ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Recent Trends in Stability Testing of Pharmaceutical Products: A Review.

Parkar Bhagyashree*[1], Ghude Karishma[1], Acharekar Sampada[1], Pandit Ankita[1] Chandankar Pratibha[2], Vilegave Kailash[3].

[1]Shivajirao S. Jondhale College of Pharmacy, Asangaon, (Shahapur) 421601, Maharashtra, India.
[2]Department of Chemistry, S.S.Jondhale College of Polytechnic, Asangaon 421601, Maharashtra, India.
[3]Research Scholar, JJT University, Chudela 333053, Rajasthan, India.

ABSTRACT

A stability study is a routine procedure which ensures the maintenance of pharmaceutical product safety quality and efficacy throughout the shelf life. Stability studies at a developmental stage provides a data base that may be of value in selection adequate formulation to determine shelf life, container closure system and storage conditions for development of new product. In a stability study, the effects of variation in temperature, time, humidity, light intensity and partial vapor pressure on the pharmaceutical product are investigated. These pharmaceutical products are followed by the guidelines issued by International Conference on Harmonization (ICH), World Health Organization (WHO) or other agencies. This review presents the importance of stability testing for any pharmaceutical product. An important point in conducting stability studies are storage conditions which are derived from real climatic conditions. As stability study is tool in cGMP, indirectly to attribute quality product which will increase reputability of company in global market. In this review work we traced the point on recent trends in stability study, recent guidelines, climatic zones, sampling time and plan, estimation of self life, and some stability specifications for pharmaceutical products mentioned.

Keywords: Stability study; Current Good Manufacturing Practices (cGMP); World Health Organization (WHO); International Conference on Harmonization (ICH).

Corresponding author

INTRODUCTION [1]

"The capability of a particular formulation in a specific container/closed system, to remain within its physical, chemical, microbiological, therapeutic, and toxicological specifications throughout its shelf life" is stability. "Stability is official defined as "the time lapse during which the drug product retains the same properties & characters that is processed at the time of manufacture. Stability testing evaluates the effects of environmental factors on the quality of the drug substance or a formulated product which is utilized for prediction of its shelf life, determine storage and labeling instructions. In a stability study, the effects of variation in temperature, time, humidity, light intensity and partial vapor pressure on the pharmaceutical product are investigated.

In current good manufacturing practices (cGMP) the word "current" refers to the present good manufacturing practices regulations, not the past or future regulations. When conditions for production are less than those currently accepted and generally practiced by industry, the final product may be deemed to be adulterated from a regulatory perspective. cGMP standards refer to conditions under which the product is produced, not the condition of the final product. Products may be deemed to be adulterated if they are not produced in conformance with cGMP. So stability study is tool of cGMP, indirectly to attribute quality product which will increase reputability of company in global market.

Importance Of Stability Testing [2,3]

Stability testing of drugs quality assures patients well-being. It ensures the safety of pharmaceutical dosage form in concern with the patients suffering from the diseases. Stability studies at a developmental stage provides a data base that may be of value in selection adequate formulation to determine shelf life, container closure system and storage conditions for development of new product. Stability studies evaluate the appearance and physical attributes (e.g. color, caking, hardness, phase separation, re-suspendability), potency, and purity of a drug product throughout its stated shelf-life and are essential to determine the quality of a modified or repacked drug product. Stability testing should be conducted on the dosage form packaged in the container closure system proposed to be used in the clinical trial. The testing parameters will vary with different dosage forms; stability studies should include testing of those attributes of the pharmaceutical product that are susceptible to change during storage and are likely to influence quality, safety and efficacy.

TERMINOLOGY COMMONLY USED DURING STABILITY STUDIES [4]

Commitment Batch

Production Batches of a drug substance for which the stability studies are initiated or completed post approval through a commitment made in the registration application.

Drug substance

The unformulated drug substance that may produce subsequently be formulated with excipient to produce the dosage form.

Pilot Scale Batch

A batch of a drug substance manufactured by the procedure fully representative of and stimulating that to be applied to a full production scale batch.

Primary Batch

A batch of drug substance used in a formal stability study , from which stability data are submitted in a registration application for a purpose of establishing a re test period or shelf life respectively . However primary batch may be a production batch.

TYPES OF STABILITY TESTING

Commonly, four types of stability tests are employed: real-time stability tests and accelerated stability tests, retained sample stability testing, cyclic temperature stress testing.

