



REVIEW ARTICLE

A Review on Stability Studies of Pharmaceutical Products

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ABSTRACT

Stability studies ensuring the maintenance of product quality, safety and efficacy throughout the shelf life are considered a pre-requisite for the acceptance and approval of any pharmaceutical product. These studies are required to be conducted in a planned way following the guidelines issued by ICH, WHO and or other agencies. Importance of various methods followed for stability testing of pharmaceutical products, guidelines issued for stability testing and other aspects related to the stability of pharmaceutical products have been presented in a concise manner in the present review.

KEYWORDS

Stability, Types of Stability Studies, Stability Guidelines, Stability Testing

INTRODUCTION

Stability of pharmaceutical product is defined as “the capacity of a drug substance or drug product to remain within specifications established to ensure its identity, strength, quality, and purity throughout the retest or expiration dating period”. Instability of the drug can cause an undesired change in performance that leads to product failures. Expiration period is a valuable quality attribute for all pharmaceutical dosage forms. The expiration date should be preferably accompanied by a detail of specific storage.

Stability studies are the one of the most critical steps during the development of drug process because it assures the identity, potency, and purity of ingredients as well as formulated products. The stability of finished pharmaceutical product depends on

environmental factors such as ambient temperature humidity, and light as well as product related factors for example chemical and physical properties of active substances and pharmaceutical excipients, the dosage form and its composition, the manufacturing process, the nature of the container closure system and properties of packing material.¹

Determination of shelf life of the drug product is the main objective of stability studies. The stability refers to storage time allowed before any degradation product in dosage form achieves a sufficient level to represent a risk to the patient. Based on this time, the product shelf life or expiration date is determined.

Stages of Stability Studies

Stability study is performed at various stages of the drug development process. There are 6 different stages:

Stage 1: Early stage, i.e., stress and accelerated testing with drug substances.

Stage 2: Stability on pre-formulation batches.

Stage 3: stress test done on scale-up batches.

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Stage 4 : Accelerated and long-term testing for registration purposes.

Stage 5 : Enduring stability testing.

Stage 6: follow up studies.²

Importance of Stability Studies

- Product instability of active drug may lead to under medication due to lowering concentration of the drug in the dosage form.
- During decomposition of active drug, the toxic product may be formed.
- Instability may be due to changing in physical appearance through the principles of kinetics are used in predicting the stability of the drug.
- 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

Objectives of Stability Studies

- The purpose of stability testing is to provide evidence on how the quality of drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light.
- To select adequate (from the viewpoint of stability) formulations and container closure Systems.
- To determine shelf-life and storage conditions.
- To substantiate the claimed shelf-life.
- To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product.
- The main aim of accelerated stability study to predict the stability profile of a drug product that prediction of the shelf life of the product before launching into the market.

Types of Drug Stability

Physical Stability

This implies that the drug product remains unchanged throughout its shelf life with no alteration in its physical properties that include its appearance, organoleptic properties, hardness, brittleness, and particle size. This stability is essential to ensure drug efficacy, safety and should be maintained during all the stages of the drug product formulation, manufacturing, packaging, storage and carefully monitored and evaluated.

Chemical Stability

This refers to the lack of any alteration in the chemical composition of the drug formulation. The chemical stability of drug is of great importance since it becomes less efficient as it undergoes degradation via chemical reactions such as hydrolysis, oxidation, and photolysis. Such results can lead to decrease in the active ingredient concentrations of the drug as well as the formation of undesired by-products. This, in turn, can cause the drug to have lower or no therapeutic effect or even to contain a harmful or toxic substance. The chemical degradation can also happen to preservatives and excipients included in the drug products as well as their packages leading to the same unwanted chemical instability. It has been noticed that the solid dosage forms are more stable than liquid dosage forms since they undergo slower chemical degradation.

Microbiological Stability

This refers to the sterility of the drug formulation and lack of contamination by different types of microorganisms (e.g., fungi and bacteria). Naturally, microbial growth in a drug product can lead to severe effects. Because of their high moisture content, solutions and water-based semi-solids drugs are more liable to suffer from microbial contamination. This makes the addition of antimicrobial preservatives to those drug dosage forms essential to ensure their sterility. To prevent the contamination of the formulation during the

storage, it is preferable to use single dose container.³

Therapeutic Stability

The therapeutic effect remains unchanged.

Toxicological Stability

No significant increase in toxicity occurs.¹

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 primary purpose was to bring in uniformity in testing from manufacturer to manufacturer. These guidelines include fundamental issues related to stability, the stability data requirements for application dossier and the steps for their execution. Such guidelines were initially issued in the 1980s.

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 a consortium formed with inputs from both regulatory and industry from the European Commission, Japan, 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 multidisciplinary (also called as Q, S, E, and M) guidelines. The World Health Organization (WHO) 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. 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 Table 1.

Series of guidelines related to stability testing has also been issued by the Committee for Proprietary Medicinal Products (CPMP) under the European Agency for the Evaluation of Medicinal Products (EMA) to assist those seeking marketing authorization for medicinal products in European Union.⁴

Table 1: 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 : Photostability 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

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 on 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 2.^{4,5}

Table 2: Climatic zones for stability testing

Climatic zone	Climatic definition	Major countries/region	MAT*/Mean annual partial water vapor pressure	Long-term testing conditions
I.	Temperate	United Kingdom, Northern Europe, Russia, United states	<15°C / < 11hPa	21°C/45%RH
II.	Subtropical and Mediterranean	Japan, Southern Europe	>15-22°C / > 11-18hPa	25°C/60%RH
III.	Hot and Dry	Iraq, India	>22°C / < 15hPa	30°C /35%RH
IV.	Hot and humid	Iran, Egypt	>22°C / > 15-27hPa	30°C /65%RH
	Hot and very humid	Brazil, Singapore	>22°C / > 27hPa	30°C /75%RH

MAT*- Mean annual temperature measured in open air

Drug Shelf Life

Shelf life or expiration date of a drug defines the time interval that the average drug characteristics such as strength and purity of the drug are expected to remain within the approved specifications after manufacture. Because of the existence of batch to batch variation, the actual shelf life of different batches might differ and must be treated as a random variable, which depends on drug stability, temperature, humidity, exposure to light, and class of container among other possible variables. Thus, the design of any stability study should establish a shelf life that is applicable to all future batches of the drug manufactured under similar circumstances.

