

A Review on Stability Guidelines by ICH and USFDA Guidelines for New Formulation and Dosage form

Anilkumar S. Chinchole^{1*}, B.N.Poul², C.V. Panchal¹, D.V. Chavan¹

¹Department of Quality Assurance,

Maharashtra College of Pharmacy, Nilanga, Latur, Maharashtra, India

²Principal of Maharashtra College of Pharmacy, Nilanga

Maharashtra College of Pharmacy, Nilanga, Latur, Maharashtra, India

*anilc14@gmail.com



ABSTRACT

Stability guidelines for new drug substance and new pharmaceutical formulations as per ICH and USP for the evaluation and consistency for new drug and pharmaceutical dosage form. The brief understanding of these guidelines can be easily recognized by this article. Stability testing Provide a 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. To establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions. Because physical, chemical or microbiological changes might impact the efficiency and security of the final product. To minimize the Adverse Effects of Instability In Drug Products Loss of potency of drug such as Change in concentration of active drug, Alteration of bioavailability, Loss of content uniformity, Loss of pharmaceutical elegance and patient acceptability, Formation of toxic degradation products.

Keywords: Stability Guidelines, ICH, USFDA Guidelines, New Formulation and Dosage form

INTRODUCTION

Stability studies means?

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^[1].

Protocol of Stability

Prior to the submission of an original or supplemental NADA, an applicant may wish to submit a stability protocol for comment before committing to studies that will become a permanent part of the NADA. The protocol should contain an outline of the proposed plan to be used in generating stability data. The protocol should describe the type of product being tested, sampling process, duration and

frequency of testing, number of samples and replicates per time interval, storage conditions (length of storage, type of storage, temperatures and packaging), methods of analysis (description or reference of published methods) with accompanying support data, if available, and other tests. The information listed in these guidelines should be incorporated as appropriate in the development of a plan.

GENERAL STABILITY CONSIDERATIONS

1. Definition of Active Ingredient

The active ingredient of an animal drug preparation is defined as that chemical whose biological, physiological, pharmacological, or chemical activities are claimed on the label to be beneficial for animals in normal or

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pathological conditions (diagnosis, prognosis, treatment, prophylaxis, therapy) or for animal production.

2. Strength (Potency)

The strength of a drug substance may be its concentration (quantity of the drug per unit measure), its potency, or both. The potency of a drug is a measurable (quantitative) extent of the biological, physiological, pharmacological, or chemical activities of the drug per unit weight or volume of the drug preparation.

Drug preparations are considered stable if the active ingredient can maintain its strength at the level specified on the label for the maximum anticipated shelf-life (the time period from the date of manufacture until administration to the animal) under environmental conditions likely to be encountered in actual use. However, few, if any, drug preparations maintain their full label-claimed strength under specified conditions. Therefore, allowances are made for some unavoidable deviations from drug levels declared on the label by designating specific limits for tolerable deviations.

A drug product is considered unstable when the drug substance (active ingredient) loses sufficient potency to adversely affect the safety or efficacy of the drug or falls outside labeled specifications as shown by stability-indicating methods. To properly evaluate the stability of a drug product, it is essential to determine the storage conditions under which the drug strength can be maintained in order to provide a safe and efficacious drug product. As a guide in determining drug strength in pharmaceutical dosage forms, the following is recognized by the scientific community: "Although there are exceptions, 90% of the labeled potency is generally recognized as the minimum acceptable potency level."

3. Drug Preparation

The active ingredient should be formulated in any drug preparation at 100% of label claim. An overage of the active ingredient may be permitted in a product should the need exist. All overages should be justified. The assay limits must account for the overage. The overage should not exceed the limits of 5% for antibiotics and 3% for non-antibiotic chemicals as established by the Center for Veterinary Medicine.

4. Chemical and Physical Properties

Strength is not the only criterion of drug product stability. Maintenance of various chemical and physical properties to preserve the effectiveness and safety of the drug is also important. Properties, such as physical appearance, crystalline form, particle size, solubility, disintegration rate, pH, sterility, viscosity, palatability (taste and odor), may be stability related and thus require testing and the setting of specific storage conditions and limits. In addition, tests may also be needed to determine the absence or presence of harmful degradation products.

