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A CRUCIAL COMPONENT OF PHARMACEUTICAL QUALITY ASSURANCE IS DRUG STABILITY TESTING.

Gungan Shashwat Kerketta*

Usha Martin University Angara Ranchi Jharkhand.

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***Corresponding Author**
Gungan Shashwat Kerketta
Usha Martin University Angara Ranchi Jharkhand.

ABSTACT

A crucial component of pharmaceutical quality assurance is drug stability testing. A crucial part of pharmaceutical quality control is stability testing, which makes sure that medications maintain their identity, safety, and efficiency over the course of their intended shelf lives in a variety of storage environments. Ensuring pharmaceutical products' safety, shelf life, and efficacy is imperative. Stability testing is done to determine how stable drug substances as well as products are in different environments, such as different temperatures, humidity levels, light levels, and pH levels. These studies aid in determining suitable storage conditions and expiration dates as well as valuable information about the possible deterioration of medications. There are 2 main types of stability testing: long-term and accelerated. Long-term studies are carried out at room temperature and under normal storage conditions, while accelerated studies are conducted at higher temperatures and/or humidity to simulate aging over time. The type of stability testing that is conducted depends on the specific drug and its expected shelf life.

KEYWORDS: International Conference of Harmonization guidelines, Stability studies, pharmaceutical products, Storage Conditions, Expiry Date, CPMP Guidelines, and ICH Guidelines.

INTRODUCTION[1-4]

Ensuring drug quality through stability testing: A Cornerstone of Pharmaceutical Development

Stability testing as a Keystone for Ensuring Drug Quality in Pharmaceutical Development Assuring pharmaceutical products' quality, effectiveness, and safety over the duration of their planned shelf life, stability testing is essential to the pharmaceutical development process.

Although it is a complex procedure that requires a large investment of money, time, and scientific knowledge, its importance in fostering confidence and guaranteeing the success of a pharmaceutical product cannot be overstated.

Stability study data is essential for regulatory submissions because it shows regulatory agencies that the drug product satisfies quality criteria and can be given to patients in a safe way. Furthermore, stability testing is essential for verifying that different batches of the same medication product have similar stability profiles and for monitoring batch-to-batch consistency.

The significance of stability testing in pharmaceutical product development[5-10]

The importance of stability testing is multifaceted:

1. **Determining shelf Life and Storage conditions:** A drug product's shelf life, or the amount of time it maintains its intended therapeutic characteristics and satisfies all quality standards, is determined by stability testing. It also offers insights into suitable storage settings, guaranteeing that the pharmaceutical product stays stable during distribution and usage.
2. **Ensuring drug Efficacy and Safety:** Stability testing assists in identifying possible drug substance or product degradation routes, keeping harmful by-products from forming that could compromise drug efficacy or put patients' safety at risk.
3. **Preserving brand reputation:** Stability testing conserves the patient's health and the reputation of the manufacturer by guaranteeing that pharmaceutical products fulfill quality standards for the duration of their shelf life. It stops the discharge of inefficient or possible
4. **Tracking Batch-to-Batch Consistency:** It is essential to conduct stability testing to make sure that several batches of the same medication product have stability profiles that are similar. For the medication product to remain effective and of high quality for the duration of its shelf life, consistency is crucial.
5. **Directing formulation development:** Information from stability testing is useful in choosing formulations, excipients, and container-closing techniques that maximize pharmaceutical products' stability. The growth of stable and efficient pharmaceutical products depends on this knowledge.
6. **Comprehending API Degradation:** Stability testing aids in clarifying the processes by which active pharmaceutical ingredients (APIs) deteriorate, facilitating the creation of mitigation plans, and maintaining the quality of drug products.

