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Regulatory Requirements and Innovation: A Comparison of Stability Study in the United States Food and Drug Administration (USFDA) and the Gulf Cooperation Council (GCC)

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ABSTRACT
Stability studies form a crucial aspect of the pharmaceutical development process and play a vital role in establishing the quality, safety and efficacy of the drug product. The core objective of a stability study is to ascertain the shelf-life of a drug product and to understand how best to design the drug product and its container-closure system so as to ensure that the same maintain suitable physical and chemical properties during the proposed shelf-life period. Since stability studies are inherently crucial to the lifecycle of a pharmaceutical formulation, the process and its requirements are subject to stringent regulations and specifications by regulatory authorities around the globe. A multitude of guidelines have been published in this regard by various regulatory authorities entailing concepts, techniques and protocols associated with stability testing, with the aim of aiding drug manufacturers generate accurate and viable stability data. Most of these guidelines, however, are based on the International Council for Harmonisation (ICH) stability guidelines and have been adapted by individual regulatory authorities to complement the climatic conditions of the respective regions, two such examples being the United States Food and Drug Administration (USFDA) and the Gulf Cooperation Council (GCC). Therefore, the present work aims to briefly discuss the stability guidelines applicable in each region and identify any similarities and differences, whilst examining the documentation requirements related to stability studies as well as the dossier requisites to be adhered to during drug product registrations.
Key words: Stability study, USFDA, GCC, ICH, WHO.

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INTRODUCTION

In the field of pharmaceutical sciences, drug safety as a concept has forever been an essential factor to be considered at the time of drug manufacture as well as post-manufacture. Given the significance that is laid on drug safety as a whole, several measures are employed by pharmaceutical manufacturers to analyse and assess the quality and efficacy of drugs at various lifecycle phases. Though most of these tests are not widely known, as opposed to measures like clinical studies, they are of equal importance. Stability study is one such example.

Stability studies are termed as a set of complex procedures that involve the application of considerable scientific expertise, to carry out tests in a time-bound manner, aimed at understanding and enhancing the quality, efficacy, and safety of a drug formulation in varied environmental as well as exposure-based conditions. To be more accurate, they can be defined as "the capability of a said drug product in a particular container or closure system to remain within its specified physical, chemical, microbiological, toxicological and informational specifications throughout its period of storage and use".[1] Stability testing usually involves procedures that ascertain how the quality of a drug product correspondingly shows variation with time in varied environmental conditions such as temperature, light and humidity. Further, they help identify possible physical, chemical and micro-organism induced changes that the drug product can undergo on storage, thereby furnishing data on the robustness of the finished pharmaceutical product. This enables pharmaceutical manufacturers to establish the shelf life and recommended storage conditions of a drug formulation along with the subsequent retest periods.[2]

Owing to the unequivocal importance of stability testing in establishing safety and efficacy profiles of drug products, regulatory authorities world-over require drug manufacturers to carry out the requisite tests at the time of drug development to furnish sufficient evidence of the stable nature of the formulation in various environmental conditions. Although a number of international and national regulatory agencies have issued guidance documents for the conduct of stability studies, it is seen that predominantly, most major regulatory markets follow ICH and WHO stability guidelines as these guidelines are inherently developed in a harmonised manner thereby enabling the generation of right-first-time stability data by drug manufacturers. In order to further aid drug manufacturers in their endeavour to deliver right-first-time stability data, regulatory authorities across the world have adopted, designed and modified these requirements to further suit their respective regions and countries.[3]

Although guidelines for stability testing around the world have been based on the ICH and WHO guidelines, the manner of adoption of these guidelines and the subsequent interpretation of the same by individual regulatory authorities respectively has potentially opened the door for a discussion on how these guidelines vary in different pharmaceutical

jurisdictions. A compelling example for such a discussion will be a comparison between the dossier requirements for stability studies prescribed by the USFDA and the GCC, as these regions represent differing economic, cultural and geographical conditions. For the purpose of drawing conclusive parallels across similar parameters, the comparison shall be carried out using sustained-release oral dosage forms as subject formulations.