Estimation of Shelf Life

The goal of shelf life estimation is to predict the time when the drug stability is no longer within the approved specification limit. Estimation of the expiration date of every newly released drug product in the market is one of the essential stages required by law to prove its safety. The

shelf life is determined from the data obtained from the long-term storage studies. The data is first linearized, and test for goodness of fit is applied. The linearized data is then analyzed to see that the slope and the intercepts are matching. For determination of the significance of the difference in case of slope or intercept, statistical tests like t-test should be applied. The data is available in the form of only five data points, i.e., 0, 3, 6, 9 and 12 months, either pooled from the three batches or from the three individual batches if they are not fit for pooling. In case data is not fit for pooling, stability estimates are to be made on the worst batch. The shelf life/expiry date is determined from the regression line of this five-point data based on a calculation of 95% one-sided confidence limit. For reading the expiry date, 90% drug concentration is considered as the lowest specification limit and the point where the extension line cuts the 95% confidence limit line is taken as an expiry date. Because shelf life derived from the intersection of the lower 90% confidence bound and 90% potency value has a 95%

confidence level, therefore there is only a 5% chance that our estimate of the shelf life will be too high. For new drugs, it is a general practice to grant only two-year expiry initially, which is based on satisfactory one-year long-term and 6 months accelerated stability data. The expiry date for third and later years is allowed only on production of real-time data for the subsequent year. Most pharmaceutical products are characterized by only one shelf life. However, in some cases a product may be, e.g. a freeze-dried (lyophilized) protein product may have only 1 shelf life, say 2 years and for the product stored in the dry condition have 2 shelf life, say 2 days, for the product when it has been reconstituted with the appropriate vehicle and is ready for injection.⁴

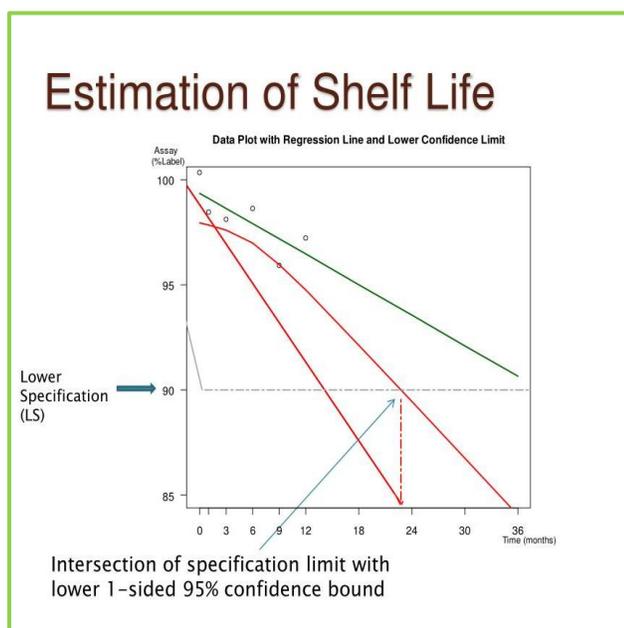


Figure 1: Estimation of shelf life

The expiration date period must be obtained through a rigorous experimental analysis with several batches of the product. The analytical procedures and conclusions derived from the analysis have to be carefully monitored and well supervised.

In order to predict the shelf life, accelerated studies are used for estimating the rate of chemical and physical degradation. For this, the order of reaction has to be determined. For example, a zero order equation represents a linear relationship between the drug

characteristic and time, whereas in the first order the logarithmic transformation of the drug characteristic which is a linear function of time. After the order of the reaction is determined, the Arrhenius equation is then applied to decide the relationship between the rate of degradation and the temperature, as Arrhenius equation describes the linear relationship between log (degradation) and reciprocal of the absolute temperature.³

Drug Dosage Forms and Stability

The stability of drug product with respect to physical, chemical, microbiological, therapeutic and toxicological characteristics is a specific dosage form that differs from one dosage form to another.

FDA guideline requires specific tests of stability depending on the dosage form of the drug, in order to be maintained particular characteristics of particular dosage form throughout its shelf life to ensure its efficacy and safety. Hardness, brittleness, and dissolution are examples of such characteristics that are mainly specific to solid dosage forms. Special tests are available to test these characteristics and are usually conducted during the drug manufacture process which shows the different essential drug characteristics for various dosage forms.

Hardness is one of the essential physical properties of the solid dosage forms and commonly used as a measurement for the tablet strength. The tablet strength should be evaluated during its formulation and manufacturing process to ensure its stability and resistance to breakdown throughout the different steps of packaging, shipping, and dispensing as well as the possible abuse by the consumer. Hardness in the pharmaceutical industry is defined as the force required to break the tablet in the diametrical compression test. This test implies placing the tablet between two anvils where one of the anvils is moved against the tablet until it breaks and the force at which the tablet breaks is the hardness.

