STABILITY STUDIES OF PHARMACEUTICAL & COSMETIC PRODUCTS

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Dedicated to
the Pharmacists
who have developed
stable pharmaceutical products

Preface

Whether a drug or a cosmetic, it should be of quality, efficacious and safe upto the recommended date of expiry or best use before date. How does a manufacturer of a drugs or cosmetics assures that? It is by carrying out stability studies. The purpose of stability studies is to monitor changes that may occur while storing drug substances and drug products over time at different storage conditions.

There are international, regional and national guidelines on stability studies of pharmaceutical products. However, there are no Indian guidelines for carrying out stability studies on drugs or cosmetics. WHO guidelines are international guidelines. These guidelines are applicable to both new drugs as well as existing drugs. The ICH guidelines are applicable to new drug substances and their formulations. ICH guidelines are applicable in ICH region (i.e. US, Europe and Japan).

ASEAN has framed stability studies guidelines for pharmaceutical products and are applicable in all ASEAN countries. National stability studies guidelines are applicable to the country to which these belong.

If a manufacturer of drugs desires to have certificate of pharmaceutical product (COPP) under the WHO certification scheme, he will be required to carryout stability study on drug products according to the WHO stability guidelines. When a drug manufacturer wants to export drugs to ASEAN countries, regulatory authorities of these countries would require stability studies according to the ASEAN stability studies guidelines.

Considering these requirements, I have compiled the information on WHO, ICH and ASEAN stability studies guidelines. Before carrying out stability studies, a pharmaceutical chemist should have sufficient knowledge about the factors which influence stability of pharmaceutical and cosmetic products and also about developing stability indicating methods (SIM). Chapters on these topics have been included in the book.

There are no formal guidelines for carrying out stability studies on cosmetics. European Association of Cosmetics and Perfumery Manufacturer, COLIPA has framed guidelines for stability studies on cosmetic products. National Health Surveillance Agency of Brazil has published cosmetic products stability guide which has useful information to carry out stability studies on cosmetics. Based on these information, a chapter has been added in this book on the stability studies of cosmetic products.

I hope, this book will be useful to pharmaceutical & cosmetic chemists, pharmacy faculty & students and regulatory officers. I look forward to readers and critics for their opinion on the book. I am thankful to all those who have helped me in collecting information. I am especially thankful to the WHO for permitting to reproduce WHO Stability Studies Guidelines for pharmaceutical products and the Director General, Executive Board of the Health Ministries Council for GCC States for permitting to reproduce GCC Stability Testing Guidelines.

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Regulatory Requirements for Stability Studies

1. INTRODUCTION

All regulations regulating pharmaceutical products whether national, regional or international have requirements for stability studies of pharmaceutical products. Stability is an essential factor in quality, safety and efficacy of pharmaceutical products. If pharmaceutical product is not of sufficient stability, it can result in change in physical characteristics (like hardness, dissolution rate, phase separation etc) and/or chemical characteristics (formation of degradation products). Microbiological instability of a product could also be hazardous.

The object of stability studies is to provide evidence of how the quality of active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP) varies with time under the influence of a number of environment factors such as temperature, humidity, light. The stability studies program also include the study of product related factors that influence its quality e.g. interaction of API with excipients, container closure systems and packaging materials. In fixed dose combinations (FDCs), interaction between two or more APIs has also to be considered.

Another important object of stability studies is to determine the shelf-life or re-testing period of API or FPP.

The stability studies consist of a series of tests in order to determine the stability of an API or FPP i.e. maintenance of the specification of the API or FPP in its specified packaging material and stored in the established storage conditions.

Various national, regional and international bodies have issued guidelines for conducting stability studies on pharmaceutical products. Some of the important guidelines are:

International

World Health Organization (WHO) – Stability testing of active pharmaceutical ingredients and finished pharmaceutical products – appearing in Annex-2 to WHO Technical Report Series No. 953, 2009.

Regional

International Conference on Harmonization of Technical Requirement for Registration of Pharmaceutical for Human Use (ICH).

ICH Q1A (R2) – Stability Testing of New Drug Substances and Products

ICH Q1B – Stability Testing: Photostability Testing of New Drug Substances and Products

ICH Q1C – Stability Testing for New Dosage Forms

ICH Q1D – Bracketing and Matrixing Design for Stability Testing of New Drug Substances and Products

ICH Q1E – Evaluation for Stability Data

ICH Q1F – Withdrawn

Association of South East Asian Nations (ASEAN) – Guidelines on Stability Study of Drug Product.

