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PHARMACEUTICAL STABILITY STUDIES AND THEIR REGULATORY SUBMISSION REQUIREMENTS: A REVIEW

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ABSTRACT

One of the crucial elements in the development of new medications and formulations is the stability testing of pharmaceutical products. These tests are conducted to ensure that pharmaceutical products maintain their quality, efficacy, and safety over time. These studies must be conducted meticulously, following standards established by organizations such as the International Council of Harmonization (ICH), the World Health Organization (WHO), or other relevant regulatory bodies. For pharmaceutical substances and products, there exist various stability categories and diverse testing methodologies. Stability studies are conducted to assess storage conditions, determine shelf life, and establish recommended labeling guidelines. The stability data of pharmaceutical drug products is typically submitted in eCTD Module 3, primarily in sections 3.P.8.1., 3.P.8.2., and 3.P.8.3. As outlined in the ICH guideline Q1A (R2), stability studies often play a pivotal role as a pathway activity for regulatory submission and approval. This article provides comprehensive insights into various types of stability studies, testing procedures, storage conditions, climatic zones, stability guidelines, and submission requirements in accordance with regulatory standards.

Keywords: Common technical document; Drug product; International council of harmonization; Quality; Stability study process; World health organization; Stability guideline

INTRODUCTION

The ability of a drug to sustain its physiological, biochemical, microbiological & biopharmaceutical constituents during its retention period, to established restrictions. is called stability **[1]**. Pharmaceutical products shelf life when the substances concentration falls to 90 % **[2]**. Technically speaking, "shelf life" refers to the products

stability and is expressed as the products expiration date **[3]**. The duration of a pharmaceutical's dosage forms seems to be affected by a variety of external factors, such as sunlight, radiation, climate and humidity **[4]**. Then again to formulation's numerous physical and chemical active ingredients, the type such as both the storing as well as the containers coverings environment affect pharmaceutical medicinal substances and medicinal products **[5]**. For example, Some of the stability tests include cyclic temperature strip testing, actual test procedures, rapid testing procedures, preserved tests on samples & ways to evaluate stability studies to determine drug stability **[6]**. Any substance or drug product requiring regulatory approval must provide all Study results on reliability in Standard Scientific Documentation (CTD) type for regulatory review **[7]**. Similarly techniques and information that should be included in stability studies testing recommendations have been published by a number of world wide, regional and national regulatory bodies and agencies so that procedures can produce stability data that is accurate the first time **[8]**. This review paper provides a thorough explanation of significance of studies of stability or their various varieties, testing methodologies and the regulatory procedures to the submission of drug material and drug products **[8]**.

Stability testing categories of pharmaceuticals

Various Stability testing categories of pharmaceuticals represents in **Figure 1**.

