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Comprehensive Review of ICH Stability Guidelines: Q1A to Q1F

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Abstract-The International Council for Harmonization (ICH) has played a pivotal role in establishing globally accepted stability guidelines for pharmaceutical products, ensuring their quality, efficacy, and safety throughout their shelf-life. This review paper critically examines the evolution, principles, and significance of ICH stability guidelines in the context of pharmaceutical development and regulatory approval processes. The paper begins by tracing the historical development of ICH stability guidelines, highlighting key milestones and collaborative efforts that have shaped the current regulatory landscape. It explores the rationale behind the establishment of stability testing, emphasizing the importance of maintaining product quality, identifying degradation pathways, and establishing appropriate storage conditions. The ICH stability guidelines, comprising Q1A(R2), Q1B, Q1C, Q1D, Q1E, and Q1F documents, provide harmonized global standards that guide the design, execution, and evaluation of stability studies for new drug substances and drug products. A comprehensive analysis of the ICH stability testing framework is provided, encompassing the various zones (I to IV) and their corresponding climatic conditions. The intricate interplay between stress testing, accelerated stability studies, and long-term stability studies is examined, shedding light on their roles in predicting product behavior over time. Furthermore, the review delves into the parameters evaluated during stability studies, including physical, chemical, and microbiological attributes, and their relevance in assessing product stability.

Keywords- ICH stability guidelines, Stability testing, Shelf life, Regulatory standards, accelerated stability

I. INTRODUCTION

1. ICH Guideline on stability

ICH is the short form of "International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use" (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry of Europe, Japan and the US to discuss scientific and technical aspects of drug registration. [1] ICH reduced the duplication of testing carried out during the research and development of newhuman medicines. ICH's mission is to achieve greater harmonization in the interpretation andapplication of technical guidelines and its requirements for pharmaceutical product registration. [2]

2. Objective of ICH:

- To increase international harmonization of technical requirements to ensure that safe, effective and high-quality medicines are developed.
- To harmonization technical requirements for registration or marketing approval.
- To promote public health.
- To prevent unnecessary duplication of clinical trials on human.
- To minimize the use of animal testing without compromising safety and effectiveness of drug.

- To develop and register pharmaceuticals in the most efficient and cost effective manner.

3. Members of ICH Guideline:

- ICH is comprised of representatives from six parties that represent the regulatory bodies and research based industry in the European Union, Japan and the USA.
- IN Japan, the members are the Ministry of Health, Labour and Welfare (MHLW), and the Japan Union (EU), the Japan Pharmaceutical Manufacturers Association (JPMA).
- In Europe, the members are the European Union (EU), and the European Federation of Pharmaceutical Industries and Associations.
- In the USA, the members are the Food and Drug Administration (FDA) and the Pharmaceutical Research and Manufacturers of America (PhRMA).
- Additional members include Observers from the World Health Organization (WHO), European Free Trade Association (EFTA), and Canada. The Observers represents non-ICH Countries and regions. [3]

4. History of ICH:

The Need to Harmonize

- The realization that it was important to have an independent evaluation of medicinal products before they are allowed on the market was reached at different times in different regions. However in many cases the realization was driven by tragedies, such as that with thalidomide in Europe in the 1960s.
- For most countries, whether or not they had initiated product registration controls earlier, the 1960s and 1970s saw a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicinal products. [2, 4]

5. Initiation of ICH:

The birth of ICH took place at a meeting in April 1990, hosted by EFPIA in Brussels. Representatives of the regulatory agencies and industry associations of Europe, Japan and the US met, primarily, to plan an International Conference but the meeting also discussed the wider implications and terms of reference of ICH. At the first ICH Steering Committee (SC) meeting of ICH the Terms of Reference were and it was decided that the Topics selected for harmonization would be divided into Safety, Quality and Efficacy to reflect the three criteria which are the basis for approving and authorizing new medicinal products. [4]

6. New Codification as per November 2005:

In November 2005, the ICH Steering Committee adopted a new codification system for ICH Guidelines. The purpose of this new codification is to ensure that the numbering / coding of ICH Guidelines are more logical, consistent and clear.

Because the new system applies to existing as well as new ICH Guidelines a history box has been added to the beginning of all Guidelines to explain how the Guideline was developed and what is the latest version.

With the new codification revisions to an ICH Guideline are shown as (R1), (R2), (R3) depending on the number of revisions. Annexes or Addenda to Guidelines have now been incorporated into the core Guidelines and are indicated as revisions to the core Guideline (e.g., R1).

7. Working Products:

- **Guidelines:** ICH has originated over 50 harmonized Guidelines aiming at eliminating gemination in the development and registration process, so that a single set of reports can be generated to demonstrate the quality, safety and efficacy of a new pharmaceutical product.
- **CTD:** The Common Technical Document (CTD) describes the common format for the formulation of a well-Integrated CTD for applications that will be submitted to regulatory bodies.
- **eCTD:** The Electronic Common Technical Document (eCTD) has been prepared for the electronic submission of the Common Technical Document (CTD) from applicant to drug regulator, in order to provide international electronic communication through the provision of Electronic Standards for the Transfer of Regulatory Information (ESTRI).
- **MedDRA:** The Medical Dictionary for Regulatory Activities (MedDRA) Terminology has also been developed under the aegis of International conference on harmonization. [5]

8. ICH Guidelines:

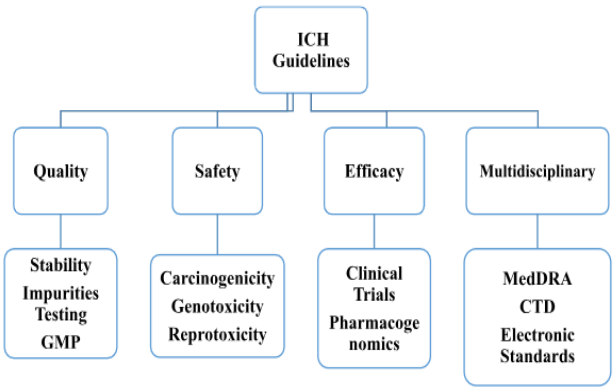

Fig 1. ICH Guidelines. [1]