5. Added Substances

Stability data on substances that are added to a drug preparation to enhance its stability, usefulness, physical or chemical properties or as an aid in manufacturing may be required. The type of substance(s) used, its purpose, and its relationship to the active drug ingredient(s) and total drug preparation will determine if testing for the substance is required. Examples of added substances that may commonly be used are antioxidants, antibacterials, absorbants (bentonite), etc.

6. Product Changes

Changes made in the composition (formulation) or dosage form of the original or succeeding product(s) present a new drug product and will require generation of new stability data. Data

requirements will depend on the nature and degree of change.

Any change requires an evaluation as to the effect on the stability of the products.

7. Correlation with Efficacy and Toxicity Studies

Stability studies supporting an application should be performed on the drug preparation in its final formulation whose efficacy and safety has been demonstrated. Any change made in an approved preparation requires consideration of the effects on the efficacy and safety of the "changed" drug product. Degradation Products Degradation products that occur during storage (under shelf-life testing) should be identified. These products should be thoroughly investigated and evaluated for safety and toxicology purposes. The presence of degradation products may require additional safety and efficacy studies.

8. Product Stability Parameters

The established regulatory registration (NADA or NDA) specifications or Compendial standards are to be used for determining the stability of the products. There can be only one set of standards. Samples of products (from production lots) on stability should be representative of those in the market place. Expiration dating is based on the ability of the product to be measured over a certain period of time against the established specifications or standards^[1,2].

STABILITY^[1,9]

In stability is defined as "the extent to which a preparation retains, within specified limits, and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of compounding." This chapter defines beyond-use date as "the date after which a compounded preparation is not to be used and is determined from the date the preparation is compounded. Stability testing is

used to determine a beyond-use date, which is required by USP guidelines to be on the label or package of a compounded preparation. The terms stability, shelf life, and beyond-use date can be used interchangeably when referring to compounded preparations. The term expiration date is used when referring to manufactured products. Pharmaceutical Compounding Sterile Preparations states, "It should be recognized that the truly valid evidence of stability for predicting beyond use dating can be obtained only through product-specific experimental studies." It is important to remember that the analytical method employed is key to determining stability versus potency. Once again, a stability-indicating method must be used to establish stability. Furthermore, a potency test that used stability-indicating methods can be used to determine stability as well as Stability testing usually includes method development, method validation, and a stability study. The method must separate the active ingredient from its degradants and impurities, as well as any other excipients potency in the preparation. This is done by force degrading the active ingredient and inactive ingredients to ensure that no degradants interfere with the analysis. In the process of force degradation, the compound is exposed to high heat and humidity, UV radiation, an acid, a base, and peroxide. It is this step that differentiates a stability indicating test from a simple potency test.

Stability can be determined from this type of study, simply because stability-indicating methods were used in the analysis. Method validation ensures that the method meets certain criteria. The typical analytical characteristics used in method validation include accuracy, precision, specificity, detection limit, quantitation limit, linearity, range, and ruggedness, as outlined in. The stability study includes storing the preparation in stability chambers, testing it at predetermined time points, and then

determining stability. These time points may be specified by the compounder or dictated by the particular compound. Once again, it is crucial to understand that the methods used to determine stability must be stability indicating. Quality assurance programs are essential to establishing appropriate standards for compounded preparations. The specific program implemented is up to the compounding pharmacy but should include a standard operating procedure, documentation, verification, and testing as outlined in USP Chapter. The standards of the Pharmacy Compounding Accreditation Board state that “a pharmacy must provide documentation of the basis for its determination of the beyond-use date assigned to its compounded preparation.”

ICH GUIDELINES ^[2]

1. Stability Testing of New Drug Substances and Products Q1A(R2)
2. Stability Testing: Photostability Testing of New Drug Substances and Products Q1B
3. Stability Testing for New Dosage Forms(Q1C)
4. Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products(Q1D)
5. Evaluation for Stability Data(Q1E)
6. Stability Data Package for Registration Applications in Climatic Zones III and IV (Q1F)².

STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS ^[2,3]

INTRODUCTION

Objectives of the Guideline

The following guideline is a revised version of the ICH Q1A guideline and defines the stability data package for a new drug substance or drug product that is sufficient for a registration application within the three regions of the EC, Japan, and the United States. It does not seek necessarily to cover the testing for registration in or export to other areas of the world.

The guideline seeks to exemplify the core stability data package for new drug substances

and products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated. Alternative approaches can be used when there are scientifically justifiable reasons.

