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Review Article

A REVIEW ON STABILITY TESTING GUIDELINES OF PHARMACEUTICAL PRODUCTS

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ABSTRACT

Stability studies must be carried out according to the guidelines provided by the International Conference of Harmonization, World Health Organization, and other agencies in a scheduled manner. The pharmaceutical product's stability can be defined as the ability, within its physical, chemical, microbiological, toxicology, protective, and informational requirements of a particular formulation in a specific container-closure system. It also guarantees that the performance, safety, and efficacy are maintained throughout the shelf life of any pharmaceutical product which is considered as pre-requisite for acceptance and approval. Different stability test methods have originated with the need for constant monitoring of drugs and products for their quality and purity. In this review, we have included the types of stability of drugs substances, the relevance of different methods used to test the stability of the pharmaceutical product, guidelines issued to test the stability of pharmaceuticals, stability testing protocols which describes the main components of a well-controlled and regulated stability test and other aspects of stability.

Keywords: Stability studies, International Conference of Harmonization guidelines, Pharmaceutical products, Shelf life.

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INTRODUCTION

Pharmaceutical product stability is a complex process collection that requires considerable time, expense, use, and scientific expertise to develop pharmaceutical formulation effectiveness, quality, and safety [1]. Any alteration that occurs after its preparation in a pharmaceutical product that adversely affects a patient's fitness for use in the quality of the product is of interest in the stability screening of pharmaceutical researchers and regulators [2]. The pharmaceutical stability test is defined according to the International Conference of Harmonization (ICH) guidelines as a systemic test conducted in pharmaceutical products to demonstrate that drug quality is subject to various environmental factors such as temperature, humidity, and light for setting a drug test period or a pharmaceuticals shelf life and to recommend a good storage condition [3]. The USP defines the stability of the pharmaceutical product as "extension within certain limits" and uses the same characteristics and attributes as it had when its products were made [4]. The stability of active drugs and formulation is determined at an early phase of the drug development process [5]. The identity, strength, and pureness of components, as well as the stability and pharmaceutical analysis of manufactured products, are essential in determining and ensuring product quality [6]. The stability of chemical products plays an essential role in reactions to chemical degradation such as oxidation, reduction, hydrolysis, and racemization. The pharmaceutical product stability also influences factors such as the concentration of reactants, pH, radiation, catalysts, raw materials, and the period between development and use of the product. Physical changes due to impacts, abrasion and temperature fluctuations such as freezing or shearing can also impact drug stability, leading to the loss of the active pharmaceutical components [7]. Forced degradation, including degradation of drug products and drug substances under conditions greater than accelerated conditions, assess the stability of the molecules and therefore produce degradation products [8]. A pharmaceutical product stability test is designed to ensure the effectiveness, safety, and quality of the active drug substances and dose type and to assess shelf life or date of expiration to support branded claims [9]. Studies on stability must be carefully performed in compliance with legislation regulated by ICH, World Health Organization (WHO), and similar bodies [10].

Importance of stability testing [11-16]

1. Determining conditions of shelf life and processing for the development of new goods
2. Toxic products may be formed during the decomposition of active drugs
3. Ensuring that the brand is fit for use as long as they are in the market with all functionally acceptable attributes to protect the manufacturer's reputation
4. To ensure that no modifications in the production or formulation method have been implemented that can negatively impact product stability
5. It offers a database that can be of value for current product growth when choosing excipients, formulations, and closure schemes for containers
6. Developing an understanding of API's degradation that can affect the quality of the pharmaceutical product
7. It is the only way to assures whether the drug is within the acceptance criteria or not.

Factors affecting drug stability [17-19]

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 hydrolyzed solution drugs is influenced by pH and reduces the effective drugs that are formulated using buffers at the pH of optimum stability.

Excipients

Starch and povidone excipients have greater water content and affect stability by enhancing the formulations of water content. Furthermore,

there are chemical interactions between excipients and drugs that lead to a reduction of instability.