- "**Q" Guidelines** -These are Quality Guidelines, Harmonization achievements in the Quality With the new codification revisions to an ICH Guideline are shown as (R1), (R2), (R3) depending on the number of revisions.
- **"S" Guidelines -**These are Safety guidelines which includes a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity.
- **"E" Guidelines**- Efficacy guidelines concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/ pharmacogenomics techniques to produce better targeted medicines.
- **"M" Guidelines-** Multidisciplinary guidelines are the cross-cutting topics which do not fit uniquely into one of the quality, safety and efficacy categories. It includes the ICH medical terminology (MedDRA), The Common Technical Document (CTD) and the development Electronic Standard for the transfer of regulatory information (ESTRI). [6]

9. ICH Quality guideline:

Table 1. ICH Quality guideline. [6]

ICH Guidelines	Tittle
Q1A-Q1F	Stability
Q2	Analytical Validation
Q3A-Q3D	Impurities
Q4A-QB	Pharmacopoeias
Q5A-Q5E	Quality of Biotechnological Products
Q6A-Q6B	Specifications
Q7	Good Manufacturing Practice
Q8	Pharmaceutical Development
Q9	Quality Risk Management
Q10	Pharmaceutical Quality System
Q11	Development and Manufacture of Drug Substances
Q12	Lifecycle Management
Q13	Continuous Manufacturing of Drug Substance and Drug Products
Q14	Analytical Procedure Development

10. Organization of ICH

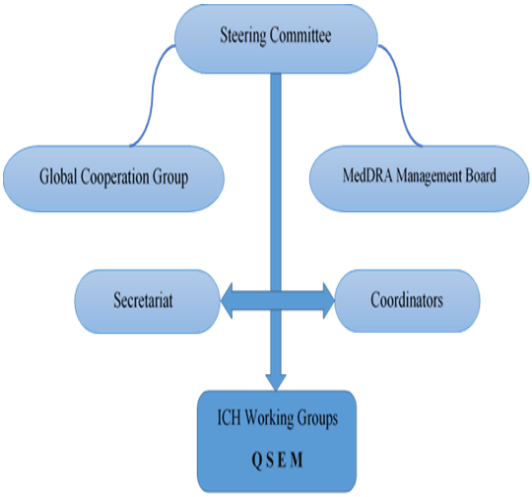

Fig 2. Organization of ICH. [4]

11. Scope of guideline:

The quality of the drug substance and product is determined by;

- Design
- Development
- In-process control
- Process validation

II. STABILITY STUDIES

1. Objectives of stability:

- The stability study is to determine shelf life of the drug product.
- The stability refers to storage time allow before degradation product in dosage form.
- The purpose of the stability is to provide the quality of drug substance (API).

Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety and efficacy. [7] Stability defined according to ICH guidelines is, the purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions. [8]

Stability of a pharmaceutical product the capability of a particular formulation in a specific container or closure system to remain within its physical, chemical, microbiological, therapeutic, toxicological, protective and informational specifications.[9]

The main objective of stability study is to provide evidence for the report submitted on the effects of various factors (above mentioned) on the drug under different conditions and to establish shelf life for the drug and recommended storage conditions. Also, it provides necessary data for the shipping and distribution of the drug product. It is intended to study basically three ensured stabilities i.e. physical, chemical and microbiological. [10]

A drug product which is not of sufficient stability can result in change in physical (like hardness, dissolution rate, and phase separation. Evaluation of drug substance or drug product is to drug quality as it determines the efficacy of any drug or dosage form. Stability testing provides evidence that the quality of drug substance or drug product changes with time under the influence of various environmental conditions such as temperature, relative humidity etc. [11]

2. 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 the product will retain fitness for use with respect to all functionally relevant attributes for as long as they are on the market. [12, 13]

Fig 3.Climatic zones. [3]

3. Factor affecting drug stability:

- Oxygen
- Temperature
- PH
- Moisture
- Light
- Concentration

3.1 Oxygen- Oxidation is the most important part of the drug degradation. Oxygen is present in atmosphere and exposure to oxygen will decompose the drug substance that is not in their most oxidized state through auto-oxidation.

3.2 Temperature- High temperature increase oxidation, reduction and hydrolysis reaction which lead to drug degradation.

3.3 PH-Acidic and alkaline pH influences the rate of decomposition of the drug. Many drugs are stable between pH 4 to 8. Weak acidic and basic drug shows good solubility because they are ionized and decompose faster.

3.4 Moisture-In chemical reaction water catalysis as oxidation, reduction and hydrolysis reaction.

3.5 Light- Drug stability affects the energy or thermal give effect which leads to oxidation.

3.6 Concentration- Rate of degradation is constant for the solution of the same drug with different concentration. [14]

4. Climatic Zones:

Partition of the world into four temperature classes based on kinetic of monthly temperatures.

III. STABILITY TESTING

1. Objective of Stability Testing:

To provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as Temperature, Humidity, Light & enables recommended storage condition, re-testing period &shelf life to be established.

2. Scope of Stability Testing:

- Provide evidence as to how the quality of the drug product varies with time.
- Establish shelf life for the drug product.
- Determine recommended storage conditions.
- Determine container closure system suitability.
- Safety point of view of patient.[3]

IV. ICH GUIDELINES FOR STABILITY TESTING

1. (Q1A) Stability Testing of New Drug Substances and Products:

The stability data package for new drug substance or drug product that is sufficient for a registration application within the region of EC, Japan and United states.

