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AN OVERVIEW: STABILITY STUDY OF PHARMACEUTICAL PRODUCTS AND SHELF LIFE PREDICTION

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ABSTRACT
Stability studies ensuring the maintenance of product quality, safety and efficacy throughout the shelf life are considered as 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 stability of pharmaceutical products have been presented in a concise manner in the present review. Stability is the extent to which a product retains, within the specified limits, throughout its period of storage and use, the same properties and characteristics possessed at the time of its packaging. Stability testing thus evaluates the effect of environmental factors on the quality of a drug substance or a formulated product which is utilized for prediction of its shelf life, determine proper storage conditions and suggest labeling instructions. Current trends in stability testing also described.

KEYWORDS: Stability, Stability studies, Stability testing, Shelf Life.

INTRODUCTION
Stability testing of pharmaceutical products is a complex set of procedures which involve considerable cost, time consumption and scientific expertise in order to build in quality, efficacy and safety in a drug formulation. Scientific and commercial success of a pharmaceutical product can only be ensured with the understanding of the drug development process and he myriad tasks and milestones that are vital to a comprehensive development plan. Stability testing is termed as a complex process because of involvement of a variety of factors influencing the stability of a pharmaceutical product. These factors include stability of the active ingredient (s); interaction between active ingredients and excipients, manufacturing process followed, type of dosage form, container/closure system used for packaging and light, heat and moisture conditions encountered during shipment, storage and handling.[1]

A pharmaceutical product may undergo change in appearance, consistency, content uniformity, clarity (solution), moisture contents, particle size and shape, pH, package integrity thereby affecting its stability. Such physical changes may be because of impact, vibration, abrasion, and temperature fluctuations such as freezing, thawing or shearing etc.[2]

The chemical reactions like solvolysis, oxidation, reduction, racemization etc. that occurs in the pharmaceutical products may lead to the formation of degradation product, loss of potency of active pharmaceutical ingredient (API), loss of excipient activity like antimicrobial preservative action and antioxidants etc. Stability of a pharmaceutical product can also be affected because of microbiological changes like growth of microorganisms in non sterile products and changes in preservative efficacy.[3]

The **USP** defines the stability of pharmaceutical product as "extent to which a product retains within specified limits" and throughout its period of storage and use (i.e. its shelf life) the same properties and characteristics that it possessed at the time of its manufacture.[4]

Stability study is a vital stake of the drug development process. Stability is the only way that assures whether the drug is within acceptance criteria or not. Stability comes into focus when the quality and efficiency of the drug are concerned. Literal meaning of stability is the capacity of a drug product to remain within specifications established to ensure its identity, strength quality and purity. Instability of the drug can cause undesired change in performance that causes product failures.[5]

In the present review importance of various methods followed for stability testing of pharmaceutical products, guidelines issued for stability testing and other aspects

related to stability of pharmaceutical products have been presented in a concise manner.

HISTOLOGICAL BACKGROUND

Jordan was the one to give the name for Stability testing in the pharmaceutical companies. The need arose when regional office organized a workshop for validation of expiry dates of drug in Amman.The workshop ordered every medical authority to collaborate with every pharmaceutical company to guide them about the importance of drug stability and expiry date.[6]

Thus International Conference on Harmonization thus took a step to implement these guidelines. FDA issued its first stability guidance in 1987.Considerable efforts were taken, to harmonize the stability practices within the ICH region then after in the early 1990. As a result to the efforts, International Conference on Harmonization (ICH) was established in 1991 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.[7]

Work on stability of pharmaceutical products was initiated by the WHO in 1988 and the WHO Guidelines on Stability Testing for Well Established Drug Substances in Conventional Dosage Forms were adopted in 1996 by the WHO Expert Committee on Specifications for Pharmaceutical Preparations following extensive consultation.

In 2000, discussions began between the International Conference on Harmonization (ICH) expert working group Q1 (stability) and the WHO to harmonize the number of stability tests and conditions employed worldwide.[7,8]

Table 01: Objectives of Stability Testing.

Objective	Type of study	Use
To select adequate (from the viewpoint of stability) formulations and container-closure systems	Accelerated	Development of the product
To determine shelf-life and storage conditions	Accelerated and real-time	Development of the product and of the registration dossier
To substantiate the claimed shelf-life	Real-time	Registration dossier
To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product	Accelerated and real-time	Quality assurance in general, including quality control

With the approval of the drug regulatory authority, a tentative (provisional) shelf-life is often established, provided that the manufacturer has undertaken, by virtue of a signed statement, to continue and complete the required studies and to submit the results to the registration authority.