Real-Time Stability Tests [1,5,13]

In real-time stability tests, a product is stored at recommended storage conditions and monitored for a period of time ($t_{estimation}$) Real-time tests store the product at recommended storage conditions and monitors the product until it fails the specification. Real-time stability should typically be done at 0, 3, 6, 9, 12 months on the first year, every 6 months on the second year and once every year afterwards. In accelerated stability studies, the product is stored at elevated stress conditions (such as temperature and humidity). Product will degrade below its specification, at some time, denoted $t_{(specification)}$, and we must also assure that it is less than or equal to t_{est}. The estimated value of $t_{(specification)}$can be obtained by modeling the degradation pattern. Good experimental design and practices are needed to minimize the risk of biases and reduce the amount of random error during data collection. Testing should be performed at time intervals that encompass the target shelf life and must be continued for a period after the product degrades below specification. It is also required that at least three lots of material be used in stability testing to capture lot-to-lot variation, an important source of product variability.

Accelerated Stability Tests [1, 5]

In accelerated stability testing; a product is stored at elevated stress conditions. Accelerated stability testing should at the minimum be done at 0, 3 and 6 months. Degradation at the recommended storage conditions can then be predicted by using known relationships between the acceleration factor and the degradation rate. Degradation at recommended storage conditions could be predicted based on the degradation at each stress condition and known relationships between the acceleration factor and the degradation rate. A product may be released based on accelerated stability data, but the real-time testing must be done in parallel to confirm the shelf-life prediction. Sometimes the amount of error of the predicted stability is so large that the prediction itself is not useful. Design your experiments carefully to reduce this error. It is recommended that several production lots should be stored at various acceleration levels to reduce prediction error. Increasing the number of levels is a good strategy for reducing error.

Retained sample stability testing [1,5]

This is a usual practice for every marketed product for which stability data are required. Retained sample stability testing is a usual practice for every marketed product for which stability data is required. Cyclic temperature stress testing is designed on the product knowledge to showcase likely conditions in market place storage.

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.

Cyclic temperature stress testing [1,5]

Cyclic temperature stress tests are designed on Knowledge of the product so as to mimic likely conditions in market place storage. The period of cycle mostly considered is 24 hours since the diurnal rhythm on earth is 24 hour, which the marketed pharmaceuticals are most likely to experience during storage. The minimum and maximum temperatures for the cyclic stress

Testing is recommended to be selected on a product by-product basis and considering factors like recommended storage temperatures for the product and specific chemical and physical degradation properties of the products. It is also recommended that the test should normally have 20 cycles.

Guidelines For Stability Testing [1,3]

To assure that optimally stable molecules and products are manufactured, distributed and given to the patients, the regulatory authorities in several countries have made provisions in the drug regulations for the submission of stability data by the manufacturers. Its basic purpose was to bring in uniformity in testing from manufacturer to manufacturer. These guidelines include basic issues related to stability, the stability data requirements for application dossier and the steps for their execution. Such guidelines were initially issued in 1980s. These were later harmonized (made uniform) in the International Conference on 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 European commission, Japan and USA. The World Health Organization (WHO), in 1996, modified the guidelines because the ICH guidelines did not address the extreme climatic conditions found in many countries and it only covered new drug substances and products and not the already established products that were in circulation in the WHO umbrella countries. In June 1997, US FDA also issued a guidance document entitled 'Expiration dating of solid oral dosage form containing Iron. WHO, in 2004, also released guidelines for stability studies in global environment (WHO, 2004). ICH guidelines were also extended later for veterinary products. A technical monograph on stability testing of drug substances and products existing in India has also been released by India Drug Manufacturers Association. Further, different test condition and requirements have been given in the guidance documents for active pharmaceutical ingredients, drug products or formulations and excipient. The codes and titles covered under ICH guidance have been outlined in the. **Table. 1**

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

Climatic Zones for Stability Testing [11]

Countries Belonging To Various Stability Zones described in **Figure.1, Table. 3 and Table. 4**

Selection of Batches [4, 6, 2, 12]

Data from formal stability studies should be provided on at least three primary batches of the drug substances. The batches should be manufactured to a minimum of pilot scale by the same synthetic route as and using a method of manufacture and procedure that stimulates the final process to be used for production batches. The overall quality of the batches of drug substance placed on formal stability studies should be representative of the quality of the material to be made on a production scale. At the time of submission, stability data should be provided for batches of the same formulation and dosage form in the container closure system proposed for marketing.

