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AN OVERVIEW OF STABILITY TESTING GUIDELINEs OF PHARMACEUTICAL PRODUCTs

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ABSTRACT:

Stability studies must be carried out according to guidelines set forth by the ICH, WHO, and/or other authorities in an organized manner. Stability testing's main goal is to learn how to create drug products and their packaging so that they have the right physical, chemical, and microbiological characteristics for a specified shelf life when kept and used in accordance with labels(4). For the acceptance and approval of any pharmaceutical product, stability studies of the product are required to ensure the maintenance of product quality, safety, and efficacy during the Stability studies must be carried out according to guidelines set forth by the ICH, WHO, and/or other authorities in an organized manner life . In this review, we have included the importance of stability testing, various method of stability testing, types of the Stability of drug substance(1).

KEYWORD: : Stability testing, stability studies, pharmaceutical products, ICH guidelines.

INTRODUCTION:

pharmaceutical product Stability is a complex process collection that requires considerable time, expense, use & Scientific expertise to develop pharmaceutical Formulation effectiveness quality & Safety. Scientific commercial success of a pharmaceutical product can only be secure with the under Standing of the drug dev. process & the multitude lasts milestones that are vital to a comprehensive development plan(1,5). A pharmaceutical product's capacity to maintain its physical, chemical, microbiological, toxicological protective & informational Specifications in a certain container or closure system is known as stability Regulatory agencies demand stability testing as a crucial component of pharmaceutical development programs in order to build & maintain high quality goods(2,4). Various stages of the drug development process include stability studies. In the early stages of medication development, accelerated stability studies are carried out to ascertain the rate of product deterioration if stored for a longer period of time under particular circumstances(17).

IMPORTANCE OF STABILITY TESTING:

> Due to the decrease of the drug's dose form product instability of the active ingredient may result in under medication.
> The drug or product may produce harmful byproducts when it breaks down.
> It is the only way to know for sure if a medicine meets the requirements for acceptance or not.
> Gaining knowledge of how API deterioration can impact the standard of the pharmaceutical product .
> Evaluating the state of product shelf life and the processing the development of new products.
> The main justification for stability testing is the concern for the use during the stability period and the health of the patient with the disease under test. However, system effectiveness and drift control for the items are designed.
> By guaranteeing that the product will remain fit for use with respect to all functionally relevant attribute for as long as they are on the market ,the manufacturer reputation will be protected.

TYPES OF STABILITY STUDIES ON DRUG SUBSTANCE:

The standard for acceptable levels of physical ,chemical, microbiological, therapeutic, and toxicological stability tests are set forth in a thorough pharmacopoeia protocol (USP).

• Physical Stability

• Chemical Stability

• Microbiological Stability

• Therapeutic Stability

• Toxicological Stability

Physical Stability :

The original physical characteristics , including color ,dissolution, palatability , and suspend ability ,have been preserved(34).

Physical Stability is crucial for the efficacy and safety of the product because it may have an impact on uniformity and release rate(4).

Chemical Stability:

Drug's chemical Stability decline as degradation occur the active ingredient's chemical properties and measurable strength are within the specified range(4,34).

Microbiological Stability:

Medication propensity for resistance to sterility and microbial growth is referred to as their Microbiological Stability . within certain parameters , the anti microbial agent used in the formulation retained their efficacy. The sterile drug products may be in danger as a result of this microbial instability(34).

Therapeutic stability :

The Therapeutic outcome want's change(4,34).

Toxicological stability:

Significantly , enhance toxicity does not happen(4,34).

TYPE OF STABILITY TESTING:

Stability testing are four different types:

1) Long term stability
2) Intermediate stability
3) Accelerated stability

Table 1 : Type of stability studies

Study	Storage condition	Minimum time period covered by data at submission
Long term	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

METHOD OF STABILITY TESTING:

Stability testing is common practice used on pharmacological substance and Product as different phases of drug development. The four types of stability testing process have been based on the objective and involved . these are

1) Real-time stability testing

2) Accelerated stability testing

3) Retained sample stability testing

4) Cyclic temperature stress testing.

Real time Stability testing:

Testing for stability in real time stability testing typically lasts longer than the test term to allow for appreciable product deterioration under advised storage circumstances(4). The duration of the product test is determined by its stability, which indicates unequivocally that it is neither deteriorated or broken down over an extended length of time due to inter-assay variance. During the testing process, samples are taken at regular intervals to ensure that data is obtained at the right frequency and the analyst can detect daily decline. By adding the one batch of reference material for which stability characteristic have been determined , the data can be increased. The tools and reagents used in this should remain consistency throughout the stability testing(1,35).

Accelerated stability testing :

A product is strained at many high temperatures and the quantity of heat input necessary to send the product to a condition that accelerates degradation in an accelerated stability test.

After that, this data is projected to estimate shelf life or utilized to contrast the relative stability of different formulations. This typically gives a head start on a product's shelf life, cutting down on the amount of time needed

for development. During accelerated stability testing, stress conditions such as moisture, light, agitation, gravity, pH, and packing are applied in addition to temperature. For statistical reasons, treatment is recommended in terms of accelerated stability predictions at four different stress levels; nevertheless, for thermolabile and protein portions, relatively accurate stability predictions are obtained when denaturing stress temperature is avoided(36,37).