IN THE DEVELOPMENT PHASE

In this phase accelerated stability tests provide a means of comparing alternative formulations, packaging materials, and/or manufacturing processes in short-term experiments.

As soon as the final formulation and manufacturing process have been established, the manufacturer carries out a series of accelerated stability tests which will enable the stability of the drug product to be predicted and its shelf-life and storage conditions determined. Real-time studies must be started at the same time for confirmation purposes.[4]

FOR THE REGISTRATION DOSSIER

For the registration of dosage form the manufacturer is required to submit information on the stability of the product derived from tests on the final dosage form in its final container and packaging. The data submitted are obtained from both accelerated and real-time studies. Published and/or recently obtained experimental supporting stability data on the stability of active ingredients and related formulations may also be submitted.[4,9]

IN THE POST-REGISTRATION PERIOD

To substantiate the expiry date and the storage conditions previously projected the manufacturer must carry out on-going real-time stability studies. The data needed to confirm a tentative shelf life must be submitted to the registration body. Other results of on-going stability studies are verified in the course of GMP inspections.

Once the product has been registered, additional stability studies are required whenever major modifications are made to the formulation, manufacturing process, packaging or method of preparation. The results of these studies must be communicated to the competent drug regulatory authorities.[4,12]

Table 02. Potential adverse effects of instability in pharmaceutical products[10, 11]

Potential Adverse Effect	Explanation/ Reason	Example	Stability Parameter Tested
Loss of Active Ingredient	Degradation of API in product resulting in less than 90% drug as claimed on label - unacceptable quality	Nitroglycerine tablets	Time elapsed before the drug content no onger exceeds 90%
Increase in concentration of active Ingredient	Loss of vehicle perfusion bags sometimes allow solvent to escape and evaporate so that the product within the bag shows an increase in concentration.	Lidocaine gel, products in perfusion bags	Stability in final container
Alteration in bioavailability	Changes in rate and extent of absorption on storage	…….	Dissolution/release studies
Loss of content uniformity	Loss of contents as a function of time	Suspension	Ease of re-dispersion or sedimentation volume
Decline of microbiological status	Increase in number of viable microorganisms already present in the product.	Multiuse cream	Total bioburden after storage
Loss of pharmaceutical elegance and patient acceptability	Speckling caused by the interaction of the drug containing amine group with a minor component in the lactose resulting in the formation of a chromatophore	Slight yellow or brown speckling on the surface of tablet containing spray-dried lactose	Visual Examination
Formation of toxic degradation products	Degradation of the drug component	Formation of Epianhydrotetracycline from tetracycline, Protein drugs	Amount of degradation products during shelf life
Loss of package integrity	Change in package integrity during storage or distribution	Plastic screw cap losing back-off-torque	Specific package integrity tests
Reduction of label quality	Deterioration of label with time and cause the ink to run and thus adversely affect legibility	Plasticizer from plastic bottle migrates into the label	Visual examination of the label

TYPES OF STABILITY TESTING

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 is 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 Depending upon the aim and steps followed, stability testing procedures have been categorized into the following four types.[2]

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.[2,12]

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.[2] 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.

For statistical reasons, the treatment in accelerated stability projections is recommended to be conducted at four different stress temperatures.[13,21]

The concept of accelerated stability testing is based upon the Arrhenius equation (1) and modified Arrhenius equation

$$k = Ae^{-E_a/(RT)}$$

$$\ln(k) = \frac{-E_a}{R}\frac{1}{T} + \ln(A)$$

Where K = degradation rate
A = frequency factor/s,
ΔE =activation energy (kJ/mol)
R = universal gas constant (0.00831kJ/mol)
T=absolute temperature (K)

As modified.

$$k = A(T/T_0)^n e^{-E_a/(RT)}$$

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.[2,6, 22]

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. 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.[2, 21]

CLIMATIC ZONE

The intended market and the climatic conditions in the area in which the drug product will be used should be taken into account for the design of the stability testing program. Four climatic zones can be distinguished for the purpose of worldwide stability testing, as follows:

Table 03: ICH Stability Zones.