7. **Regulatory Compliance and Approval:** Stability data is a mandatory requirement for regulatory submissions, demonstrating to regulatory bodies that the drug product meets the required quality standards and can be safely administered to patients

Factors influencing drug stability[11-13]

Numerous factors that can affect a drug's physical, chemical, and therapeutic qualities might also affect its stability. Comprehending these variables is essential to guaranteeing the effectiveness and caliber of pharmaceutical items for the duration of their shelf life.

1. **Temperature:** Changes in temperature have a big impact on how stable drugs are. Drug degradation is often accelerated by higher temperatures, especially during hydrolysis processes. Preserving medicine quality therefore requires regular and suitable storage temperature maintenance.
2. **Moisture:** Drug stability may suffer as a result of moisture. Drugs that are soluble in water are especially prone to absorbing moisture, which can cause chemical and physical changes that reduce their effectiveness. Drug stability must be preserved by employing moisture-resistant packaging and regulating humidity levels.
3. **pH:** The pH of the drug environment plays a critical role in its stability. Changes in pH can alter the ionization state of the drug molecule, affecting its solubility, absorption, and distribution. Formulating drugs in buffers at their optimal pH can help maintain stability and ensure consistent therapeutic activity.
1. **Excipients:** Excipients, the inactive ingredients in drug formulations, can interact with the active pharmaceutical ingredient (API) and influence its stability. Certain excipients, such as starch and povidone, can increase moisture content, potentially accelerating drug degradation. Careful selection and testing of excipients are essential for maintaining drug stability.
2. **Light exposure:** Exposure to light, particularly ultraviolet (UV) radiation, can break down certain drugs and render them ineffective. Protecting drug products from direct sunlight and using light-resistant packaging can help maintain their stability and efficacy.
3. **Oxygen exposure:** Oxygen in the air can cause oxidative degradation of drugs, particularly those containing double bonds or unsaturated side chains. Packaging and storage strategies that minimize oxygen exposure can help preserve drug stability.
4. **Chemical incompatibilities:** Interactions between the drug substance and other components of the formulation, such as excipients or preservatives, can lead to chemical instability. Careful compatibility testing is crucial for ensuring drug products' stability.

Types of stability of drug substances[5,14]

Drug development and quality control depend heavily on the stability of drug ingredients, which guarantees that the medication will retain its intended qualities for the duration of its shelf life. Stability comes in four primary forms:

1. **Physical stability:** The term 'physical stability' describes a drug's capacity to hold onto its physical properties over time, including size, shape, color, and texture. For patients to receive consistent medication delivery and to be safe, physical stability must be maintained.
2. **Chemical stability:** A drug substance's capacity to preserve its active form and chemical integrity over time is referred to as chemical stability. Drug efficacy and safety may be jeopardized by the production of inactive or potentially hazardous compounds as a result of chemical degradation.
3. **Microbiological stability:** Microbiological stability is referred to as the ability of a drug substance to resist the growth of microorganisms, such as bacteria, fungi, and viruses. Maintaining microbiological stability is essential for preventing product contamination and ensuring patient safety.
4. **Therapeutic stability:** It is the ability of a drug substance to maintain its therapeutic activity and efficacy over time. Therapeutic degradation can lead to a loss of potency or a change in pharmacological effects, compromising the effectiveness of the drug

Types of stability studies[15]

Stability studies are a very important component of pharmaceutical quality assurance, evaluating drug substances & products' stability under various storage conditions. These studies provide valuable insights into a drug product's shelf life and help determine appropriate storage recommendations. The four main types of stability studies are:

1. **Long-term stability studies:** These studies are conducted under real-time conditions, typically at the recommended storage temperature and humidity specified for the drug product. The duration of long-term studies is usually equal to or longer than the proposed shelf life.
2. **Intermediate stability studies:** These studies are carried out at elevated temperatures as well as humidity levels compared to long-term studies. This accelerated environment simulates the effect of long-term storage in a shorter period. Intermediate studies provide preliminary data on the potential stability of the drug product and help guide the design of long-term studies.