Drug Substance:

1.1 General: Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation. [24]

1.2 Stress Testing: Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation Pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance (API) and the type of drug product involved. [28] Stress testing is likely to be carried out on a single batch of the drug substance (API). It should include the effect of temperatures (in 10°C increments (e.g., 50°C, 60°C, etc.) above that for accelerated testing), humidity (e.g., 75% RH or greater) where appropriate, oxidation, and photolysis on the drug substance. The testing should also evaluate the susceptibility of the drug substance to hydrolysis across a wide Range of pH values when in solution or suspension. [29]

1.3 Selection of Batches: Data from stability studies on at least three primary batches of the drug substance (API) should normally be provided. The batches should be manufactured to a minimum of pilot scale by the same synthesis route as production batches, and using a method of manufacture and procedure that simulates the Final process to be used for production batches. The overall quality of the batches of drug substance (API) placed on stability studies should be representative of the quality of the material to be made on a production scale. [29] For existing active substances that are known to be stable, data from at least two primary batches should be provided.

1.4 Container Closure System: The stability studies should be conducted onthe drug substance packaged in a containerclosure system that is the same as or simulate the packaging proposed for storage anddistribution. [29]

1.5 Specification: Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and or efficacy. The testing has appropriate, the physical, chemical, biological, and microbiological attributes. Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed will depend on the results from validation studies. [24]

1.6 Testing Frequency: For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance. For drug substances with a proposed re-test period of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period or shelf- life. At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six month study is recommended. [6]

1.7 Storage Conditions: In general a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and if its sensitivity to moisture. Storage condition tolerances are defined as the acceptable variations in temperature and relative humidity of storage facilities for stability studies. The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be

continued for a period of time sufficient to cover the proposed re-test period. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping). [24]

1.7.1 Table 1. General case:

Table 2. Drug Substance for all Studies

Study	Storage condition	Minimum time period covered by data at submission
Long term	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH	12 months
Intermediate	30 °C ± 2 °C/75% RH ± 5% RH	6months
Accelerated	30 °C ± 2 °C/75% RH ± 5% RH	6months

- Whether long-term stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH
- If 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is the long-term condition there is no intermediate condition.

If long –time studies are conducted at 25 °C ± 2 °C/60% RH and "significant change" occurs at any time during 6 months testing at the accelerated storage condition and evaluated against significant change. The initial application should include a minimum of 6 months data from a 12month study at the intermediate storage condition.

1.7.2 Drug substances intended for storage in a refrigerator:

Table 3. Drug substances intended for storage in a refrigerator.

Study	Storage condition	Minimum time period covered by data at submission
Long term	5 °C ± 3 °C	12 months
Long term	25 °C ± 2 °C/60% RH ± 5% RH	6 months

Data on refrigerated storage should be assessed according to the evaluation section of these guidelines. If significant change occurs between 3- and 6-months' testing at the accelerated storage condition, the proposed re-test period should be based on the data available at the long-term storage condition. If significant change occurs within the first three months' testing at the accelerated storage condition a discussion should be provided to address the effect of short-term excursions outside the label storage condition, e.g. during shipping or handling.

This discussion can be supported, if appropriate, by further testing on a single batch of the API for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test an API for the whole 6 months when a significant change has occurred within the first 3 Months.

1.7.3 Drug substances intended for storage in a freezer.

Table 4. Drug substances intended for storage in a freezer.

Study	Storage condition	Minimum time period covered by data at submission
Long term	-20 °C ± 5 °C	12months

In the case of any drug substance intended for storage in a freezer, the re-test period or shelf-life should be based on the long-term data obtained at the long-term storage condition. In the absence of an accelerated storage condition for APIs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. 5 °C ± 3 °C or 25 °C ± 2 °C or 30 °C ± 2 °C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition, e.g. during shipping or handling.

1.7.4 Drug substance intended for storage below -20°C

Drug substances intended for storage below -20 °C should be treated on a case-by-case basis.

1.8 Stability commitment: When the available long-term stability data on primary batches do not cover the proposed re-test, period granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the re-test period or shelf-life. The submission includes long-term stability data on the number of production batches covering the proposed re-test period, a post-approval commitment is considered unnecessary. Otherwise one of the following commitments should be made:

If the submission includes data from stability studies on the number of production batches a commitment should be made to continue these studies through the proposed re-test period. If the submission includes data from stability studies on fewer than the number of production batches a commitment should be made to continue these studies through the proposed re-test period and to place additional production batches, to a total of at least three, in long-term stability studies through the proposed re-test period. If the submission does not include stability data on production batches, a commitment should be made to place the first two or three production batches on long-term stability studies through the proposed re-test period.

1.9 Evaluation: The purpose of the stability study is to establish, based on testing a minimumof the number of batches unless otherwisejustified and authorized, of the Drug Substance (API) and evaluating the stability information(including, as appropriate, results of the physical, chemical, biological andmicrobiological tests), a re-test period applicable to all future batches of thedrug substances API manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch willremain within specification throughout the assigned re-test period.The data may show so little degradation and so little variability that it isapparent from looking at them that the requested re-test period will begranted. [24] An approach for analyzing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g. p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero-time intercepts for the individual batches. [6]

1.10 Statements and labelling: A storage statement should be established for display on the label based on the stability evaluation of the Drug Substance (API). Where applicable specific instructions should be provided, particularly for APIs that cannot tolerate freezing or excursions in temperature. Terms such as "ambient conditions" or "room temperature" should be avoided. A re-test period should be derived from the stability information, and a retest date should be displayed on the container label if appropriate. [6]

2. Drug Product:

2.1 General: The design of the formal stability studies for the drug product should be based on knowledge of the behavior and properties of the drug substance and from stability studies on the drug substance and on experience gained from clinical formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated. [17]

2.2 Photostability Testing: Photostability testing should be conducted on at least one primary batch of the drug product if appropriate. The standard conditions for photostability testing are described in ICH Q1B. [6]

2.3 Selection of Batches: Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. Two of the three batches should be at least pilot scale batches and the third one can be smaller, if batches of the drug product should be manufactured by

using different batches of the drug substance. [17]

2.4 Container Closure System: Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the drug product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively. [24]

2.5 Specification: Specification, which is a list of tests, reference to analytical procedures, and proposed acceptance criteria, including the concept of different acceptance criteria for release and shelf life specifications, is addressed in ICH Q6A and Q6B. Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). Analytical procedures should be fully validated and stability indicating. [17]

2.6 Testing Frequency: For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life. At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. [6] Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design. [24] When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

2.7 Storage Conditions:

2.7.1 General case

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use. Stability testing of the drug product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product.