The Arrhenius equation predicts the accelerated stability studies with ease.

$$K = Ae^{(-Ea)/RT}$$

Where,

K= Specific rate constant

A= Frequency factor or Arrhenius factor

E a =activation energy

R= Real gas constant 4.184 j/mol. K

T= Absolute temperature, k

The temperature between degradation rate and storage temperature is expressed by this equation.
For some degradation processes, the Arrhenius equation can be used to project stability based on the deterioration rate seen at high temperature.

Retained sample stability testing :
This is standard procedure for any product that is commercialized and needs stability data. Stability samples are chosen for this investigation in order to be kept in storage for at least one batch per year. It is advised to gather stability samples from two batches if there are more than 50 batches being marketed. Tests are conducted on stability samples at prearranged intervals. For this reason, it is customary to test a product at 3, 6, 9, 12, 18, 24, 36, 48, and 60 months if its shelf life is five years. This is standard procedure for any product that is commercialized and needs stability data. Stability samples are chosen for this investigation in order to be kept in storage for at least one batch per year. It is advised to gather stability samples from two batches if there are more than 50 batches being marketed. Because it tests the product in real-world settings as well as under idealized retained sample storage conditions, this kind of stability sampling testing is by its very nature more realistic. A modified way of verifying stability is the examination of market samples, which entailed taking samples that were already available and assessing the stability attributed to them. Since these tests put the product to the test in both real-world settings and the idealized retained sample storage situation, they are by nature more realistic(38).

Cyclic temperature stress testing :
Stress testing in cycles When developing or troubleshooting for stability testing, temperature is a very helpful aspect for pharmaceutical scientists, however it is not good for ordinary product testing. Using this approach, cyclic temperature stress tests are created with product knowledge to replicate possible market storage circumstances. The sampling in this experiment is thought to be done in cycles of twenty-four hours, or what is known as the earth's 24-hour rhythm. It is advised that the lowest and maximum temperatures for the cyclic stress test be chosen product-by-product, taking into account things like the product's suggested storage temperature and unique physical and chemical degradation characteristics. Additionally, it is advised that the test typically consist of 20 cycles. This is not how advertised products are typically tested(1,2,4).

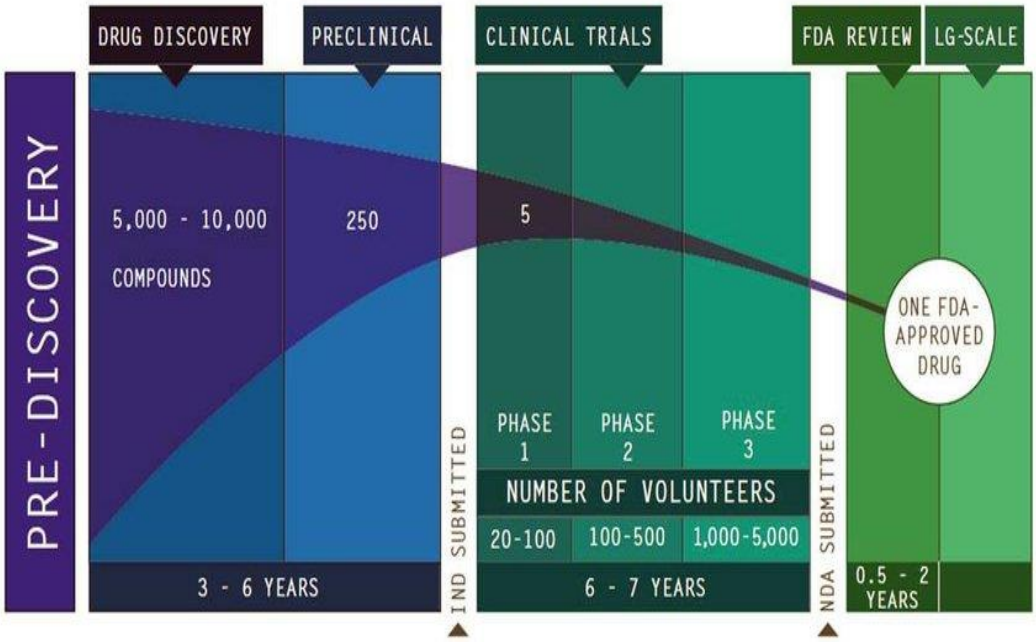

Fig.1 Stability during various stages of drug development process

Table 2 : codes and titles used in ICH guidelines

ICH codes	Guideline titles
Q1A	Stability testing of new drug substances and products (second revision))
Q1B	Photo stability testing of new drug substances 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	Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
Q6B	Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological/Biological Products

Q1A: stability testing of new drug substances and products : The standard establishes the stability data package for a new drug substance or drug product that is necessary for a registration application within the three regions of the EC, Japan, and the US. It is an updated version of the ICH Q1A standard. The guideline covers the data that must be included in applications for registration of novel molecular entities and related pharmaceutical products. The information required to be submitted for variants, clinical trial applications, shortened or abridged applications, etc., is not currently covered by this guideline(14,15).