3. **Accelerated stability studies:** These studies are performed at even higher temperatures as well as humidity levels than intermediate studies. Accelerated studies provide a rapid assessment of the drug product's stability under extreme conditions and can help identify potential degradation pathways.
4. **In-use stability studies:** These studies assess the stability of the drug product after it has been opened and exposed to environmental factors. In-use stability studies are particularly important for multi-dose products and provide guidance on appropriate handling and storage practices after the initial opening.

Table 1: Types of stability studies.

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C±2°C and 60% RH±5% RH or 30°C±2°C and 65% RH±5% RH	12 months
Intermediate	30°C±2°C and 65% RH±5% RH	6 months
Accelerated	40°C±2°C and 75% RH±5% RH	6 months”

Types of stability testing methods

It is a very important component of pharmaceutical development as well as quality assurance, ensuring that drug substances and products maintain their intended properties throughout their shelf life.[16]

There are four main types of stability testing methods

1. **Real-time stability testing**[17]

Real-time stability testing is a critical component of pharmaceutical development and quality assurance, providing invaluable insights into drug substances & products’ stability under real-world storage conditions. It involves storing the drug product at the recommended storage temperature as well as humidity for an extended period, typically equal to or longer than the suggested shelf life.

The primary objective of real-time stability testing is to assess the stability of the drug product under actual storage conditions and establish its shelf life. By monitoring the drug substance or product for degradation or changes in physical characteristics over time, real-time studies provide the most accurate data on the product's stability profile.

The duration of real-time stability studies is dictated by drug product's inherent stability as well as the desired shelf life. A sufficiently long test period is essential to ensure that any potential degradation is detected and that the product's stability can be confidently established.

To differentiate between genuine product instability and day-to-day assay variability, real-time stability studies employ trend analysis techniques. By collecting data at appropriate intervals, trend analysis can reveal subtle changes in the drug product's stability profile, distinguishing between genuine degradation and inherent assay variations.

The reliability of real-time stability data hinges on the use of stable reference materials and consistent instrument performance. Reference materials, such as reagents and standards, should be regularly evaluated to ensure their stability throughout the testing period. Additionally, instrument calibration and maintenance procedures must be strictly followed to minimize drift and variability arising from equipment changes or performance fluctuations.

2. Accelerated stability testing[18,19]

A vital tool in pharmaceutical development is accelerated stability testing (AST), which offers quick insights into the stability of drug ingredients and products under stress-simulation scenarios. In contrast to real-time stability testing, AST can accelerate the degradation of the drug product by exposing it to high temperatures, high humidity, or other environmental stressors. This enables a more thorough evaluation of the product's stability to be completed in a shorter amount of time.

Predicting the drug product's long-term stability and estimating its shelf life under typical storage conditions are the main goals of AST. Scientists are able to extrapolate the product's performance under more benign conditions over a prolonged time period by monitoring the rate of degradation at elevated stress levels. This capacity for prediction aids in the formulation of well-informed decisions.

Rapid stability assessment is essential for screening possible formulations and spotting possible stability issues early on in the drug development process, which is where AST is especially helpful. AST has the potential to drastically cut development time and costs by eliminating unstable formulations early on.

Carefully choosing the stress conditions and figuring out the right stress levels are important aspects of AST study design. The following are typical stressors: pH, light exposure, temper-

ature, humidity, and mechanical agitation. In order to expedite degradation while maintaining relevance to actual storage conditions, the stress levels were selected.

A correlation between the observed degradation rate and the stress level is established by statistical analysis of the AST data. The product's stability under less extreme conditions over a prolonged period of time can then be predicted using this relationship.

To ensure the reliability of AST data, it is crucial to compare the results with real-time stability studies. This comparison helps validate the predictive capability of AST and provides a more comprehensive understanding of the product's stability profile.