Zone	Type of Climate
Zone I	Temperate zone
Zone II	Mediterranean/subtropical zone
Zone III	Hot dry zone
Zone IV	Hot humid/tropical zone
Zone IVb	ASEAN testing conditions hot/higher humidity

Table 04: Long Term Testing Conditions.

Climatic Zone	Temperature	Humidity	Minimum Duration
Zone I	21ºC ± 2ºC	45% rH ± 5% rH	12 Months
Zone II	25ºC ± 2ºC	60% rH ± 5% rH	12 Months
Zone III	30ºC ± 2ºC	35% rH ± 5% rH	12 Months
Zone IV	30ºC ± 2ºC	65% rH ± 5% rH	12 Months
Zone IVb	30ºC ± 2ºC	75% rH ± 5% rH	12 Months
Refrigerated	5ºC ± 3ºC	No Humidity	12 Months
Frozen	-15ºC ± 5ºC	No Humidity	12 Months

Table 05: Accelerated and Intermediate Testing Conditions.

Test type	Temperature	Humidity	Minimum Duration
Accelerated Ambient	40ºC ± 2ºC	75% rH ± 5% rH	6 Months
Accelerated Refrigerated	25ºC ± 2ºC	60% rH ± 5% rH	6 Months
Accelerated Frozen	5ºC ± 3ºC	No Humidity	6 Months
Intermediate	30ºC ± 2ºC	65% rH ± 5% rH	6 Months

Guidelines for stability studies objectives of these guidelines

These guidelines seek to exemplify the core stability data package required for registration of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs), replacing the previous WHO guidelines in this area. However, alternative approaches can be used when they are scientifically justified. Further guidance can be found in International Conference on Harmonisation (ICH) guidelines and in the WHO guidelines on the active pharmaceutical ingredient master file procedure.[16]

Guidelines for active pharmaceutical ingredient general case

Information on the stability of the API is an integral part of the systematic approach to stability evaluation. Potential attributes to be tested on an API during stability testing are listed in the examples of testing parameters will be described in the lower part of this guideline.

Table 06: Long term, Intermediate and Accelerated testing condition for General case.

Study	Storage condition	Storage condition
Long-term	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12 months or 6 months
Intermediate	30 °C ± 2 °C/65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

Whether long-term stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30°C ±2 °C/65% RH ± 5% RH or 30°C ± 2 °C/75% RH ± 5% RH is determined by the climatic condition under which the API is intended to be stored.

Testing at a more severe long-term condition can be an alternative to testing condition, i.e. 25 °C/60% RH or 30 °C/65% RH.

If 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH is the long-term condition there is no intermediate condition.[17,18]

ACTIVE PHARMACEUTICAL INGREDIENTS INTENDED FOR STORAGE IN A REFRIGERATOR

Table 07: Active pharmaceutical ingredients intended for storage in a refrigerator.

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5 °C ± 3 °C	12 months
Accelerated	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 months

Whether accelerated stability studies are performed at 25 ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe long term condition can be an alternative to storage testing at 25 °C/60%RH or 30 °C/65%RH.[17]

GUIDELINE FOR FINISHED PHARMACEUTICAL PRODUCT GENERAL CASE

Table 08: Long term, Intermediate and Accelerated testing condition for General case.

Study	Storage condition	Storage condition
Long-term	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12 months or 6 months
Intermediate	30 °C ± 2 °C/65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

Whether long-term stability studies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH is determined by the climatic zone in which the FPP is intended to be marketed. Testing at a more severe long-term condition can be an alternative to storage at 25 °C/60% RH or 30°C/65% RH.

If 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during six months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. In this case the initial application should include a minimum of six months' data from a 12-month study at the intermediate storage condition.[16,17]

FPPS PACKAGED IN SEMI-PERMEABLE CONTAINERS

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below.

Table 09: Stability studies for FPPS Packaged Semi-permeable Containers.

Study	Storage condition	Minimum time period covered by data at submission
Long-term	25 °C ± 2 °C/40% RH ± 5% RH or 30 °C ± 2 °C/35% RH ± 5% RH	12 months
Intermediate	30 °C ± 2 °C/65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/not more than (NMT) 25% RH	6 months

Whether long-term stability studies are performed at 25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH is determined by the climatic condition under which the FPP is intended to be marketed. Testing at 30°C/35% RH can be an alternative to the storage condition at 25 °C/40% RH. [16,17]

FPPS INTENDED FOR STORAGE IN A REFRIGERATOR

Table 10: Stability studies for FPPS Packaged Semi-permeable Containers intended for storage in a refrigerator.