The Gulf Cooperation Council (GCC) States – Guidelines for Stability Testing of Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs).

National

USA – Guideline for Submitting Documentation for Stability of Human Drugs and Biological (US FDA)

Australia – Australian Regulatory Guidelines for Prescription Medicines, Appendix 14: Stability Testing (TGA)

2. REQUIREMENTS UNDER LEGISLATION IN INDIA AND USA

2.1 Requirements under the Drugs and Cosmetics Rules in India

In India, pharmaceutical industry is regulated under the Drugs and Cosmetics Act and rules made under this act i.e. The Drugs

and Cosmetics Rules 1945 (as amended, time to time). Rules 71(6) and rule 76(7) of the Drugs and Cosmetic Rules, 1945 read as under:

> "The applicant shall, while applying for a licence to manufacturer patent or proprietary medicines, furnish to the licensing authority evidence and data justifying that patent or proprietary medicines:
>
> (i) contain the constituent ingredients in therapeutic or prophylactic quantities as determined in relation to the claims or conditions for which the medicines are recommended for use or claimed to be useful;
>
> (ii) are safe for use in the context of the vehicles, excipients, additives and pharmaceutical aids used in the formulation and under the conditions in which the formulations for administration and use are recommended;
>
> (iii) are stable under the conditions of storage recommended;
>
> (iv) contain such ingredients and in such quantities for which there is therapeutic justification; and
>
> (v) have the approval in writing, in favour of the applicant to manufacture drug formulations falling under the purview of new drug as defined in Rule 122-E, from the licensing authority as defined in clause (b) of Rule 21."

These rules form a part of the conditions for grant of licence to manufacture drugs for sale/distribution. Although these rules mention patent/proprietary medicines, but their spirit is applicable to even pharmacopoeial drug formulations and formulations manufactured under chemical name (generics). The Rules 71(7) and 76(8) stipulate that the licensee shall comply with the requirements of "Good Manufacturing Practices" as laid down in Schedule M.

> Para 16.10 of Part 1 of Schedule M states as under:
>
> "The quality control department shall conduct stability studies of the products to ensure and assign their shelf life at the prescribed conditions of storage. All records of such studies shall be maintained."

It may be seen that no distinction has been made between drugs or their formulations under trade name (patent/proprietary medicines) and formulations under chemical name (generics) thereby meaning that stability studies are applicable to all formulations.

Rule 96 stipulates that drugs specified in Schedule P and their preparations including fixed dose combinations (FDCs) shall bear on their lables the date of manufacture and the date of expiry of potency and the period between the dates of manufacture and expiry shall not exceed that laid down in the Schedule P. It means that the maximum shelf-life that can be given is the period mentioned in the Schedule P.

For other drugs (drugs not specified in Schedule P) the rule stipulates that the period between date of manufacture and date of expiry shall not exceed 60 months (5 years). It means that in case of drugs not mentioned in Schedule P can have a maximum shelf-life of 5 years.

However, a provision has been made under this rule that the shelf-life mentioned above can be extended by the Licensing Authority specified in clause (b) of Rule 21 (i.e. Drugs Controller General India) provided a manufacturer produces satisfactory evidence to justify such extension.

All these provisions recommend to carry out stability studies. For the maximum shelf-life of a drug mentioned in Schedule P, readers may refer to the Schedule P of the Drugs and Cosmetics Rules, 1945.

2.2 Requirements under Code of Federal Regulations (CFR) in U.S.A.

Under the CFR of U.S., there are more elaborate requirements for stability studies. These are reproduced below for the information of readers.

Title 21 – Food and Drugs

Chapter 1 – Food Drug Administration

Department of Health and Human Services

Sub-chapter C – Drugs: General

Part 211 – Current Good Manufacturing Practices for Finished Pharmaceuticals

Sub-part I – Laboratory Controls

Sec. 211.166 – Stability Testing

(a) There shall be a written testing program designed to assess the stability characteristics of durg products. The results of such testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include:

(1) Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimate of stability;

(2) Storage conditions for samples retained for testing;

(3) Reliable, meaningful, and specific test methods;

(4) Testing of the drug products in the same container – closure system as that in which the drug product is marketed;

(5) Testing of the drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted.