3. Retained sample stability testing[20]

It is a standard practice in the pharmaceutical industry, employed for every marketed product that requires stable data collection. It involves selecting stability samples from at least 1 batch per year for long-term storage. Stability samples from 2 batches are advised when the number of marketed batches surpasses fifty. Initially, stability samples from each batch may be collected and tested. However, at a later stage, this number may be reduced to 2-5% of marketed batches.

For products with a shelf life of five years, stability testing is usually conducted at predetermined intervals, such as 3, 6, 9, 12, 18, 24, 36, 48, and 60 months. This standardized approach, known as the constant interval technique, ensures that comprehensive stability data is gathered on stored samples.

Retained sample stability testing plays a critical role in making sure the stability and efficacy of drug products throughout their shelf life. By periodically evaluating stability samples from marketed batches, pharmaceutical companies can monitor the long-term stability of their products and make informed decisions regarding shelf-life claims and storage recommendations. This continuous monitoring process helps safeguard patient safety and maintains public confidence in the quality of pharmaceutical products.

4. Cyclic temperature stress testing[2,21]

It is a specialized stability testing technique that simulates potential temperature fluctuations encountered by drug products during storage and distribution. While not routinely used for product testing, it serves as a valuable tool for pharmaceutical scientists in product development and troubleshooting.

The design of cyclic stress testing protocols is guided by the product's characteristics and intended storage conditions. The most common cycle duration is twenty-four hours, mimicking the diurnal temperature variations experienced by pharmaceuticals during storage. Both minimum and maximum temperatures employed in the test are carefully selected based on product-specific factors, including recommended storage temperatures and the product's susceptibility to physical and chemical degradation.

Typically, cyclic stress testing involves subjecting the drug product to 20 cycles of temperature variation. This repeated exposure to temperature fluctuations helps assess the product's resilience to potential environmental stresses and provides insights into its stability under real-world storage conditions

Guidelines for stability testing[22]

The regulatory landscape of stability testing: ensuring product stability for patient safety

Stability testing plays a very important role in ensuring the quality as well as the efficiency of pharmaceutical products throughout their shelf life. To maintain consistency in stability testing practices across different countries and streamline the regulatory process, regulatory authorities have established comprehensive guidelines for stability data submission.

The evolution of stability testing regulations

The need for standardized stability testing procedures was recognized in the 1980s, leading to the development of initial guidelines. These guidelines addressed fundamental stability testing principles and outlined the stability data requirements for regulatory applications.

The International Conference on Harmonization (ICH) Guidelines

Recognizing the global nature of the pharmaceutical industry, the ICH was established to harmonize stability testing guidelines across major regulatory regions – the European Union, Japan, as well as the US. This harmonization effort aimed to overcome regulatory hurdles and facilitate the international registration of pharmaceutical products.

Addressing extreme climatic Conditions and Beyond

In 1996, the WHO (World Health Organization) modified the ICH guidelines to address the unique climatic conditions prevalent in many countries. This modification ensured that stability testing practices were relevant to a broader range of global environments.

Expanding stability testing guidelines

The scope of stability testing guidelines has expanded beyond new drug substances as well as products to encompass existing products already in circulation. Additionally, specialized guidelines have been developed for stability testing of APIs, drug products, formulations, and excipients.

A comprehensive regulatory framework

The establishment of harmonized stability testing guidelines has played a very important role in making sure the consistent assessment of product stability across different regulatory jurisdictions. This harmonization has facilitated the movement of pharmaceutical products between countries, ultimately enhancing patient access to safe and effective medicines

Table "2: Code and Title used in ICH Guidelines. [1,3]

Q1A	Stability testing of New Drug Substances and Products (Second revision
Q1B	Stability testing Photo stability 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.
Q1E	Evaluation of stability data
Q1F	Stability data package for Registration Applications in Climatic Zones III and IV.
Q5C	Stability testing of Biotechnological/Biological Products"

ICH Stability Testing Guidelines: Ensuring drug product stability

The ICH of Technical Requirements for Pharmaceuticals for Human Usage has created a comprehensive set of guidelines for drug substances & products' stability testing. These guidelines offer a framework for assessing the stability profile of pharmaceutical products and ensuring their safety and efficiency throughout their shelf life.