Table 3: Drug characteristics for different dosage forms

Dosage form	Drug Characteristic
Tablets	Appearance, friability, hardness, color, odor, moisture, strength, dissolution.
Capsules	Strength, moisture, color, appearance, shape, brittleness, dissolution.
Emulsions	Appearance, color, odor, pH, viscosity, strength.
Oral solution and suspension	Appearance, strength, pH, color, odor, redispersibility, dissolution, clarity.
Oral powder	Appearance, pH, dispersibility, strength.
MDI aerosols	Strength, delivered dose per actuation, number of metered doses, color, clarity, particle size, loss of propellant, pressure, valve corrosion, spray pattern.
Topical and ophthalmic preparations	Appearance, clarity, color, homogeneity, odor, pH, re-suspendibility, consistency, particle size distribution, strength, weight loss.
Small volume parenterals and large volume parenterals	Strength, appearance, colour, clarity, particulate matter, sterility, pyrogenicity, Ph.
Suppositories	Strength, softening range, appearance, dissolution.

Shelf life is mostly related to the primary drug characteristics such as the strength. The strength of a drug product is defined as either the concentration of the drug substance or its potency which refers to the therapeutic activity of the drug product. FDA guideline considers the drug strength as a quantitative measure of the active ingredient of a drug product as well as other elements that require quantitation, such as alcohol and preservatives.

If a drug is designed to be used as an additive to another drug product such as parenteral or aerosols, FDA requires that stability study should be conducted on the dosage form made of the mixture of both drugs rather than each component alone.

The stability of the characteristics of a drug product for a particular dosage form may be influenced by storage conditions, such as temperature, humidity, light, or air, and by package types such as high-density polyethylene (HDPE).³

Factors Affecting Drug Stability

To maintain drug stability, it is essential to thoroughly understand the drug structure and its characteristics along with the impact of different physical, chemical, microbiological, toxicological, and environmental factors upon the drug formulation. This ensures providing optimal storage conditions and modes of transportation of the drug products and identifying the precautions that should be taken

to prevent or minimize the loss of activity. For example, knowing the effect of temperature on a specific drug can help avoiding its damage by keeping it under a suitable temperature during its storage and shipment.

Basically, both environmental factors such as heat, moisture, light, and oxygen and product-related factors such as formulation composition, manufacturing, and packaging can influence the drug product stability by inducing alterations of its physicochemical properties. Such influence can expedite the degradation of drug products. The degradation usually varies depending on the dosage form although different formulations can be influenced by the same factor quite similarly. Factors that commonly affect the stability of various dosage forms are summarized below:

A. Liquid Dosage Form

Liquid dosage forms stability is influenced by the following factors:

a) pH

pH changes the rate of hydrolysis in liquid form. Some drugs undergo hydrolysis at a rapid rate in the presence of strong acids and bases. Weakly acidic and basic drugs show good solubility and decompose faster when they are ionized, and that is why it is essential to determine the pH at which the stability is most significant.

b) Temperature

As temperature increases, the hydrolysis rate of drugs in solution is also increased. Some drugs are not stable even at room temperature, so it became necessary to provide cold storage conditions to maintain drug stability. Examples of these drugs include injecting penicillin and insulin.

c) Ionic Strength

Some drug solutions require electrolytes to be added to adjust their tonicity. But this was found to have an impact on the stability.

d) Solvent

In some drugs, its water content is replaced

with a solvent such as alcohol or propylene glycol to avoid hydrolysis. However, if such a procedure is applied to other drugs, it can actually increase the rate of degradation.

e) Oxygen

The presence of oxygen promotes oxidation in some drugs. Proper packing keeps the oxygen content of the solution less and leaving very little space in the bottle above the drug product are methods to fight against oxidation. In some cases, nitrogen or carbon dioxide can be used in place of oxygen.

f) Surfactant

Non-ionic, cationic and anionic surfactants, when added to solution-containing drugs, form a micelle, and the drug particles become trapped in the micelle. The hydrolytic groups such as OH cannot penetrate this micelle cover to reach the drug particles, and hence hydrolysis rate is decreased.

B. Solid Dosage Form

Solid dosage forms stability is influenced by the following factors:

a) Moisture

When solid water-soluble drugs get exposed to moisture, they undergo decomposition in a similar way as the liquid dosage forms. For example, moisture can induce hydrolytic cleavage of ester or amide linkages in the drugs. Hence, the moisture should be avoided during manufacture and storage, and packaging should be selected carefully.

b) Excipients

The decomposition of the drug is proportionally related to the water content of its excipients. Excipients that have high moisture content are Starch, povidone, and magnesium trisilicate. The chemical interactions between the excipients in solid dosage forms can increase the degradation rate.

c) Temperature

Temperature can affect the drug or its excipients either directly by inducing melting or polymorphism or indirectly influence the drug

decomposition through changing the relative humidity.

d) **Light and Oxygen**

Many drugs can undergo photodecomposition or oxidation and hence, such drugs should be kept away from light and oxygen. Since water contains oxygen, moisture should be avoided by storing the medications under dry conditions.

C. Semi-Solid Dosage Form

The chemical stability of ointments and creams is mainly based on the base in their formulation. For example, hydrocortisone decomposes quickly in polyethylene glycol base making its shelf life to be only 6 months. Moreover, dilution of some highly potent ointments such as steroids to make them safer and hence, the choice of diluents should be made carefully as it influences the stability. The stability of these drugs can also be influenced by their incorporation into gel structures by causing increased degradation. However, the viscosity has only a minimum influence on the drug stability.¹¹

Others Factors Affecting Stability

Several factors affect the stability of dosage forms. These include

1. **Storage time:** The longer the storage time, the more the degradation of drug and the more the deterioration of dosage forms.
2. **Storage condition:** storage conditions such as storage temperature and percentage relative humidity at the storage place affect the stability of dosage forms adversely.
3. **Type of dosage forms:** The chemical stability of drug depends on the type of dosage forms. The liquid dosage forms such as solutions exhibit more degradation of the drug than semisolid and solid dosage forms.
4. **Container and closure system:** container-closure systems adversely affect the stability of drug and dosage forms. The plastic containers and rubber closures are reported to absorb antioxidants and preservatives from solution in contact with

them leading to destabilization and microbial attack.⁶

Mechanism of Drug Degradation

Drug products of different dosage forms such as liquid, solid, and Semisolid dosage forms can usually undergo some kind of chemical degradation or breakdown with time. Such change in the dosage form may change either the physical drug appearance such as discoloration or its chemical structure with a consequent difference in its potency or safety. Several modes of degradation have been identified include; hydrolysis, oxidation, isomerization, photochemical decomposition, and polymerization.

