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STABILITY TESTING OF PHARMACEUTICAL PRODUCTS

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ABSTRACT

Stability testing is a crucial part of the pharmaceutical development process that ensures the safety, efficacy, and quality of a drug product throughout its shelf life. This testing involves subjecting the product to various environmental condition, such as temperature, humidity, and light, to evaluate how these factors affect its physical, chemical, and microbiological properties. Stability studies help determine the appropriate storage conditions, expiration date, and packaging requirements for a pharmaceutical product. The tests are typically conducted under accelerated, intermediate, and long-term conditions, with samples analyzed at predefined intervals. The data obtained from stability testing also play a critical role in a regulatory approval process, providing evidence that the product remains within specifications throughout its intended shelf life. Furthermore, stability testing is an ongoing process that continuous post-market to monitor any potential changes or degradation that may occur during distribution or consumer us. This paper reviews the principles, methodologies, and importance of stability testing, highlighting its role in ensuring the reliability of pharmaceutical products in the market.

KEYWORDS: *Stability testing, ICH Guideline, Shelf life*

INTRODUCTION

Stability testing of pharmaceutical products is a complex set of procedures which involve considerable cost, time consumption and scientific expertise in order to build in quality, efficacy and safety in a drug formulation. Scientific and commercial success of a pharmaceutical product can only be ensured with the understanding of the drug development process and he myriad tasks and milestones that are vital to a comprehensive development plan. Stability testing is termed as a complex process because of involvement of a variety of factors influencing the stability of a pharmaceutical product. These factors include stability of the active ingredient (s); interaction between active ingredients and excipients, manufacturing process followed, type of dosage form, container/closure system used for packaging and light, heat and moisture conditions encountered during shipment, storage and handling.

Stability studies are carried out at various stages of the drug development process. At early stages of drug development, accelerated stability studies are performed to determine the rate of degradation of the product if stored for longer period under specific conditions. After that, forced degradation study is carried out to check the effect of external stressed conditions on the drug product.

The stability of finished pharmaceutical products depends, on the one hand, on environmental Factors such as ambient temperature, humidity and light, and, on the other, on product-related Factors, e.g. the chemical and physical properties of the active substance (API) and of pharmaceutical excipients, the dosage form and its composition, the manufacturing process, The nature of the container-closure system and the properties of the packaging materials for established drug substances in conventional dosage forms, literature data on the decomposition process and degradability of the active substance are generally available together with adequate analytical methods. Thus, the stability studies may be restricted to the dosage forms.

FACTORS AFFECTING DRUG STABILITY[4]

- Stability of the Active Pharmaceutical Ingredient (API) from storage
- Interaction between the API and excipient –during Formulation Development
- Selection of dosage form
- Manufacturing process of drug product
- Selection of container closure packaging system
- Effect of storage (temperature, humidity and light)
- Selection of marketing image
- Handling of the finished products

IMPORTANCE OF STABILITY STUDIES

- Product instability of active drug may lead to under medication due to lowering concentration of the drug in dosage form.
- During decomposition of active drug toxic products may be formed.
- Instability may be due to changing in physical appearance though the principles of kinetics are used in predicting the stability of drug there different between kinetics and stability study.
- To protect the reputation of the manufacturer by assuring that the product will retain fitness for use with respect to all functionally relevant attributes for as long as they are on the market.

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Table 1: Types of Stability Studies

Study Type	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

TYPE OF STABILITY OF DRUG SUBSTANCE

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

Chemical Stability: Each active ingredient retains its chemical integrity and labelled potency within the specified limits. The Chemical stability of drug is of great importance since it becomes less effective as it undergoes degradation. Also drug decomposition may yield toxic by-products that are harmful to the patient.

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

Therapeutic Stability: The therapeutic effect remains unchanged.

Toxicological Stability: No significant increase in toxicity occurs.

GUIDELINES FOR STABILITY TESTING

To assure that optimally stable molecules and products are manufactured, distributed and given to the patients, the regulatory authorities in several countries have made provisions in the drug regulations for the submission of stability data by the manufacturers. Its basic purpose was to bring in uniformity in testing from manufacturer to manufacturer. These guidelines include basic issues related to stability, the stability data requirements for application dossier and the steps for their execution. Such guidelines were initially issued in 1980s.

These were later harmonized (made uniform) in the International Council for Harmonization (ICH) in order to overcome the bottleneck to market and register the products in other countries. The ICH was established in 1991, it was a consortium formed with inputs from both regulatory and industry from European commission, Japan and USA and various guidelines for drug substance and drug product came into existence regarding their quality, safety and efficacy. These guidelines are called as quality, safety, efficacy and multi-disciplinary (also called as Q, S, E and M) guidelines.