(b) An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

(c) For homeopathic drug products, the requirements of this section are as follows:

(1) There shall be a written assessment of stability based at least on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use.

(2) Evaluation of stability shall be based on the same container-closure system in which the drug product is being marketed.

(d) Allergenic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements of this section.

[43 FR 45077, Sept., 29, 1978, as amended at 46 FR 56412, Nov. 17, 1981]

3. REQUIREMENTS UNDER WHO GMP

In the WHO GMP, requirements for stability have been mentioned under the element "17 Good Practices in Quality Control" and are given below:

"17.23. Quality control should evaluate the quality and stability of finished pharmaceutical products.

17.24. Quality control should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

17.25. A written programme for ongoing stability determination should be developed and implemented to include elements such as:

(a) a complete description of the drug involved in the study;

(b) the complete set of testing parameters and methods describing all tests for potency, purity and physical characteristics and documentary evidence that these tests indicate stability;

(c) provision for the inclusion of a sufficient number of batches;

(d) the testing schedule for each drug;

(e) provision for special storage conditions;

(f) provision for adequate sample retention;

(g) a summary of all the data generated, including the evaluation and the conclusion of the study.

17.26. Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials etc."

Thus, it may be seen that there are requirements to conduct stability studies not just once but on the ongoing basis.

4. REQUIREMENTS UNDER EU GMP

Requirements and guidelines for stability of finished products are given under the elements, "Good Quality Control Laboratory Practice" under the sub-element "on going stability programme under the EU GMP." The purpose of ongoing stability programme has been stated to be monitoring the product over its shelf life and to determine that the product remains and can be expected to remain, within specifications under the labeled storage conditions. The requirements and the guidelines under EU GMP are referred for the information of readers.

On-going stability progamme

6.23 After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of impurities or dissolution profile) associated with the formulation in the marketed package.

6.24 The purpose of the on-going stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.

6.25 This mainly applies to the medicinal product in the package in which it is sold, but consideration should be given to the inclusion in the programme of bulk product. For example, when the bulk product stored for a long period before being packaged and/or shipped from manufacturing site to a packaging site, the impact on the stability conditions. In addition, consideration should be given to intermediate that are stored and used over prolonged periods. Stability, studies reconstituted product are performed during product development and need not to be monitored on an on-going basis. However, when relevant, the stability of reconstituted product can also be monitored.

6.26 The on-going stability programme should be described in a written protocol following the general rules of Chapter 4 and results formalize as a report. The equipment used for the on-going stability programme (stability chambers among others) should be qualified and maintained following the general rules of Chapter 3 and Annex 15.

6.27 The protocol for an on-going stability programme should extend to the end of the shelf life period and should include, but not to limited to, the following parameters:

- number of batch (es) per strength and different batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test methods;
- acceptance criteria;
- reference to test methods;
- description of the container closure system(s);
- testing intervals (time points);
- description of the conditions of storage (standardized ICH conditions for long-term testing, consistent with the product labeling, should be used);
- other applicable parameters specific to the medicinal product.

6.28 The protocol for the on-going stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorization dossier provided that this is justified and documented in the protocol (for example the frequency of testing, or when updating to ICH recommendations).

6.29 The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year). For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk-benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.

6.30 In certain situations, additional batches should be included in the on-going stability programme. For example, an on-going stability study should be conducted after any significant change

or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.

6.31 Results of on-going stability studies should be made available to key personnel and, in particular, to the qualified person (s). Where on-going stability studies are carried out at a site other than the site of manufacturer of the bulk or finished product, there should be written agreement between the parties concerned. Results of on-going stability studies should be available at the site of manufacturer for review by the competent authority.

6.32 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with chapter 8 of the GMP Guide and in consultation with the relevant competent authorities.

6.33 A summary of all the data generated, including any interim conclusion on the programme, should be written and maintained. This summary should be subjected to periodic review.