Scope of the Guideline

The guideline addresses the information to be submitted in registration applications for new molecular entities and associated drug products. This guideline does not currently seek to cover the information to be submitted for abbreviated or abridged applications, variations, clinical trial applications, etc. Specific details of the sampling and testing for particular dosage forms in their proposed container closures are not covered in this guideline.

Further guidance on new dosage forms and on biotechnological/biological products can be found in ICH guidelines Q1C and Q5C, respectively.

General Principles

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 re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.

The choice of test conditions defined in this guideline is based on an analysis of the effects of climatic conditions in the three regions of the EC, Japan and the United States. The mean kinetic temperature in any part of the world can be derived from climatic data, and the world can be divided into four climatic zones, I-IV. This guideline addresses climatic zones I and II. The principle has been established that stability information generated in any one of the three

regions of the EC, Japan and the United States would be mutually acceptable to the other two regions, provided the information is consistent with this guideline and the labeling is in accord with national/regional requirements.

GUIDELINES

Drug Substance

General

Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation.

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 and the type of drug product involved.

Stress testing is likely to be carried out on a single batch of the drug substance. 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. Photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in ICH Q1B.

Selection of Batches

Data from formal stability studies should be provided on at least three primary batches of the drug substance. The batches should be manufactured to a minimum of pilot scale by the same synthetic route as, 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 placed on formal stability studies should be representative of the quality of the material to be made on a production scale.

Container Closure System

The stability studies should be conducted on the drug substance packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.

Specification

Specification, which is a list of tests, reference to analytical procedures, and proposed acceptance criteria, is addressed in ICH Q6A and Q6B. In addition, specification for degradation products in a drug substance is discussed in Q3A.

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 should cover, as 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.

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. 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. Where an expectation (based on development experience) exists that results from accelerated studies 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.

Storage Conditions

In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the

lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

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).

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
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 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

**If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and “significant change” occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. Testing at the intermediate storage condition should include all tests, unless otherwise justified. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

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
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

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	12 months

Drug substances intended for storage below - 20°C

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

Stability Commitment

One of the following commitments should be made:

1. If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue these studies through the proposed re-test period.
2. If the submission includes data from stability studies on fewer than three 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, on long term stability studies through the proposed re-test period.
3. 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 re-test period.

Evaluation

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug substance and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological, and microbiological tests), a re-test period applicable to all future batches of the drug substance manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned re-test period.

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested re-test period will be granted. Under these circumstances, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

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. If it is inappropriate to combine data from several batches, the overall re-test period should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any 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 of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the real time data from the long term storage condition beyond the observed range to extend the re-test period can be undertaken at approval time, if justified. This justification should be based on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, existence of supporting stability data, etc. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should cover not only the assay, but also the levels of degradation products and other appropriate attributes.

Drug Product

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.

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.

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 justified. Where possible, batches of the drug product should be manufactured by using different batches of the drug substance.

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.

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. In addition, specification for degradation products in a drug product is addressed in Q3B.

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. Whether and to what extent replication should be performed will depend on the results of validation studies.

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. 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.

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.

Storage Conditions

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, 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. In general, this testing need not be repeated on commitment batches.

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 shelf life. 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).

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
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 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

**If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

Stability Commitment

Where 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:

1. 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.

2. 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.

3. 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.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

Where intermediate testing is called for by a significant change at the accelerated storage condition for the primary batches, testing on the commitment batches can be conducted at either the intermediate or the accelerated storage condition. However, if significant change occurs at the accelerated storage condition on the commitment batches, testing at the intermediate storage condition should also be conducted.

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.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing data of 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. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

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.

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.

STABILITY TESTING: PHOTOSTABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS Q1B ^[2,4]

General

The ICH Harmonized Tripartite Guideline covering the Stability Testing of New Drug

Substances and Products (hereafter referred to as the Parent Guideline) 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.

Preamble

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:

1. Tests on the drug substance;
2. Tests on the exposed drug product outside of the immediate pack; and if necessary ;
3. Tests on the drug product in the immediate pack; and if necessary ;
4. Tests on the drug product in the marketing pack.

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 unless otherwise justified. 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.

Option 2

For option 2 the same sample should be exposed to both the cool white fluorescent and near ultraviolet lamp.

1. A cool white fluorescent lamp designed to produce an output similar to that specified in ISO 10977(1993) ; and
2. 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.