Q1A (R2): Stability Testing of New Drug Substances and Products

ICH Q1A(R2) provides guidance on stability testing for new drug substances & products, outlining the factors to consider and the data to be submitted in registration applications. When assessing how the quality of pharmacological products or substances varies over time due to environmental influences including humidity, light, and temperature, stability testing is essential.[23,24]

Q1B: Examining the photostability of novel pharmaceutical Ingredients and Goods

Photostability testing, which assesses how exposure to light affects a drug substance or product, is the main focus of ICH Q1B. Because light can change the characteristics of a product

and degrade active pharmaceutical ingredients, photostability is a crucial component of stress testing.[25]

Q1C: Testing for stability of novel dosage forms

Stability testing for new dosage forms, or products with the same active ingredient as a prevailing product but a different delivery system, dosage form, or route of administration, is covered by ICH Q1C. To make sure that the active ingredient's stability is preserved when incorporated into a new dosage form, stability testing is crucial.[26]

Q1D: Bracketing and Matrixing Design

ICH Q1D suggests the usage of matrixing and bracketing designs to optimize stability studies. Bracketing involves testing only the extreme variants of a factor, such as the lowest and highest strength or container size, and assuming that intermediate levels are stable. Matrixing involves testing selected subsets of samples at specific time points to lower the overall number of samples required.[27,28]

Q1E: Evaluation of stability data

ICH Q1E provides guidance on how to evaluate stability data and make recommendations for retest periods or shelf life. This includes considering factors such as the degradation rate, the presence of impurities, and the overall stability profile of the drug substance or product.[29]

Q1F: Stability Data Package for Registration Applications in Climatic Zones III and IV

ICH Q1F addresses stability testing for drug products intended for use in climatic zones III & IV, which are regions with hot and humid climates. Additional stability testing is often needed for these regions to account for their unique environmental conditions.[30]

Q5C: Stability Testing of Biotechnological/Biological Products

ICH Q5C provides guidance on stability testing for biotechnological/biological products, which are products that contain active ingredients produced by living organisms. These products may have unique stability profiles due to their complex nature, and specific stability testing considerations are necessary.[31,32]

Good Manufacturing Practice (GMP) Guide for APIs[33]

This paper offers GMP guidelines for API manufacturing within an appropriate quality management system. It aims to make sure that APIs meet the needed quality standards for consistent composition and purity.

The guide defines ‘manufacturing’ as encompassing all operations involved in the product lifecycle, including receipt, production, labeling, relabelling, packaging, repackaging, release, quality control, storage, and distribution of APIs as well as related control activities.

It is significant to notice that neither environmental protection nor production worker safety is covered in this guide. These aspects are considered the manufacturer's inherent responsibilities as well as are regulated by national laws. Furthermore, the pharmacopeia requirements for registration, filling, and adjustment are not defined in this guide. It focuses on the manufacturing of APIs for pharmaceutical goods intended for human use.

The Committee for Proprietary Medicinal Products (CPMP) within the EMA (European Medicines Agency) has issued guidelines for stability testing to support those seeking authorization to market medicinal products in the European Union. These guidelines, summarized in Table 4, provide recommendations for conducting stability testing under various climatic conditions.[36]

Climatic zones for stability testing[34]

Based on temperature and humidity, Futscher and Schumacher suggested in 1972 to divide the world into 4 climatic zones: Zone I, Zone II, Zone III, and Zone IV, temperate climate, subtropical and Mediterranean climates, hot and humid climate, hot and dry climate, and temperate climate, respectively. The WHO guidelines for stability monitoring also outline recommendations for conducting stability testing under these four climatic zone storage conditions.