The mode of degradation that will take place is determined by the type of the chemical groups that are present in the drug molecules. Some drugs can undergo more than one mode of degradation.

Hydrolysis

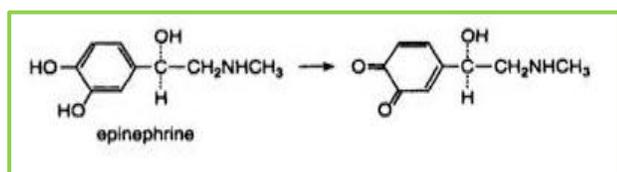
Hydrolysis as a term means splitting in water. Hydrolytic degradation occurs for a drug that is a derivative of carboxylic acid or contains a molecular group that is based on this moiety such as an ester, amide, lactone, lactam, imide, or Carbamate. Examples of such drugs include acetylsalicylic acid, physostigmine, and methyldopa.

Hydrolysis can be catalyzed by Hydrogen ions (specific acid-catalysis) or hydroxyl ions (specific base-catalysis) and also by a buffer that contains acidic or basic species. To stabilize the drug against acid-base catalyzed hydrolysis, several ways are available. The most common one is to formulate the drug at a pH of maximum stability that is determined values. Hydrolysis can also be by the addition of non-aqueous solvents such as alcohol, glycerine or propylene glycol. Making the drug less soluble is another method to suppress degradation, and this is done by using additives such as citrates, dextrose, sorbitol, and gluconate. Adding a compound that forms a complex with the drug or solubilization of a

drug by surfactants can increase the stability of many drugs.

Oxidation

This is another very common way of drug degradation. It can occur simultaneously with hydrolysis. Oxidation occurs by either loss of an electropositive atom, radical, or electron or addition of an electronegative atom or radical. Oxidation process usually involves combining oxygen with free radicals via quite slow chain reactions. These free radicals typically result from organic compounds by the action of light, heat or trace metals. An example includes catechols such as methyl dopa and epinephrine are readily oxidized to quinones.



Drugs that can degrade by oxidation include phenolic compounds such as morphine, phenyl epinephrine, and catecholamine. One method that is commonly used to prevent oxidation and stabilize the drugs is to store them under anaerobic condition. This requires replacing oxygen in the containers with nitrogen or carbon dioxide. Also, since heavy metals such as iron, cobalt, and nickel can act as catalysts for oxidation process, avoiding the use of containers made from these metals during their storage or manufacture can be a protective method against oxidation. Other methods involve reducing the storage temperature and adding small amounts of antioxidants or reducing agents who were proven to be helpful in many cases.

Isomerisation

Isomerisation refers to the process of changing of the drug into its optical or geometric isomers. Such isomers are usually of no therapeutic efficacy. As an example, adrenaline can undergo racemization where it converts from its levo-rotary form into less active isomer. Isomerisation can be catalyzed by low pH. Also, vitamin A can isomerize from its active

form of all-trans into the less productive Cis-isomer.

Photo-Chemical Degradation

Light exposure can initiate chemical degradation of some drug products. The photochemical reactions can be either oxygen dependent (photo-oxidation) or independent on oxygen (such as dehydrogenation, rearrangement, and dimerization). Sodium nitroprusside which is a treatment of acute hypertension has to be protected from light. If the solution is protected from light, it is stable for at least 1 year; if exposed to normal room light, it has a shelf life of only 4 hours.

Other examples of drugs that can rapidly degrade by ultraviolet light are phenothiazines, hydrocortisone, and ascorbic acid compounds. In some cases, photochemical degradation can be manifested as discoloration of the drug.

An efficient way to prevent photo-degradation of drugs is by the use of amber colored glass containers for solution dosage forms. Other means include the use of cardboard outer, aluminum foil over wraps and film coating that can absorb light for tablets as well as storage of photosensitive drug products in the dark.³

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 prerequisite for starting stability testing and is necessarily a written document that describes the critical components of a regulated and well-controlled stability study. Because the testing condition is based on the 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 on 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 IV b, the stability program must include all these zones.

Stability protocol should contain the following information:

- Number of batches
- Containers and closure
- The orientation of container storage
- Sampling time points
- Sampling plan
- Test storage conditions
- Test parameters
- Test methodology
- Acceptance criteria

Batches

Stability studies at developmental stages are generally carried out on a single batch while studies intended for registration of a 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 represent a random sample from the population of pilot or production batches.

Containers and Closures

The testing is done on the product in immediate containers and closures proposed for marketing. The packaging materials include aluminum strip packs, blister packs, Alu- Alu packs, HDPE bottles, etc. This may also include secondary packages, 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.

The 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 into the container-closure.

Sampling Time Points

The 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. The test schedule for stability testing of a new product has been presented in the table.

In case the same product of different strengths, multiple sizes are 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

Table 4: Test schedule for stability testing of new products

Environment	Sampling time points (months)	Method & climatic zones
25 ⁰ C / 60 % RH	3, 6, 9, 12, 18, 24, 36	Long term for zones I and IV
30°C / 35% RH	3, 6, 9, 12, 18, 24, 36	Long term for zones III
30°C / 65% RH	3, 6, 9, 12, 18, 24, 36	Long-term for zone IV a, or intermediate condition for zones I and II
30°C / 75% RH	3, 6, 9, 12, 18, 24, 36	Long-term for zone IVa, or intermediate condition for zones I and II
40°C / 75% RH	3,6	Accelerated condition for all zones

factors, e.g., strength, package size, are tested at all the 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 matrixed include batches, strengths with the identical formulation, container sizes, fill sizes and intermediate time points.