Following points are to be considered during submission of the information in the registration dossier to the International Regulatory Agencies

- Data from 3 primary batches required (Batch number, date of manufacturing and size of each batch should be stated)
- Primary batches could be from pilot/plant scale
- Plant/Pilot batches should be similar (process, equipment, route should be similar)

Container Closure System [1, 2, 6, 14,]

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

include secondary packs, but not shippers. Products in all different types of containers/closures, whether meant for distribution or for physician and promotional samples, are to be tested separately. Any available studies carried out on the medicinal product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively. However, for bulk containers, testing in proto type containers is allowed, if it simulates the actual packaging.

Orientation of storage of containers

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

Sampling time points [1]

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

In case the same product of different strengths, multiple sizes, etc. is required to be tested, reduced stability testing plans can be worked out, which involves less number of test points. The reduced testing plans are based on bracketing and Matrixing statistical designs. Bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all-time points as in a full design. On the other hand, Matrixing involves testing of a subset of the total number of possible samples for all combinations at a specific time point. Subsequently, another subset of samples for all factor combinations is tested. The factors that can be matrixed include batches, strengths with identical formulation, container sizes, fill sizes, and intermediate time points. Test Schedule for stability testing of new products is described in **Table. 5**

Sampling Plan [1]

Sampling plan for stability testing involves, planning for the number of samples to be charged to the stability chambers and sampling out of the charged batch so as to cover the entire study. The first step should be the development of the sampling time points followed by the number of samples needed to be drawn at each pull point for complete evaluation of all test parameters and finally adding up to get the total number of samples. For example there would be a requirement of about 100 tablets per pull out in a long term or accelerated stability studies including 10 each for assay, hardness and moisture determination, 6 each for dissolution and disintegration and 50 for friability. This multiplied by the total number of pull outs will give the total number of tablets required for a study. This is followed by the development of a sampling plan, which includes the selection of the containers representing the batch as a whole but in an unbiased manner. A stratification plan has been suggested whereby from a random starting point every *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 [1,5]

The stability package should be stored under the specified storage conditions as defined in the protocol, or the conditions found in the manufacturers warehouse. The stability study should be conducted over the longest period of time that the excipient supplier warrants the product will continue to conform to the specification in the commercial package using the recommended normal warehousing or specified storage

conditions. Extrapolation of data from these stability studies to justify a warranty period in excess of the duration of the stability study should be scientifically justified.

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 are described in: **Table. 6**

Test Parameters [5]

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

Estimation of Shelf Life, Expiry date [7]

The time period during which an Active Pharmaceutical Ingredient (API) or a Finished Pharmaceutical Product (FPP) is expected to remain within the approved shelf-life specification, provided that it is stored under the conditions defined on the container label. After recording the data, the final step is the estimation of shelf life or expiry date.

The guidelines suggest an approach, which is different from the conventional approach of stability testing

Conventionally

- Multi- temperature accelerated studies
- Arrhenius approaches were used for estimation of shelf life, but there are several drawbacks in Arrhenius approach.

a. It applicable only for cases where drug degradation is reasonable and rate or order of reaction can be determined.
b. In this approach, linear regression is applied even though the data is not linear.
c. Errors associated with determination of drug content are not included.

Above critical temp degradation mechanism may change and in this case also Arrhenius approach becomes invalid

$$\mathbf{K = Se^{-Ha}/RT} \quad \text{.....} \quad \mathbf{(1)}$$

Where, K= Specific rate of degradation

R = gas constant (1.987 calories degree mole)
T = absolute temperature
S = Frequency factor

By integrating Arrhenius equation……..

$$\mathbf{In\ k = -\frac{\Delta Ha}{RT} + In\ S} \quad \text{.....} \quad \mathbf{(2)}$$

Converting To $\log_{10}$

$$\log k = \frac{\Delta Ha}{2.303}\frac{1}{T} + \log s \quad \text{..... (3)}$$

From equation (c) a plot of log k verses 1/T Yields a slope equal to

$\frac{-\Delta Ha}{2.303R}$ From which the value for the heat of activation can be calculated.