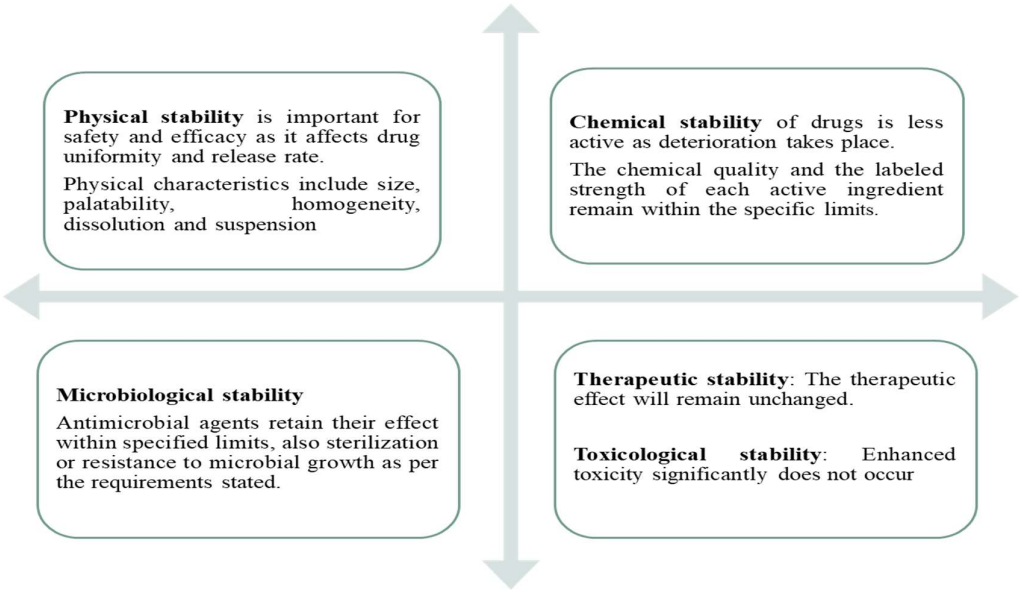

Figure 1: Stability testing categories of Pharmaceuticals

Types of Stability studies

Pharmaceutical stability research according to different time periods and variables including temperature, relative humidity and stability investigations **[17]**. The sample is run through tests to assess its long-term stability. At predefined periodic or altering the additional parameter conditions as appropriate **[18]**. As given below, **Table 1**, which shows types of stability tests, storage requirements and shelf life for pharmaceutical medication product dosage forms and **Table 2** indicates case studies, storage conditions and time all of which are crucial for maintain the drug's efficacy products displays consequently various stability research, their storage settings and associated time periods.

Table 1: Types of stability studies [19, 20]

Various Stability Studies	Conditions	Time Period Minimum
Long Term	25±2°C and 60±5% RH	12 months
Intermediate	30±2°C and 65±5% RH	6 months
Accelerated	40±2°C and 75±5% RH	6 months

Table 2: Drug items should be assessed while being stored [21-22]

Sr.No	Case	Study	Conditions	Time period
1.	General	Long term Intermediate Accelerated	25°C±2°C/60% RH 30°C±2°C/65% RH±5%RH 40°C±2°C/75% RH±5%RH	12 months 6 months 6 months
2.	Stored in refrigerator	Long term Intermediate	5°C±3°C 25°C±2°C/60% RH±5% RH	12 months 6 months
3.	Stored in freezer	Long term	-20°C±5°0C	12 months

Stability testing methods

At different stages during the process of developing a product. Checking for stability is performed on all pharmaceutical products **[23]**. The accelerated stability research can be used to anticipate pharmaceutical drugs' quick breakdown **[24]**. Depending on the objective and the steps done as well as four many types of consistency testing processes.

1. **Stability testing in real time**
2. **Rapidly conducted stability tests**
3. **Testing the stability of retained samples**
4. **Stress testing at cyclic temperatures**

1. Stability testing in real time

To be able to account for substantial product deterioration in suggested container settings, real-time stability evaluations is often carried out over a long period of time **[25]**. When collecting test samples at regular intervals, the appropriate frequency of data collection enables analytics to detect daily decline **[26]**.

2. Rapidly conducted stability tests

Higher temperatures are used for this form of stability studies testing to assess how pharmaceutical product decomposes **[27]**. Stability studies projections are made for the accelerated stability studies at four distinct stress temperatures **[28]**. This test method's objective is to swiftly determine how long a

specific medicine may maintain its natural qualities and qualities when subjected to extremely unfavourable situations **[29]**.

3. Testing the stability of retained samples

For any product on the market that requires stability, this is standard practice. By selecting one batch to test for one year, stability is determined in this from testing **[30]**. The maximum Any product's shelf life can be presumed to be 5 years, as test samples often last for 3, 6, 9, 12, 18, 24, 36, 48 and 60 months., if the number of samples is greater than 50 **[31]**.The constant interval method is another name for this testing approach **[32]**.

4. Stress testing at cyclic temperatures

The use of this technique for product sampling is less common. For product understanding, cyclic temperature stress tests are used in this method to simulate expected market storage conditions **[33]**. In these tests, sampling is assumed to be governed by a 24-hour cycle known as the Earth's 24-hour rhythm **[34]**.

Guidance of stability studies

The pharmaceutical preparation that will be given to the patient should be optimally stable and all goods are produced in accordance with the recommended standards put out by the WHO, FDA and ICH. The preparation and marketing of the preparation are critically dependent on ICH **[35, 36]**. The ICH was established in 1991 and is a partnership made up of inputs from the China, the European Commission, as well as the US industry along with terms of regulations. As a result, a number of recommendations for the quality of medicinal substances and medicinal products, safety, efficacy and trans disciplinary development have emerged **[37-39]**. A drug regulating body for India is called CDSCO and it is based in New Delhi. The legal criteria differ from one nation to another **[40]**. **Table 3** lists the codes and titles used in ICH guidelines which are useful as testing of pharmaceutical drug product testing.

Table 3: ICH guidelines codes and title [41, 42]

ICH codes	Guideline Titles
Q1A	Stability testing of new drug substances and products`
Q1B	Photo stability testing of new drug substance and products
Q1C	Stability testing of new dosage form
Q1D	Bracketing and Matrixing designs for the stability testing of drug substances and products.
Q1E	Evaluation of stability data
Q1F	Stability data package for registration applications in climatic zones III and IV
Q5C	Stability testing for biotechnological/biological products
Q6A	Specification: test procedures and acceptance criteria for new drug substance and new drug products: chemical substance.
Q6B	Specification: Test procedures and acceptance criteria for new drug substance and new drug products: Biotechnological/biological products.

