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AN OUTLINE: STABILITY INVESTIGATION ON NEW DRUG PRODUCTS

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ABSTRACT

The pharmaceutical product's stability can be explained as the ability, within its physical, chemical, microbiological, toxicology, protective, and informational requirements of a particular formulation in a specific container-closure system. Stability studies ensuring the maintenance of product quality, safety, and efficacy throughout the shelf life are considered prerequisites for the acceptance and approval of any pharmaceutical product. These studies must be conducted in a planned way following the guidelines issued by ICH, WHO, and or other agencies. The stability studies of pharmaceutical products are one of the very important parameters for the growth of new drugs and new formulations. Guidelines provide for stability testing and other detail related to the stability of pharmaceutical products have been presented concisely in the present review.

KEYWORDS

Stability, Types of stability studies, Stability guidelines and Stability testing.

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INTRODUCTION

Stability testing of pharmaceutical products is a complex set of procedures require substantial cost, time consumption, and scientific expertise to build in quality, efficacy, and safety in a drug formulation. The most valuable steps during the developmental stages include pharmaceutical analysis and stability studies to determine and assure the identity, potency, and purity of ingredients and those of the formulated product[1]. The stability of pharmaceutical ingredients and the products containing them depends on (a) the chemical and physical properties of the materials concerned and (b) environmental factors such as temperature, humidity, and light and their effect on

the substances in the product[2]. The United States pharmacopeia defines the stability of the pharmaceutical product as an "extension within certain limits" and uses the same characteristics and attributes as it had when its products were made. Any alteration that occurs after its preparation in a pharmaceutical product that adversely affects a patient's fitness for use in its quality is of interest in the stability screening of pharmaceutical researchers and regulators[3]. For the stability of pharmaceutical products, it is essential to consider the totality of the product drug-excipients, pack, and label. All of these elements can play an important role in using the drug delivery system[4]. The stability of a pharmaceutical product can also be affected because of microbiological changes like the growth of microorganisms in non-sterile products and changes in preservative efficacy[5].

FACTORS AFFECTING DRUG STABILITY[6]

Temperature

The stability of a drug substance is affected by changes in temperature; when the temperature is increased, it causes an increase in the hydrolysis rate of drugs.

Moisture

Some physical and chemical dosage changes when the water-soluble solid dose is absorbed into any moisture surface and therefore loses its properties.

pH

The deterioration rate of hydrolysed solution drugs is influenced by pH and reduces the effective drugs formulated using buffers at the pH of optimum stability.

Excipients

Starch and povidone excipients have greater water content and affect stability by enhancing water content formulations. Furthermore, there are chemical interactions between excipients and drugs that lead to a reduction of instability.

Light

When exposed to light, the rate of decomposition increases. Certain drugs are photosensitive, and their stability can be measured when exposed to light or stored in the dark by comparing their stability. Photosensitive medicines must be packed in a glass amber bottle and held in a dark place.

TYPES OF STABILITY STUDIES[7]

Physical Stability

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

Chemical Stability

Each active ingredient retains its chemical integrity and is labeled potency within the specified limits. A drug's chemical stability is of great importance since it becomes less effective as it undergoes degradation. Also, drug decomposition may yield toxic by-products harmful to the patient.

Microbiological Stability

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

Therapeutic Stability

The therapeutic effect remains unchanged.

Toxicological Stability

No significant increase in toxicity occurs.

Other types of stability studies are given in (Table No.1).

CLIMATIC ZONE FOR STABILITY TESTING[8-10]

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 based on these regions' mean annual temperature and relative humidity data. Based upon this data, long-term or real-time stability testing conditions and accelerated stability testing conditions have been derived (Table No.2).

GUIDELINES FOR STABILITY TESTING[11-13]

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 to submit stability data by the manufacturers. Its basic purpose was to bring uniformity in testing from manufacturer to manufacturer. These guidelines include basic issues related to stability, the stability data requirements for the application dossier, and the steps for their execution. They have initially issued such guidelines in the 1980s. These were later harmonized (made uniform) in the International Council for Harmonization (ICH) to overcome the bottleneck to market and register the products in other countries. The ICH was established in 1991. It was a consortium formed with inputs from both regulatory and industry from the European Commission, Japan, and the USA. Various guidelines for drug substance and drug products came into existence regarding their quality, safety, and efficacy. These guidelines are called quality, safety, efficacy and multi-disciplinary (also called Q, S, E, and M) guidelines. 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. It only covered new drug substances and products and not the already established products in circulation in the WHO umbrella countries. In June 1997, the United States Food and Drug Administration (US FDA) also issued a guidance document entitled 'Expiration dating of a solid oral dosage form containing Iron. WHO, in 2004, also released guidelines for stability studies in the global environment7. 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 Association8 Further, different test conditions and requirements have been given in the guidance documents for active pharmaceutical ingredients, drug products or formulations, and excipients. The codes and titles covered under ICH guidance have been outlined in the (Table No.3 and Table No.4).