Sampling Plans

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 the 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 the 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 pullouts 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 nth container is taken from the filling or packaging line (n is chosen such that the sample is spread over the whole batch).

Test Storage Conditions

For accelerated stability testing, the sample is stored under isothermal conditions and for long-term stability testing, the containers are stored on open shelves in ventilated areas. 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 presented in Table.

Table 5: Stability test storage conditions for drug products

Intended storage condition	Stability Test Method	ICH Test temperature and humidity (Period in months)	WHO Test temperature and humidity (Period in months)
Room temperature	Long-term	25±2°C/60±5% RH (12)	25±2°C/60±5% RH or 30±2°C/65±5% RH
	Intermediate	30±2°C/65±5% RH (6)	30±2°C/65±5% RH (6)
	Accelerated	40±2°C/75±5% RH (6)	40±2°C/75±5% RH (6)
Refrigerator	Long-term accelerated	5°C/ambient (12) 25±2°C/60±5% RH (6)	5±3°C 25 ±2°C/60±5% RH or 30 ±2°C/65±5% RH
Freezer	Long term	-20°C/ambient (12)	-20°C±5°C

The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months'

testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

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.

Microbial 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.

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.

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 Q3 B (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.^{4,5,7}

Conduct of Stability Studies

The stability study is conducted by keeping the drug substance or the product in their proposed final packs (e.g. Aluminium strip, blister pack, Alu-Alu pack, HDPE container etc.), or prototype containers in the case of bulk drugs, in sufficient numbers in the stability chambers set at appropriate storage conditions as per the protocol. The samples are then withdrawn, as per the stability protocol, at the prescribed sampling intervals and are then analyzed by a suitable method. The sampling should preferably be from an unopened container. As far as possible the samples are placed for testing as soon as they have been prepared and analyzed without delay after they have been withdrawn. Delay in placing the samples and analysis of withdrawn samples is known to affect the results. However, if there is an unavoidable delay, then the samples are frozen until they are subjected to analysis. In order to minimize the effect of day-to-day variability on the results, the following two approaches are followed. Samples are drawn in replicate. One of the samples is tested, and others are kept at temperatures sufficiently low to prevent further drug loss and then all the samples are subjected to analysis on the same day at the end of study (i.e. after withdrawal of the last sample).

The second approach is to freeze the initial samples till the expiration period and test them

at appropriate times by using them as internal standards in the assays.^{4,7}

Presentation and Recording of Stability Data

Stability data is recorded in an organized, comprehensive and cumulative format. The stability data table is the means for reporting the results of the stability study in a concise format for ease of review and interpretation. The data is recorded in a proper tabular format, and all-encompassing information on a batch is recorded at one place. Similar sheets are prepared for each batch. When, it is not possible to collect a sample precisely at the designed time (i.e., 3, 6, 9, 12 months, etc.), the sample may be withdrawn conveniently, and the actual time of collection should be indicated in the format sheet. The data can be grouped by storage condition and time interval to present the stability as a function of time for each environmental state studied. Data can be presented in multiple tables taking care that it is easily interpretable. In addition, a graphical presentation of stability data versus time for the test data can be used to illustrate trends in data and may be helpful for data evaluation. A graphical presentation of the data, however, cannot replace the tabular presentation for a regulatory filing. The results of the statistical analysis, wherever appropriate and analysis of impurities should also be discussed.^{4,7}

Mean Kinetic Temperature

The Mean kinetic temperature is the 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 cycles of higher and lower temperature. It is an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variation. The MKT takes into account seasonal and daily temperature variations during a year. It expresses the cumulative thermal stress undergone by a product at varying temperatures during storage and distribution. The concept of MKT is applied in order to provide assurance that the actual storage conditions will not affect the

stability and shelf life of the product adversely. This is based upon the fact that the degradation rate constants are temperature dependent. A controlled room temperature maintained thermostatically to the usual working environment of 20°C to 25°C results in a mean kinetic temperature calculated to be not more than 25°C. This concept is applied to pharmacies, hospitals, distribution and storage areas and vehicles and warehouses. Articles may be labeled for storage at “controlled room temperature” or at “up to 25°C”, or any other relevant word/phrase based on the same mean kinetic temperature. The distribution of the countries and regions of the world into four different climatic zones has been on the basis of the mean kinetic temperature. Mean kinetic temperature is calculated by two methods, i.e. USP method and FDA method. In the USP method, MKT is derived from the average storage temperatures recorded over a 1-year period and the running average derived from the average of weekly high and low temperatures recorded over the preceding 52 weeks. This result in entering 52 data points and calculation is done by Hayne’s equation, which is derived from Arrhenius equation and relates degradation rate constants at different temperatures to the activation energy.

$$T_K = \frac{\frac{\Delta H}{R}}{-\ln \left(\frac{t_1 e^{\left(\frac{-\Delta H}{RT_1}\right)} + t_2 e^{\left(\frac{-\Delta H}{RT_2}\right)} + \dots + t_n e^{\left(\frac{-\Delta H}{RT_n}\right)}}{t_1 + t_2 + \dots + t_n} \right)}$$

where MKT is the mean kinetic temperature; ΔH is the energy of activation, in kJ/mole; R is the universal gas constant, 83.144kJ/mole (5-240 kJ/mole); T1 is the arithmetic mean of the highest and lowest temperatures recorded during the first time period (e.g., the first week); T2 is the arithmetic mean of the highest and lowest temperatures recorded during the second time period (e.g., the second week); Tn is the arithmetic mean of the highest and lowest temperatures recorded during the nth time period (e.g., nth week), n being the total number of average storage temperatures recorded during the annual observation period; and all

temperatures T being absolute temperatures in degrees Kelvin (K).