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5 °C ± 3 °C	12 months
Accelerated	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 months

Whether accelerated stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to the storage condition at 25°C/60% RH or 30 °C/65% RH.[17,18]

EXAMPLES OF TESTING PARAMETERS

SECTION I: FOR ACTIVE PHARMACEUTICAL INGREDIENTS

In general, appearance, assay and degradation products should be evaluated for all active pharmaceutical ingredients (APIs). Other API parameters that may be susceptible to change should also be studied where applicable.[6]

SECTION II: FOR FINISHED PHARMACEUTICAL PRODUCTS

The following list of parameters for each dosage form is presented as a guide to the types of tests to be included in a stability study. In general, appearance, assay and degradation products should be evaluated for all dosage forms, as well as the preservative and antioxidant content if applicable.[6]

a. TABLETS

Dissolution (or disintegration, if justified), water content and hardness/ friability.

b. CAPSULES

Hard gelatin capsules

brittleness, dissolution (or disintegration, if justified), water content and level of microbial contamination.

Soft gelatin capsules

dissolution (or disintegration, if justified), level of microbial contamination, pH, leakage and pellicle formation.

c. ORAL SOLUTIONS, SUSPENSIONS AND EMULSIONS

Formation of precipitate, clarity (for solutions), pH, viscosity, extractabilities, level of microbial contamination. Additionally for suspensions, dispersibility, rheological properties, mean size and distribution of particles should be considered.

d. POWDERS AND GRANULES FOR ORAL SOLUTION OR SUSPENSION

Water content and reconstitution time, Reconstituted products (solutions and suspensions) should be evaluated as described above under "Oral solutions suspensions and emulsions", after preparation according to the recommended labeling, through the maximum intended use period.

e. METERED-DOSE INHALERS AND NASAL AEROSOLS

Dose content uniformity, labeled number of medication actuations per container meeting dose content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate, level of microbial contamination, valve delivery (shot weight), extractables/ leachables from plastic and elastomeric components, weight loss, pump delivery, foreign particulate matter and extractables/leachables from plastic and elastomeric components of the container, closure and pump. Samples should be stored in upright and inverted/on-the-side orientations.

For suspension-type aerosols, microscopic examination of appearance of the valve components and container's contents for large particles, changes in morphology of the API particles, extent of agglomerates, crystal growth, foreign particulate matter, corrosion of the inside of the container or deterioration of the gaskets.

f. NASAL SPRAYS: SOLUTIONS AND SUSPENSIONS

Clarity (for solution), level of microbial contamination, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet and/ or particle size distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign particulate matter and extractables/ leachables from plastic and elastomeric components of the container, closure and pump.

g. TOPICAL, OPHTHALMIC AND OTIC PREPARATIONS

Included in this broad category are ointments, creams, lotions, paste, gel, solutions, eye drops and cutaneous sprays.

• Topical preparations should be evaluated for clarity, homogeneity, pH, suspendability (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible), level of microbial contamination/sterility and weight loss (when appropriate).

• Evaluation of ophthalmic or otic products (e.g. creams, ointments, solutions and suspensions) should include the following additional attributes: sterility, particulate matter and extractable volume.

• Evaluation of cutaneous sprays should include: pressure, weight loss, net weight dispensed, delivery rate, level of microbial contamination, spray pattern, water content and particle size distribution (for suspensions).

h. SUPPOSITORIES

Softening range, disintegration and dissolution (at 37°C).

i. SMALL VOLUME PARENTERALS (SVPS)

Color, clarity (for solutions), particulate matter, pH, sterility, endotoxins.

• The stability studies for Suspension for injection should include, in addition, particle size distribution, dispersibility and rheological properties. The stability studies for Emulsion for injection should include, in addition, phase separation, viscosity, mean size and distribution of dispersed phase globules.

j. LARGE VOLUME PARENTERALS (LVPS)

Color, clarity, particulate matter, pH, sterility, pyrogen/endotoxin and volume.

k. TRANSDERMAL PATCHES[6, 14, 19]

In vitro release rates, leakage, level of microbial contamination/sterility, and adhesive forces.

