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A Review of Regulatory Guidelines on Stability Studies

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ABSTRACT

Stability could be an essential quality attribute; so, the stability program plays a very important role while manufacturing fresh pharmaceutical products. Particularly, this is in regard with the pharmaceutical preparations or formulations, which are to be distributed in various strengths and various types of packages for the purpose of marketing. It involves many samples to be tested at a given cost, and also involves testing large number of samples of various strengths, package types, many batches of different storage conditions, testing parameters and testing intervals. To design a successful stability-testing program, there are many regulatory guidance documents that should be consulted. These guidance documents provide information on how to conduct a stability program to ensure that appropriate data are generated in support of a new drug substance or product. This paper discusses the various guidelines governing the stability studies, particularly the FDA (Food and Drug Administration), ICH (The International Conference on Harmonization), CPMP (Committee for Proprietary Medicinal Products), & WHO (Word Health Organization)-their rules, regulations, and recommendations regarding stability studies. In this paper, details regarding the formation of International Conference on Harmonization, the regions involving it, the suggestions made by them, and the various guidelines issued by it, relating not only to stability studies but many other aspects relating to it, and an overview of various ICH stability guidelines, their names and the codifications, have been described briefly.

Keywords: Stability Studies, Regulatory Guidelines, FDA, ICH, CPMP, WHO.

INTRODUCTION

Stability may be an essential criterion for confirming quality and approval of the various manufactured preparations. So, stability studies may be an important element of manufacturing trade. Manufacturing industries depend upon the information on stability studies to assign shelf-life for the formulation manufactured and distributed for the purpose of marketing and also to make sure of the potency and safety of the drugs [1].

Stability studies on of drugs revolves around various details pertaining to the research and development process, such as preparation of formulation, performing analytical studies on it, and its quality check-and all of these have great influence on the regulatory aspects, starting from the synthesis of drug to formulation of the drug, its approval and marketing. Stability studies should be carried out on all the batches of a product and on various aspects. The resultant data obtained should be satisfactory enough to fulfil all the parameters till the end of its shelf-life or expiry period, and thus becomes capable to be approved and registered by the regulatory bodies. Stability of a drug is an important criterion to confirm the medicinal integrity [1].

Present study summarizes various guidelines related to stability testing and their significance for the testing protocols.

Need and Purpose of regulatory guidelines

In order to make sure that good products are prepared, which may be potent enough to last till their stability period, marketed well and reaches the people in need on time, authorities in many countries have stressed that the information regarding the potency or stability of drug or shelf-life period of the same should be made available by the manufacturers. The intention was to usher in similar testing methods by all manufacturers. The guidance embody the simplest problems associated with potency of drugs/stability, the information on how to apply for manufacture of a product by providing the necessary information regarding the potency or stability or shelf-life of the product and the methods to bring them into action. These types of guidance were first released in 1980s [2].

Brief history

FDA issued its first guidance in 1987 [1]. Food and Drug Association guidelines have stressed upon:

1. Incorporating study designs on stability of drugs, establishing accurate expiration date, the methods of storage and the care to be taken during storage of drugs.

2. To submit the data on the stability study of investigational new drugs, biologicals, new drug applications, and the biological product license application.

Subsequently, various regulatory authorities of various countries developed their own guidelines. These guidelines had various discrepancies and did not conform with each other, so a strong need was felt to harmonize the guidelines. Efforts were made in 1990s to bring uniformity in the stability practices in the ICH regions (United States, Europe and Japan)[1]**.** At a later date they were made uniform within the ICH, in order to promote and make registration of the products in different places. The International Conference on Harmonisation, was a union where suggestions were given regularly from regulatory as well as manufacturing industries of ICH regions (i.e., The three countries like, Europe, Japan & United States). ICH guidelines were also extended later for veterinary products [2,3].