The CPMP stability guidelines incorporate the parent guidelines for ICH tripartite regions (Japan, the European Union, and the US) and the WHO guidelines for “climatic Zones I & II and climatic zones III & IV. Additionally, the CPMP guidelines recommend dividing Climatic Zone IV into two subzones: Climatic Zone IVB: in this zone, 30°C/75 percent RH is the long-term test condition; Climatic Zone IVA: 30°C/65 percent RH is the standard for long-term” testing circumstances. The goal of this section is to standardize and streamline global stability testing procedures.

Stability testing protocols[9,35]

A well-defined stability testing protocol is essential before initiating stability tests. The main elements of controlled & regulated stability research are outlined in this protocol, which func-

tions as a written document. The particulars of the protocol's content are dependent upon the kind of drug substance or product under examination, taking into account elements like the compound's intrinsic stability, dose form, and container closure system. It should be specified in the protocol if the medication is new or already available.

Table "3: The CPMP stability guidelines. [1,3,36]

Code	Title	Climatic Zone	Temperature	Relative Humidity
CPMP/QWP/576/96 Rev.1	Guidelines for conducting stability tests before approving changes to a marketing authorization	I	25°C ± 2°C	60% ± 5% RH
CPMP/QWP/6142/03	Guidelines for stability testing drugs and active ingredients produced in climatic zones III and IV that are intended for the EU market	II	30°C ± 2°C	65% ± 5% RH
CPMP/QWP/609/96 Rev.1	Guidelines for conducting stability tests before approving changes to a marketing authorization	IIIA	37°C ± 2°C	75% ± 5% RH
CPMP/QWP/122/02 Rev.1	Guidelines for assessing the stability of currently used active ingredients and related finished goods	IIIB	40°C ± 2°C	75% ± 5% RH
CPMP/QWP/072/96	Guidelines for the beginning of the completed dosage form's shelf life	IVA	30°C ± 2°C	65% ± 5% RH
CPMP/QWP/2934/99	Guidelines for human medication stability testing during use	IVB	30°C ± 2°C	75% ± 5% RH"

Table "4: Climatic zone and long-term testing conditions.[1,3,37]

Climatic Zone	Climate/Definition	Major countries/region	MAT*/mean annual partial water vapor pressure	Long-term testing conditions
I	Temperate	UK, United States, Russia, Northern Europe	≤15°C/≤11 hPa	21°C/45% RH
II	Subtropical and Mediterranean	Southern Europe, Japan	>15–22°C/>11–18 hPa	25°C/60% RH
IIIa	Hot and Dry	India, Iraq	>22°C/≤15 hPa	30°C/35% RH
IIIb	Hot and Humid	Egypt, Iran	>22°C/>15–27 hPa	30°C/65% RH
IVa	Hot and very Humid	Singapore, Brazil	>22°C/>27 hPa	30°C/75% RH"

Essential components of a stability protocol[3,9,35,38,39]

A well-defined stability protocol is crucial for conducting reliable and meaningful stability testing of pharmaceutical products. The protocol serves as a comprehensive roadmap for the entire stability study, ensuring consistency and adherence to established guidelines.

1. **Number of batches**
   - Specify the number of batches to be tested. This typically includes at least three batches to ensure adequate representation of the product's variability.
2. **Containers and Closures**
   - Clearly define the types of containers and closures used for the product. This includes the material, size, and design of both containers and closures.
3. **Orientation of storage**
   - Specify the orientation in which the product containers will be stored during the stability study. This is especially crucial for items like liquids and suspensions that could be orientation-sensitive.
4. **Sampling time points**
   - Outline the specific time points at which samples will be withdrawn from the stability study for analysis. These time points should be strategically chosen to provide sufficient data for assessing the product's stability profile.
5. **Sampling plan**
   - Describe the detailed sampling plan, including the number of samples to be taken at every time point and the method for selecting samples.

