Regulation on Stability Test of Pharmaceuticals

[Enforcement Date: Dec.17, 2019] [MFDS Notification No. 2020-132, Partially Amended on Dec.17, 2019]

Article 1(Purpose) The purpose of this regulation is to set forth the standard related to stability testing of drugs and quasi-drugs (hereinafter referred to as "pharmaceuticals") submitted in accordance with Articles 31 and 42 of the Pharmaceutical Affairs Act and Article 9 Paragraph 1 Subparagraph 3 of the Regulation on Safety of Medicinal Products, etc.

Article 2(Definitions) The definitions of the terms used in this regulation shall be as follows:

① The term "stability testing (hereinafter referred to as "testing")" means a test performed to assess the stability of quality with the passage of time, in order to establish storage condition and shelf-life, etc. of pharmaceuticals.

② The term "long-term testing" means a test performed for a long period of time to verify the physicochemical and biological stability of pharmaceuticals to establish shelf-life (or expiration date) under the set storage conditions.

③ The term "stress testing" means a test performed to elucidate the degradation process and degradation products of pharmaceuticals under stress conditions.

④ The term "accelerated testing" means a test performed to assess the effect of short-term accelerated conditions deviating from storage conditions of the long-term test on the stability of pharmaceuticals.

⑤ The term "intermediate condition testing" means a test performed under intermediate conditions when significant changes are found during an accelerated test.

⑥ The term "semi-permeable container" means a container which allows passage of solvent but not the solute (e.g., plastic bags and flow-density polyethylene (LDPE) bags for large volume parenteral (LVPs), low-density polyethylene ampoules, bottles or vials, etc.).

⑦ The term "shelf-life, etc." means the shelf-life, expiration date or re-testing period.

⑧ The term "biological products etc." means biological products, recombinant DNA products and cell culture derived products, cell-therapy products and gene-therapy products.

Article 3(Standards for Testing) ① Standard for Long-term Testing

1. Batch Selection

a. The same composition, formulation and container closure system as the product to be marketed shall be used. However, there may be exceptions for cases those that do not affect stability.

b. In principle, testing shall be performed on more than 3 batches.

2. Storage conditions: Testing shall be performed under the following conditions depending on the

temperature, but if a storage temperature is already established, then it may be used.

a. Drugs to be stored at room temperature: Conditions shall be 25±2°C and relative humidity of 60±5% or 30±2°C and relative humidity of 65±5%. However, for semi-permeable containers, conditions shall be 25±2°C and relative humidity of 40±5% or 30±2°C and relative humidity of 35±5%.

b. Drugs under refrigerated storage: Conditions shall be 5±3°C.

c. Drugs under frozen storage: Conditions shall be -20±5°C.

3. Testing period: New drug shall be tested for at least 12 months, and pharmaceuticals required for data submission shall be tested for at least 6 months. However, testing period may be determined separately depending on the nature of pharmaceuticals.

4. Testing frequency: Testing shall be performed every 3 months over the first year after initiation, every 6 months over the second year, and then annually.

5. Testing items: In principle, all items established in the Specification & Test Method shall be tested. However, in case of omitting certain items, a clear reason for such omission shall be provided.

② Standard for Stress Testing

1. Testing conditions: The 3 conditions of light, temperature and humidity shall be set, taking into account the characteristics of the sample. However, if the sample is a drug substance, the testing shall be performed to include testing conditions (light, temperature, pH) for aqueous solutions.

2. Testing items: Important items for quality control shall be tested, production of degradation products shall be assessed and quantified, and information on the physicochemical properties, toxicity and pharmacological test data, etc. of significant degradation products shall be submitted.

3. Batch selection, testing period, etc., shall be set appropriately according to the characteristics of the sample and testing conditions.