Oxygen

Oxygen presence facilitates oxidation in some products. Products with a higher decomposition rate are stabilized when exposed to oxygen by substituting carbon dioxide and nitrogen for oxygen in the storage container.

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 of drug substances [20]

Physical stability

Physical stability is important for safety and efficacy as it affects drug uniformity and release rate. Physical characteristics include size, palatability, homogeneity, dissolution, and suspension.

Chemical stability

Chemical stability of drugs is less active as deterioration takes place. The chemical quality and the labeled strength of each active ingredient remain within the specific limits [11].

Microbiological stability

Antimicrobial agents retain their effect within specified limits, also sterilization or resistance to microbial growth as per the requirements stated.

Therapeutic stability

The therapeutic effect will remain unchanged.

Toxicological stability

Enhanced toxicity significantly does not occurs.

STABILITY TESTING METHOD

Stability tests are a routine operation used in the various phases of product development for drug substances and products. Early stages use accelerated stability tests to measure the type of degraded products found following long-term storage. The main objectives of the pharmaceutical stability test are to ensure that products remain on the market for the duration of their acceptable fitness or quality and are fit for consumption until the last pharmaceutical unit is used [21]. Stability testing procedures are divided into four groups.

1. Real-time stability testing
2. Accelerated stability testing
3. Retained sample stability testing
4. Cyclic temperature stress testing.

Real-time stability testing

It is conducted to allow substantial product degradation for a longer length of the trial period under storage circumstances. The test period relies on product stability which must remain sufficiently long to clearly show that no observable degradations occur and that degradation must be separated from the variability of the inter-assay. Trend analysis can differentiate instability from day-to-day ambiguity during the test by gathering information at an appropriate frequency. Reference material stability involves reagent stability and instrument quality consistency to be used during the stability studies. However, process efficiency and regulation of drift and irregularity arising from reaction and instrument modifications need to be controlled [22].

Accelerated stability testing

The quantity of heat input required for product failure is calculated when a product is stressed at various elevated temperatures (more warm than ambient). This test is performed to make the product situation more degrading. These data are intended to compare or predict the alternative formulations relative stability. It provides an early indication of the product quality and thereby shortens the development plan.

During accelerated stability testing, the stress conditions applied are humidity, heat, turbulence, weight, pH, and packaging. The samples are stressed, cooled, and then concurrently tested since the analysis period is brief and by comparing with the real-time stability testing, the probability of measurement instability is decreased. Further, unstressed product contrast with stressed material in accelerated stability testing is produced in the same test and the stressed sample recovery shall be given as an unpressured percentage of sample recovery.

For statistical purposes, treatment is suggested in accelerated stability predictions at four distinct stress levels, whereas for thermolabile and protein parts, when denaturing stress temperature is avoided relatively precise predictions of stability are achieved [23,24].

"Accelerated stability testing theory is based on Arrhenius equation 1 and modified Arrhenius equation 2:"

$$\ln K = \ln A + \frac{\Delta E}{RT}$$

Where,

K = Degradation rate/s
A = Frequency factor/s
ΔE = Activation energy (KJ/mol)
R = Universal gas constant (0.00831 KJ/mol)
T = Absolute temperature (K)
Log (k2/k1) = –Ea/2.303R (1/T2–1/T1)

Where,

k1 and k2 = Rate constants
T1 and T2 = Temperature expressed in degree kelvins
Ea = Activation energy
R = Gas constant.

These equations define the relationship between degradation rate and storage temperature. Arrhenius equation determines the stability projection of degradation rates observed for certain degradation processes at high temperatures. The rate of degradation at lower temperatures can be estimated at "stress" [25].

Retained sample stability testing

The retained sample stability test is practice for each item on the marketed for which stability information is needed. Stability samples were chosen in this research for the retained storage of one batch a year at least. It is suggested to take stability samples from two batches if the number of batches marketed reaches 50 batches.