This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points and, if full shelf life long term data will not be available before submission, at 12 months or the last time point for which data will be available.

The long-term testing cover a minimum of 12 should months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Data from the accelerated storage condition and if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping). [24]

Table 5. Drug Substance for all Studies.

Study	Storage condition	Minimum time period covered by data at submission
Long term	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH	12months
Intermediate	30 °C ± 2 °C/65% RH ± 5% RH	6months

Accelerated	30 °C ± 2 °C/75% RH ± 5% RH	6months

General case Study Storage condition Minimum time period covered by data at submission Long term* 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH 12 months Intermediate** 30°C ± 2°C/65% RH ± 5% RH 6 months.

5% RH.± 2°C/65% RH ± 5% RH or 30°C ± 2°C/60% RH ±Accelerated 40°C ± 2°C/75% RH ± 5% RH 6 months *It is up to the applicant to decide whether long term stability studies are performed at 25 5% RH is the long-term condition, there is no intermediate condition.± 2°C/65% RH ±**If 30°C.

2.7.2 Drug products packaged in impermeable containers:

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological and microbiological stability. Drug products stored in semi–permeable container have low relative humidity environment. Long term 25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

For long-term studies conducted at 25°C ± 2°C/40% RH ± 5% RH, additional testing at the intermediate storage condition should be performed under the general case to evaluate temperature at 30°C if change other water loss occurs during the 6 months testing at accelerated storage condition.

2.7.3 Drug products packaged in semi-permeable containers:

Table 6. Drug products packaged in semi-permeable containers.

Study	Storage condition	Minimum time period covered by data at submission
Long term	25 °C ± 2 °C/40% RH ± 5% RH or 30 °C ± 2 °C/35% RH ± 5% RH	12months
ntermediate	30 °C ± 2 °C/65% RH ± 5% RH	6months
Accelerated	40 °C ± 2 °C/not more than (NMT) 25% RH	6months

2.7.4 Drug products intended for storage in a refrigerator:

Table 7. Drug products intended for storage in a refrigerator.

Study	Storage condition	Minimum time period covered by data at submission
Long term	5 °C ± 3 °C	12 months
Accelerated	25 °C ± 2 °C/60% RH ± 5% RH	6 months

If the drug product is packaged in a semi-permeable container, appropriate information should be provided to extend of water loss. If change occurs between 3 and 6 months testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long-time storage condition.

2.7.5 Drug substances intended for storage in a freezer.

Table 8. Drug substances intended for storage in a freezer.

Study	Storage condition	Minimum time period covered by data at submission
Long term	-20 °C ± 5 °C	12months

2.7.6 Drug substances intended for storage below -20°C

Drug Products intended for storage below -20°C should be treated.

2.8 Stability Commitment: The submission includes long term stability data from three production batches covering the proposed shelf life, a post approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made: If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months.

If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue the long term studies through the proposed shelf life and the accelerated studies for 6 months, and to place additional production batches, to a total of at least three, on long term stability studies through the proposed shelf life and on accelerated studies for 6 months. If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long term stability studies through the proposed shelf life and on accelerated studies for 6 months. [17]

2.9 Evaluation: The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug product, a shelf life and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. The nature of the degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve. [17]

2.10 Statements/Labeling:A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug product. Where applicable, specific instruction should be provided, particularly for drug products that cannot tolerate freezing. Terms such as "ambient conditions" or "room temperature" should be avoided. There should be a direct link between the label storage statement and the demonstrated stability of the drug product. An expiration date should be displayed on the container label. [6]

V.(Q1B) STABILITY TESTING: PHOTOSTABILITY TESTING OF NEW DRUG SUBSTANCE AND PRODUCTS

1. General:

The ICH Harmonized Tripartite Guideline covering the Stability Testing of New Drug Substances and Products notes that light testing should be an integral part of stress testing. This document is an annex to the Parent Guideline and addresses the recommendations for Photostability testing.

2. Preamble:

The intrinsic photostability characteristics of new drug substances and products should be result in unacceptable change. Normally, photostability testing is carried out on a single batch of material selection as described under Selection of Batches in the Parent Guideline.

The guideline primarily addresses the generation of Photostability information for submission in Registration Applications for new molecular entities and associated drug products. The guideline does not cover the photostability of drugs after administration (i.e. under conditions of use) and those applications not covered by the Parent Guideline. Alternative approaches may be used if they are scientifically sound and justification is provided.

A systematic approach to Photostability testing is recommended covering, as appropriate, studies such as:

- Tests on the drug substance
- Tests on the exposed drug product outside of the immediate pack; and if necessary
- Tests on the drug product in the immediate pack; and if necessary
- Tests on the drug product in the marketing pack. [6]

3. Light Sources:

The light sources described below may be used for photostability testing. The applicant should either maintain an appropriate control of temperature to minimize the effect of localized temperature changes or include a dark control in the same environment.

For both options 1 and 2, a pharmaceutical manufacturer/applicant may rely on the spectral distribution specification of the light source manufacturer.