A 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 (EMEA) to assist those seeking marketing authorization for medicinal products in European Union.2 These are listed in (Table No.5).

STABILITY TESTING METHOD[14,15]

Stability testing is a routine procedure performed on drug substances and products and is employed at various stages of product development. In the early stages, accelerated stability testing (at relatively high temperatures and humidity) determines the degradation products that may find after long-term storage. Testing under less meticulous 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. Depending upon the aim and steps followed, stability testing procedures have been classified into the following four types:

Real Time stability testing

Real-time stability testing is normally performed for a long duration to allow significant degradation of the product under the recommended storage conditions. The period for the test of the product depends on the stability of the product, which tells that the product is not degraded or decomposed for a long time from inter-assay variation. Testing the samples are collected at regular intervals such that the data is collected at the appropriate frequency such that the analyst can distinguish the degradation day-today. The data can be increased by including the single batch of reference material for which stability characteristics have been established. The reagents and the instruments used should be consistent throughout the stability testing. The control of drift and discontinuity results in the changes of both reagents and instruments should be monitored[16].

Accelerated Stability Testing

Accelerated stability testing refers to methods that may estimate product stability by-product storage under conditions that accelerate degradation, commonly by increasing temperature. Stress conditions that accelerate change fall under the general headings of temperature, light, moisture, agitation, gravity, pH, packaging, and method of manufacture. The accelerated method is often used to provide an early indication of product shelf life and shorten the development schedule[17]. This may permit, in some circumstances, the prediction of the stability of the product at ordinary shelf temperature from data obtained by stress testing. A reasonable statistical treatment in accelerated stability projections based on the Arrhenius equation normally requires that at least four stress temperatures be used. Many accelerated stability testing models are based on the Arrhenius equation[18].

$k = Ae^{-Ea/RT}$

K is a rate constant at temperature T (in degrees Kelvin), Ea is the activation energy, and R is the gas constant. This equation describes the relationship between storage temperature and degradation rate. The Arrhenius equation permits a projection of stability from the degradation rates observed at high temperatures for some degradation processes.

Retained sample stability testing

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 product knowledge to showcase likely conditions in marketplace storage. This study selected stability samples for retained storage for at least one batch a year. 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.

Cyclic temperature stress testing

Cyclic temperature stress tests are designed on Knowledge of the product to mimic likely conditions in marketplace storage. The period of cycle mostly considered is 24 hours since the daily rhythm on earth is 24 hours, 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[19].

PROTOCOL FOR STABILITY TESTING

The stability testing protocol is a requirement for preliminary stability testing. It is a written document that portrays the necessary part of stability studies, like tests to be performed and a planned testing schedule. The protocol is required for batches of clinical, formulation development, registration, and marketed product to develop a stability profile of the product. The protocol depends on types of dosage form and proposed container closure system. As well as protocol depends on the drugs formulated newly or is already is in the market. The protocol should also include the regions where the medicine is planned to be marketed proposed by ICH, namely climatic zones I-IV and extreme tropical zones[20].

A well-designed stability study protocol should include the following information

Number of batches

For batches at developmental stages, for registration of novel product or unstable established product, for stable and well-established batches only single batch, 1st three production batches and even two batches are subjected to stability studies respectively. If not submitted in the original drug

application, the first three batches of drug product manufactured post-approval should be set on long-term studies using the identical protocol as in the approved drug application.

Containers and closures

The selection of containers and closure is crucial, and stability studies are done in an immediate containers-closures system intended for marketing. The packaging materials include aluminium strip packs, blister packs, HDPE bottles, etc., including secondary packs except for shippers. Products in all different containers/closures, whether for distribution or physician and promotional samples, must be tested separately. If bulk containers stimulate the actual packaging, testing in prototype containers is acceptable.

The orientation of storage of containers

To permit the product's full interaction with the container closure, samples of liquid or semisolid form like a solution, suspension, emulsion, etc., are kept upright and placed either inverted or tilted. This orientation helps to know when the drug comes in contact with the containers and the closure consequences in leaching chemical substances from the closure components or adsorption of product components into the container-closure system.

Testing time points

Testing frequency should be enough to establish the stability profile of the drug product where the testing point interval at the long-term storage condition should be each three months over the 1st year, every six months over the 2nd year, and yearly after that throughout the estimated expiration date. But for the accelerated storage conditions, at least 3 testing points, including the initial and ending points. The test program has been presented for stability studies of new products in (Table No.6).

Test parameters

The stability testing protocol is a subset of product specifications, consisting of a list of tests similar to product specifications. Some tests are not required to be repetitive during stability testing. Those tests are requisite at the period of product release different physical parameters for different dosages from (Table No.7).