The Heat Of activation (ΔHa) represents the energy the reacting molecule must acquire to undergo reaction shown in **Figure 2**

So due to the drawbacks in Arrhenius approach the ICH, CGMP and Food Drug Administration (FDA) guideline suggest 'shelf life determination should be based on real time testing data rough application of appropriate statistical technique. Some types of stability and conditions maintained during shelf life of the product is shown in the **Table 8**

Re-Test Period [7, 16]

The period of time during which the drug substance is expected to remain within its specification therefore, can be used in the manufacture of given product. Provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be re-tested for compliance with the specification and then used immediately

Conformance Period [1, 8]

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 extractability reservoir.

Stability Specification [4]

Specification (Release specification)

In this specification of stability include Physical, chemical and biological& acceptance criteria that determine the suitability of drug product at the time of its release.

Specification (stability specification)

This specification used to determine suitability of a drug substance throughout its re-test period, or shelf life of product described in .**Table. 9**

Photo-Stability Testing [9, 10, 12]

Photostability testing should be conducted on at least one primary batch of the drug product if appropriate. Proof that the products do not or not significantly change within a certain period of use must, among other things, is provided through the photo-stability test with light. For this purpose, binder offers the complete solution on the market - the KBF with standard equipment of ICH-conforming lighting. (Series KBF 720, with 700 l inner chamber volume).The stability cabinet is shown in **Figure 3.**

The special international ICH guideline Q1B was created for proving photo-stability. Since the fulfillment of this guideline must now mandatorily be documented by the authorities without exception, pharmaceutical companies are faced by new challenges in this regard in their test practices. For the new photo-stability tests, samples must be exposed to a light amount of 1.2 million Lux x hours, as well as UV radiation of 200 Watt x hours /m^2, in climatic chambers with ICH lighting.

But what is the most objective method of proving these light values? The fundamental prerequisite for reliable recording is the integration and display of the light values on the regulator, as in the binder KBF series with ICH lighting. This includes the automatic shutoff of the lamps (VIS and UV separately) when the freely selectable dosage values are reached. Reliable recording of the light amounts is provided at binder with Light Quantum Control, two spherical light sensors which, due to their direction-independent characteristics, function more precisely than planar sensors.

However, the following should be decisive for the testing authorities: binder chambers possess APT-COM™ Data Control System software and therefore, excellent options for documenting the test conditions in every phase. The information from the light sensors flows into this system, providing optimal proof.

Products [17]

The primary objective of this study is investigation and identification of stable storage condition for drug in the solid state and identification of compatible excipient for a formulation.

Studies on drug products carried out in a sequential manner of testing the fully exposed product then processing as necessary to the product in the immediate pack and then in the marketing pack. After the testing the drug product should be adequately protected from the exposure to light. The product should be exposed to the light conditions described under the procedure in section I.C.

To confirmed the Photostability characteristic of the product as described in the parent guidelines, only one batch of product is tested during the development phase and state that if the product is photostable or photolabile.

The testing should normally only be conducted on directly exposed drug products. It may be appropriate to taste certain products such as infusion, liquids,dermal creams etc. to support their Photostability in use

Recent Trends in stability testing [1]

Current trend in multifunctional pharmaceutical companies are to define condition for stability testing for global marketing. For this companies are creating their protocols to single set of conditions that covers extreme environmental condition. The specific changes for global testing includes increase in duration of accelerated testing period from 6-12 months and conduct of additional tests at 50^0c/75% RH for 3 months (mischler et al 2004).It avoids the repetition of stability testing for the region and efficient optimum use of resources as all tests are done in one laboratory testing under combination of 3 environmental factors vise, temperature, humidity and light has been reported to result in stronger deleterious effect on drug substances and products than humidity condition only

Table 1: Codes and titles used in ICH Guidelines

ICH CODE	GUIDELINE TITLE
Q. I (A)	Stability testing of new drug substances and products(second revision)
Q,I (B)	Stability testing : Photostability testing of new drug substances and products
Q.I (C)	Stability testing of new dosage forms
Q.I (D)	Bracketing & Matrixing Designs for stability testing of Drug Substances & Products
Q I.(E)	Evaluation of stability data
Q I.(F)	Stability data package for registration application in climatic zones III &IV
Q 5.(C)	Stability testing of Biotechnological/Biological Products