Option 1 Any light source that is designed to produce an output similar to the D65/ID65 emission standard such as an artificial daylight fluorescent lamp combining visible and ultraviolet (UV) outputs, xenon, or metal halide lamp. D65 is the internationally recognized standard for outdoor daylight as defined in ISO 10977 (1993). ID65 is the equivalent indoor indirect daylight standard. For a light source emitting significant radiation below 320 nm, an appropriate filter(s) may be fitted to eliminate such radiation. [6]

Option 2 The same sample should be exposed to both the cool white fluorescent and near ultraviolet lamp.A cool white fluorescent lamp designed to produce an output similar to that specified in ISO 10977(1993); And A near UV fluorescent lamp having a spectral distribution from 320 nm to 400 nm with a maximum energy emission between 350 nm and 370 nm; a significant proportion of UV should be in both bands of 320 to 360 nm and 360 to 400 nm. [6]

4. Procedure:

The samples should be exposed to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200-watt hours/square meter to allow direct comparisons to be made between the drug substance and drug product. If protected samples (e.g., wrapped in aluminum foil) are used as dark controls to evaluate the contribution of thermally induced change to the total observed change, these should be placed alongside the authentic sample. [17]

5. Drug Substance:

For drug substances, photostability testing should consist of two parts: forced degradation testing and confirmatory testing. The purpose of forced degradation testing studies is to evaluate the overall photosensitivity of the material for method development purposes and degradation pathway elucidation. This testing may involve the drug substance alone and in simple solutions/suspensions to validate the analytical procedures. In these studies, the samples should be in chemically inert and transparent containers. In these forced degradation studies, a variety of exposure conditions may be used, depending on the photosensitivity of the drug substance involved and the intensity of the light sources used. [6]

For development and validation purposes it is appropriate to limit exposure and end the studies if extensive decomposition occurs. For photo stable materials, studies may be terminated after an appropriate exposure level has been used.

6. Presentation of Samples:

Presentation of samples should be taken to ensure that the physical characteristics of the samples under test are taken into account and efforts should be made, such as cooling and placing the samples in sealed containers, to ensure that the effects of the changes in physical states such sublimation, evaporation or melting are minimized. All such precautions should be chosen to provide minimal interference with the exposure of samples under test. Possible interactions between the samples and any material used for containers or for general protection of the sample should also be considered and eliminated wherever not relevant to the test being carried out. Solid drug substances should be spread across the container to give a thickness of typically not more than 3 millimeters. Drug substances that are liquids should be exposed in chemically inert and transparent containers. [25]

7. Analysis of Samples:

The end of the exposure period, the samples should be examined for any changes in physical properties (e.g., appearance, clarity, or color of solution) and for assay and degradants by a method suitably validated for products likely to arise from photochemical degradation processes. Where solid drug substance samples are involved, sampling should ensure that a representative portion is used in individual tests. Similar sampling considerations,

such as homogenization of the entire sample, apply to other materials that may not be homogeneous after exposure.

8. Drug Product:
Normally, only one batch of drug product is tested during the development phase, and then the photostability characteristics should be confirmed on a single batch selected as described in the Parent Guideline if the product is clearly photostable or photo labile. If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted. [25]

For some products where it has been demonstrated that the immediate pack is completely impenetrable to light, such as aluminum tubes or cans, testing should normally only be conducted on directly exposed drug product. It may be appropriate to test certain products such as infusion liquids, dermal creams, etc., to support their photostability in-use. The extent of this testing should depend on and relate to the directions for use, and is left to the applicant's discretion. The analytical procedures used should be suitably validated.

VI. (Q1C) STABILITY TESTING FOR NEW DOSAGE FORMS

1. General:
The ICH harmonized Tripartite Guideline on Stability Testing of New Drug Substances and Products was issued on October 27, 1993. This document is an annex to the ICH parent stability guideline and addresses the recommendations on what should be submitted regarding stability of new dosage forms by the owner of the original application, after the original submission for new drug substances and products. [17]

2. New dosage form:
A new dosage form is defined as a drug product which is a different pharmaceutical product type, but contains the same active substance as included in the existing drug product approved by the pertinent regulatory authority.

Such pharmaceutical product types include products of different administration route (e.g., oral to parenteral), new specific functionality/delivery systems (e.g., immediate release tablet to modified release tablet) and different dosage forms of the same administration route (e.g., capsule to tablet, solution to suspension). [6]

VII. (Q1 D) BRACKETING AND MATRIXING DESIGNS FOR STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS

1. General:
The study design is one in which samples for every combination of all design factors are testing at all the time points. A reduced design is one in which samples for every factor combination is not all tested at all the time points. Any reduced design should have ability to adequately predict the retest period or shelf life. [17]

2. Applicability of Reduced Designs:
Reduced designs can be applied to the formal stability study of most types of drug products although additional explanation should be provided for certain complex drug delivery system where there are a large number of potential drug device interaction. [27]

Whether bracketing or matrixing can be applied depends on the circumstances, as discussed in detail below. The use of any reduced design should be justified. In certain cases, the condition described in this guideline is sufficient justification for use, while in other cases, additional justification should be provided.
The type and level of justification in each of these cases will depend on the available supporting data. Data variability and product stability, as shown by supporting data, should be considered when a matrixing design is applied. [17]

3. Bracketing:
The design of stability schedule such that only samples at the extremes of certain design factors, e.g. strength and package size, are tested at time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. [6]

Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g. for a Tablet range made with different compression

weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system. [27]

3.1 Drug factors: Design factors are variables (e.g. strength, container size and fill) to be evaluated in a study design for their effect of product stability.

3.1.1 Strength

- Bracketing can be applied to studies with multiple strength of identical or closely related formulations. For example
- Capsules of different strength made different fills plug sizes from the same powder blend
- Tablets of different strengths manufactured by compressing varying amounts of the same granulation.
- Oral solutions of different strengths with formulations that differ only in minor excipients (e.g. colorants, flavorings). [17]

3.1.2 Container closure sizes or fills

Bracketing can be applied to studies of same container closure system where either container sizes or fill varies while other remains constant. However, if not bracketing design is considered where both containers size and fills vary, it should not be assumed that the largest and smallest containers represent the extremes of all packaging configurations. [27]

Table 9. Example of a Bracketing Design.