The FDA recommends the method of entering both the individual highest and the lowest temperatures (rather than averages) in the equation for the calculation of MKT. This results in entering 104 data points, in contrast to USP's 52 points. If temperatures are electronically recorded at many times during a day, and all the values are used in the calculation of MKT, then there is no difference between the USP and FDA method.^{4,7}

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 proper recording, safety and alarm devices. In addition, photostability chambers are also available and utilized both with and without temperature and humidity control. Two types of light sources are usually employed in photostability chambers, one is the combination of cool white and near UV fluorescent tubes, while second is 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 an hour). The visible light intensity is estimated using a lux meter. The calculation is made on how many hours of exposure are needed.⁷

Stability Testing Methods

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 primary 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 marketplace available for supply to the patients and will be fit for their consumption until the patient uses the last unit of the product.

Depending on 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 stability testing

The primary 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 marketplace 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 usually performed for the 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 trend analysis is able to identify 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 provides for the stability of reagents as well as the consistency of the performance of the instrument to be used throughout the period of stability testing.

Shelf life Determination based on Real-Time Testing

Another method which involves real-time testing and statistical analysis followed for determining shelf life.

- 1) Keep three batches for stability study at least for 1 year at one fixed temperature.
- 2) Test them at 0, 1, 3, 6, 9, and 12 months for drug content. At each testing time test a number of samples, so that mean and standard deviation value of the result is obtained.
- 3) Now plot the graph of %drug content on Y axis and time on X-axis along with the confidence intervals. Where the lower 95% confidence curve intersects minimum potency, there fix shelf life.

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. To assess the stability of a formulated product, it is usual to expose it to high-stress condition, i.e. condition of temperature, humidity, and light intensity that cause break down. High-stress conditions enhance the deterioration of the product, and so reduce the time required for testing.

A significant change occurs due to accelerated testing are

- A 5% potency loss from the initial assay value of a batch.
- Any specified degradants are exceeding its specified limit.
- The product is exceeding its pH limits.
- Dissolution is exceeding the specified limits for 12 capsules or tablets.
- Physical changes under accelerated conditions of temperature and humidity.
 1. Under the light, both primary and secondary packaging affected, and fading of container color and the print is fading.
 2. Effervescent tablet: gain of moisture, loss of integrity.
 3. Capsule: colour fading in the blister and sticking in a glass bottle.
 4. Powder: spread within strip pockets.
 5. Suppositories : softening
 6. Change in viscosity of a gel, jelly, cream, and ointment
 7. Lozenges: melting

Prediction of shelf life from accelerated stability data based on the principle of chemical kinetics demonstrated by

• Garret and carper method

Shelf life determination based on Arrhenius plot (garret and carper method). The mathematical prediction of shelf life is based on the application of the Arrhenius equation, which indicates the effect of temperature on the rate constant k , of a chemical reaction of thermodynamic temperature $1/T$ is a straight line.

If the slope of this line is determined from the results of temperature by extrapolation, the k value obtained. This k value is substituted inappropriate. Order of reaction allows the amount of decomposition after a given time.

Preliminary experiments are there for necessary to determine this order.

$$K=Ae^{-E_a/RT}$$

$$\text{Log } K=\text{log}A-E_a/2.303*RT$$

Where, k = rate constant

R= gas constant=1.987cal/mole

T= absolute temperature

A= frequency factor

E_a= energy of activation

Garret and Carper Method

1. Keep several samples of the drug product at least three temperatures such as 40°C,50°C and 60°C.
2. Determine the drug content at all three storage points by taking a number of samples and make the mean drug content. We do this for a few weeks.
3. At each temperature, we plot a graph between time and log percent drug remaining. If the decomposition is first order, this gives a straight line. If it is zero order, percent drug remaining versus time will give a straight line.
4. Next, we take the log K or log of reaction constant on Y-axis and 1/T x
5. 10³ on X-axis and draw the best fit line. This line is the Arrhenius Plot, extrapolate this line to get k at 25°C and from this we calculate the shelf-life.

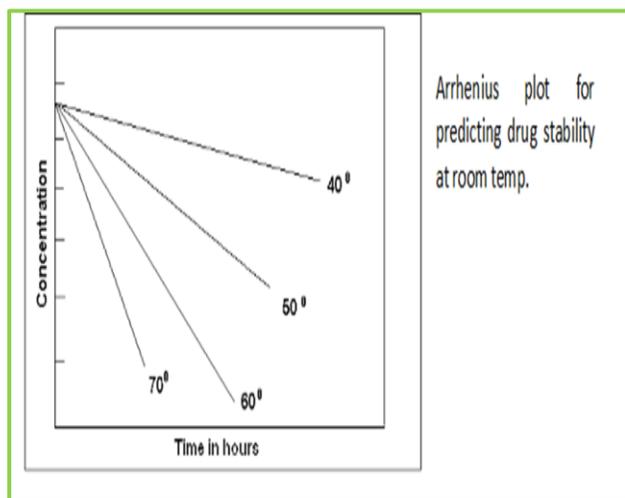
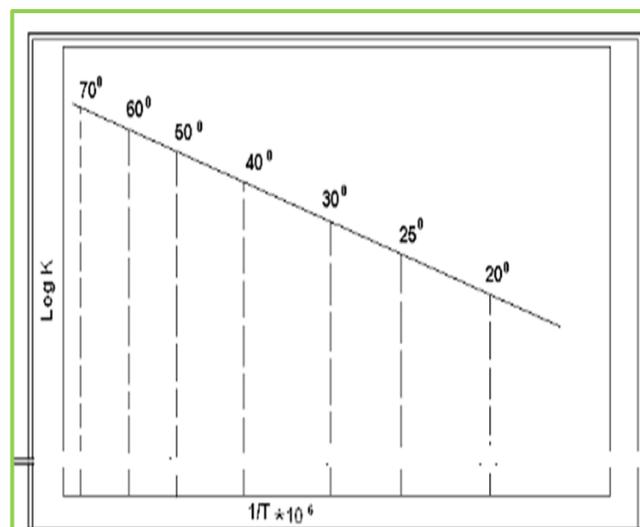