When a product is launched in the market, stability samples of each batch may have decreased at a later stage to only 2–5% of marketed batches. If a product has a shelf life of 5 years, testing samples at 3, 6, 9, 12, 18, 24, 36, 48, and 60 months is conventional, so the stability samples are evaluated at predetermined intervals. This standard technique is known as the constant interval techniques to collect stability information on stored samples [26].

Cyclic temperature stress testing

Cyclic stress testing temperature is a very useful factor in the pharmaceutical scientist's development or troubleshooting for stability testing but not for routine product testing [3].

From the knowledge of the product, cyclic temperature stress tests are designed to mimic possible market place storage conditions. Since the diurnal cycle is 24 h on earth so, the period of cycle mostly considered is 24 h which are most likely experienced by the marketed pharmaceuticals during storage. In cyclic stress testing, minimum and maximum temperatures are recommended which have to be chosen based on the product and should consider factors such as suggested product storage temperatures and special physical and properties of chemical degradation of the product. It also suggests that there are normally 20 cycles in the test [27].

Stability testing equipment

The stability chamber is the equipment used for stability testing and is environmental specialist chambers which can stimulate storage condition and real-time stability, accelerated stability, and protocol for the long term and enables evaluation of product stability. Both reach-in styles and walk-in are accessible to the rooms. Small chambers are preferred for rapid testing because product retention time in these cabinets is much less, while long-term tests prefer walk-in chambers. Due to the need for years of continuous use, it is expected that these chambers will be reliable, robust, and equipped with appropriate recording, safety, and alarm devices. Furthermore, there are also picture stabilization chambers that can be used with and without control of temperature and moisture. In the photostability chamber, 2 types of light sources are used.

1. Cool white and near UV fluorescent tubes are combined
2. Daylight artificial lamps (e.g., metal halide or xenon).

A maximum of 1.2 million lux hours of exposure is needed. The visible light intensity and how many hours of exposure required are measured using a lux meter [6,15].

Guidelines for stability testing

In 1980, these guidelines were issued, and later the ICH harmonized (made uniform) to solve the bottleneck for marketing and registration in other nations. In the drug regulation, the regulatory authority in several nations has created regulations for the producers to submit stability information to ensure that molecules and products are generated with optimum stability, circulated, and provided to the patient. These guidelines aimed to introduce consistency in testing from supplier to supplier and also involve fundamental problems linked to stability, stability information for application dossier requirements, and implementation steps [15].

In 1991, ICH was established which was a consortium created by the European Commission, Japan, and the USA with inputs from both regulatory and business. These guidelines are referred to as guidelines for quality, safety, efficacy, and multidisciplinary (also referred to as QSEM) [27]. In 1996, these guidelines were modified by the WHO because ICH guidelines did not address the extreme climatic conditions in many nations, but only new drug substances and products were covered and not the product already in use which was circulated in the entire nations by the WHO.

In June 1997, the United States Food and Drug Administration (USFDA) also issued guidance documents entitled "Expiration dating of solid oral dosage form containing Iron." In 2004, WHO also issued guidelines for worldwide environment stability research [28,29]. These ICH guidelines for veterinary products were subsequently expanded. The Indian Drug Manufacturers Association also published a technical monograph on drug and product stability testing in India [30].

In the guidance documents, various test conditions and requirements for active pharmaceutical ingredients (APIs), drug products, or formulation and excipients have been established. The codes and titles for stability research covered by the ICH guidelines were presented in Table 1.

Q1A (R2): Stability testing of new drug substances and products

These guidelines address that new molecular entities and associated drug product information must be submitted in the registration application. Stability testing aims to provide evidence on how the quality of the drug substances or drug product changes over time under the influence of multiple environmental factors such as temperature, light, humidity, and also to establish a retest or shelf life for drug substance or drug product and recommend the storage conditions [31,32].