Benefits of Regulatory harmonization

Regulatory harmonization offers several direct advantages to each authority passing regulations, and also the manufacturing trade having useful benefits needed to protect the health of the people. The main advantages are, avoidance of repetition of clinical trials in human beings, thereby minimizing the testing on animals and without side-lining the safety and effectiveness, regulating or forming the process for assessing new drug applications; and minimizing the time of development and the costs incurred for developing the drugs [2,3]. Slow but great evolvement in the International Conference on harmonization from the time of its implication in 1990, has taken place and in its initial period of coming into effect, ICH has seen good development particularly in the fields of safety, quality and efficacy aspects. Activities took place on various important topics like multidisciplinary topics, which included MedDRA (Medical Dictionary for Regulatory Activities) and the CTD (Common Technical Document) [1,24,5].

Revision & Codification of ICH guidelines

In November 2005, the International conference on harmonization Steering Committee allotted new codes to the ICH Guidance's. The intention of allotting new codes was to make sure; no confusion occurs and it makes things easy for practical implementation. Based on the number of times the revisions were made, codes like (R1), (R2), (R3) were assigned. This was done to make the ICH codification of guidelines clearer to all. Many annexures have also currently been added to the main guidance and are termed as revisions to the main or core guidance (e.g., R1) [1,2,4,5].

General Categories of International Conference on Harmonization Guidance

The ICH guidance is classified into four groups and codes have been allotted depending on these groups [1,4,5].

"Q" Guidelines: These are Quality Guidelines. Harmonization achievements inside the standard area embody vital milestones just like the methods of understanding studies on stability of drugs, setting of minimum thresholds required for testing impurities in the drugs involved in the studies, and to assess the quality of the products manufactured as per the Good Manufacturing Practice (GMP) risk management [2,4,5]. The "Q" guidelines released by the ICH are listed in the **Table 1.**

Table 1: Showing ICH 'Q' Guidelines

"Q" Guidelines	
Q1 A – Q1 F	Stability Guidelines
Q2	Analytical validation
Q3 A – Q3 D	Impurities
Q4 – Q4 B	Pharmacopoeias
Q5 A – Q5 E	Quality of Biotechnological products
Q6 A – Q6 B	Specifications
Q7	Good Manufacturing Practices
Q8	Pharmaceutical Development
Q9	Quality Risk Management
Q10	Pharmaceutical quality system
Q11	Development and manufacture of Drug Substances
Q12	Lifestyle Management

Source: (ICH.org)

"S" Guidelines: These are Safety guidelines which includes guidance's on safety, to rule out serious problems like cancer, gene toxicity, and toxicity to the kidneys. The "S" guidelines released by the ICH are listed in the **Table 2.**

Table 2: Showing ICH 'S' Guidelines

"S" Guidelines	
S1 A – S1 C	Carcinogenicity studies
S2	Genotoxicity studies
S3 A – S3 B	Toxicokinatics and Pharmacokinatics
S4	Toxicity testing
S5	Reproductive Toxicology
S6	Biotechnologycal Products
S7 A – S7 B	Pharmacology studies
S8	Immunotoxicology studies
S9	Nonclinical Evaluation for anticancer Pharmaceuticals
S10	Photosafety Nonclinical safety Testing Evaluation
S11	Nonclinical safety Testing

Source: (ICH.org)

"E" Guidelines: Efficacy guidelines governing the method of designing trials, carrying on trials, the safety steps adopted and the submission of report regarding the clinical trials undertaken. In addition, it governs the different important types of medicinal products which are got by adopting various biotechnological procedures. In addition, the usage of pharmacokinetics and pharmacogenomics techniques in manufacturing best medicines [2,4,5]. The "E" Guidelines released by the ICH are listed in the **Table 3**.