RECOMMENDED LABELING STATEMENTS ACTIVE PHARMACEUTICAL INGREDIENTS[16, 17]

The statements that should be used if supported by the stability studies for active pharmaceutical ingredients (APIs) are listed in Table 11.

EXPIRATION DATE/SHELF LIFE

An expiration date is defined as the time up to which the product will remain stable when stored under recommended storage conditions. Thus, an expiration date is the date beyond which it is predicted that the product may no longer retain fitness for use. If the product is not stored in accordance with the manufacturer's instructions, then the product may be expected to degrade more rapidly. Shelf life is the time during which the product, if stored appropriately as per the manufacturer's instructions, will retain fitness for use (>90% of label claim of potency). The expiration date is also defined as the date placed on the container/labels of a drug product designating the time during which a batch of the product is expected to remain within the approved shelf life specifications, if stored under defined conditions and after which it should not be used.[3,15]

ESTIMATION OF SHELF LIFE

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. Table below gives the different possibilities in the pattern of the concentration-time data of the three batches. The data is pooled accordingly and used for estimation of the common slope.

Table 11: Recommended labeling statements for active pharmaceutical ingredients (APIs).

Testing condition under which the stability of the API has been demonstrated	Recommended labeling statement
25 °C/60% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 25 °C"
25 °C/60% RH (long-term) 30°C/65% RH (intermediate, failure of accelerated)	"Do not store above 25 °C"
30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
30 °C/75% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
5 °C ± 3 °C	"Store in a refrigerator (2 °C to 8 °C)"
-20 °C ± 5 °C	"Store in freezer"

Table 12. Recommended labeling statements for Finished pharmaceutical products[16,18]

Testing condition under which the stability of the FPP has been demonstrated	Recommended labeling statement
25 °C/60% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 25 °C"
25 °C/60% RH (long-term) 30°C/65% RH (intermediate, failure of accelerated)	"Do not store above 25 °C"
30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
30 °C/75% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
5 °C ± 3 °C	"Store in a refrigerator (2 °C to 8°C)"
-20 °C ± 5 °C	"Store in freezer"

Table 13: Additional labeling statements for use where the result of the stability testing demonstrates limiting factors[16,17]

Limiting factors	Additional labeling statement, where relevant
FPPs that cannot tolerate refrigeration	"Do not refrigerate or freeze"
FPPs that cannot tolerate freezing	"Do not freeze"
Light-sensitive FPPs	"Protect from light"
FPPs that cannot tolerate excessive heat, e.g. suppositories	"Store and transport not above 30 °C"
Hygroscopic FPPs	"Store in dry condition"

Table 14: Pattern of concentration-time data and pooling decision[6, 20]

Slope	Intercept	Variation Factor	Pooling
Identical	Identical	Nil	Yes
Identical	Different	Batch e.g. unequal initial drug concentrations	No
Different	Identical	Storage e.g. difference in the rate of drug loss	No
Different	Different	Interactive Forces-Both batch and storage factor	No

For determination of significance of 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 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 years. Most pharmaceutical products are characterized by only one shelf life. However, in some cases a product may have two e.g. a freeze-dried (lyophilized) protein product may have only 1 shelf life, say 2 years, for the product stored in the dry condition and a 2nd shelf life, say 2 days, for the product when it has been reconstituted with the appropriate vehicle and is ready for injection.[6,21]

Shelf life can be predicted Based on the principle of chemical kinetics demonstrated by
-Garret and Carper method
-Free and Blythe 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. And this k value is substituted in appropriate order of reaction allows the amount of decomposition after a given time. Preliminary experiments are there for necessary to determine this order.