Q1B: Photostability testing of new drug substances and products

The ICH Harmonized tripartite guideline on new drug substances and stability testing for products (referred to as parent guidelines) states that light testing should be an essential component of stress testing. This document is an appendix to the parent guideline and discusses the guidelines for photostability evaluation. Photostability testing is performed on one batch of selected materials in compliance with the parent guidelines [33].

Q1C: Stability testing for new dosage forms

These guidelines address a recommendation made by the original applicant on the stability of new dosage forms following the original application for new drug substances and products.

The new dosage form is defined as a pharmaceutical product containing the same active substance as the existing drug product approved by the regulatory authority differing in the route of administration (e.g., oral to parental), new delivery system (e.g., tablet to modified tablet immediate release), and different dosage forms of the same dosage route (e.g., capsule to tablet, a solution to suspension). The parent stability guideline should be the concept of stability for a new dosage [34].

Q1D: Bracketing and matrixing design

This guideline proposes the use of bracketing and matrixing instability research. This guideline proposes the use of bracketing and matrixing instability research. Bracketing is described as designing a timetable for stability where only specimens are always tested to the extreme layout variables such as strength, container size, or complete design filling. The structure also presumes that any intermediate level of stability is the stability of the test ends. Matrixing is defined as the development of a stability schedule in which selected subsets of the total number of samples should be tested for all combinations of factors at a specified time point and specific sample subsets should be checked later. The design assumes that each sample's stability at a given time is the strength of all samples [35,36].

Q1E: Evaluation of stability data

This guideline defines when and how to consider extrapolation when recommending a re-assessment duration for the drug substance or drug product shelf life that goes beyond the period covered by "long-term storage conditions information accessible from the stability research." The design and performance of the official stabilization research should follow the parent guideline values. The stability research aims to develop standards for the retest or shelf life and storage of all future batches produced and packaged

Table 1: Codes and titles used in ICH guidelines

ICH Codes	Guideline titles
Q1A	Stability testing of new drug substances and products (second revision)
Q1B	Photostability testing of new drug substances and products
Q1C	Stability testing of new dosage forms
Q1D	Bracketing and matrixing designs for stability testing of drug substances and products
Q1E	Evaluation of stability data
Q1F	Stability data package for registration applications in climatic Zones 3 and 4
Q5C	Stability testing of biotechnological/ biological products

under comparable conditions based on the minimum testing of three batches of drug substances or products. The degree of variability on individual batches also impacts the assurance that a future production batch will remain within acceptance requirements during its retest or shelf life [37].

Q1F: Stability data package for registration applications in climatic Zone III and IV

In February 2003, these documents were accepted by the ICH Steering Committee and then enforced in the ICH regions. This guideline sets the storage requirements for stability testing in climatic zone III (hot and dry) and IV (hot and humid). To promote access to medicinal products by reducing the number of storage conditions, it specifies harmonized international stability testing requirements. In general cases, accelerated and long-term storage conditions recommended for climatic zone III and IV are shown in Table 2 (described in the parent guideline).

Long-term and accelerated storage conditions for aqueous material packed in semi-permeable containers recommended storage conditions for climatic zone III and IV is shown in Table 3 (described in parent guideline) [38].

Q5C: Stability testing of biotechnological/biological products

This guidance refers to well-defined polypeptides and proteins, their products, and derivatives that are isolated from body fluids, tissues, cell cultures, or developed using r-DNA technology. The document thus includes the development and submission of stability information for products such as cytokines (interferons, interleukins, colony-stimulating factors, tumor necrosis factors), erythropoietin's, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulin's, monoclonal antibodies, and vaccines consisting of well-characterized proteins or polypeptides [39,40].