③ Standard for Accelerated Test

1. Batch selection: Refer to the standard for long-term testing.

2. Storage conditions: Testing shall be performed under the following conditions:

a. Drugs to be stored at room temperature: Conditions shall be 40±2°C and relative humidity of 75±5% or considering appropriate humidity for the given temperature, more than 15°C above the storage temperature set for long-term testing. However, for semi-permeable containers, conditions shall be 40±2°C and relative humidity of 25% or below.

b. Drugs under refrigerated storage: Conditions shall be 25±2°C and relative humidity of 60±5%.

c. Drugs under frozen storage: Conditions shall be determined separately depending on the individual product.

3. Testing period: Testing shall be performed for more than 6 months.

4. Testing frequency: Testing shall be performed at least 3 times including the initial time point. In case a significant change is observed in an accelerated testing during drug development, testing shall be performed at least 4 times.

5. Testing items: Refer to the standard for long-term testing.

④ Standard for Intermediate Condition Testing

For drugs to be stored at room temperature, intermediate conditions test shall be performed when significant changes are observed during an accelerated test. However, if a long-term test was performed at 30±2°C and relative humidity of 65±5% (or at 30±2℃ relative humidity of 35±5% for semi-permeable containers), the long-term testing can be used in place of intermediate condition testing.

1. Batch selection: Refer to the standard for long-term testing.
2. Storage conditions: Conditions shall be 30±2°C/ and relative humidity of 65±5%. However, for semi-permeable containers, testing shall be performed at 30±2°C and relative humidity of 65±5%.
3. Testing period: To determine shelf-life, etc. based on the results of the intermediate condition testing, data from intermediate conditions testing performed for more than 12 months are required.
4. Testing frequency: Testing shall be performed at least 4 times including the initial and final time points.

⑤ Significant changes in an accelerated testing or an intermediate condition testing are as follows:

1. Drug substance: Does not conform to specifications
2. Drug product
   a. There is a variation in content of more than 5% compared to the initial value;
   b. The degradation product exceeds the acceptance criteria;
   c. The results of the pH or dissolution test do not conform to the specification set for the corresponding dosage form;
   d. The results of the appearance, physical properties, functional test (e.g., color, phase separation, degree of resuspension, caking, hardness, dosage unit per spray, etc.) do not conform to the specification.

⑥ Despite paragraphs ① through ⑤, testing for new drugs shall be performed according to Annex 4 "Stability Testing Standard for New Drugs", Annex 5 "Stability Testing of New Dosage Forms for New Drugs", and Annex 6 "Photostability Testing of New Drugs".

Article 4(Exemption of Testing) Part of the testing may be omitted as the following for products with the same active pharmaceutical ingredient(s) and dosage form (including products with different strengths of active pharmaceutical ingredient). However, this excludes products deemed to have a special dosage form:

① Testing is performed based on a bracketing design according to Annex 1.

② Testing is performed based on a matrix design according to Annex 2.

③ Despite paragraphs ① through ②, testing for new drugs shall be performed according to [Annex 7] Bracketing and Matrixing Designs for New Drugs.

Article 5(Standard for Establishing Shelf-life, etc.) ① Generally, shelf-life, etc. shall be established within the actual long-term testing period.

② Shelf-life, etc. may be established according to the method described in Annex 3 based on the results of the long-term testing and accelerated testing. However, this is not applicable for biological products.

③ When determining shelf-life, etc. based on a bracketing design, if there is a discrepancy between the test results on the product containing the maximum dose of active pharmaceutical ingredient (or the maximum fill volume of the container) and the product containing the minimum dose of active pharmaceutical ingredient (or the minimum fill volume of the container), then shelf-life, etc. shall be established based on the results of the product with inferior stability.

④ Despite paragraphs ① through ③, new drugs shall be evaluated according to Annex 8 "Evaluation of Stability Data".

⑤ Matters regarding the establishment of shelf-life, etc that are out of scope of prescribed paragraphs ① through ③ shall follow the "Regulation on Pharmaceuticals Approval, Notification and Review"(MFDS Notification).