Strength		50mg			75mg			100mg		
Batch		1	2	3	1	2	3	1	2	3
Container Sizes	15ml	T	T	T				T	T	T
	100ml									
	500ml	T	T	T				T	T	T

3.2 Design considerations and potential risks: The study design can be maintained to support the bracketed intermediates. A commitment should be provided to carry out stability studies on the marketed extremes post-approval.

3.3 Design Example: An example of a bracketing design is given in Table 8. This example is based on a product available in three strengths and three container sizes. In this example, it should be demonstrated that the 15 ml and 500 ml high-density polyethylene container sizes truly represent the extremes. The batches for each selected combination should be tested at each time point as in a full design.

4. Matrixing:

The Matrixing is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point. At a subsequent time, point, another subset of samples for all factor combinations would be tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and possibly, in some cases, different container closure systems. [17]

When a secondary packaging system contributes to the stability of the drug product, matrixing can be performed across the packaging systems. Each storage condition should be treated separately under its own matrixing design.

4.1 Design factor: Matrixing designs can be applied to strengths with identical or closely related formulations. For Example1) Capsules of different strength made different fills plug sizes from the same powder blend. 2) Tablets of different strengths manufactured by compressing varying amounts of the same granulation. 3) Oral solutions of different strengths with formulations that differ only in minor excipients (e.g.colourants, flavorings). [27]

4.2 Design considerations: A matrixing design should be balanced as possible so that combination of factors is tested to the same extent over the intended duration of the study and through the last time point to submission. However, due to achieve a full testing at certain time points are matrixed, all selected factor combinations should be tested at the initial and finial time points, while only certain fractions of the designated combination should be tested at

each intermediate time point. In addition, data from at least 3 times points, including initial, should be available for each selected combination through the first 12 months of the study.

4.3 Design Examples: Examples of matrixing designs on time points for a product in two strengths (S1 and S2) are shown in Table 9. The terms "one-half reduction" and "one-third reduction" refer to the reduction strategy initially applied to the full study design. For example, a "one-half reduction" initially eliminates one in every two time points from the full study design and a "one-third reduction" initially removes one in every three. In the examples shown in Table 9, the reductions are less than one-half and one-third due to the inclusion of full testing of all factor combinations at some time points discussed in section (Design considerations). These examples include full testing at the initial, final, and 12-month time points. The ultimate reduction is therefore less than one-half (24/48) or one-third (16/48), and is actually 15/48 or 10/48, respectively. [27]

4.4 Applicability and Degree of Reduction : The following, although not an exhaustive list, should be considered when a matrixing design is contemplated:

- Knowledge of data variability
- Expected stability of the product
- Availability of supporting data
- Stability differences in the product within a factor or among factors and
- Number of factor combinations in the study

Table 10. Examples of Matrixing Designs on Time Points for a Product with Two Strengths.

Time point (months)			0	3	6	9	12	18	24	36
STRENGTH	S1	Batch1	T	T		T	T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T	T		T
	S2	Batch 1	T		T		T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T		T	T

"One-Half Reduction"

Time point (months)			0	3	6	9	12	18	24	36
STRENGTH	S1	Batch 1	T	T		T	T		T	T
		Batch 2	T	T	T		T	T		T
		Batch 3	T		T	T	T	T	T	T
	S2	Batch 1	T		T	T	T	T	T	T
		Batch 2	T	T		T	T		T	T
		Batch 3	T	T	T		T	T		T

"One-Third Reduction"

In general, a matrixing design is applicable if the supporting data indicate predictable product stability. Matrixing is appropriate when the supporting data exhibit only small variability. If the supportive data show large variability, a matrixing design should not be applied.

If a matrixing design is considered applicable, the degree of reduction that can be made from a full design depends on the number of factor combinations being evaluated. The more factors associated with a product and the more levels in each factor, the larger the degree of reduction that can be considered. However, any reduced design should have the ability to adequately predict the product shelf life. [27]

4.5 Potential Risk: Due to the reduced amount of data collected, a matrixing design on factors other than time points generally has less precision in shelf life estimation and yields a shorter shelf life than the corresponding full design. In addition, such a matrixing design may have insufficient power to detect certain main or interaction effects, thus leading to incorrect pooling of data from different design factors during shelf life estimation. If there is an excessive reduction in the number of factor combinations tested and data from the tested factor combinations cannot be pooled to establish a single shelf life, it may be impossible to estimate the shelf lives for the missing factor combinations. A study design that matrixes on time points only would often have similar ability to that of a full design to detect differences in rates of change among factors and to establish a reliable shelf life. This feature exists because linearity is assumed and because full testing of all factor combinations would still be performed at both the initial time point and the last time point prior to submission. [27]

5. Data Evaluation:

Stability data from studies in a reduced design should be treated in the same manner as data from full design studies.

VIII. (Q1E) EVALUATION OF STABILITY DATA

1. General Principles:

The purpose of a stability study is to establish, based on testing a minimum of three batches of the drug substance or product, a retest period or shelf life and label storage instructions applicable to all future batches manufactured and packaged under similar circumstances.

Although normal manufacturing and analytical variations are to be expected, it is important that the drug product be formulated with the intent to provide 100 percent of the labeled amount of the drug substance at the time of batch release. If the assay values of the batches used to registration application are higher than 100 percent of label at the time of batch release, after taking into account manufacturing and analytical variations, the shelf life proposed in the application can be overestimated. On the other hand, if the assay value of a batch is lower than 100 percent of label claim at the time of batch release, it might fall below the lower acceptance criterion before the end of the proposed shelf life.