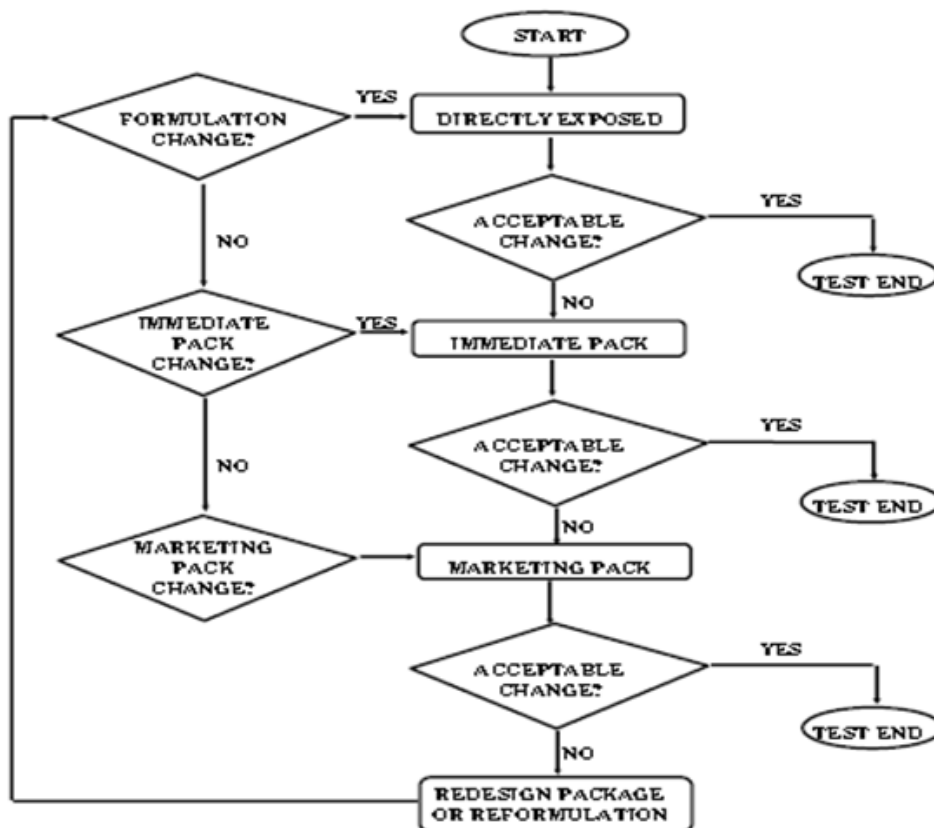
Procedure

For confirmatory studies, 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.

Samples may be exposed side-by-side with a validated chemical actinometric system to ensure the specified light exposure is obtained, or for the appropriate duration of time when conditions have been monitored using calibrated radiometers/lux meters. An example of an actinometric procedure is provided in the Annex.

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.

**DECISION FLOW CHART FOR
PHOTOSTABILITY TESTING
OF DRUG PRODUCTS**



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/or degradation pathway elucidation. This testing may involve the drug substance alone and/or 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. For development and validation purposes it is appropriate to limit exposure and end the studies if extensive decomposition occurs. For photostable materials, studies may be terminated after an appropriate exposure level has been used. The design of these experiments is left to the applicant's discretion although the exposure levels used should be justified.

Presentation of Samples

Care 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/or placing the samples in sealed containers, to ensure that the effects of the changes in physical states such as

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.

As a direct challenge for samples of solid drug substances, an appropriate amount of sample should be taken and placed in a suitable glass or plastic dish and protected with a suitable transparent cover if considered necessary. 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.

Analysis of Samples

At 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. The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark controls if these are used in the test.

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 photolabile. If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted.

For some products where it has been demonstrated that the immediate pack is completely impenetrable to light, such as aluminium 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.

EVALUATION FOR STABILITY DATA (Q1E) ^[2,5]

INTRODUCTION

Objectives of the Guideline

This guideline is intended to provide recommendations on how to use stability data generated in accordance with the principles detailed in the ICH guideline "Q1A(R) Stability Testing of New Drug Substances and Products" (hereafter referred to as the parent guideline) to propose a retest period or shelf life in a registration application. This guideline describes when and how extrapolation can be considered when proposing a retest period for a drug substance or a shelf life for a drug product that extends beyond the period covered by "available data from the stability study under the long-term storage condition" (hereafter referred to as long-term data).

