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Review Article

Overview of Regulatory Guidelines for Stability study of Pharmaceuticals: Review

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ABSTRACT

The safety, efficacy and quality of a pharmaceutical product plays a crucial role in product development, stability study ensures the following about the product. Shelf life of a product is consider for its acceptance and approval. These stability studies are conducted by following guidelines issued by international regulatory agencies such as ICH, WHO etc. These guidelines provide a plan to conduct the stability study, various methods are involved in performing stability studies. The environment plays an important role in quality of a product, the stability studies helps to retain product specified limits throughout its period of storage and use. Which helps in determined its shelf life. In this overview the guidelines and trends of stability testing are briefly described.

INTRODUCTION

Stability is an essential criterion for confirming quality and approval of the various manufactured preparations. Pharmaceutical 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. Stability studies 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 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. In order to make certain that good products are prepared, which may be potent enough to last till their shelf life time, marketed

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well and reaches to the people on time, regulatory authorities in many countries have emphasize 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 commission the similar testing methods by all pharmaceutical 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.

STABILITY STUDY: HISTORY IN BRIEF

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

A. Incorporating study designs on stability of drugs.
B. Establishing accurate expiration date.
C. The methods of storage and the care to be taken during storage of drugs.
D. To submit the data on the stability study of investigational new drugs,
E. Biological, new drug applications, and the biological product license application.

Along these lines, different administrative specialists of different nations adopted their own rules. These rules had different disparities and didn't adjust with one another, so a solid need was felt to fit the rules. Endeavors were made in 1990s to acquire consistency the solidness rehearses in the ICH areas (Joined together States, Europe and Japan). Sometime in the future they were made uniform inside the ICH, to advance and make enlistment of the items in better places. The Global Meeting on Harmonization, was an association where ideas were given routinely from administrative as well as assembling enterprises of ICH areas (i.e., the three nations like, Europe, Japan and US). ICH rules were additionally expanded later for veterinary items

International Conference on Harmonization (ICH) was established in 1991 and different guidelines for drug substances came into existence regarding their quality, safety, efficacy and multi-disciplinary (also called as Q, S, E, M) guidelines.

Categorization of ICH guidelines

In November 2005, the Global meeting on harmonization Controlling Board of trustees distributed new codes to the ICH Direction's. The aim of designating new codes was to ensure; no disarray happens furthermore, it makes things simple for useful execution. In view of the number of times the amendments were made, codes like (R1), (R2), and (R3) were doled out. This was finished to make the ICH codification of rules more clearly to all. Numerous annexures have likewise presently been added to the fundamental direction and are named as modifications to the principal or center direction (e.g., R1) The ICH guidance is classified into four groups and codes have been allotted depending on these groups.

Q Guidelines

Table 1: Q - Guidelines & codes

Q1A-Q1F	Stability Guidelines
Q2	Analytical validation
Q3A-Q3D	Impurities
Q4-Q4B	Pharmacopoeias
Q5A-Q5E	Quality of Biotechnological products
Q6A-Q6B	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

Table 2: S - Guidelines

S1A – S1C	Carcinogenicity studies
S2	Genotoxicity studies
S3A-S3B	Toxicokinetic and Pharmacokinetics
S4	Toxicity testing
S5	Reproductive Toxicology
S6	Biotechnological Products
S7 A- S7B	Pharmacology studies
S8	Immunotoxicology studies
S9	Nonclinical Evaluation for anticancer Pharmaceuticals
S10	Photo safety Nonclinical safety Testing Evaluation
S11	Nonclinical safety Testing

Table 3 – E Guidelines

E1	Clinical safety for drugs used in long term treatment.
E2 A- E2F	Pharmacovigilance
E3	Clinical study reports
E4	Dose response studies
E5	Ethnic factor
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 Evaluation by Therapeutic Category
E12	Clinical Evaluation
E14	Definitions in Pharmacogenetics and Pharmacogenomics
E15	Qualifications for gwnomic Biomarkers
E16	Multi-regional Clinical Trials
E18	Genomic sampling methodologies
E1	Clinical safety for drugs used in long term treatment.
E2 A- E2F	Pharmacovigilance

Table 4 – 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)

CLIMATIC ZONES

The International Council for Harmonization (ICH) has established four distinct stability zones to guide the pharmaceutical industry in the stability testing of drugs. These zones represent different climatic conditions worldwide to ensure that pharmaceutical companies test products under environmental conditions similar to where they will be stored and used. Each zone has specific temperature and humidity conditions that simulate

the climatic environment of various geographic regions.

Table 5 – ICH Stability Zones & Testing conditions

Zone	Temperature	Humidity	Description	Minimum Duration
Zone I	21^0C	45%	Temperate Zone	12 Months
Zone II	25^0 C	60%	Mediterranean/Subtropical Zone	12 Months
Zone III	30^0 C	35%	Hot/Dry Zone	12 Months
Zone IV	30^0 C	65%	Hot Humid/Tropical Zone	12 Months
Zone IVb	30^0 C	75%	Hot/Higher Humidity Zone	12 Months

The WHO Guidelines for stability

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 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. Guidance on stability testing in global environment were also released by the World Health Organization in the year, 2004. 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.

CONCLUSION

Steadiness testing is presently the vital procedural part in the drug improvement program for another medication as well as new definition. Steadiness tests are done so that suggested capacity conditions and time span of usability can be remembered for the mark to guarantee that the medication is protected and successful all through its rack life. Over a timeframe and with expanding experience and attention, the administrative prerequisites have been made progressively severe to accomplish the above objective in all potential circumstances to which the item may be oppressed during its rack life. Therefore, the dependability tests ought to be completed following legitimate logical standards and after understandings of the ongoing administrative necessities and according to the climatic zones. Present review summarizes the significant land marks in the improvement of the rules for steadiness studies. It is trusted that a prepared to begin reference is produced by the review. FDA, ICH, CPMP, and WHO rules of explicit circumstances for dependability studies and explicitly, ICH Q1A (R2) are required to have been considered for solidness study.

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