Table 3: Showing ICH 'E' Guidelines

"E "Guidelines	
E1	Clinical safty for drugs used in long term treatment.
E2 A- E2 F	Pharmacovigilance
E3	Clinical study reports
E4	Dose responce studies
E5	Ethinic factors
E6	Good clinical practice
E7	Clinical trials in Geriatric Population
E8	General considerations for clinical trials
E9	Statistical Principals of clinical trials
E10	Choice of control group for clinical trials
E11	Clinical trials in Pediatric Population
E12	Clinical Evaluation by Therapeutic Category
E14	Clinical Evaluation
E15	Definitions in Pharmacogenetics and Pharmacogenomics
E16	Qualifications for gwnomic Biomarkers
E17	Multi-regional Clinical Trials
E18	Genomic sampling methodologies

Source: (ICH.org)

"M" Guidelines: Multidisciplinary guidance are the cross-cutting topics that don't work unambiguously within the standard groups governing the Safety and efficacy groups. It comprises of the International Conference on Harmonization medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI) [2,4,5]. The "M" Guidelines released by the ICH are listed in the **Table 4**.

Table 4: Showing ICH 'M' Guidelines

"M" Guidelines	
M1	MedDRA terminologies
M2	Electronics standards
M3	Nonclinical Safety Studies
M4	Common Technical document
M5	Data Elements and standards for drug dictionaries
M6	Gene therapy
M7	Genotoxic impurities
M8	Electronic common technical document (eCTD)

Source: (ICH.org)

GUIDELINES FOR STABILITY STUDIES

ICH and FDA Stability Regulatory Guidelines

Introduction

Stability testing for product registration is one of the areas covered by international conference on harmonization (ICH) guidance documents. The ICH jointly governs the regulators and the industries involved in research from E U, United States, as well as Japan focusing on all its technical requirements for medicinal products containing new drugs. This organization was initiated in the early 1990s and stability testing was one of the first topics to proceed through the stepwise process to recognition by the regulatory bodies from all three region [6].

Stability studies are currently an important method adopted within the manufacturing industries to develop brand new drug and new products. Stability study is often applied to suggest the conditions favourable to store the products and it highlights the fact that, the potency period or the expiry date of the drug has to be shown on the outer cover of packaging of the drugs for marketing, suggesting the drug to be safe and potent in its efficacy till its expiry date mentioned on the outer cover of the packaged product. are applied to suggested storage conditions and shelf life may be displayed on the label to confirm that the drug is safe and effective throughout its shelf life. Regulatory necessities are done more and more tight to attain the maximum goal in every potential condition to that the drug may well be placed throughout its shelf life. Hence the stability studies may be conducted after adopting good scientific principles, by properly knowing the present regulations governing the same and also keeping in mind the climatic zones [4].

Guidelines: A series of guideline documents were developed in order to clearly mention the stability information needed to register the new drug substances and products within the ICH regions. The stability studies performed to support product registration should comply with these guidance documents. Currently, there are five guidance documents available. They begin with:

Q1A, stability testing of new drug substances and products [2,6,7], which provides the basic protocol for stability studies for registration. For both new drug substances and new drug products, this guidance states the number and the types of batches, stability container closure systems, storage conditions, and time points that should be studied to support registration. It specifies that appropriate tests, analytical methods, and proposed acceptance criteria should be used, but references the ICH guidance documents on specifications and impurities for more detailed information. In addition to the general guidance on stability studies needed for registration, this document discusses stress testing of new drug substances and the required commitment to provide additional information on stability studies under taken on at least three production batches through the suggested retest time or till the expiry date, if not submitted in the original registration document [2,6,7].

The remaining four documents supplement this general protocol guidance. There is guidance **Q1B,** photo stability testing of new drug substances and products [2,6,8]. This document provides instruction for carrying out photo stability studies on new drug substances and drug products to show that light exposure will not negatively impact the materials. The testing outlined is performed on one batch from the registration stability study and is a stepwise approach with exposed drug substance, exposed drug formulation, drug formulation soon after packaging, and the drug formulation packaged, for its distribution, as necessary.

Guidance **Q1C,** stability testing of new dosage forms [2,6,9], was written to clarify the requirements for a new dosage form or line extension by the holder of the original submission. In this case, the requirements from Q1Aare followed, but less data may be required at the time of submission. In the parent guidance, Q1A, there is a mention of using bracketing or matrixing to reduce the amount of testing associated with the registration stability program.