STABILITY TESTING

Based on the phase of drug development or stage of drug development, the objective of a stability study can be determined. In the initial stages of development, a stability study is aimed at ascertaining the intrinsic rigidity of the drug product and the possibility of it reacting with other excipients. This phase also seeks to assess the possibility of acidity, alkalinity, humidity, oxidation on exposure to atmosphere and light, affecting the stability of the product. Following this, stability testing will seek to determine the extent of the stable nature of the physico-chemical properties of the drug product, which in turn helps in discerning the potential decomposition routes. This is primarily achieved by the conduct of accelerated stability studies.

Apart from this, stability testing carried out during the pre-formulation phase of a drug product aims at listing out solvents that can be employed in pre-clinical toxicological investigations Similarly, during the conduct of clinical studies, stability studies are employed to affirm the stability and data-integrity of all batches of drug formulations tested during the trials. In the case of New Drug Applications (NDA), manufacturers are required to submit data supporting claims of stability of the drug formulation over a specified period of time, under prescribed storage conditions.[4] A stability study can include a wide set of elements ranging from physico-chemical properties, presence/absence of excipients, type of packaging, transportation, storage to a predisposition to oxidation, reduction, hydrolysis or racemization. Additionally, stability studies intend to determine the possible effects that chemical reactions like solvolysis and racemization may result in such as the formation of degradation product, reduced effectiveness of active pharmaceutical ingredient, reduced excipient effectiveness like degrading the antioxidant property, etc.[5]

On the basis of main aim of the stability testing, i.e. to provide sufficient evidence of product quality over the duration of shelf-life and consumption, stability testing can be categorised into four different categories.

Real-time stability testing

Real-time stability testing is carried out by pharmaceutical manufacturers with the intention of permitting significant drug-product degradation under pre-determined storage conditions. This test is usually performed for prolonged durations, in order to signify the lack of credible degradation occurring in adverse conditions for the drug product. A trend-analysis method is employed where data will be collected at pre-determined frequencies and the same is used to differentiate between day-to-day uncertainty and any possible instability. The duration for a real-time study may range from a minimum of 6 months upto 5 years, based on the characteristics of the drug product being tested.

Accelerated stability testing

As the name suggests, accelerated stability testing is employed by subjecting the formulation under elevated conditions of stress, such as extremely high temperatures (higher than ambient), moisture, light, pH, etc., which is likely to cause product degradation at a rapid rate. The objective of this method of testing is to quickly estimate the duration for which a given pharmaceutical product can maintain its inherent quality characteristics and properties when exposed to severely adverse conditions. Although the product is subjected to extreme conditions, the same is done under laboratory conditions with controlled changes in each of the applicable parameters. Additionally, accelerated studies aid pharmaceutical manufacturers in releasing drug products early into the market upon the successful completion of the study.

Data generated through accelerated studies is acknowledged by international regulatory authorities, but it is only accepted when the same can be reproduced by 'long-term test' samples to prove the shelf-life of the drug product. Therefore, accelerated stability studies are normally carried out in a concurrent manner with the accelerated stability test.[6]

Retained sample stability testing

This category of stability testing is conducted for all drug products that are marketed actively. It involves carrying out prescribed tests on a minimum of one batch a year of the final drug product retained for storage. This is applicable when the overall number of batches marketed is 50 or less than 50. In cases where the number of batches marketed is in excess of 50, the guidelines state that two batches of the retained final drug product shall be tested. In this method, testing is carried out at pre-determined time intervals based on the shelf life of the drug product to be tested. A more modified version of this test includes the use of samples collected from the pharmaceutical market, thereby ensuring that the products tested are from a more realistic scenario as compared to ideal storage-retained drug product samples.[7]

Cyclic temperature stress testing

Cyclic temperature stress testing is not generally carried out for all drug products made available in the market. This method is based on the principle of temperature-based stress tests, planned on the basis of drug formulation information available in a cyclic manner. To best mimic, the conditions experienced by marketed products, this test is carried out in a 24-hr cycle (in conjunction with the diurnal-rhythm of earth's 24-hr rotation cycle). Whilst deciding the temperature range to be utilised in this test, a product-to-product approach is adopted which shall include consideration for aspects such as storage temperature suggested on the label, as well as any other relevant properties of the formulation. Finally, in the event of the conduct of this test, manufacturers are recommended to carry out a test comprising of a minimum of 20 cycles.[8]

A fundamentally key aspect of stability testing is the storage condition of the drug product. Stability tests must accurately mimic the exposure-conditions of the drug product, right from the initial stages of manufacturing to the latter stages of storage. Since storage conditions of a product are found to directly correspond to real-life climatic conditions, the ICH and the WHO have geographically divided the earth into five distinct zones. These zones are as stated in Table 1.