Drug Substances and drug product -
1) Stress testing :It aids in the identification of probable degradation products, but only those that arise during prolonged and rapid storage. It establishes the molecule's intrinsic stability and its pathway of destruction. It validates the analytical procedure's indicating power, which is dependent on the specific drug substance and drug product type, and is tested on a single batch(15).
2) Selection of batch : at least three main groups , its was produced at least on a pilot scale , using the same artificial path , the manufacturing process and procedure should mirror the ultimate product, the standard of quality that will be produced on a large scale(14).
3)Container closure system : It is important to talk about the decision and justification behind choosing the container closure method for the commercial goods. The drug product's intended usage and the container's suitability should be taken into account.
4) Closing system for shipping and storage, encompassing the storage and When applicable, a delivery container for a drug product in bulk(14). The product is tested in the suggested retail closures and immediate containers. Aluminum blister packs, Alu-Alu packs, aluminum strip packs, HDPE bottles, and other materials are used in the packaging(17).
5) Specifications: The specifications cover all the tests needed for different dosage forms, as well as the accepted analytical process and its stability indication, which are covered in ICH Q6A and Q6B. The profile of the material as it is utilized in the pre-clinical and clinical batches should be used to determine the limits of acceptability. The material used in pre-clinical investigations and clinical trials should be utilized as a basis for the justification of the inclusion of individual and total upper limits for impurities and degradation products(16,25,26,28).
6) Storage condition : The following conditions apply to storage: room temperature, refrigerator, freezing and thawing, and moisture residue. Conditions of storage for zones 1, 2, 3, and 4.The climate zone in which the product is anticipated to be sold or for which regulatory permission is being sought will determine the best storage condition.

Q1B:Photo stability testing of new drug substances and products: Light testing need to be an integral aspect of stress testing, according to the ICH Harmonized tripartite guideline on novel drug substances and stability testing for products (also known as the parent guidelines). This paper addresses the photo stability evaluation guidelines and is an appendix to the parent guideline. One batch of carefully chosen materials is subjected to photo stability testing in accordance with the parent specifications(4).

Q1C:Stability testing of new dosage form :To make clear what was required for a new dosage form or line extension by the original submission's holder, stability testing of new dosage forms was written. The requirements from Q1A are met in this instance, albeit there might be less data needed at the time of submission. Using bracketing or matrixing to cut down on the amount of testing related to the registration stability program is mentioned in the parent advice(12).

Q1D:Bracketing and matrixing design for stability testing of drug substances and products: Bracketing -It is the stability schedule's design to test only samples at the extremes of a given design factor (such as strength or container size) during the whole design process. The design makes the assumption that the stability of the tested extremes represents the stability of any intermediate levels Matrixing -The process of creating a stability schedule using matrixing involves choosing a portion of all potential samples to test at a given time interval for each factor combination. Another subgroup of the sample for every factor combination would be evaluated at a later time point. The design makes the assumption that, at any given time, the stability of every evaluated subset of samples represents the stability of all samples(10).

Q1E:Evaluation of stability data: The assessment of stability data that must be included in registration applications for novel molecular entities and related pharmaceutical products is covered by this guideline. Retest intervals and shelf life for pharmaceutical substances and drug products meant for storage at or below "room temperature" are recommended by the guideline. It covers stability investigations using full or reduced designs and single- or multi-factor systems.

Q1F:Stability data package for registration applications in climatic zones 3 and 4 :The storage conditions for stability testing in countries located in Climatic Zones III (hot and dry) and IV (hot and humid), i.e., countries not covered by ICH Q1 A (R2) Stability Testing for New Drug Substances and Drug Products, are defined by the ICH Q1 F Stability Data Package for Registration Applications in Climatic Zones III and IV. In order to streamline drug accessibility by lowering the variety of storage settings, ICH Q1 F outlined standardized worldwide stability testing standards. WHO surveyed its member states during the talks that resulted in the establishment of the recommendation to establish agreement on 30°C/65% RH as the long-term storage conditions for hot and humid region(4).

Q5C:Stability testing for biotechnological/biological products: This guideline covers clearly characterized proteins and polypeptides, as well as their byproducts and derivatives, that are produced using r-DNA technology or extracted from tissues, cell cultures, bodily fluids, or other sources. Thus, the document covers the creation and submission of stability data for goods like insulin, monoclonal antibodies, erythropoietin, plasminogen activators, blood plasma factors, growth hormones and growth factors, cytokines (interferons, interleukins, colony-stimulating factors, tumor necrosis factors), and vaccines made of well-characterized proteins or polypeptides.

CONCLUSION: In the pharmaceutical development program , stability testing is now the primary process factor for a new medicine or new formulation. Stability tests are preformed to make sure the medication is safe and effective for the duration of it's designated shelf life under storage and shelf life circumstances. As a result, the stability test ought to be carried out in accordance with accepted scientific methods and an understanding of the climate zone, present regulatory requirements, and both.

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