Figure 2: Arrhenius plot for predicting drug stability at room temperature



If the reaction is following zero order, Expiration date at 25°C C = Initial potency – minimum potency / reaction rate at 25°C.

$$T_x = Y_0 - Y_x / K_0$$

If the reaction is following the first order, Expiration date at 25°C C (t_x) = log initial potency – log minimum potency / reaction rate at 25

$$T_x = \text{logo} - \text{log} Y_x / K_1$$

Where, Y₀ = initial potency

Y_x = final potency

K₀ = zero order reaction

K₁ = first order reaction

Limitation of Arrhenius Relationship for Stability Prediction

- There are varieties of the situation in which Arrhenius equation can be erroneous or invalid.
- Higher temperature may evaporate solvents thus producing unequal moisture concentration at a different temperature.
- At higher temperature stability for drugs sensitive to the presence of moisture and oxygen.
- For dispersive systems viscosity decrease as a temperature increases and physical characteristic may alter and result in potentially significant errors in predicting of stability.⁸

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 the 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 a 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 marketplace 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.

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 marketplace 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 typically have 20 cycles.⁷

Photostability Testing of Drugs

For drug substances, photostability testing

should consist of two parts: forced degradation testing and confirmatory testing. The purpose of forced degradation testing studies is to evaluate the overall photosensitivity of the material for method development purposes and/or degradation pathway elucidation. This testing may involve the drug substance alone and/or in simple solutions/suspensions to validate the analytical procedures.

In these studies, the samples should be in chemically inert and transparent containers. In these forced degradation studies, a variety of exposure conditions may be used, depending on the photosensitivity of the drug substance involved and the intensity of the light sources used. For development and validation purposes it is appropriate to limit exposure and end the studies if extensive decomposition occurs.

For photo stable materials, studies may be terminated after an appropriate exposure level has been used. The design of these experiments is left to the applicant's discretion although the exposure levels used should be justified.

Under forcing conditions, decomposition products may be observed that are unlikely to be formed under the conditions used for confirmatory studies. This information may be useful in developing and validating suitable analytical methods. If in practice it has been demonstrated they are not formed in the confirmatory studies; these degradation products need not be further examined.

Permeable

The intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable change. Usually, photostability testing is carried out on a single batch of a material selected as described under Selection of Batches in the Parent Guideline. Under some circumstances, these studies should be repeated if certain variations and changes are made to the product (e.g., formulation, packaging). Whether these studies should be repeated depends on the photostability characteristics determined at the time of initial filing and the type of variation

and/or change made.

The guideline primarily addresses the generation of photostability information for submission of Registration Applications for new molecular entities and associated drug products. The guideline does not cover the photostability of drugs after administration (i.e., under conditions of use) and those applications not covered by the Parent Guideline. Alternative approaches may be used if they are scientifically sound and justification is provided.

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

- i. Tests on the drug substance
- ii. Tests on the exposed drug product outside of the immediate pack; and if necessary
- iii. Tests on the drug product in the immediate pack, and if necessary

The extent of drug product testing should be established by assessing whether or not acceptable change has occurred at the end of the light exposure testing as described in the Decision Flow Chart for Photostability Testing of Drug Products. Acceptable change is change within limits justified by the applicant. The formal labeling requirements for photolabile drug substances and drug products are established by national/regional requirements.

Light Sources

The light sources described below may be used for photostability testing. The applicant should either maintain appropriate control of temperature to minimize the effect of localized temperature changes or include a dark control in the same environment unless otherwise justified. For both options 1 and 2, a pharmaceutical manufacturer/applicant may rely on the spectral distribution specification of the light source manufacturer.

Option 1:

Any light source that is designed to produce an output similar to the D65/ID65 emission

standard such as an artificial daylight fluorescent lamp combining visible and ultraviolet (UV) outputs, xenon, or metal halide lamp. D65 is the internationally recognized standard for outdoor daylight as defined in ISO 10977 (1993). ID65 is the equivalent indoor indirect daylight standard. For a light source emitting significant radiation below 320 nm, an appropriate filter(s) may be fitted to eliminate such radiation.

Option 2:

For option 2 the same sample should be exposed to both the cool white fluorescent and near the ultraviolet lamp.

1. A cool white fluorescent lamp designed to produce an output similar to that specified in ISO 10977(1993).
2. A near UV fluorescent lamp has a spectral distribution from 320 nm to 400 nm with a maximum energy emission between 350 nm and 370 nm; a significant proportion of UV should be in both bands of 320 to 360 nm and 360 to 400 nm.

Procedure

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

Samples may be exposed side-by-side with a validated chemical actinometric system to ensure the specified light exposure is obtained, or for the appropriate duration of time when conditions have been monitored using calibrated radiometers/lux meters. An example of an actinometric procedure is provided in the Annex.

If protected samples (e.g., wrapped in aluminum foil) are used as dark controls to evaluate the contribution of thermally induced change to the total observed change, these should be placed alongside the authentic sample.