Climatic Zones for stability studies

These stability assessments cannot vary from location to place and are carried out globally [43]. The WHO has broken down the environmental conditions resulting from long-term storage settings and listed the accurate climatic zones or their usage in studies on the stability of pharmaceutical goods **[44]**. **Table 4** shows various climatic zones for pharmaceuticals with their country specific regions and their temperature and relative humidity. Each country and each climatic zone have different temperature and different relative humidity.

Table 4: Climate zones for storing pharmaceuticals at room temperature [45-48]

Sr.No	Zone	Major Countries	Temp.	RH
I	Temperate	US, UK, Russia, Northern Europe	21°C	45%
II	Tropical/Middle Eastern	Southern Europe, japan	25°C	60%
III	Hot/Dry	India, Iraq	30°C	35%
IV(A)	Hot/Humid	Iran, Egypt	30°C	70%
IV(B)	Hot/Very Humid	Brazil, Singapore	30°C	75%

Stability Study Protocol

One of the steps in the medication development process is stability testing. For the majority of the prepared formulated items, storage conditions and packing are closed using stability data from the stability studies **[49]**. The pharmaceuticals now available on the market and the newly developed drugs may also have an impact on the regimens **[50]**. The following details out to be included in a well- designed stability protocol.

1. Quantity of batches
2. Closures and containers
3. Container storage orientation
4. Time for sampling point
5. Testing Containers Condition
6. Testing variable

1. Quantity of batches

It seems to be challenging to complete stability tests in a single step, stability testing is carried out in batches **[51]**. Stability tests are run on one batch of an item that unaffected by any responses. Studies on stability on three batches seem to be conducted to determine whether the ingredients are unstable when the medicine is first registered **[52]**. Any time among the lots exhibits unstable activity, the stability of the remaining 6 lots is tested; if returning to unsteady activity, the entire formulation must be discarded because it cannot be delivered **[53]**. Initially 3 batches after approval that lasts a long time studies utilising that similar procedure along with the valid medication submissions, should be available instead of the first data, which is not a complete manufacturing batch **[54]**. Primary stability data are not acceptable using laboratory-collected data **[55]**. A random sample is drawn from a series of

pilot or production lots thanks to lot selection **[56]**.

2. Closures and containers

Once the items should be packaged in a appropriate medium, the selection of containers, and closures are essential **[57]**. As is the research of consequently consistency of containers and closures. Aluminium strips, blister packs, Alu-Alu packs and other items are examples of packing materials **[58]**. Secondary packaging may also be included, but not the shipper **[59]**. All products packed with closures should undergo stability tests because an inappropriate container could cause the drug's physical degradation, Prototype containers are accepted for bulk containers **[60]**. The prepared medicine is put in appropriate containers while packing is being completed since unsuitable containers could contaminate the product and diminish the drug's shelf life **[61]**.

3. Container storage orientation

For stability investigations, samples of semi-solid and solution-based medication preparations must be positioned vertically such it's a drug comes into contacting the containers **[62]**. This makes it easier such as understand how and to medicine degrades when it comes into contact with the containers due to a chemical change. The loss or absorption of water may be the source of this deterioration **[63]**.

4. Time for sampling point

To assess the stability profile of such a novel medicinal substance, testing is crucial at specific intervals. Items with a limited shelf life forecast for the initial year, monthly, followed by six months the coming year and every year thereafter **[64]**. At 3 time intervals, at most, such as should have been 0, 3 and 6 months. used in accelerated stability studies **[65]**. Stability retention testing, which uses fewer points, can be used to test the same product with variations in strength, size, etc. Statistical crossfading with framing designs are consequently foundation such as reduced testing programmes **[66]**. Only when specimens are examined for specific design elements, including strength and pack size any more three time intervals as in a whole design, is framing considered a design, the strength, batches, container sizes and intermediate points are just examples of factors that can be manipulated **[67]**. **Table 5** shows the various test schedules for evaluating the stability of new products mainly in that schedule involves the environmental factors, sample techniques and climates.

Table 5: Test schedule for stability testing of new products [68-70]

Environment	Sampling Time Points	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 zoneIVa, or intermediate condition for zones I and II
30°C/75%RH	3,6,9,12,18,24,36	Long term for zoneIVa, or intermediate condition for zones I and II
40°C/75%RH	3,6,9,12,18,24,36	Accelerated condition for all zones

5. Sample Storage Condition

Storage requirements are chosen depending on the climates of the marketing regions for the goods **[71]**. ICH, CPMP and WHO have all provided general recommendations for storage conditions **[72]**.