A systematic approach should be adopted in the presentation and evaluation of the stability information. The stability information should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including those related to particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms). The basic concepts of stability data evaluation are the same for single- versus multifactor studies and for full- versus reduced-design studies.

Data from formal stability studies and, as appropriate, supporting data should be evaluated to determine the critical quality attributes likely to influence the quality and performance of the drug substance or product. Each attribute should be assessed separately, and an overall assessment should be made of the findings for the purpose of proposing a retest period or shelf life.

The retest period or shelf life proposed should not exceed that predicted for any single attribute. Appendix B provides (1) information on how to analyze long term data for appropriate quantitative test attributes from a study with a multifactor, full or reduced design, (2) Information on how to use regression analysis for retest period or shelf life estimation, and (3) examples of statistical procedures to determine pool ability of data from different batches or other factors. Additional guidance can be found in the references listed; however, the examples and references do not cover all applicable statistical approaches.

In general, certain quantitative chemical attributes (e.g., assay, degradation product and Preservative content) for a drug substance or product can be assumed to follow zero order kinetics during long-term storage1. Data for these attributes are therefore amenable to the type of statistical analysis described in Appendix B, including linear regression and pool ability testing. Although the kinetics of other quantitative attributes (e.g., pH, dissolution) is generally not known, the same statistical analysis can be applied, if appropriate. Qualitative attributes and microbiological attributes are not amenable to this kind of statistical analysis. [17, 28]

2.Data presentation:

Data should be presented in an appropriate format (e.g., tabular, graphical, narrative) and an evaluation of such data should be included in the application. The values of quantitative attributes at all the time points should be reported as measured (e.g., assay as percent of label claim). If a statistical analysis is performed, the procedure used and the assumptions underlying the model should be stated and justified. A tabulated summary of the outcome of statistical analysis and/or graphical presentation of the long-term data should be included.

3. Extrapolation:

Extrapolation is the practice of using a known data set to infer information about future data. Extrapolation to extend the retest period or shelf life beyond the period covered by long-term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition. Any extrapolation should be performed such that the extended retest period or shelf life will be valid for a future batch released with test results close to the release acceptance criteria.

The extrapolation of stability data assumes that the same change pattern will continue to apply beyond the period covered by long-term data. When estimating a regression line or curve to fit the long-term data, the data themselves provide a check on the correctness of the assumed change pattern, and statistical methods can be applied to test the goodness of fit of the data to the assumed line or curve.

Thus, a retest period or shelf life granted on the basis of extrapolation should always be verified by additional long-term stability data as soon as these data become available. Care should be taken to include in the protocol for commitment batches a time point that corresponds to the end of the extrapolated retest period or shelf life. [28]

4. Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products Intended for Room Temperature Storage:

A systematic evaluation of the data from formal stability studies should be performed. For drug substances or products intended for storage at room temperature, the assessment should begin with any significant change at the accelerated condition and, if appropriate, at the intermediate condition, and progress through the trends and variability of the long-term data. The circumstances are delineated under which extrapolation of retest period or shelf life beyond the period covered by long-term data can be appropriate.

4.1 No significant change at accelerated condition:

The no significant change occurs at the accelerated condition, the retest period or shelf life would depend on the nature of the long-term and accelerated data.

4.2Long-term and accelerated data showing little or no change over time and little or no variability: long-term data and accelerated data for an attribute show little or no change over time and little or no variability, it might be apparent that the drug substance or product will remain well within the acceptance criteria for that attribute during the proposed retest period or shelf life. In these circumstances, a statistical analysis is normally considered unnecessary but justification for the omission should be provided. Extrapolation of the retest period or shelf life beyond the period covered by long-term data can be proposed. The proposed retest period or shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data. [28]

4.3Long-term or accelerated data showing change over time and variability:If the long-term or accelerated data for an attribute show change over time and/or variability within a factor or among factors, statistical analysis of the long-term data can be useful in establishing a retest period or shelf life. Where there are differences in stability observed among batches or among other factors (e.g., strength, container size and/or fill) or factor combinations (e.g., strength-by-container size and/or fill) that preclude the combining of data, the proposed retest period or shelf life should not exceed the shortest period supported by any batch, other factor, or factor combination. Extrapolation beyond the period covered by long-term data can be proposed; however, the extent of extrapolation would depend on whether long-term data for the attribute are amenable to statistical analysis.

4.4 Data not amenable to statistical analysis: The long-term data are not amenable to statistical analysis, but relevant supporting data are provided, the proposed retest period or shelf life can be up to one and-a-half times, but should not be more than 6 months beyond, the period covered by long-term data. Relevant supporting data include satisfactory long-term data from development batches that are (1) made with a closely related formulation to, (2) manufactured on a smaller scale than, or (3) packaged in a container closure system similar to, that of the primary stability batches.

4.5 Data amenable to statistical analysis: If long-term data are amenable to statistical analysis but no analysis is performed, the extent of extrapolation should be the same as when data are not amenable to statistical analysis. However, if a statistical analysis is performed, it can be appropriate to propose a retest period or shelf life of up to twice, but not more than 12 months beyond, the period covered by long-term data, when the proposal is backed by the result of the analysis and relevant supporting data. [28]

4.6 Significant change at accelerated condition: The significant change* occurs at the accelerated condition, the retest period or shelf life would depend on the outcome of stability testing at the intermediate condition, as well as at the long-term condition.

- Softening of a suppository that is designed to melt at 37ºC, if the melting point is clearly demonstrated.
- Failure to meet acceptance criteria for dissolution for 12 units of a gelatin capsule or gel-coated tablet if the failure can be unequivocally attributed to cross-linking. However, if phase separation of a semi-solid dosage form occurs at the accelerated condition, testing at the intermediate condition should be performed. Potential interaction effects should also be considered in establishing that there is no other significant change. [17]

4.7 No significant change at intermediate condition: If there is no significant change at the intermediate condition, extrapolation beyond the period covered by long-term data can be proposed; however, the extent of extrapolation would depend on whether long-term data for the attribute are amenable to statistical analysis.