General Principles

The design and execution of formal stability studies should follow the principles outlined in the parent guideline. 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. The degree of variability of individual batches affects the confidence that a future production batch will remain within acceptance criteria throughout its retest period or shelf life.

The decision tree in Appendix A outlines a stepwise approach to stability data evaluation and when and how much extrapolation can be considered for a proposed retest period or shelf life. Appendix B provides (1) information on how to analyze long-term data for appropriate quantitative test attributes from a study with a multi-factor, 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 poolability 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 products, preservative content) for a drug substance or product can be assumed to follow zero-order kinetics during long-term storage ^[1]. Data for these attributes are therefore amenable to the type of statistical analysis described in Appendix B, including linear regression and poolability 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.

Data presentation

Data for all attributes 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 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.

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. Whether extrapolation of stability data is appropriate depends on the extent of knowledge about the change pattern, the goodness of fit of any mathematical model, and the existence of relevant supporting data. 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.

An extrapolation of stability data assumes that the same change pattern will continue to apply beyond the period covered by long-term data. The correctness of the assumed change pattern is critical when extrapolation is considered. 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.

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 as illustrated in this section. Stability data for each

attribute should be assessed sequentially. 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.

Long-term and accelerated data showing little or no change over time and little or no variability

Where the 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. Justification can include a discussion of the change pattern or lack of change, relevance of the accelerated data, mass balance, and/or other supporting data as described in the parent guideline. Extrapolation of the retest period or shelf life beyond the period covered by long-term data can be proposed.

Long-term or accelerated data showing change over time and/or 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. Alternatively, where the

differences are readily attributed to a particular factor (e.g., strength), different shelf lives can be assigned to different levels within the factor (e.g., different strengths).

Significant change at accelerated condition

Where 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 37°C, 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.

Significant change at intermediate condition

Where 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 could be called for.

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

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 as described in Section 2.4 for drug substances or products intended for room temperature storage, except where explicitly noted in the section below. The decision tree in Appendix A can be used as an aid.

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.

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., $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ or $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$) 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).

Drug 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.

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 analyse data from commitment batches to verify or extend the originally approved retest period or shelf life.

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.

Data Analysis For Bracketing Design Studies

The statistical procedures described in Section B.3 can be applied to the analysis of stability data obtained from a bracketing design study. For example, for a drug product available in three strengths (S1, S2, and S3) and three container sizes (P1, P2, and P3) and studied according to a bracketing design where only the two extremes of the container sizes (P1 and P3) are tested, six sets of data from the 3x2 strength-size combinations will be obtained. The data can be analyzed separately for each of the six combinations for shelf life estimation according to Section B.3.2.1, or tested for poolability prior to shelf life estimation according to Section B.3.2.2.

The bracketing design assumes that the stability of the intermediate strengths or sizes is represented by the stability at the extremes. If the statistical analysis indicates that the stability of the extreme strengths or sizes is different, the intermediate strengths or sizes should be considered no more stable than the least stable extreme. For example, if P1 from the above bracketing design is found to be less stable than P3, the shelf life for P2 should not exceed that for P1. No interpolation between P1 and P3 should be considered.

Data Analysis For Matrixing Design Studies

A matrixing design has only a fraction of the total number of samples tested at any specified time point. Therefore, it is important to ascertain that all factors and factor combinations that can have an impact on shelf life estimation have been appropriately tested. For a meaningful interpretation of the study results and shelf life estimation, certain assumptions should be made and justified. For instance, the assumption that the stability of the samples tested represents the stability of all samples should be valid. In addition, if the design is not balanced, some factors or factor interactions might not be estimable. Furthermore, for different levels of factor combinations to be poolable, it might have to be assumed that the higher order factor interactions are negligible. Because it is usually impossible to statistically test the assumption that the higher order terms are negligible, a matrixing design should be used only when it is reasonable to assume that these interactions are indeed very small, based on supporting data.

The statistical procedure described in Section B.3 can be applied to the analysis of stability data obtained from a matrixing design study. The statistical analysis should clearly identify the procedure and assumptions used. For instance, the assumptions underlying the model in which interaction terms are negligible should

be stated. If a preliminary test is performed for the purpose of eliminating factor interactions from the model, the procedure used should be provided and justified. The final model on which the estimation of shelf life will be based should be stated. The estimation of shelf life should be performed for each of the terms remaining in the model. The use of a matrixing design can result in an estimated shelf life shorter than that resulting from a full design.