Guidance **Q1D**, bracketing and matrixing designs for stability testing of drug substances and drug products [2,6,10], was written to provide more detailed guidance on the topic. This guidance discusses when each of these techniques may be considered and provides examples of them. It also discusses the potential risks with using these reduced testing designs.

The fifth guidance, **Q1E**, evaluation of stability data [2,6,11], provides additional information relating to the method of evaluating and analysis of the information generated, statistically following the Q1A guideline. This document provides a stepwise process for evaluating stability data and extrapolating that information acquired to suggest the expiry date of the product. It discusses the application of linear regression, pool ability tests, and statistical modelling to stability data for registration.

To supplement these guidance documents for the study of biotechnology products, an additional guidance was written. **Q5C,** quality of biotechnological products: stability testing of biotechnological/ biological product [2,6,12], gives additional details for the stability testing of biotechnological/biological products for product registration.

These guidance documents provide only the core requirements of the registration stability program. They do not provide all of the detail necessary to develop and manage the stability program in support of new product registration. Additionally, the abbreviated applications for registration of generic drug products is out of scope of the ICH documents but general principles may be taken from these guidance documents when studies to support registration are developed. In the past, the FDA provide additional stability guidance in a document issued in the year 1987, guideline for submitting documentation for the stability of human drugs and biologics [13]. This document was followed by a draft FDA guidance issued in the year 1998, guidance for industry: stability testing of drug substances and drug products [14].

It combined the **ICH Q1AR2** with many different International Conference on Harmonization guidance's. This guidance became a basic referral guidance to all those carrying on studies on stability of drugs. International Conference on Harmonization issued Q1F guidance in the year 2004, which suggested stability study programmes carried on in order to support zone 3 and 4. Later on, the Association of South East Asian Nations (ASEAN) voiced regarding the conditions necessary for extremely hot and humid climate that are to be followed and implemented [1].

Both of the documents (the stability guidance passed in the year 1987, and the stability draft guidance passed in the year 1998), were withdrawn by the Food and Drug Association, in the year, June 2006.

As a consequence, the ICH Q1F guideline withdrawn by the International Conference on Harmonization in July in the year 2006. As a part of the initiation taken by the agency, pharmaceutical current good manufacturing practices (cGMPs) for the 21st century came into being [1,15,16].

The QbD, quality-by-design concepts in drug development introduced by the Food and Drug Association became the most discussed topic of all times [1].

The names of the guidelines and their respective codes assigned to them by the International Conference on Harmonization guidance have been shown in the **Table 5** for easy reference [2,3].

Table 5: Codes and Titles Used in ICH Guidelines

ICH Code	Guideline title
Q1A	Stability testing of New Drug Substances and Products (Second Revision)
Q1A (R2)[2]	Stability testing of new drug substances and products[2]
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 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

Source: (ICH.org)

The guidelines took into account the climatic regions, besides various factors that effected the stability. Specific guidelines were drafted for each of the product for specific drug delivery system. Moreover, guidelines for inferences from the accelerated studies were also framed.

CPMP Stability Guidelines:

Series of guidance associated with stability studies involving stability of drugs are additionally released by the Committee for Proprietary medicinal products (CPMP) which comes under the European Agency for the Evaluation of Medicinal Products (EMEA) in order to assist those people seeking marketing authorization for medicinal products in European Union beyond their adoption of the ICH guidance [3,6].

These guidance documents are as follows:

Guidance **CPMP/QWP/122/02,** Stability Testing of Existing Active Substances and Related Finished Products [17].

Guidance **CPMP/QWP/576/96,** Stability Testing for applications for variations to a marketing authorization [18], provides necessary information required to carry out studies on stability of drugs, that should be generated in support of variations made to a marketing authorization. It provides some examples of variations and the types and amounts of stability data that would be expected to support them.