- **Data not amenable to statistical analysis:** The long-term data for an attribute are not amenable to statistical analysis, the proposed retest period or shelf life can be up to 3 months beyond the period covered by long-term data, if backed by relevant supporting data.
- **Data amenable to statistical analysis:** When the long-term data for an attribute are amenable to statistical analysis but no analysis is performed, the extent of extrapolation should be the same as when data are not amenable to statistical analysis. However, if a statistical analysis is performed, the proposed retest period or shelf life can be up to one-and-half times, but should not be more than 6 months beyond, the period covered by long-term data, when backed by statistical analysis and relevant supporting data.

4.8Significant change at intermediate condition: The significant change occurs at the intermediate condition, the proposed retest period or shelf life should not exceed the period covered by long-term data. In addition, a retest period or shelf life shorter than the period covered by long-term data. [28]

5. Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products Intended for Storage below Room Temperature:

5.1 Drug substances or products intended for storage in a refrigerator: Data from drug substances or products intended to be stored in a refrigerator should be assessed according to the same principles for drug substances or products intended for room temperature storage, except where explicitly noted in the section below.

5.2 No significant change at accelerated condition: The no significant change occurs at the accelerated condition, extrapolation of retest period or shelf life beyond the period covered by long-term data can be proposed based on the principles except that the extent of extrapolation should be more limited. If the long-term and accelerated data show little change over time and little variability, the proposed retest period or shelf life can be up to one-and-a-half times, but should not be more than 6 months beyond, the period covered by long-term data normally without the support of statistical analysis.

The long-term or accelerated data show change over time and/or variability, the proposed retest period or shelf life can be up to 3 months beyond the period covered by long-term data if (1) the long-term data are amenable to statistical analysis but a statistical analysis is not performed, or (2) the long-term data are not amenable to statistical analysis but relevant supporting data are provided. Where the long-term or accelerated data show change over time and/or variability, the proposed retest period or shelf life can be up to one-and-a-half times, but should not be more than 6 months beyond, the period covered by long-term data if (1) the long term data are amenable to statistical analysis and a statistical analysis is performed, and (2) the proposal is backed by the result of the analysis and relevant supporting data. [17]

5.3 Significant change at accelerated condition: If significant change occurs between 3- and 6-months' testing at the accelerated storage condition, the proposed retest period or shelf life should be based on the long-term data. Extrapolation is not considered appropriate. In addition, a retest period or shelf life shorter than the period covered by long-term data could be called for. If the long-term data show variability, verification of the proposed retest period or shelf life by statistical analysis can be appropriate. If significant change occurs within the first 3 months' testing at the accelerated storage condition, the proposed retest period or shelf life should be based on long-term data. Extrapolation is not considered appropriate. A retest period or shelf life shorter than the period covered by long-term data could be called for. If the long-term data show

variability, verification of the proposed retest period or shelf life by statistical analysis can be appropriate.

In addition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition (e.g., during shipping or handling). This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance or product at the accelerated condition for a period shorter than 3 months. [28]

5.4 Drug substances or products intended for storage in a freezer: For drug substances or products intended for storage in a freezer, the retest period or shelf life should be based on long-term data. In the absence of an accelerated storage condition for drug substances or products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition (e.g., during shipping or handling). [17]

5.5Drug substances or products intended for storage below -20°C: For drug substances or products intended for storage below -20°C, the retest period or shelf life should be based on long-term data and should be assessed on a case-by-case basis. 2.6 General Statistical Approaches where applicable, an appropriate statistical method should be employed to analyze the long-term primary stability data in an original application. The purpose of this analysis is to establish, with a high degree of confidence, a retest period or shelf life during which a quantitative attribute will remain within acceptance criteria for all future batches manufactured, packaged, and stored under similar circumstances.

In cases where a statistical analysis was employed to evaluate long-term data due to a change over time and/or variability, the same statistical method should also be used to analyze data from commitment batches to verify or extend the originally approved retest period or shelf life. Regression analysis is considered an appropriate approach to evaluating the stability data for a quantitative attribute and establishing a retest period or shelf life.

The nature of the relationship between an attribute and time will determine whether data should be transformed for linear regression analysis. The relationship can be represented by a linear or non-linear function on an arithmetic or logarithmic scale. In some cases, a non-linear regression can better reflect the true relationship. An appropriate approach to retest period or shelf-life estimation is to analyze a quantitative attribute (e.g., assay, degradation products) by determining the earliest time at which the 95 percent confidence limit for the mean intersects the proposed acceptance criterion. For an attribute known to decrease with time, the lower one-sided 95 percent confidence limit should be compared to the acceptance criterion. For an attribute known to increase with time, the upper one-sided 95 percent confidence limit should be compared to the acceptance criterion. For an attribute that can either increase or decrease, or whose direction of change is not known, two-sided 95 percent confidence limits should be calculated and compared to the upper and lower acceptance criteria.

The statistical method used for data analysis should take into account the stability study design to provide a valid statistical inference for the estimated retest period or shelf life. The approach described above can be used to estimate the retest period or shelf life for a single batch or for multiple batches when the data are combined after an appropriate statistical test. [28]

IX.CONCLUSIONS

As the pharmaceutical industry growing day by day, there is a great need of developing guidelines those will create harmonization. ICH is formed to develop and implement harmonized guidelines that will reduce the time required for registration of a pharmaceutical product.

ICH guidelines are mainly categorized into four types (Quality, Safety, Efficacy, and Multidisciplinary) which will cover almost all areas required for registration of a pharmaceutical product. Provide information regarding common stability data that should be submitted in registration process. Stability studies should be planned on the basis of pharmaceutical R+D and regulatory requirements. Forced degradation studies reveal the intrinsic chemical properties of API, while formal stability studies establish the rest date.

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