K=Ae-Ea/RT
Log K=Log A - Ea/2.303*RT

Where,
K= rate constant
R= gas constant =1.987 cal/mole
T = absolute temperature
A = frequency factor
Ea = energy of activation
T10% = (2.303/K)*(log100/90)
T90% = (2.303/K)*(log100/10)

Garret and Carper method)
1. Keep several samples of the drug product at at least three temperatures, such as **40ºC, 50 ºC and 60ºC.**

2. Determine the **drug content at all three storage points** by taking a number of samples and take 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 10-3 on X axis** and draw a best fit line. This line is the Arrhenius Plot, **extrapolate** this line to get **k at 25 ºC** and from this we calculate the shelf-life.[6, 20, 21]

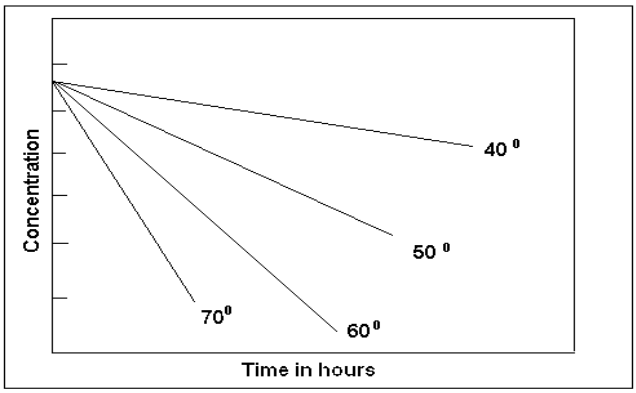

Fig.01: Arrhenius plot for predicting drug stability at room temperature.

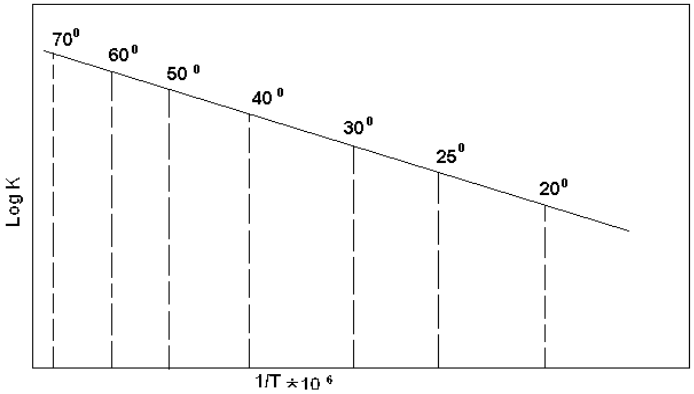

Fig.02: Arrhenius plot for predicting drug stability at room temperature.

If the reaction is following zero-order.

Expiration date at 25 ºC = Initial potency – minimum potency / reaction rate at 25 °C
tx =Yo - Yx/ Ko
If the reaction is following first order.
Expiration date at 25 oC (tx) = Log initial potency – log minimum potency/reaction rate at 25 ºc
tx =log Yo – log Yx / K1.

Where
Yo = initial potency
Yx = final potency
Ko = zero order constant
K1 = first order constant.[2,6,12]

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 you have a mean and a standard deviation value of the result.

3. NOW plot the graph of % drug content on Y axis and time on X axis along with confidence intervals. Where the lower 95% confidence curve intersects minimum potency, there you fix the shelf life.[2, 6]

CONFORMANCE PERIOD

The conformance period is determined from the intersection of the lowest (or highest) acceptable value of the stability parameter and the 95% confidence bound of the regression line. Shelf life assigned to a product is equal to, or less than, the conformance period and is usually a convenient rounded off number (e.g. 7 days, 1 month, 1 year, 18 months, or 2, 3, or 5 years). e.g. if for 3 separate pharmaceutical products we obtained conformance periods of 13.2, 26.1 and 39.4 months, we would probably assign shelf lives of 12, 24 and 36 months to the 3 products. The difference between conformance period and the assigned shelf life is that conformance period provides an extra stability reserve.[6, 15]

CURRENT TRENDS IN STABILITY TESTING

Current trend, especially amongst the multinational pharmaceutical companies, is to define conditions for stability testing for global marketing. For this the companies are orienting their protocols to single set of conditions that covers extreme environmental conditions. The specific changes for global testing include increase in duration of accelerated testing period from 6 to 12 months, and conduct of additional tests at 50°C/75% RH for 3 months .The concept behind this change is to avoid repetition of stability testing for other regions and efficient and optimum use of resources as all tests are done in one laboratory. Moreover testing under combination of three environmental factors, viz., temperature, humidity and light, has been reported to result in stronger deleterious effect on drug substances and products, than under temperature and humidity conditions only.[6, 22]

CONCLUSION

Stability testing is now the key procedural component in the pharmaceutical development program for a new drug as well as new formulation. 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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