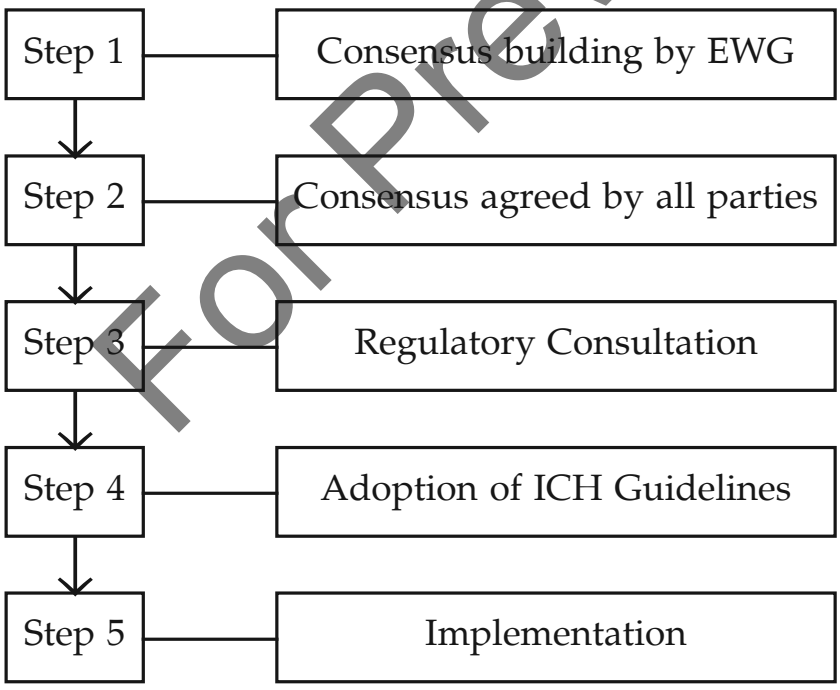
5. ICH GUIDELINES

5.1 Development ICH Stability Guidelines

ICH guidelines are applicable to new drugs. Stability being a critical quality attribute, stability program plays an important role when developing new pharmaceutical products. If the product is to be marketed in several strengths and packages, the number of sample becomes quite large for testing and consequently becomes quite costly. Prior to early 1990, multinational pharmaceutical companies were performing an enormous amount of stability testing seeking approvals in more than one country. Therefore, the compilation of a common set of stability requirements for marketing authorization was considered on top priority by the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) when it was formed in 1990.

Regulatory authorities, representatives from pharmaceutical industry from European Union (EU), Japan and United States (US) with observers from the Canadian and Swiss Health Authorities and the WHO chose stability testing as one of the first issues to be discussed and harmonized. Following this decision, an ICH Guidelines on Stability Testing (QIA) was subsequently developed and published in 1993 and was adopted throughout ICH region. Other countries followed these guidelines in principle (e.g. Canada, Australia, Switzerland).

Development of an ICH guideline consists of five main steps. In the first step, consensus building begins after the steering committee adopts a concept paper. In the step 2, consensus is agreed by all parties of Expert Working Group (EWG) members. In the step 3, the draft document is consulted with all ICH regional regulatory agencies. In the fourth step, the Steering Committee agrees and it is recommended for adoption by the regulatory bodies of three regions. Step 5 is the final step and in this step, the guideline is implemented.



5.2 ICH Stability Guidelines

5.2.1 ICH Q1A (R2) – Stability Testing of New Drug Substances and Products

The parent document was finalized in 1993 and was recommended for adoption in three regions of ICH. The document

was revised and was approved by the Steering Committee in 2000 and was recommended for adoption by the participating regions. Another revision was carried out and the same was approved by the Steering Committee in 2003.

The document has three elements: Introduction, Guidelines and Glossary. In the first element, objective of the guideline, scope of guideline and general principles have been given. The choice of test conditions given in the guidelines is based on an analysis of the affects climatic conditions in the three regions (EC, Japan, US). Mean Kinetic Temperature (MKT) can be derived for any part of the world from the climatic data and the world can be divided into four climatic zones (Zone I to Zone IV). The guideline, however, addresses climatic zone I and II only.

There are guidelines for both drug substances and drug products. Some important requirement are given below:

Stress testing

Stress testing of drug substance is necessary, as it can help in identifying the likely degradation products. In turn, it can help in establishing degradation pathways and intrinsic stability of molecule. What stress testing should be done will depend on the drug substance and the type of drug product.

Stress testing may be carried out on single batch of drug substance. It should include the effects of:

- temperature (in 10°C increments e.g. 50°C, 60°C);
- humidity (e.g. 75% RH or more);
- oxidation, where appropriate;
- photolysis, where appropriate;
- hydrolysis across a wide range of pH values, when in solution or suspension.

Stability commitment

More often than not, available long term data may not cover the re-test date in some of drug substances and shelf-life in case of drug products. In such circumstances, a commitment should be made to carry out the stability study post approval. For details, readers may refer to chapter 3 of this book.