Q7: Good manufacturing practice (GMP) guide for APIs

This document (Guide) provides guidance on GMP for APIs manufacturing under a suitable quality management framework. It guarantees that APIs meet the requirements of consistency and purity criteria that they possess. This guide describes "manufacturing" as relating to all operations involving product receipt, manufacture, labeling, re-labeling, packaging, repackaging, quality control, shipment, storage, and distribution of APIs and related control. As a whole, this document does not address the safety aspects of production workers or environmental protection issues. Such checks are the manufacturer's intrinsic obligations and are regulated by national laws. This guide does not define pharmacopeia requirements for registration, filling, or adjustment. This guide refers to the production of APIs for human drug products. It also includes APIs generated through chemical synthesis, extraction, cell culture/fermentation, recovery from natural sources, or any combination of these processes [41].

Table 2: Long-term and accelerated storage conditions for climatic zone III and IV

Study	Storage condition	The minimum time covered by data at submission
Long-term	30°C±2°C/65% RH±5% RH	12 months
Accelerated	40°C±2°C/75% RH±5% RH	6 months

Table 3: Long-term and accelerated storage conditions for aqueous material

Study	Storage conditions	The minimum time covered by data at submission
Long-term	30°C±2°C/35% RH±5% RH	12 months
Accelerated	40°C±2°C/not more than 25% RH±5% RH	6 months

The committee for proprietary medicinal products (CPMP)

In the framework of the European Agency for the Evaluation of Medicinal Products (EMEA), CPMP has issued a set of stability testing recommendations to assist those seeking authorization to sell medicinal products in the European Union. The CPMP stability guidelines are shown in Table 4.

Stability testing for climatic zone

In 1972, Futscher and Schumacher suggested the possibility of dividing the earth into four temperature and humidity-based zones, namely Zone I (temperature climate), Zone II (subtropical and Mediterranean climates), Zone III (hot and dry climate), and Zone IV (hot and humid climate) [43]. The WHO guidelines for stability monitoring, including four climatic zones storage conditions, outline guidelines for stability monitoring. The guidelines for stability testing assessments are based on the parent guidelines and guidelines for WHO. In climatic Zones I and II and climatic Zone III and IV, the parent guideline outlines the stability information package for tripartite ICH regions (European Union, Japan, and the United States) [44]. In the world, four climate zone has been divided to harmonize and simplify worldwide stability testing (Grimm W, 1998). The Current Climatic Zone IV was recommended to divide into two zones, that is, Climatic Zone IVA where 30°C/65% RH remains the standard for long-term testing conditions and Climatic Zone IVB where 30°C 75% RH becomes the long-term test condition. The climatic zone and long-term testing are shown in Table 5.

Based on this long-term stability data, stability in real-time and accelerated conditions for stability testing have been derived [45].

Protocol for stability testing

Stability testing protocol is a pre-condition for initiation of stability tests and is essentially a written document describing the main components of a well-controlled and regulated stability test. The protocol relies upon the drug substance type or the product because it depends on the compound's intrinsic stability, dosage form, and process of closing the container implied. It is also possible to determine whether the drug is new or already on the market. Stability tests are designed to determine a pharmaceutical

Table 4: The CPMP stability guidelines [42]

CPMP code	Guideline title
CPMP/QWP/576/96 Rev.1	Guideline on stability testing for applications for variations to a marketing authorization
CPMP/QWP/6142/03	Guideline on stability testing for active substances and medicinal products manufactured in climatic zones III and IV to be marketed in the EU
CPMP/QWP/609/96 Rev.1	Note for guidance on a 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 the 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 the following reconstitution

Table 5: Climatic zone and long-term testing conditions

Climatic zone	Climate/definition	Major countries/region	MAT*/mean annual partial water vapor pressure	Long-term testing conditions
I	Temperature	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	30°C/75% RH

Table 6: Test schedule for stability testing of new products [27-31]

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

product expiry date and shelf life [46]. The protocol should also include the areas where the product is expected to be put on the market, for example, where it is planned for use in climatic Zones I-III, IVa, and IVb [47].

