left(\frac{k_2}{k_1} \right) = \frac{-E_a}{2.303R} \left(\frac{1}{T_2} - \frac{1}{T_1} \right)$$

in the above equation (2) where k_1 and k_2 are rate constants at temperatures T_1 and

T_2 expressed in degree kelvins;

E_a is the activation energy;

R is the gas constant.

These equations describe the relationship between storage temperatures and degradation rate. Using Arrhenius equation, projection of stability from the degradation rates observed at high Temperatures for some degradation processes can be determined. When the activation energy is known, the degradation rate at low temperatures may be projected from those observed at "stress" temperatures.^{14,15,16} The stress tests used in the current ICH guideline (e.g., 40% for products to be stored at controlled room temperature) were developed from a model that assumes energy of activation of about 83 kJ per mole.¹³

A common practice of manufacturers in pharmaceutical industries was to utilize various shortcuts such as Q rule and bracket tables for prediction of shelf life of the products but these methods are not official either in ICH or FDA. The Q rule states that a product degradation rate decreases by a constant factor Q_{10} when the storage temperature is decreased by 10°C. The value of Q_{10} is typically set at 2, 3 or 4 because

these correspond to reasonable activation energies. This model falsely assumes that the value of Q does not vary with temperature. The bracket table technique assumes that, for a given analyte, the activation energy is between two limits (e.g., between 10 and 20 kcal). As a result, a table may be constructed showing days of stress at various stress temperatures. The use of a 10 to 20 kcal bracket table is reasonable because broad experience indicates that most analytes and reagents of interest in pharmaceutical and clinical laboratories have activation energies in this range.^{12,13}

Retained Sample Stability Testing: This is a usual practice for every marketed product for which stability data are required. In this study, stability samples, for retained storage for at least one batch a year are selected. If the number of batches marketed exceeds 50, stability samples from two batches are recommended to be taken. At the time of first introduction of the product in the market, the stability samples of every batch may be taken, which may be decreased to only 2% to 5% of marketed batches at a later stage. In this study, the stability samples are tested at predetermined intervals i.e. if a product has shelf life of 5 years, it is conventional to test samples at 3, 6, 9, 12, 18, 24, 36, 48, and 60 months. This conventional method of obtaining stability data on retained storage samples is known as constant interval method.^{12,17} Stability testing by evaluation of market samples is a modified method which involves taking samples already in the market place and evaluating stability attributes. This type of testing is inherently more realistic since it challenges the product not just in the idealized retained sample storage conditions, but also in the actual marketplace.¹²

Cyclic Temperature Stress Testing: This is not a routine testing method for marketed products. In this method, cyclic temperature stress tests are designed on knowledge of the product so as to mimic likely conditions in market place storage. The period of cycle mostly considered is 24 h since the diurnal rhythm on earth is 24 h, which the marketed pharmaceuticals are most likely to experience during storage. The minimum and maximum temperatures for the cyclic stress testing is recommended to be selected on a product by-product basis and considering factors like recommended storage temperatures for the product and specific chemical and physical degradation properties of the products. It is also recommended that the test should normally have 20 cycles.^{12,17}

CONCLUSION

Stability testing of pharmaceutical products the key procedural contribution in the development program for a new drug as well as new formulation. Any deviation from the established stability profile could affect the quality, safety and efficacy thorough understanding of the stability of the drug substance and drug product is important to "build the quality in". Stability tests are carried out so that recommended storage conditions and shelf life can be included on the label to ensure that the medicine is safe and effective throughout its shelf life. Over a period of time and with increasing experience and attention, the regulatory requirements have been made increasingly stringent to achieve the above goal in all possible conditions to which the product might be subjected during its shelf life. Therefore, the stability tests should be carried out following proper scientific principles and after understanding of the current regulatory requirements and as per the climatic zone.

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