Table 2: CGMP Guidelines for stability

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

Table 3: FOR ZONE I &ZONE II

PRODUCT	TYPE OF STUDY		
	Accelerated	Intermediate	Long Term
	40^0 C/75%RH	30 ^{0}C /60% RH	25^0C /69% RH
Liquid in glass bottles, vials, scaled glass ampules, which provide an impermeable barrier to water loss.	40^0C/ ambient humidity	30 ^{0} C / ambient humidity	25 ^{0} C/ambient humidity
Drug products in semi permeable containers	40^0 C/15%RH	30^0 C/40%RH	25^0 C/40%RH
Drug product intended to be stored at refrigerator temperature	25^0 C/60% RH or 25 C /ambient humidity for liquid products		5+3 ^{0} C with monitoring but not control of humidity
Drug products intended to be stored at freezer temperature	5 + 3 ^{0}C/ ambient humidity		- 15+ 5 ^{0} C

Table 4: Zone III and IV

PRODUCTS	TYPES OF STUDY	
	Accelerated	Long Term
Solid oral dosage form, for reconstitution. Dry & lyophilized powder in glass vials	40^0 C/75%RH	30^0 C & 30^0 C/70% RH
Liquid in glass bottles, vials, scaled glass ampules , which provide an impermeable barrier to water loss	40^0 C/ ambient humidity	
Drug products in semi permeable containers	40^0 C/15%RH	30^0 C/40%RH
Drug product intended to be stored at refrigerator temperature	25^0 C & 35^0 C/75% RH or 30 C /ambient humidity for liquid products	5+3^0 C with monitoring but not control of humidity
Drug products intended to be stored at freezer temperature	5 + 3^0 C/ ambient humidity	-15+ 5^0 C

Table 5: Test Schedule for stability testing of new products

Environment	Sampling Time Points(months)	Method & Climatic Zone
25^oc/60%RH	3, 6, 9, 12, 18, 24, 36	Long term for zones I and IV
30^oC/35%RH	3, 6, 9, 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 IV a, or intermediate condition for zones I and II
40°C/75% RH	3,6	Accelerated condition for all zones

Table 6: Recommended stability storage conditions for various products in Zone I-IV

Product	Zone	Accelerated	Intermediate	Long-term
Solid oral dosage forms, solids for reconstitution, dry and lyophilized powders in glass vials	Zone I/II Zone III/IV	40^0C/75% RH 40^0 C/75% RH	30^0 C/65% RH ----------	25^0 C/60% RH 30^0 C/65% RH
Liquids in glass bottles, vials , or sealed glass ampoules , which provide an impermeable barrier to water loss	Zone I/II Zone III/IV	40^0C/ambient humidity 40^0C/ambient humidity	30^0 C/ambient Humidity ----------	25^0 C/ambient Humidity 30^0 C/ambient Humidity
Drug products in semi permeable and permeable containers, large volume parenteral (LVPs), small volume parenteral(SVPs), ophthalmic, optics, and nasal sprays packaged in semi permeable containers, such as plastic bags, semi rigid plastic containers, ampoules, vials and bottles with or without droppers/ applicators, which may be susceptible to water loss	Zone I/II Zone III/IV	40^0 C/NMT25%RH 40^0C/NMT 25%RH		25^0 C/40% RH 25^0 C/40% RH
Drug products intended to be stored at refrigerator temperature	Zone I/II Zone III/IV	25^0 C/60% RH or 25^0C/ambient humidity for liquid products 25°C/60% RH or 30 °C /65%RH,whichever is available 25°C/ambient humidity or 30°C /ambient humidity for liquid products , whichever is available		5^0 C ±3^0 C with monitoring but not control of humidity
Stability storage conditions for drug products intended to be stored at freezer temperature	Zone I-IV	5^0 C ±3^0 C ambient Humidity		-20^0 C ±5^0 C

Table 7: Some dosage forms and their physical parameters

Dosage form	Physical parameters
1.Solutions	a) Change of color b) Change of odor c) Clarity d) Appearance(precipitate, cloudiness) e) pH
2. Suspensions	a) Appearance (precipitate, cloudiness) b) pH c) Color , odor d) Redispersibility
3. Tablets	a) Appearance b) Friability c) Hardness d) Color , odour e) Dissolution f) Moisture absorption