Test storage conditions

Stability studies on the finished product should provide adequate information on storage, subsequent use, and reconstitution or dilution of the product, if appropriate. The expiration date on labelling is based on the storage condition at which long-term testing is conducted. The storage condition is selected based on the climatic zones where the product is anticipated to be marketed or proposed to be filed for regulatory acceptance. The storage condition recommended by ICH and WHO are given in (Table No.8).

"Specified degradation products" defines those degradation products included in the specification of product with specific acceptance criteria where it can be identified or unidentified. Specified identified degradation products should be included along with specified unidentified degradation products estimated to be present at a level greater than (>) the identification threshold given in (Table No.9).

IMPURITIES IN NEW DRUG PRODUCTS

As per ICH Q3B guidelines, the impurities present in new drug products are also referred to as degradation products of the drug substances or reaction products with an excipient and immediate container closure system. It is unnecessary to monitor and specify in new drug products those impurities present in the new drug substance unless they are also degradation products. Degradation might occur during manufacturing and stability studies of the drug product.

EXPIRATION DATE OR SHELF LIFE

Every drug product bears an expiration date on its label, which clearly states the time where the product remains stable and can be dispensed when stored under the manufacturer’s recommended storage condition. To ensure the product's stability to the labeled expiration date, strict adherence to the instructed storage requirement is necessary. Thus, the expiration date mentioned in the label applies

when these products are stored only as per requirement set by the manufacturer until it is dispensed to the consumer.

ESTIMATION OF SHELF LIFE

Based on real-time testing

The data obtained from the studies of long-term storage condition is used for the determination of shelf life**.**

Based on accelerated testing

Shelf life can be predicted based on the principle of chemical kinetics. In this method, the determination of shelf-life is carried out by the Arrhenius plot.

CURRENT TRENDS IN STABILITY TESTING

The Current trends in stability studies characterize the environment for stability testing for worldwide marketing, especially amongst the multinational pharmaceutical industries. To comply with this and establish a single set of conditions covering extreme environmental conditions, the pharmaceutical industries are orienting their protocols.

Extending the accelerated testing period from six to twelve months and conducting further tests at 50°C/75% RH for three months are some examples of specific changes for global testing. An amalgamation of 3 environmental factors mainly causes drug product degradation, viz., temperature, humidity, and light, rather than temperature and humidity conditions only[21].

Table No.1: Types of stability studies

S.No	Study Type	Storage condition	Minimum time period covered by data at submission
1	Long Term	25°C±2°C and 60% RH±5% RH or 30°C±2°C and 65% RH±5% RH	12 months
2	Intermediate	30°C±2°C and 65% RH±5% RH	6 months
3	Accelerated	40°C±2°C and 75% RH±5% RH	6 months

Table No.2: Climatic zone and long-term testing conditions

Climatic Zone	Climate/Definition	Major Countries/Region	MAT*/Mean annual partial water vapour pressure	Long-term testing conditions
I	Temperate	UK, Northern Europe Russia, United states	≤15°C/≤11 hPa	21°C/45% RH
II	Subtropical and Mediterranean	Japan, Southern Europe	>15–22°C/>11–18 hPa	25°C/60% RH
III	Hot and Dry	Iraq, India	>22°C/≤15 hPa	30°C/35% RH
IV a	Hot and humid	Iran, Egypt	>22°C/>15–27 hPa	30°C/65% RH
IV b	Hot and very Humid	Brazil, Singapore	>22°C/>27 hPa	0°C/75% RH

Table No.3: Codes and titles used in ICH Guidelines

S.No	ICH Code	Guideline title
1	Q1 A(R2)	Stability testing of New Drug Substances and Products
2	Q1B	Stability testing: Photo stability testing of New Drug Substances and Products
3	Q1C	Stability testing of New Dosage Forms
4	Q1D	Bracketing and Matrixing Designs for stability testing of Drug Substances and Products
5	Q1E	Evaluation of stability data
6	Q1F	Stability data package for Registration Applications in Climatic Zones III and IV
7	Q5C	Stability testing of Biotechnological/Biological Products

Table No.4: ICH Q1A summary of stability parameters

S.No	Study Type and Condition		Storage Condition	Time Period (Months)	Comments
1	General Case	Long-term	25 °C±2°C/60% RH±5% RH Or 30°C±2°C/65% RH±5% RH	12	Must cover retest or shelf life period at a minimum and includes storage, shipment and subsequent use.
		Intermediate	30°C±2°C/65% RH±5% RH	6	
		Accelerated	40°C±2°C/75% RH±5% RH	6	
2	Refrigeration	Long-term	5°C±3°C	12	Must cover retest or shelf life period at a minimum and includes storage, shipment and subsequent use.
		Accelerated	25°C±2°C/60% RH±5% RH	6	
3	Freezer	Long term	-20°C±5°C	12	Must cover shelf life period at a minimum and includes storage, shipment and subsequent use.