6. **Test storage conditions**
   - Clearly define the specific storage conditions under which the stability study will be conducted. This includes temperature, humidity, and light exposure conditions.
7. **Test parameters**
   - List the specific parameters that will be evaluated for each sample. This may include physical characteristics, chemical properties, and biological activity.
8. **Test methodology**
   - Describe the detailed methodology for each test to be performed. This includes the equipment, reagents, and analytical procedures.
9. **Acceptance criteria**
   - Define the acceptance criteria for each test. These criteria should be on the basis of the product's specifications and regulatory requirement

Table "5: Stability test storage conditions for drug products.[24,39]

Intended Storage Condition	Stability Test Method	ICH Test Temperature and Humidity (Period in Months)	WHO Test Temperature and Humidity (Period in Months)	Intended Storage Condition
Room Temperature	Long term	25±2°C/60±5% RH (12)	25±2°C/60±5% RH or 30±2°C/65±5% RH or 30±2°C/75±5% RH (12)	Room Temperature
Room Temperature	Intermediate	30±2°C/65±5% RH (6)	30±2°C/65±5% RH (6)	Room Temperature
Room Temperature	Accelerated	40±2°C/75±5% RH (6)	40±2°C/75±5% RH (6)	Room Temperature
Refrigerated	Long term	5°C/ambient (12)	25±2°C/60±5% RH (6)	Refrigerated
Refrigerated	Accelerated	25±2°C/60±5% RH (6)	25±2°C/60±5% RH (6)	Refrigerated
Freezer	Long term	-20°C/ambient (12)	-20±5°C"	Freezer

Steps in stability studies[40]

1. **Formulating the preparation:** Validate the formulation and container selection before initiating a stability study. Ensure no known incompatibilities or content/container interactions exist. Conduct preliminary studies if necessary. Use active ingredients from the same batch for all stability studies.

2. **Choice of concentration tested:** Use the concentration intended for therapeutic use unless a single concentration is known to be clinically effective. Study the stability of at least 2 concentrations: one low and one high. Pharmacists ought to choose the higher and upper concentrations after determining the effective therapeutic range. If there is a noticeable difference between low and high concentrations, think about doing intermediate-concentration research.
3. **Number of testing:** Test at least three units to acquire a minimum of three independent measurements. If at all possible, create a single preparation unit for every sample time point. If it isn't likely to utilize distinct units for every sampling time point, use preparations from different batches for three different experiments.

4. **Storage conditions**

- **Ambient temperature**: Unless the active ingredient is known to be heat unstable, do the test at a temperature close to 25°C. Use an environmental chamber if available to maintain 25°C±2°C conditions.
- **Refrigeration:** Consider a study at 5°C if the literature recommends refrigeration, the active ingredient is thermo-sensitive, or analyses at 25°C show rapid degradation.
- **Freezing-Thawing**: If the literature suggests freezing, the active ingredient degrades quickly at room temperature or after refrigeration or residual moisture is an issue, take into consideration conducting a study at -20°C. Maintain -20°C±5°C during testing.
- **Residual moisture:** Test at 25°C while maintaining 60% ± 5% residual moisture if an environmental chamber is available.

5. **Light:** Use day/night ambient light unless the literature indicates photosensitivity. For photosensitive molecules, protect the preparation with suitable packaging and store it in sheltered conditions.
6. **Duration of study:** Conduct real-time studies for up to 1 year. Accelerated aging studies may provide insights into degradation pathways. Follow ICH methodology for accelerated aging studies.
7. **Sampling time points:** Calculate sampling time points based on the maximum planned duration. Establish at least "five sampling time points between the initial time T0 and the maximum duration. Use sampling frequencies around 1/24th, 1/12th, ¼, ½, and ¾ of the maximum" duration.
8. **Analysis to be performed**

- Conduct a test on the active component.

- Monitor the appearance of degradation products.
- Determine other analyses based on the pharmaceutical dosage form used.
- For sterile products, add a microbiological stability study to a physicochemical stability study.