The following information should be included in the stability protocol:

- Number of batches
- Containers and closures
- The orientation of storage of containers
- Sampling time points
- Sampling plan
- Test storage conditions
- Test parameters
- Test methodology
- Acceptance criteria.

Number of batches

Stability studies are usually conducted in one single batch at the development stage, while new product or product created registration studies are conducted in the first three batches, well-established and stable batches are allowed in two different batches. In the absence of complete manufacturing information, long-term studies should include the first three batches of the drug product produced after approval using the procedure used in the authorized application for the drug product. Laboratory data collected during pharmaceutical advances are not known as primary stability data, but as data support. The random sample selection of the pilot population or production batches should generally be a random sample [48].

Containers and closures

Tests are carried out on the material in immediate containers or marketing closures. Packaging materials include aluminum strips, Alu-Alu packs, blister packs, HDPE bottles, and so on; secondary packs are also required but not shippers. Products are to be tested individually in all separate container types or closures, before delivery and marketing. However, testing in prototype containers is permitted for bulk containers if the actual packaging is stimulated [49].

The orientation of storage of containers

For studies of stability, to allow full product contact with the container closing, samples of a solution, dispersed process, and semi-solid drug material must be held upright and placed either inverted or sideways. The guiding principle helps to determine if the interaction between the pharmaceutical material or solvent and the closure results in the removal of chemical substances from the closed components or the adsorption of the product's components in the container [15,46].

Sampling time points

The stability profile of new drug products should be at the test rate. During the 1st year of products with a planned shelf life of at least 12 months, the long-term storage monitoring frequency should be every 3 months, every 6 months in the 2nd year, and annually after that for the expected shelf life. It is recommended that the initial and end stages are at least 3 times, with accelerated storage conditions as 0 or 6 months. Due to major improvements in accelerated storage conditions, a maximum of four test points, including the initial and final time points such as 0, 6, 9, and 12 months will be needed to test intermediate storage conditions.

In case the same product needs to be tested with different strengths, multiple sizes, etc., reduced testing stability plans with fewer test points can be created. The reduced research plans were based on statistical principles of matrixing and bracketing. The test schedule for stability testing of new products are shown in Table 6.

Sampling plan

Stability testing for the sampling method includes the preparation in a stabilization chamber of several samples and the evaluation of the charged batch for the entire study. For a thorough assessment of all the test parameters first, the time-points for sampling and the number of samples must be calculated at every drawn stage. About 100 tablets, 10 for each test, hardness and moisture detecting, 6 for every disintegration and dissolution, and 50 for each friability, would be sufficient for long-term or accelerated stabilization studies. This is the total number of tablets needed for the study multiplied by the number of results. The sampling plan is then established that involves the uneven choice of the containers that represent the whole batches [30].

Test storage conditions

The conditions of storage to be chosen shall depend on the climatic zone where the product is expected to be sold on the market or for which regulatory approval is sought. The ICH, CPMP, and WHO has given a general recommendation on the storage conditions. The stability test storage conditions for drug products are shown in Table 7.

Test parameters

The protocol for the stability test should specify test parameters for the stability sample analysis. A stability test that monitors the performance, purity, capacity, and identity after the storage is selected. The presentation, processing, material deterioration, dissolution, humidity, and microbial testing are therefore normal tests carried out on test samples. The batches used to study stability must fulfill all test criteria, including heavy metals used, residual solvents, and traces of combustion. Some are necessary for the release of the product, but not repeatedly for stability testing. Q6A further checks, including enantiomeric purity, polymorphic form, particle dimensions, and others, are discussed in ICH guidance.

Test methodology

The protocol presented in the official compendia must always be followed, considering that the results obtained by the official test are generally accepted better. When using alternative techniques, they

Table 7: Stability test storage conditions for drug products [32,49]

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

must be checked properly. Moreover, a drug test should have performed using a stability indication technique developed by performing stress tests on a substance in a state of forced decomposition. The method should be tested for linearity, reliability, accuracy, and precision within the scope of stability studies the drug is expected to fall. The system validated should include the limit of detection/quantification for the analysis of product degradations. After checking reproductivity and performing minimum validation, say linearity, range, etc., the method specified in the documentation should be used. Each test is subject to the recommendation of a standard test protocol [46].