6. Test parameter

Stability samples must be utilised to evaluate test parameters used in stability investigations. The sample test primarily examines the item's quality, purity, potency and identification, all of which may be affected by the climate **[73]**. In light of this, testing for sterility, preservation techniques, degradation products and microbiological appearance are all important **[74]**. Heavy metals, igniting residues, residual solvents and other test conditions should be met by stability test lots as well **[75]**. The ICH guidelines also cover these tests QA6 **[76]**.

Introduction of CTD (Common Technical Document)

The ICH M4 guideline describes the general organization of the CTD and contains a section on particle size that offers instructions on the placement and pagination of documents inside the CTD dossier **[77]**. If the set document includes numerous indications or multiple components of the investigational medicinal products, the particle size information is extremely helpful **[78]**. **Figure 2** shows The CTD triangle describes the CTD modules in different types along with that module number and name.

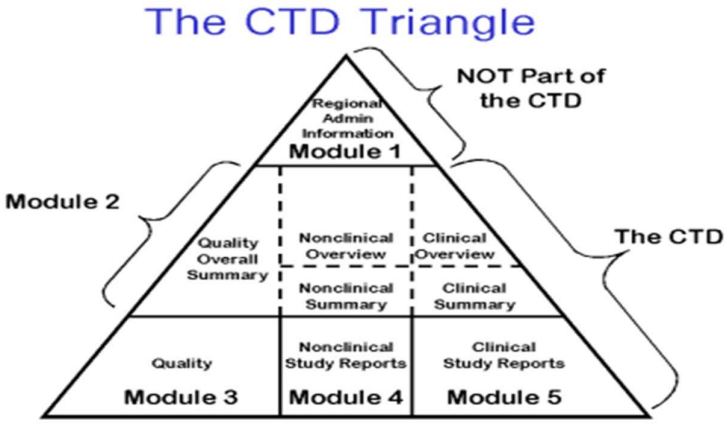

Figure 2: CTD Triangle
Image source: https://www.ich.org/page/ctd

Module 1: Regional and administrative information

Module 2: Quality Overall Summary

Module 3: Quality

Module 4: Non clinical study reports

Module 5: Clinical study reports

Module 1: Regional and administrative Information

This relates to the submission of regional and administrative information to the regulatory authorities of the country in which The applicant wants to submit a

request for marketing permission. in accordance with regulatory guidelines **[78]**. Prescription information (labels, package inserts, etc. also falls under this module. It depends on the country **[79]**.

Module 2: Quality Overall summary

Module 2 Consists of a review and overall summary of chemical, manufacturing, control (CMC), Results of nonclinical and clinical research that support the medicine's efficacy, safety and quality **[80]**. Modules 3, 4 and 5 have summaries in this one **[81]**.

Module 3: Quality

Module 3 addressing every technical and pharmacological area that could have an impact on the drug's quality. drug discovery and development report), production (GMP), evaluation and testing (GLP), packing and storing circumstances and product stability research; to formulation development department **[82]**.

Module 4: Non clinical study report

Module 4 presents a non-clinical report of contained in dossier. The content and format of module 4 are defined in ICHM4 guidelines **[83]**. Module 4 contains the pharmacology, pharmacokinetics, toxicology **[84]**.

Module 5: Clinical study report

This section contains human clinical trials and their reports to list the desired effects of the drug. It should be available to regulatory agencies along with information demonstrating the effectiveness of the medicine **[85]**. The requester is generic medication must demonstrate comparable to the bioavailability of a branded or innovative medication alone **[85]**. Healthy subjects are selected and performed in a controlled manner to perform such bioisostere studies (BA-BEs) **[86]**.

Submission type: eCTD (Electronic common technical document)

No matter the level of the regulatory filling process NDA, ANDA, supplemental NDA, etc. Stability studies are necessary **[87]**. The stability database includes inspection data produced and kept in printed or electronic reports **[88]**. Check the veracity of every aspect in the report **[89]**. Stability reports, which summaries stability data across a product's shelf life, are typically the largest non-clinical element in NDA or ANDA submission **[90]**. A statistical analysis of the currently available data should be included in the stability report, together with a description of the findings for each ICHQ1E or a claim that there are no overarching trends or just minor fluctuation in the data set **[91]**.

Data requirements for submission

The document must contain stability information in the form of module. **Table 6** shows the detailed descriptions of the modules are about submission of stability data are come under CTD module 3 and their subpart of that stability data **[92]**. This **Table**

6 also useful as a final checklist of submission of stability data submission.