Table No.5: CPMP Guidelines for Stability

S.No	CPMP code	Guideline title
1	CPMP/QWP/576/96 Rev. 1	Guideline on Stability Testing for Applications for Variations to a Marketing Authorization
2	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
3	CPMP/QWP/609/96 Rev. 1	Note for guidance on Declaration of Storage Conditions for Medicinal Products Particulars and Active Substances
4	CPMP/QWP/122/02 Rev. 1	Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products
5	CPMP/QWP/072/96	Note for Guidance on Start of Shelf Life of the Finished Dosage Form
6	CPMP/QWP/2934/99	Note for Guidance for In-Use Stability Testing of Human Medicinal Products
7	CPMP/QWP/576/96	Note for Guidance on Stability Testing for a Type 2 variation to a Marketing Authorization
8	CPMP/QWP/ 159/96	Note for Guidance on Maximum Shelf-Life for Sterile Products after First Opening or Following Reconstitution

Table No.6: Test Schedule for stability testing of new products

S.No	Environment	Sampling Time Points (Months)	Method and Climatic zone
1	25°C/ 60% RH	3, 6, 9, 12, 18, 24 and annually through the proposed shelf-life	Long term for zones I and II
2	30°C/ 35% RH	3, 6, 9, 12, 18, 24 and annually through the proposed shelf-life	Long term for zones II
3	30°C/ 65% RH	3, 6, 9, 12, 18, 24 and annually through the proposed shelf-life	Long term for zone III and IVa, or intermediate condition for zones I and II
4	30°C/ 75% RH	3, 6, 9, 12, 18, 24 and annually through the proposed shelf-life	Long term for zone IVb
6	40°C/ 75% RH	3, 6	Accelerated condition for all zones

Table No.7: Physical parameter to be evaluated for new products

S.No	Dosage Form	Physical parameters
1	Solution	Change of colour, change of odour, clarity, appearance, P^H
2	Suspensions	Appearance, pH, colour, odour, re-dispersibility
3	Tablets000	Appearance, friability, hardness, colour, odour, dissolution, moisture absorption
4	Hard gelatin capsules	Moisture, colour, appearance, brittleness, dissolution, pH
5	Soft gelatine capsule	Moisture, colour, appearance, brittleness, dissolution, pH, precipitation, cloudiness
5	Emulsions	Appearance, colour, odour, pH, precipitate, cloudiness
6	Creams and ointments	Appearance, Colour, odour, homogeneity, pH, re suspensibility, weight loss, particle size
7	Microspheres/Nanoparticles	Moisture, pH, shearing, temperature, rotation, density, particle size and shape, surface charge

Table No.8: Stability studies storage conditions for drug products.

S.No	Intended Storage condition	Stability Test Method	Storage Condition			
			ICH		WHO	
			Temperature/ humidity	Period in months	Temperature/ humidity	Period in months
1	Room Temperature	Long term	25±2°C/60±5%RH or 30±2°C/65±5%RH or 30±2°C/75±5%RH	12	25±2°C/60±5% RH	12
		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
2	Refrigerated	Long term	5±3°C	12 or 6	5±3°C	12
		Accelerated	25±2°C/60±5%RH or 30 ±2°C/65±5%RH or 30 ±2°C/75±5%RH	6	25±2°C/60±5% RH	6
3	Freezer	Long term	–20 °C ± 5 °C	12 or 6	–20 °C ± 5 °C	12

Table No.9: Reporting, identification, and qualification thresholds for impurities in new drug products

S.No	Maximum daily Dose	Reporting threshold	Identification threshold	Qualification threshold
1	>2g/day	0.10%	0.10%	0.15%
2	>100mg-2g	0.10%	0.2% or 2mg Total Daily Intake (TDI), whichever is lower	0.2% or 3mg TDI, whichever is lower
3	10mg - 100mg	0.05%	0.2% or 2mg TDI, whichever is lower	0.5% or 200µg TDI, whichever is lower
4	1mg-10mg	0.05%	0.5% or 20µg TDI, whichever is lower	1.0% or 50µg TDI, whichever is lower
5	<1mg	0.05%	1.0% or 5µg TDI, whichever is lower	1.0% or 50µg TDI, whichever is lower

CONCLUSION

It is necessary that the stability testing practices all over the world be oriented towards uniformity, which can be achieved by using international guidelines. This is because of the world trade agreement and General Agreement on Tariffs and Trade (GATT). This will prove the manufacturers have the confidence to go for international marketing at the right time to change. Stability tests are carried out to include the recommended storage condition and expiration date on the label and ensure the safety and efficacy of medicine throughout its shelf life. Therefore, the stability tests should be carried out following proper scientific principles and after understanding the current regulatory provisions and climatic zones.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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