Acceptance criteria

Before starting the stability studies, all analytical methods must be validated. Similarly, the criteria for the acceptance of the analytical findings and standards should also be developed in advance on the existence of degrading products. The acceptability criteria in the stability analysis are set in numerical limitations for the results shown in performance term such as moisture collection, viscosity, degradation, assay, and particle size and fail or pass qualitative tests such as odor, color, appearance, microbial growth, cracking, and so forth. The approval requirements for the individual and complete degradation products should also include the upper limits.

Concerning impurities in new drug materials, "ICH Guideline Q3B (R2)" discusses the degradation of the new drug formulations. When the proposed threshold is reached, active ingredient degradation products and excipients, as well as active container elements, should be registered, detected, and/or eligible. The impurity reporting level is dependent on the target dose. A maximum daily dose of 0.1% shall be less than or equal to 1 g and 0.05% shall be the minimum if the maximum daily dose is greater than 1. For a daily maximum of 1 mg and 2 mg dose, the identified threshold of impurities is between 1.0 and 0.1% [27].

Estimation of shelf life

Long-term storage data determine the shelf life. First, the data are linearized and the fits are evaluated. The linearized information is then evaluated for the gradient to match the intercept.

Table 8 contains the various possibilities for the trends of concentration period for three batches. The data were correctly aggregated for calculating the general slope [49]. Most pharmaceutical products have a single shelf life. In some circumstances, the product may be two, for example, a freeze-dried protein product (lyophilized) but may have only one shelf life of 2 years, a dry-conditioned product, and a second shelf life of 2 days [50].

Recent trends in stability testing

The recent trends are to identify stability checking requirements for global marketing, particularly among the multinational pharmaceutical company. For this purpose, the organizations are orienting their policies toward a single set of conditions, including extreme climatic conditions. International research specific changes include an enhancement from 6 to 12 months in the duration of accelerated tests and a further 50°C/75% RH test for 3 months [51,52]. This adjustment is based on the concept that stability tests are not repeated for other areas and that resources are used efficiently and optimally, as all experiments take place at a single laboratory. Besides, the combination of three variables of the climate, such as temperature, humidity, and light, indicates a more extreme effect on medicinal products than was recorded under the temperature and humidity conditions alone [53-55]. Singh *et al.* (2018) have reported that drug stability analysis is an indispensable activity to ensure the quality of drug products and safety of patients. It considers the progress toward globalization, harmonization, and stability issues that pharmaceutical scientists and regulators are likely to focus on soon [56]. Kailash *et al.* (2015) revealed the importance of stability testing for any pharmaceutical product. The author also states that the important point for performing stability studies and storage conditions is that the test should be based on real climatic conditions. As stability study is a tool in cGMP, indirectly imparts quality products to improve company reputability on the global market [57].

Table 8: Pattern of the concentration-time data and pooling decision

Slope	Intercept	Variation factor	Pooling
Identical	Identical	Nil	Yes
Identical	Different	Batch, for example, unequal initial drug concentrations	No
Different	Identical	Storage, for example, difference in the rate of drug loss	No
Different	Different	Interactive forces – both batch and storage factor	No

CONCLUSION

Stability testing has now become the main process factor for a new drug or new formulation in the pharmaceutical development program. Stability tests are carried out to ensure that the medicine in recommended storage and shelf life conditions is safe and effective throughout its shelf life. Therefore, the stability test should be conducted based on scientific principles and comprehension of current regulatory requirements and the climate zone.

AUTHORS' CONTRIBUTIONS

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CONFLICTS OF INTEREST

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Nil/Self.

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