4. Hard gelatin capsule	a) Moisture b) Color c) brittleness d) Appearance(shape) e) pH f) Dissolution
5. Soft gelatin capsule	a) Moisture b) Color c) Brittleness d) Appearance(shape) e) pH f) Dissolution g) Precipitate h) Cloudiness
6. Emulsions	a) Moisture b) Color, odor. c) Cloudiness d) Appearance(phase separation) e) pH f) Precipitate
7. Creams & ointments	a) Moisture b) Color & odor c) brittleness d) Appearance & clarity e) Homogenicity f) pH g) Resuspendibility (for lotions) h) Consistency (viscosity) i) Weight loss (plastic containers) j) Particle size

Table No 8: Types of stability and conditions maintained during shelf life of product

Types of stability	Conditions maintained during the shelf life of the product
Chemical	Retains its chemical Integrity& labeled potency
Physical	Appearance(palatability, uniformity ,dissolution,& suspendability)
Microbiological	Retain sterility effectiveness of antimicrobial agents
Therapeutic	Drug action remains unchanged.

Table 9: Stabilty Specification

SR NO	Sample Withdrawal Day	Date Of Analysis	%potency retained(Mean SD) 5C 25C/ 60% 30C/ 60% 40C/ 70% 50C ambient floure- scent xenon light UV light Humidity
1	0th day (initial)		
2	30th day(1 month)		
3	60th day(2 month)		
4	90th day(3 month)		
5	180th day(6 month)		