Table 6: Steps in stability studies.

Step	Description
Formulating the Preparation	Validate formulation and container selection. Use active ingredients from the same batch.
Choice of Concentration Tested	Use two concentrations: one low and one high. Consider intermediate concentration study if necessary.
Number of Testing	Test at least three units. Ideally, create one preparation unit per sampling time-point.
Storage Conditions	Consider ambient temperature, refrigeration, freezing-thawing, and residual moisture.
Light	Use day/night ambient light unless photosensitivity is indicated. Protect photosensitive preparations.
Duration of Study	Conduct real-time studies for up to 1 year. Consider accelerated aging studies.
Sampling Time Points	Establish at least five sampling time points between T0 and the maximum duration.

Expiration Date and Shelf life[1-3,41,42]

A pharmaceutical product's expiration date is the last date by which the manufacturer warrants that, when stored according to recommended guidelines, the product will remain fully potent and safe. It is advised to throw away the product after this date because it might no longer be as safe or effective. A product's shelf life is the length of time that it should stay stable and within tolerable limitations when stored in accordance with the suggested standards.

Calculating the shelf life

The shelf life is ascertained through stability tests, which evaluate the rate of deterioration of the drug substance or product under various storage conditions. In these studies, product samples are usually stored at various temperatures, humidity levels, and light exposure conditions, and the drug's concentration and other quality parameters are tracked.

Elements that impact shelf life

A pharmaceutical product's shelf life can be impacted by a number of factors, such as:

- **Drug substance stability:** The inherent stability of the therapeutic ingredient is a major factor in determining a product's overall shelf life.
- **Formulation**: By affecting the stability of the drug ingredient, the product's formulation—which includes the excipients and container-closure system—can also impact the shelf life.
- **Storage Conditions:** Having the proper storage conditions—including the proper humidity, temperature, and light—is essential to preserving the product's stability and increasing its shelf life.

Importance of expiration date

Adhering to the expiration date is essential for several reasons:

- **Ensuring drug efficacy:** Expired drugs may not have the same therapeutic effect as unexpired drugs, potentially leading to treatment failures.
- **Preventing adverse effects:** Degraded drug substances may produce harmful byproducts that could cause adverse reactions or side effects.
- **Maintaining regulatory compliance:** Pharmaceutical manufacturers are legally obligated to provide accurate expiration dates for their products

Goals[43]

The following are the main goals of stability testing:

1. **Determine the length of time:** That a drug product has its intended therapeutic properties and satisfies all quality standards. This is known as the shelf life.
2. **Determine and keep an eye on possible degradation pathways:** Stability testing aids in determining elements like temperature, pH, humidity, and light that can cause a drug's substance or product to deteriorate.
3. **Provide information for regulatory submissions:** Stability information, which illustrates the drug product's quality and stability under various storage circumstances, is an essential part of regulatory filings.
4. **Keep an eye on consistency from batch to batch:** Stability testing makes sure that various batches of the same medication product have consistent stability profiles.

Support post-approval modifications: Stability data is frequently needed to facilitate post-approval modifications, including.

CONCLUSION

Stability testing guarantees the quality, effectiveness, and safety of pharmaceutical products for the course of their shelf life, making it a crucial step in the medication development process. Stability studies assess the durability of pharmacological substances and products in a range of environmental settings, offering vital information for establishing suitable expiration dates and storage advice.

The successful execution of stability studies requires careful planning, adherence to established guidelines, and rigorous analytical techniques. The data generated from these studies serves as the foundation for regulatory submissions, providing assurance that the product will maintain its intended performance within the specified shelf life.

In conclusion, stability testing plays a pivotal role in safeguarding public health by ensuring that patients receive effective and safe pharmaceutical products. By continuing to refine and enhance stability testing practices, the pharmaceutical industry can further advance the quality and safety of medications worldwide

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