BRACKETING AND MATRIXING DESIGNS FOR STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (Q1D) ^[2,6]

Objectives of the Guideline

This guideline is intended to address recommendations on the application of bracketing and matrixing to stability studies conducted in accordance with principles outlined in the ICH Q1A(R) Harmonised Tripartite guideline on Stability Testing of New Drug Substances and Products (hereafter referred to as the parent guideline).

General

A full study design is one in which samples for every combination of all design factors are tested at all time points. A reduced design is one in which samples for every factor combination are not all tested at all time points. A reduced design can be a suitable alternative to a full design when multiple design factors are involved. Any reduced design should have the ability to adequately predict the retest period or shelf life. Before a reduced design is considered, certain assumptions should be assessed and justified. The potential risk should be considered of establishing a shorter retest period or shelf life than could be derived from a full design due to the reduced amount of data collected.

During the course of a reduced design study, a change to full testing or to a less reduced design can be considered if a justification is provided and the principles of full designs and reduced designs are followed. However, proper adjustments should be made to the statistical

analysis, where applicable, to account for the increase in sample size as a result of the change.

Applicability of Reduced Designs

Reduced designs can be applied to the formal stability study of most types of drug products, although additional justification should be provided for certain complex drug delivery systems where there are a large number of potential drug-device interactions. For the study of drug substances, matrixing is of limited utility and bracketing is generally not applicable.

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. Bracketing and matrixing are reduced designs based on different principles. Therefore, careful consideration and scientific justification should precede the use of bracketing and matrixing together in one design.

Bracketing

As defined in the glossary to the parent guideline, bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or fill) are tested at all 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.

The use of a bracketing design would not be considered appropriate if it cannot be demonstrated that the strengths or container

sizes and/or fills selected for testing are indeed the extremes.

Design Factors

Design factors are variables (e.g., strength, container size and/or fill) to be evaluated in a study design for their effect on product stability.

Strength

Bracketing can be applied to studies with multiple strengths of identical or closely related formulations. Examples include but are not limited to (1) capsules of different strengths made with different fill plug sizes from the same powder blend, (2) tablets of different strengths manufactured by compressing varying amounts of the same granulation, and (3) oral solutions of different strengths with formulations that differ only in minor excipients (e.g., colourants, flavourings).

With justification, bracketing can be applied to studies with multiple strengths where the relative amounts of drug substance and excipients change in a formulation. Such justification can include a demonstration of comparable stability profiles among the different strengths of clinical or development batches.

Container Closure Sizes and/or Fills

Bracketing can be applied to studies of the same container closure system where either container size or fill varies while the other remains constant. However, if a bracketing design is considered where both container size and fill vary, it should not be assumed that the largest and smallest containers represent the extremes of all packaging configurations. Care should be taken to select the extremes by comparing the various characteristics of the container closure system that may affect product stability. These characteristics include container wall thickness, closure geometry, surface area to volume ratio, headspace to volume ratio, water vapour permeation rate or

oxygen permeation rate per dosage unit or unit fill volume, as appropriate.

Design Considerations and Potential Risks

If, after starting the studies, one of the extremes is no longer expected to be marketed, 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.

Before a bracketing design is applied, its effect on the retest period or shelf life estimation should be assessed. If the stability of the extremes is shown to be different, the intermediates should be considered no more

stable than the least stable extreme (i.e., the shelf life for the intermediates should not exceed that for the least stable extreme).

Design Example

An example of a bracketing design is given in Table 1. 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.

Example of a Bracketing Design

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

Key: T = Sample tested

Matrixing

As defined in the glossary of the parent guideline, 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.

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. Matrixing should not be performed across test attributes. However, alternative matrixing designs for different test attributes can be applied if justified.

Design Factors

Matrixing designs can be applied to strengths with identical or closely related formulations. Examples include but are not limited to (1) capsules of different strengths made with different fill plug sizes from the same powder blend, (2) tablets of different strengths manufactured by compressing varying amounts of the same granulation, and (3) oral solutions of different strengths with formulations that differ only in minor excipients (e.g., colourants or flavourings).

Other examples of design factors that can be matrixed include batches made by using the same process and equipment, and container

sizes and/or fills in the same container closure system.