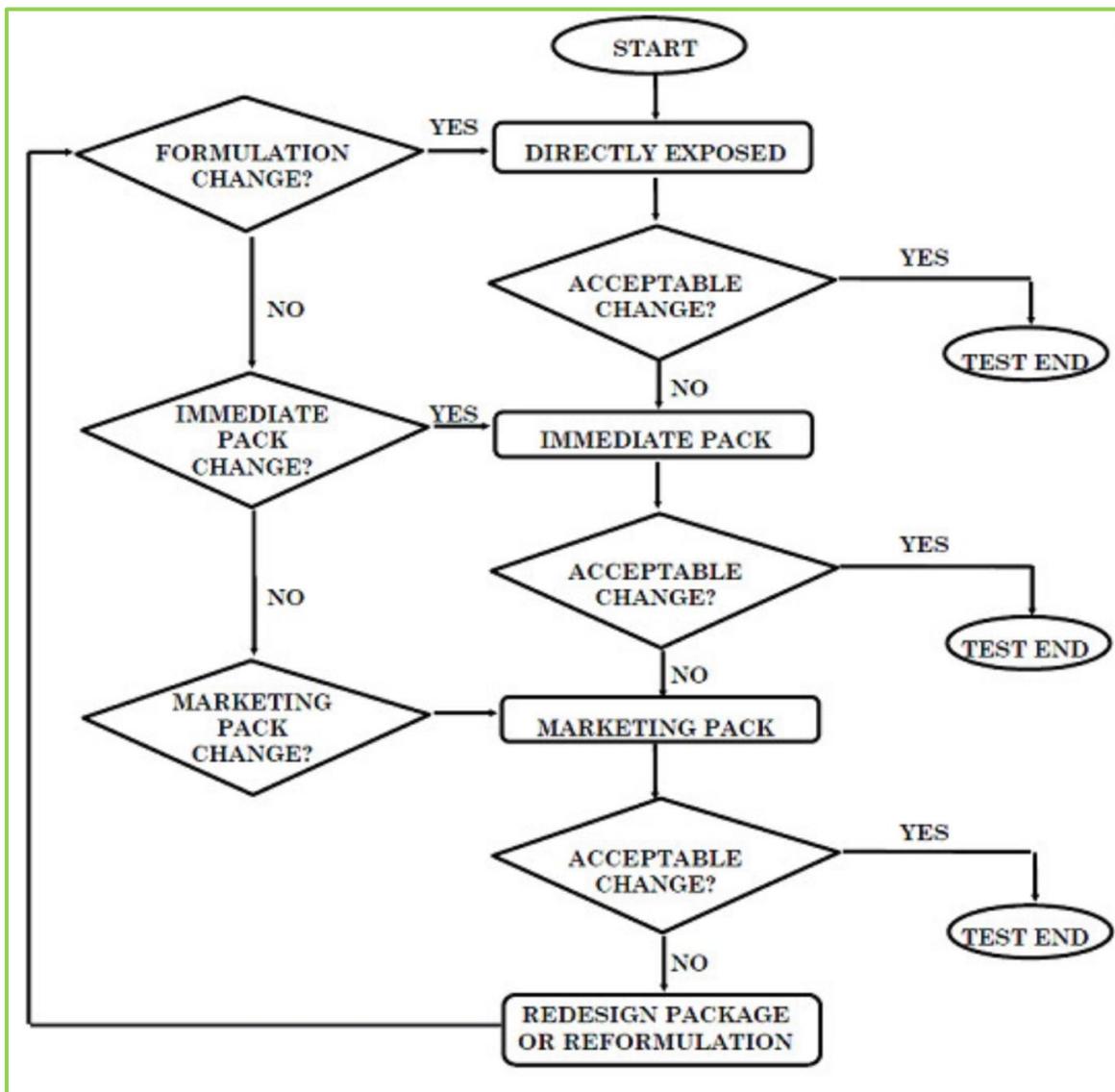


Figure 3: Decision flowchart for photostability testing of drug products

Presentation of Samples

Care should be taken to ensure that the physical characteristics of the samples under test are taken into account and efforts should be made, such as cooling and/or placing the samples in sealed containers, to ensure that the effects of the changes in physical states such as sublimation, evaporation or melting are minimized.

All such precautions should be chosen to provide minimal interference with the exposure of samples under test. Possible interactions between the samples and any material used for

containers or for general protection of the sample should also be considered and eliminated wherever not relevant to the test being carried out.

As a direct challenge for samples of solid drug substances, an appropriate amount of sample should be taken and placed in a suitable glass or plastic dish and protected with an adequate transparent cover if considered necessary. Solid drug substances should be spread across the container to give a thickness of typically not more than 3 millimeters. Drug substances that are liquids should be exposed in chemically

inert and transparent containers.

Analysis of Samples

At the end of the exposure period, the samples should be examined for any changes in physical properties (e.g., appearance, clarity, or color of solution) and for assay and degradants by a method suitably validated for products likely to arise from photochemical degradation processes.

Where solid drug substance samples are involved, sampling should ensure that a representative portion is used in individual tests. Similar sampling considerations, such as homogenization of the entire sample, apply to other materials that may not be homogeneous after exposure. The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark controls if these are used in the test.

Judgment of Results

The forced degradation studies should be designed to provide suitable information to develop and validate test methods for the confirmatory studies. These test methods should be capable of resolving and detecting photolytic degradants that appear during the confirmatory studies. When evaluating the results of these studies, it is essential to recognize that they form part of the stress testing and are not therefore designed to establish qualitative or quantitative limits for a change.

The confirmatory studies should identify precautionary measures needed in manufacturing or in the formulation of the drug product, and if the light resistant packaging is necessary. When evaluating the results of confirmatory studies to determine whether change due to exposure to light is acceptable, it is important to consider the results from other formal stability studies in order to assure that the drug will be within justified limits at the time of use.

CONCLUSION

Stability testing of pharmaceutical products is the essential procedural contribution in the

development program for a new drug as well as n, safety and efficacy thorough understanding of the stability of the drug substance and drug product is essential 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 an understanding of the current regulatory requirements and as per the climatic zone.

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