The World Health Organization (WHO), in 1996, modified the guidelines because the ICH guidelines did not address the extreme climatic conditions found in many countries and it only covered new drug substances and products and not the already established products that were in circulation in the WHO umbrella countries.

In June 1997, United States Food and Drug Administration (US FDA) also issued a guidance document entitled 'Expiration dating of solid oral dosage form containing Iron. WHO, in 2004, also released guidelines for stability studies in global environment.7 ICH guidelines were also extended later for veterinary products.

Table 2: Codes and titles used in ICH Guidelines

ICH Code	Guideline title
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 Matrix Designs for 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 of Biotechnological/Biological Products

The International Conference on Harmonization (ICH) guidelines 'stability testing of new drug substances and products requires that stress testing should be carried out to elucidate the substance. It suggests that the degradation products that are formed under the variety of condition should include the effect of temperature, humidity where appropriate oxidation, photolysis and susceptibility to hydrolysis across a wide range of pH value.

CLIMATIC ZONES FOR STABILITY TESTING

For the purpose of stability testing, the whole world has been divided into four zones (I - IV) depending upon the environmental conditions the pharmaceutical products are likely to be subjected to during their storage. These conditions have been derived on the basis of the mean annual temperature and relative humidity data in these regions. Based upon this data, long-term or real-time stability testing conditions and accelerated stability testing conditions have been derived.

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Table 3: ICH Climatic zones and long term stability conditions

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

***MAT - Mean annual temperature measured in open air.**

HISTOLOGICAL BACKGROUND

Jordan was the one to give the name for Stability testing in the pharmaceutical companies. The need arose when regional office organized a workshop for validation of expiry dates of drug in Amman .The workshop ordered every medical authority to collaborate with every pharmaceutical company to guide them about the Importance of drug stability and expiry date.

Thus International Conference on Harmonization thus took a step to implement these guidelines. FDA issued its first stability guidance in 1987.Considerable efforts were taken, to harmonize the stability practices within the ICH region then after in the early 1990. As a result to the efforts, International Conference on Harmonization (ICH) was established in 1991 and various guidelines for drug substance and drug product came into existence regarding their quality, safety and efficacy. These guidelines are called as quality, safety, efficacy and multidisciplinary (also called as Q, S, E and M) guidelines.

In 2000, discussions began between the International Conference on Harmonization (ICH) expert working group Q1 (stability) and the WHO to harmonize the number of stability tests and conditions employed Worldwide, With The approval of the drug regulatory authority.

STABILITY TESTING PROTOCOL

Stability testing is the systematic approach towards drug development process. Stability data for the drug substance are used to determine optimal storage and packaging conditions for bulk lots of the material. The stability studies for the drug product are designed to determine the expiry date or shelf life.

The protocol for stability testing is a pre-requisite for starting stability testing and is necessarily a written document that describes the key components of a regulated and well-controlled stability study. Because the testing condition is based on inherent stability of the compound, the type of dosage form and the proposed container-closure system, the protocol depends on the type of drug substance or the product. In addition, the protocol can depend on whether the drug is new or is already in the market.

A well designed stability protocol should contain the following information:

- Number of Batches
- Containers and closures
- Orientation of storage of containers
- Sampling time points
- Test storage conditions
- Test parameters
- Test methodology
- Acceptance criteria

EXPIRATION DATE/SHELF LIFE

An expiration date is defined as the time up to which the product will remain stable when stored under recommended storage conditions. Thus, an expiration date is the date beyond which it is predicted that the product may no longer retain fitness for use. Shelf life is the time during which the product, if stored appropriately as per the manufacturer's instructions, will retain fitness for use (>90% of label claim of potency). The expiration date is also defined as the date placed on the container/labels of a drug product designating the time during which a batch of the product is expected to remain within the approved shelf life specifications, if stored under defined conditions and after which it should not be used.

CONCLUSION

Stability testing is now the key procedural component in the pharmaceutical development program for a new drug as well as new formulation. Stability testing of pharmaceutical products the key procedural contribution in the development program for a new drug as well as new formulation. Any deviation from the established stability profile could affect the quality, safety and efficacy thorough understanding of the stability of the drug substance and drug product is important to "build the quality in". Stability tests are carried out so that recommended storage conditions and shelf life can be included on the label to ensure that the medicine is safe and effective throughout its shelf life. Over a period of time and with increasing experience and attention, the regulatory requirements have been made increasingly stringent to achieve the above goal in all possible conditions to which the product might be subjected during its shelf life. Therefore, the stability tests should be carried out

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following proper scientific principles and after understanding of the current regulatory requirements and as per the climatic zone.

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