These five zones are reproduced in long-term stability tests to simulate the conditions worldwide that a formulation of API is likely to be subjected to. The geographical division of five zones was carried out based on mean annual temperatures recorded in each of these regions along with the relative humidity (RH) data procured. The higher the temperature-humidity conditions, the greater the likelihood of product degradation. Further, along the lines of the aforementioned data obtained, the ICH published region-based long-term and accelerated stability conditions to be observed when carrying out stability tests for drug substances/products to be marketed in the respective zones.[9] Table 2 indicates long-term prescribed by the ICH for the five climatic zones.

Accelerated stability studies are majorly conducted by drug product manufacturers in their respective facilities or through means of an accredited external testing laboratory. These studies are typically conducted at 40°C ± 2°C and 75 % ± 5 % RH for a minimum duration

of 6 months, and these conditions are commonly accepted across all the five climatic zones. Accelerated stability testing helps discern possible degradation products that can be anticipated under long-term storage conditions and this provides manufacturers the opportunity to modify the drug product suitably in order to avoid the formation of such degradation compounds over the drug storage duration up until final consumption. During the conduct of any stability study, the drug product or formulation shall be tested in accordance with the ICH storage conditions applicable, evaluating the thermal stability of the drug as well as its reactivity to moisture. For example, if the drug in question is developed in a Zone I region and is subsequently shipped to Zone IV region for marketing via transportation channels passing through Zones I and II, then the drug product will have to be evaluated for stability in accordance with conditions prescribed for Zones I, II and IV.[10]

Apart from the aforementioned conditions, ICH also describes storage conditions to be tested in case of refrigeration of the drug substance/product. These conditions are as specified in Table 3.

STABILITY TESTING FOR SOLID ORAL DOSAGE FORMS

Since the advent of the age of modern medicines, drug delivery via the oral route has most commonly been accepted and preferred by patients and doctors alike. It can be said that most therapeutic agents are preferentially administered via the oral route owing to factors ranging from an increased patient acceptance, purported ease with which the drug is administered, accuracy in dosing and cost-effective drug manufacturing techniques. For example, conventional oral dosage forms have been found to be lacking in terms of patient compliance and also pose potential issues arising due to see-saw fluctuations in drug concentrations in the bloodstreams. As is known, maintaining optimum concentrations of the therapeutic agents in plasma within the therapeutic index is a critical factor for ensuring effective treatment.[11] Therefore, limitations associated with conventional oral dosage forms can pose poor efficiency in treatment, repetitive dosing, and unpredictable absorption, eventually resulting in any number of adverse effects. Let us take the example of sustained release dosage forms which are intended to control the rate of drug release whilst maintaining the desired drug concentration in the plasma, in a manner that is considered to be therapeutically effective and non-toxic for prolonged durations. The rationale behind the development of a sustained-release drug product is to optimise the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of the drug product, as compared to a conventional oral drug product, thereby effectively reducing dosage frequency and instances of local and systemic side-effects.[11,12]

Keeping this in mind, the manufacturers of such dosage forms give higher priority to these factors during the development of the drug product and also, any probable interactions between the formulation and the packaging used during delivery, transport, and storage are thoroughly probed.[13]

Table 1: Climatic zones for stability testing.

Climatic Zone	Conditions
Zone I	Temperate
Zone II	Sub-tropical/Mediterranean
Zone III	Hot/Dry
Zone IV a	Hot/Humid
Zone IV b	Hot/Higher humidity

Table 2: Long-term testing conditions as per climatic zones.