With justification, matrixing designs can be applied, for example, to different strengths where the relative amounts of drug substance and excipients change or where different excipients are used or to different container closure systems. Justification should generally be based on supporting data. For example, to

matrix across two different closures or container closure systems, supporting data could be supplied showing relative moisture vapour transmission rates or similar protection against light. Alternatively, supporting data could be supplied to show that the drug product is not affected by oxygen, moisture, or light.

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

“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
	S2	Batch 1	T		T		T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T		T	T

Key: T = Sample tested

“One-Third 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

Key: T = Sample tested

STABILITY TESTING FOR NEW DOSAGE FORMS (Q1C) ^[2,7]

GENERAL

The ICH harmonised 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

NEW DOSAGE FORMS

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).

Stability protocols for new dosage forms should follow the guidance in the parent stability

guideline in principle. However, a reduced stability database at submission time (e.g., 6 months accelerated and 6 months long term data from ongoing studies) may be acceptable in certain justified cases.

STABILITY DATA PACKAGE FOR REGISTRATION APPLICATIONS IN CLIMATIC ZONES III AND IV (Q1F) ^[2,8]

Objectives of the Guideline

This guideline describes an approach to broader use of the ICH guideline “Q1A(R) Stability Testing of New Drug Substances and Products” (hereafter referred to as the parent guideline) and outlines the stability data package for a new drug substance or drug product that is considered sufficient for a registration application in territories in Climatic Zones III and IV.

GUIDELINES

Continuity with the Parent Guideline

This guideline should be used in conjunction with the parent guideline and subsequently published annexes (Q1B, Q1C, Q1D, Q1E, Q5C).

The recommendations in the parent guideline and annexes should be followed unless specific alternatives are described within this guideline. The following sections of the parent guideline can be considered common to any territory in the world and are not reproduced here:

- Stress testing
- Selection of batches
- Container closure system
- Specification
- Testing frequency
- Storage conditions for drug substance or product in a refrigerator
- Storage conditions for drug substance or product in a freezer
- Stability commitment
- Evaluation
- Statements/labelling

Storage Conditions

General Case

For the “General case” (as described in the parent guideline), the recommended long-term and accelerated storage conditions for Climatic Zones III and IV are shown below:

Study	Storage condition	Minimum time period covered by data at submission
Long-term	30°C ± 2°C/65% RH ± 5% RH	12 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

No intermediate storage condition for stability studies is recommended for Climatic Zones III and IV. Therefore, the intermediate storage condition is not relevant when the principles of retest period or shelf life extrapolation described in Q1E are applied.

Aqueous-based drug products packaged in semi-permeable containers

For aqueous-based drug products packaged in semi-permeable containers (as described in the parent guideline), the recommended long-term and accelerated storage conditions for Climatic Zones III and IV are shown below:

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

As described in the parent guideline, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio (see table below for examples).

The ratio of water loss rates at a given temperature is calculated by the general formula (100 – reference % RH)/(100 – alternative % RH).

Alternative relative humidity	Reference relative humidity	Ratio of water loss rates at a given temperature
65% RH	35% RH	1.9
75% RH	25% RH	3.0

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can be used. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

Tests at elevated temperature and / or extremes of humidity

Special transportation and climatic conditions outside the storage conditions recommended in this guideline should be supported by additional data. For example, these data can be obtained from studies on one batch of drug product conducted for up to 3 months at 50°C/ambient humidity to cover extremely hot and dry conditions and at 25°C/80% RH to cover extremely high humidity conditions^[2].

Stability testing at a high humidity condition, e.g., 25°C/80% RH, is recommended for solid dosage forms in water-vapour permeable packaging, e.g., tablets in PVC/aluminum blisters, intended to be marketed in territories with extremely high humidity conditions in Zone IV. However, for solid dosage forms in primary containers designed to provide a barrier to water vapour, e.g. aluminum /

aluminum blisters, stability testing at a storage condition of extremely high humidity is not considered necessary.

CONCLUSION

The stated citation and reviewed data is considerable for comparative study and study about critical key elements that are often used in the ICH guidelines. Many guidelines has been used for various pharmaceutical operations and processes, so can't read as fast as early therefore compact and partially but important peer can be stated as above. The USFDA and ICH stability guidelines has been given appropriate and considerable data as per references mentioned so, the data available with regarding stability studies of New drug Substances and Drug Products were easy to understand and refer.

↓ REFERENCES

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