Table 6: Data requirements for submission [93-96]

Module 3.P.8.1. (Conclusion and summary for stability)	Module 3.P.8.2 (Stability commitment and stability process after approval)	Module 2.3. P. P.8.3. (Data on Stability)
Stability overview and conclusions includes results and a brief description of the results and if applicable, the recommended expiration date. ➢ Protocol Used ➢ Research Results ➢ Storage Conditions ➢ Strength ➢ Lot sequence ➢ Size ➢ Manufacturing Process type and date ➢ Container and closure system ➢ Conclusion on storage condition along with shelf life.	Stability protocol and post approval obligations. ➢ All relevant stability obligations. ➢ Both must submit stability data if the applicant differs from the pharmaceutical producer. ➢ Post –certification stability protocol commitment required. ➢ If the applicant and the manufacturer of the drug are different entities, both will provide the information. ➢ Meanwhile, after approval, of three production batches proposed shelf life submit into long-term stability research data. ➢ On the other hand, a post approval obligation necessitates the submission of data from Stability studies throughout the long period for the three production batches included in the recommended shelf life	Stability data ➢ In this part, data collected over the whole time frame of stability experiments conducted thus far are succinctly recapped. Preferably as a table. ➢ The lot number must match the test lots listed for the instability records. ➢ Dossier stability data include ➢ Accelerated, ➢ Long-term, ➢ Transient data, ➢ Lot numbers must match those of the test lot.. ➢ Results of stability studies and other test parameters relevant to each lot should be tabulated.

National standards for stability tests

Table 7 describes regulatory guidelines of stability studies testing for all regions for conducting of stability testing of pharmaceutical product testing.

Table 7: Regulatory Stability Guidelines [97-102]

Region	Regulatory agency	Title
Australia	Therapeutic Goods Administration	Stability testing for prescription medicines
Brazil	ANVISA	Guide for stability studies
Canada	Health Canada	Guidance for industry: Stability testing of existing drug substance and products
China	Chinese Pharmacopeia	Guidelines for stability testing of drug substances and preparations.
India	CDSCO	Guidelines for stability testing of pharmaceutical products
Mexico	Health department, Mexico	Stability of drug and medicines
South Africa	Medicines control council	Stability
Europe	European Medicines Agency	Guideline on stability testing: stability testing of existing active substances and related finished products

Current trends in stability research

Pharmaceutical businesses with a global reach are setting the parameters for testing for stability in the current stability studies trend **[103]**. Companies do this by focusing their procedures on one particular set of requirements and it includes extremely challenging ecological circumstances **[104]**. Additional testing will be conducted at 50°C/75% RH for 90 days and the accelerated testing duration will be increased from six to twelve months **[105]**.

Because all tests are conducted in a single facility, the idea This change is being made to prevent repeating stability evaluation of additional locations seem to be use resources as effectively and efficiently as possible **[106]**. Additionally, it has been claimed that testing under a combination of climate, hazard, as well as illumination has a better detrimental effect as of drug compounds and items than testing in temperature and humidity settings alone **[107-109]**.

CONCLUSION:

The development of novel pharmaceuticals and formulations depends heavily research on the stability of therapeutic goods, which have made and simple that forecast estimated storage of impact ecological nature conditions on item deterioration. Every departure from a stated a characteristic of stability could compromise the product's effectiveness, safety and quality. In order to verify that now the treatment is safe, effective such as the duration Stability tests are performed to determine the product's shelf life in order to identify the appropriate storage parameters and storage stability on the label. Therefore, stability testing should be carried out in accordance with good scientific practises and after having a thorough awareness of the current legal requirements and climate zones.

Abbreviations

Sr.No	Abbreviations	Term
1.	CTD	Common Technical Document
2.	RT	Room temperature
3.	RH	Relative Humidity
4.	ICH	International Council of Harmonisation
5.	WHO	World Health Organization
6.	eCTD	Electronic Common Technical Document
7.	FDA	Food and drug administration
8.	USA	United states of America
9.	CDSCO	Central Drug Standard Control Organization
10.	NDA	New Drug Application
11.	ANDA	Abbreviated New Drug Application
12.	EMEA	European Medicine Evaluation Agency
13.	CPMP	Committee for Proprietary Medicinal Products

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Conflict of Interest

The authors have no Conflict of Interest to declare**.**

Author contributions

NS conceived and organized the presented idea in review paper with the help of listed references. HD contributed in analysing and reviewing the manuscript. All authors have

critically reviewed and approved the final draft.

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Consent for publication

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