Climatic Zone	Conditions	Long-term Testing Conditions	
		Temperature	Humidity
Zone I	Temperate	21°C ± 2°C	45% RH ± 5% RH
Zone II	Sub-tropical/ Mediterranean	25°C ± 2°C	60% RH ± 5% RH
Zone III	Hot/Dry	30°C ± 2°C	35% RH ± 5% RH
Zone IVa	Hot/Humid	30°C ± 2°C	65% RH ± 5% RH
Zone IVb	Hot/Higher humidity	30°C ± 2°C	75% RH ± 5% RH

STABILITY TESTING FOR SOLID ORAL DOSAGE FORMS IN THE US AND IN THE GCC

Before the institution of the ICH guidelines, the FDA followed stability guidelines titled "Guidelines for Submitting Documentation for Stability of Humana Drug and Biologics.", which were published in the year 1987. However, from the year 1993 onwards, the USFDA together with regulatory authorities from the European Union and Japan, instituted the ICH guidelines and this lead to the implementation of ICH Q1-stability guidelines. Further, the USFDA decided to integrate all ICH guidelines that were not discussed or resolved at the ICH forum into a wholistic combined text/document. This guidance document incorporated stability study requisites to be followed at all stages of drug development, site-specific stability studies and post-approval changes (PACs). Of all ICH stability guidelines proposed and implemented, ranging from Q1A-Q1F, Q5C, the USFDA chose to adopt all with the exception of guidelines Q1F – Stability Data Package for Registration Applications in Climatic Zones III and IV. However, going ahead, Q1F was withdrawn in the year 2006. The United States of America is categorised under the temperate zone, i.e. zone 1, after analysing the effect of climatic conditions. In addition to the ICH guidelines, the USFDA adheres to stability guidelines which are not of ICH origin.[14] These include the documents specified in Table 4.

On the other hand, the GCC follows a relatively simple set of guidelines when it comes to stability testing. In the year 2005, GCC put forth a stability guideline which was of a generalised nature and applicable to all pharmaceutical products developed and manufactured in the GCC member nations. This guidance document was revised periodically with its final version 3.1 being published the year 2013 on the behest of the Executive Board of the Health Ministers' Council of GCC States. The majority of this guidance document has been based on the ICH stability guidelines and the WHO stability studies guidelines, 2009 for APIs and finished formulations. Member nations of the GCC are categorised under either climatic zone III (hot/dry climate) or IVa (hot/humid climate), on the basis of analysing the effects of climatic conditions. In GCC, the guidance title is "The GCC Guidelines for Stability Testing of

Table 3: Storage conditions for long-term and accelerated stability studies in refrigeration and freezer conditions.

Type of Study	Storage Conditions
For drug substance/product meant to be stored in refrigerators	
Long term stability testing	5°C ± 3°C
Accelerated stability testing	25°C ± 2°C / 60% ± 5% RH
For drug substance/product meant to be stored in freezers	
Long term stability testing	-20°C ± 5°C

Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs)".[15]

DISCUSSION

The mode of submission followed by both USFDA and GCC is eCTD format. The dossier requirements for stability testing in US and GCC for sustained released tablets are comprehensively in the article. The stability testing in the US should be conducted for the first three batches of the drug product simulating the production batches and the applicant shall submit data from 3 or 2 pilot-scale batches. If the size of pilot-scale batch does not follow the ICH recommendations, the applicant shall provide a justification. Whereas GCC follows ICH guidelines which recommend the stability testing of the single batch at developmental phase. For registration of finished pharmaceutical product (FPP), stability testing of at least 3 batches of initial production batch is required. In the US, at the time of submission applicant shall provide 6 months of data that include accelerated and long term condition. On the other hand in GCC, long term testing is applicable for the projected shelf life of a minimum of 12 months, once every 3 months, 6 months and once a year in 1st, 2nd and subsequent years respectively. In accelerated testing, three data collection points are instituted at 0, 3 and 6 months. Both the USFDA and GCC conduct stability testing on the proposed formulation in the proposed container for marketing. Photostability testing in the US has been recommended on one primary batch, in accordance with guidelines prescribed under ICH stability-Q1B.

The dossier of both the countries should contain stability information in the form of modules.[16,17] The modules are as follows:

Module 2.3.P.8.1 Stability summary and conclusions: This module will address the summarisation of all studies conducted with the purpose of disseminating stability. Includes a brief discussion of the outcomes and results as well with proposed shelf life mentioned, if necessary.