Guidance **CPMP/QWP/2934/99**, In-use Stability Testing of human medicinal products [19], provides necessary information required to carry out stability studies to establish the amount of time a multidose product can be used after it has first been opened.

Guidance **CPMP/QWP/159/96,** Maximum shelf-life for sterile products for human use after first opening or following reconstitution [20], states that studies should be conducted to support the practical use of sterile products. It also provides sample wording to include in user labelling specifying the appropriate hold times and storage conditions once the product is opened, diluted, or reconstituted.

Guidance **CPMP/QWP/609/96,** declaration of storage conditions: A: In the product information of medicinal products, B: for active substances [21], is an additional information (annexure) to the ICH stability guidelines documents providing uniform storage condition statements for products. On the basis of the stability data generated following the ICH guidance, an appropriate storage condition labelling statement is suggested along with additional storage statements, where relevant.

Guidance **CPMP/QWP/072/96,** start of shelf-life of the finished dosage form [22], outlines how to calculate and assign expiration date of a drug product on the basis of the date of release or date of production. The guidelines are listed for easy reference in **Table 6**.

Table 6: Codes and Titles Used in ICH Guidelines

CPMP code	Guideline title
CPMP/QWP/ 576/96 Rev.1	Guideline on Stability Testing for Applications for Variations to a Marketing Authorization
CPMP/QWP/ 6142/03	Guideline on Stability Testing for Active Substances and Medicinal Products Manufactured in Climatic Zones III and IV to be marketed in the EU
CPMP/QWP/ 609/96 Rev.1	Note for guidance on Declaration of Storage Conditions for Medicinal Products Particulars and Active Substances
CPMP/QWP/ 122/02 Rev.1	Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products
CPMP/QWP/ 072/96	Note for Guidance on Start of Shelf Life of the Finished Dosage Form
CPMP/QWP/ 2934/99	Note for Guidance for In-Use Stability Testing of Human Medicinal Products
CPMP/QWP/ 576/96	Note for Guidance on Stability Testing for a Type 2 variation to a Marketing Authorization
CPMP/QWP/ 159/96	Note for Guidance on Maximum Shelf-Life for Sterile Products after First Opening or Following Reconstitution

The WHO Stability Guidelines

The World Health Organization (WHO) has also issued guidance on the performance of stability studies [6]. World Health Organization commenced the work on stability studies in the year 1988 [1].

Guidance for stability studies of manufacturing products made up of drug substances in the conventional dosage forms were issued as annexure 5 to the World Health Organization Expert Committee on Specifications for Pharmaceutical Preparations Technical Export Series, No:863, 1996 [23].

Failure of the international conference on harmonization guidelines to raise up the extreme climatic conditions seen in many countries and its coverage only on the new drug substances and products and no guidelines available on the products already being circulated in the markets in the countries coming under the preview of the World Health Organization umbrella countries [3]. The World Health Organization brought about certain modifications in the international conference on harmonization in the year, 1996. This guidance was revised in 2003 and 2006 because of changes in the long-term storage conditions to support climate zone IV regions [24,25]. Guidance on stability testing in global environment were also released by the World Health Organization in the year, 2004 [3].

The first draft of the new World Health Organization, stability guidance's were provided for comments and suggestions in the year, April 2007. The second draft was made available in October in the year, 2007 based on the WHO eastern Mediterranean region stability guidelines [1].

The India Drug Manufacturers Association, have additionally released the technical monograph on stability testing of new drug substances and products in India. Further, other testing conditions and requirements have also been given in the guideline particularly for active pharmaceutical ingredients, drug products or formulations and excipients [3]. As for other countries not mentioned specifically, many have adopted either the ICH or the WHO guidelines as the basis for their stability testing requirement [6].

CONCLUSION

Present study sums up the important land marks in the development of the guidelines for stability studies. It is hoped that a ready to start reference is generated by the study. FDA, ICH, CPMP, & WHO guidelines of specific conditions for stability studies and specifically, ICH Q1A (R2) are needed to be taken into account for stability study.

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