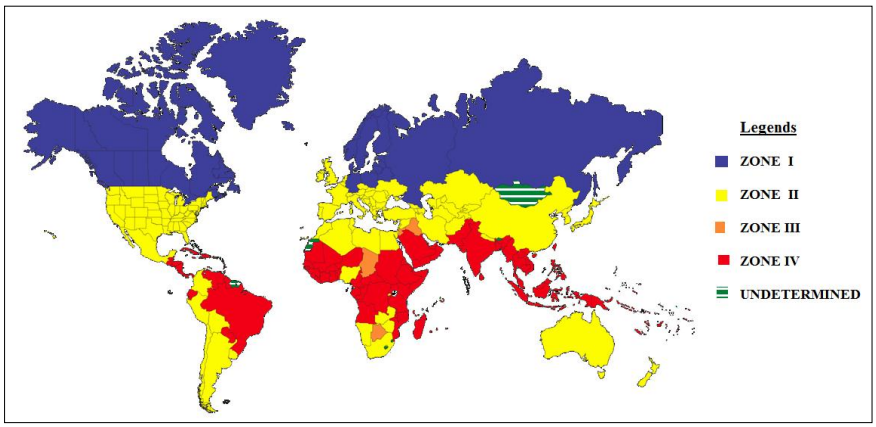

Figure 1: World View Of Climatic Zone Determination By Country

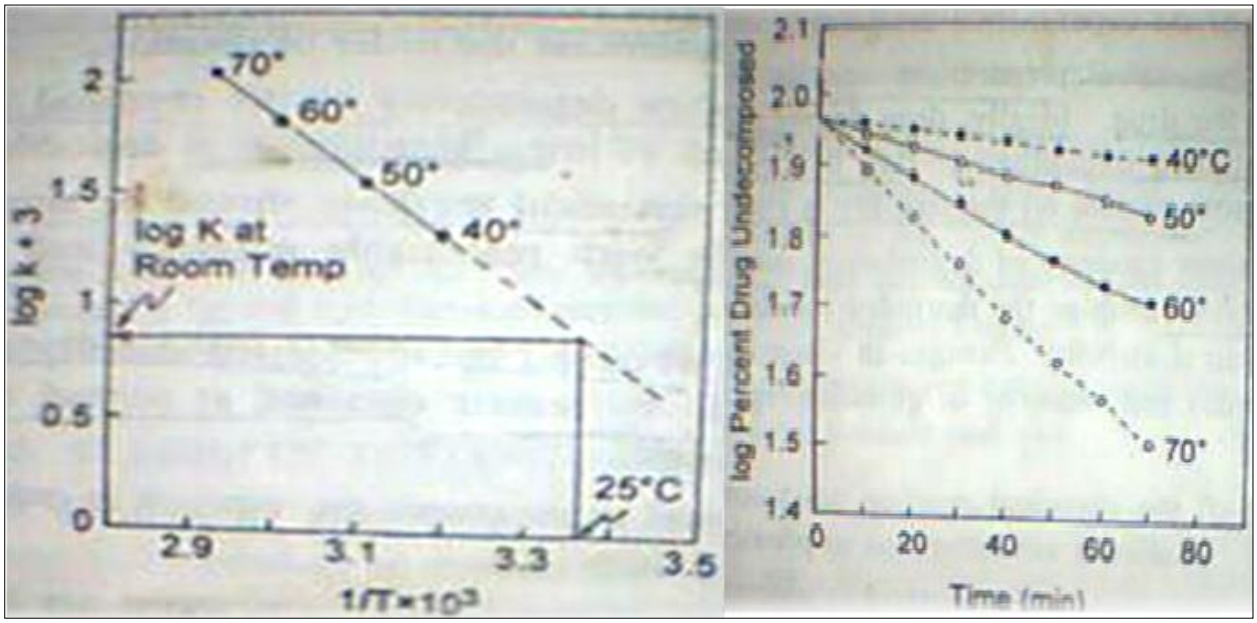

Figure 2: Estimation of shelf life and expiry date

Figure 2: Estimation of shelf life and expiry date

CONCLUSION

For new drug and new formulation stability testing is important aspect of pharmaceutical development program which is important component of it. Stability testing provides the information about storage and shelf life about the medicines, which ensures that the medicine is safe and effective throughout its shelf life and patient gets assurance cause of it. 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 this stability testing should carry out in proper manner by following scientific principles, keeping current requirements in mind and climatic zone.

REFERENCES

[1] Sanjay Bajaj. J App Pharm Sci 2012;2(3):129-138.
[2] The GCC Guidelines for Stability Testing of Drug Substances and Pharmaceutical Products, EDITION TWO ,1428 H –2007 G
[3] Ajay Malik ,Vipin Kumar,Renu,Sunil,Tarun Kumar. J Chem Pharm Res 2011;3(2):892-898.
[4] Agraval Vipul, Sharma Devesh. J Pharm Sci Innov 2012;1(2); 18-23

[5] Maninderjit Kaur, Gurpreet Kaur, Harpreet Kaur,Saurav Sharma, Overview on stability studies Institute of Pharmaceutical Sciences, District . Jalandhar, Punjab, India.
[6] Annex 2, Stability testing of active pharmaceutical ingredients and finished pharmaceutical products, © World Health Organization, WHO Technical Report Series, No. 953, 2009
[7] (http://www.authorstream.com/Presentation/kailashvilegave-1414382-preformulation-and-production-managment-by-kailash-vilegave/)
[8] (http://books.google.co.in/books?id=lK5QzB4w9QwC&pg=PA49&lpg=PA49&dq=Carstensen+JT.+Drug+Stability,+Principles+and+Practices,+Marcel+++Dekker,+New+York+(2000)&source=bl&ots=hO1adE_-rf&sig=aetZit0BpCtHtt9cBtZG5aT11eg&hl=en&sa=X&ei=1vpEVOiRI4SnmwXGqoDgBQ&ved=0CDoQ6AEwBA#v=onepage&q=Carstensen%20JT.%20Drug%20Stability%2C%20Principles%20and%20Practices%2C%20Marcel%20%20%20Dekker%2C%20New%20York%20(2000)&f=false)
[9] http://www.pharmaceutical-int.com/article/pharmaceutical-stability-testing-in-climatic-cabinets.html
[10] http://www.pharmaceutical-int.com/article/cabinets-stability-testing.html
[11] Kathy Waddle MS, Wei Pan,Phd RAC,Stability studies in Pharmaceutical Development Catelent Pharma Solution
[12] Asean Guideline on stability study of drug,Version 6.0,Update Version May 2013
[13] American Pharmaceutical Association J Pharm Sci 2002;91: 893-899.
[14] SADC GUIDELINE FOR STABILITY TESTING ,2004
[15] CPMP. Guideline on stability testing:Stability testing of existing active substances and related finished products. CPMP/QWP/122/02, 2003.
[16] ICH Q1A (R2). Stability testing guidelines: Stability testing of new drug substances and products. ICH Steering Committee, 2003
[17] ICH HARMONISED TRIPARTITE GUIDELINE, Stability testing, Photostability testing of new drug substances and products Q1B