5.2.2 ICH Q1B – Stability Testing: Photostability Testing of New Drug Substances and Products

This guideline was approved by the Steering Committee in Nov. 1996 and was recommended for adoption by the participating regional authorities. This document is an annexure to the parent guideline (ICH QIA) and addresses only the recommendations for photostability testing.

The guideline primarily addresses the generation of information on photo-stability for submission in registration application for new drug substances and new drug products. The guideline states that a systematic approach to photostability testing is recommended covering studies like:

- tests on drug substances;
- tests on the exposed drug product outside of the immediate pack, and if necessary;
- tests on drug product in the immediate pack; and if necessary;
- tests on the drug product in the marketing pack.

5.2.3 ICH Q1C – Stability Testing for New Dosage Forms

This document was approved by the Steering Committee and recommended for adoption by the participating regulatory authorities in November 1996. It is annexure to the ICH parent stability guidelines and addresses the recommendations on what should be submitted by the applicant about stability of new dosage forms.

What is new dosage form? A new dosage form has been defined in this document as "a drug product which is different pharmaceutical product type, but contains the same active substance as included in the existing drug product approved by the pertinent regulatory authority." Thus new dosage form would include products of different administration route (e.g. oral to parenteral), new specific functionality delivery system (e.g. dispersible tablets to modified release tablets) and different dosage forms of the same administration route (e.g. capsule to tablet, solution to suspension).

It has been recommended in the document that stability protocol for new dosage forms should follow, in principle, the guidelines given in parent guidelines. If justified, a reduced stability

data base may be given at the time of submission (e.g. 6 months accelerated and 6 months long term data from on going studies).

5.2.4 ICH Q1D – Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products

This document was approved by the Steering Committee and was recommended for adoption by the ICH regulatory authorities in Feb. 2002. In the parent guidelines, it has been stated that the use of matrixing and bracketing can be applied, if justified, to the testing of new drug substances and new drug products. The objective of this document is to provide guidelines on the application of bracketing and matrixing to the stability studies.

Guidelines have been discussed under the following elements:

- general;
- applicability of reduced designs;
- bracketing;
- matrixing; and
- data evaluation.

5.2.5 ICH Q1E – Evaluation for Stability Data

This document was approved by the Steering Committee and was recommended for adoption by ICH regulatory bodies in February 2003. The guideline provided in the parent guidelines (Q1A) about the evaluation and statistical analysis of stability data is brief in nature and limited in scope.

The objective of this guideline is to provide recommendations on how to use stability data generated.

In the Appendix A of this document, a decision tree is given which outlines a step wise approach to stability data evaluation and when and how much extrapolation can be considered for a proposed re-test period or shelf life. Appendix B provides information on:

- how to analyze long term data for quantitative test attributes in a study with a multifactor, full or reduced design;
- how to use regression analysis for retest period or shelf life estimation;

– example of statistical procedures to determine poolability of data from different batches or other factors.

Generally, certain quantitative chemical attributes (e.g. assay, degradation products, preservative content) for a drug substance or product may be assumed to follow zero order kinetics during long term storage. For such data, statistical analysis described in appendix B can be used. Although the kinetics of other quantitative attributes like pH, dissolution, generally is not known, but if suitable, the same statistical analysis can be employed. It may be noted that qualitative attributes and microbiological attributes are not amenable to this kind of statistical analysis.

Other than these general principles, the guidelines include recommendations on:

– data presentation;
– extrapolation;
– data evaluation for retest period or shelf-life estimation for drug substances or drug products intended for room temperature storage;
– data evaluation for re-test period or shelf-life estimation for drug substances or products intended for storage below room temperature;
– general statistical approaches.

For more information, the original document may be referred.

5.2.6 ICH Q1F – Stability Data Package for Registration Application in Climatic Zones III and IV

This document was adopted by the Steering Committee in Feb., 2003 and subsequently implemented. But some countries in climatic zone IV expressed their wish to include a larger safety margin for medicinal products to be marketed in their region. In view to this several countries revised their own stability testing guidelines, defining upto 30°C/75% RH as the long term storage condition for hot and humid regions. Because of this divergence in global stability testing requirements, ICH Steering Committee decided to withdraw ICH Q1F and to leave the defining of storage conditions in climatic zone III and IV to the respective regions and WHO.

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