Module 2.3.P.8.2 Post-approval stability protocol and commitments: This module furnishes all relevant stability commitments. In the event of the applicant differing from the formulation manufacturer, both are liable to furnishing stability data.

Module 2.3.P.8.3 Stability Data: Data generated across the entire duration of the stability study conducted thus far will be briefly summarised under this section, preferably in a tabular format. This shall necessarily include the following:

- Batch numbers shall match the test batches mentioned instability records.
- Batches used shall be from the primary batches.

Even though the USFDA and GCC follow the same dossier format, the structure of dossier varies in the following manner:

Module 2.3.P.8.1: In case of the dossier prepared by USFDA includes writeup of primary batch analysis and proposed expiration period, differences among the packages or storage conditions whereas in case of GCC, the stability summary and conclusion includes types of studies conducted, the protocol used, results of studies should be summarised, the summary should include information about storage condition, strength, batch number, size, type and manufacturing date, container and closure system, conclusions with respect to storage conditions and shelf life. In-use stability studies should be conducted in accordance with GCC guidelines.

Module 2.3.P.8.2: The post-approval stability protocol commitments are necessary for USFDA. If the applicant and drug product manufacturer are different entities, both will provide stability commitments. On the other hand, the submission for long term stability data on three production batches covering the proposed shelf-life period, post-approval commitment is necessary. If the submission includes data from stability studies on three or less than three production batches, written commitment should be made to continue these studies.

Module 2.3.P.8.3: The stability data of USFDA dossier includes accelerated, long term and intermediate data. Batch numbers should be the same as a test batch. However, in the case of GCC, results of stability studies should be presented in tabular form and the results of all testing parameters related to each batch.

Table 4: Non-ICH stability guidelines adopted by USFDA.

Organisations	Guidance Title
Office of Regulatory Affairs	CPG Sec. 480.100 Requirements for Expiration Dating and Stability Testing
Office of Regulatory Affairs	CPG Sec. 480.300 Lack of Expiration Date of Stability Data
Centre for Drug Evaluation and Research	Expiration Dating and Stability Testing of Solid Oral Dosage Form Drugs Containing Iron
Office of Regulatory Affairs	CPG Sec. 280.100—Stability requirements Licensed In Vitro Diagnostic Products
Centre for Drug Evaluation and Research, Centre for Biologics Evaluation and Research, Centre for Veterinary Medicine	Container and Closure System Integrity Testing In lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products
Centre for Biologics Evaluation and Research	Guidance for Industry: Testing Limits in Stability Protocols for Standardized Grass Pollen Extracts
Centre for Drug Evaluation and Research	Guidance for Industry: ANDAs—Stability Testing of Drug Substances and Products
Centre for Drug Evaluation and Research	Guidance for Industry: ANDAs—Stability Testing of Drug Substances and Products, Questions and Answers

CONCLUSION

Over the years, stability studies have undoubtedly emerged as an indispensable procedural component in the development of active pharmaceutical ingredients as well as finished pharmaceutical products. With due importance being given to these tests, a corresponding increase in attention to the regulatory requirements for the conduct of the same has been warranted, which has duly achieved realisation at regional, national and international levels. The passage of the ICH guidelines as well as the WHO guidelines for stability was a true breakthrough in achieving enhanced harmonisation of stability study requirements across different regions. These guidelines essentially act as a mainstay for stability requirements, providing a strong framework for individual regulatory authorities to implement them in a suitable manner based on the climatic conditions of the respective regions. As witnessed in the case of the USFDA and the GCC, both the regulatory bodies have predominantly prescribed their stability study requirements along the lines of the ICH requirements, thereby ensuring the presence of a multitude of similarities and resultantly aiding pharmaceutical manufacturers in bringing stable pharmaceutical products to the market. While a few differences are witnessed, such as the specific requirement for a photostability study in the US and the lack of intermediate testing

in the GCC, on the whole, the similarities are found to far outweigh the variances.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ABBREVIATIONS

USFDA: United States Food and Drug Administration; **GCC:** Gulf Cooperation Council, **ICH:** International Council for Harmonisation; **WHO:** World Health Organisation; **NDA:** New Drug Application; **RH:** Relative Humidity; **SR:** Sustained Release; **PACs:** Post-approval changes.

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