Article 6(Submission of Test Data) ① Stability testing data shall be data from tests performed using a verified test method by a responsible person with adequate experience and responsibility at a facility with sufficient equipment in accordance with testing standards in Article 3, and shall include the following:

1. Information on the facilities, such as the name and address of the testing institute, critical equipment used in the testing, etc
2. Name, job title, testing experience and qualifications/licenses of the responsible person for the testing
3. Product name, composition of drug substances including excipients, container closure system, manufacturing date, production scale and batch number
4. Testing period and storage (testing) conditions
5. Conclusion of the responsible person for the testing regarding test results.

Article 7(Supplementary Provision) ① These regulations set forth the standard for stability testing of pharmaceuticals. Should there be a reasonable justification, the storage conditions and testing period, etc. may be changed.

Article 8(Reexamination of Regulation) In accordance with Article 8 of [Framework Act on Administrative Regulations] and [Regulation on Issuance and Management of Decree and Rules, etc.] (Presidential Decree No. 248), the measures such as revision, etc. based on the examination of validity shall be taken by every 3 years (refers to December 31 of every third year) as of January 1st 2014.

ADDENDUM <No. 2014-59, February 12, 2014>

This regulation shall enter into force on the date of its notification.

[Annex 1] Bracketing Design

1. This is a method applied when performing stability testing on 3 or more formulations with different doses of active pharmaceutical ingredient(API) but have similar ratios in composition of API and excipients, or have equivalent concentrations of API and excipients in a unit weight (volume) but have different fill volumes. In such case, the shelf-life, etc. of the formulation with an intermediate dose or an intermediate fill volume can be determined based on data from tests performed on formulations with maximum API dose or maximum fill volume and formulation containing minimum API dose or minimum fill volume.
2. Test results from all time points are required for formulations of maximum dose (or maximum fill volume) and formulations of minimum dose (or minimum fill volume).
3. Example of bracketing design

Dose of API		50 mg			75 mg			100 mg		
Batch		1	2	3	1	2	3	1	2	3
Container fill volume	15 mL	T*	T	T				T	T	T
	100 mL									
	500 mL	T	T	T				T	T	T

* T : Test batch

a. If the API doses are 50mg, 75mg or 100mg, then the shelf-life, etc. of the 75mg formulation can be determined based on data on the 50mg and 100mg formulations.
b. If the container fill volumes are 15 mL, 100 mL and 500 mL, then the shelf-life, etc. of the 100mL formulation can be determined based on data on the 15mL and 500mL formulations.
c. For formulations that meet the conditions of both a and b, the shelf-life, etc. for the 75mg formulation and 100ml container fill volume can be determined based on data from tests as according to the table.

[Annex 2] Matrix Design

1. This is a method applied when performing stability testing on 2 or more formulations with different doses of active pharmaceutical ingredient(API) or 2 or more formulations with equivalent concentrations of API and excipients in a unit weight (volume) but have different container fill volumes. In this case, shelf-life, etc. can be determined based on test data from one or more batches obtained at any time point(excluding the initial time point, 12-month point and final time point) as representative test data for all batches. However, for biological products, this design is limited to cases where a similar reaction is observed under the storage condition even though the API doses are different.

2. Each batch shall satisfy the following conditions:

   a. There shall be test results obtained at the initial time point, 12-month point and final time point;

   b. There shall be 3 or more test results obtained between the initial and 12-month time point, including these 2 points;

   c. Tests from two consecutive time points in a single batch cannot be both omitted.

3. Example of a matrix design: For a formulation with two or more different doses of the API, “one-half reduction” and “one-third reduction” designs shall be used.

   a. One-half Reduction

      1) One in every two time points may be omitted.

      2) In Example 1, 24 or less time points may be omitted from a total of 48 points. However, since test data from the initial, 12-month and final time points are required, 15 time points were omitted.

Example 1: One-half Reduction

Time point (Months)			0	3	6	9	12	18	24	36
Strength*	Strength 1	Batch 1	T	T		T	T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T	T		T
	Strength 2	Batch 1	T		T		T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T		T	T

* Strength: the amount of API in a unit dosage form

   b. One-third reduction

      1) One in every three time points may be omitted.

      2) In Example 2, 16 or less time points may be omitted from a total of 48 points. However, since test data from the initial, 12-month and final time points are required, 10 time points were omitted.

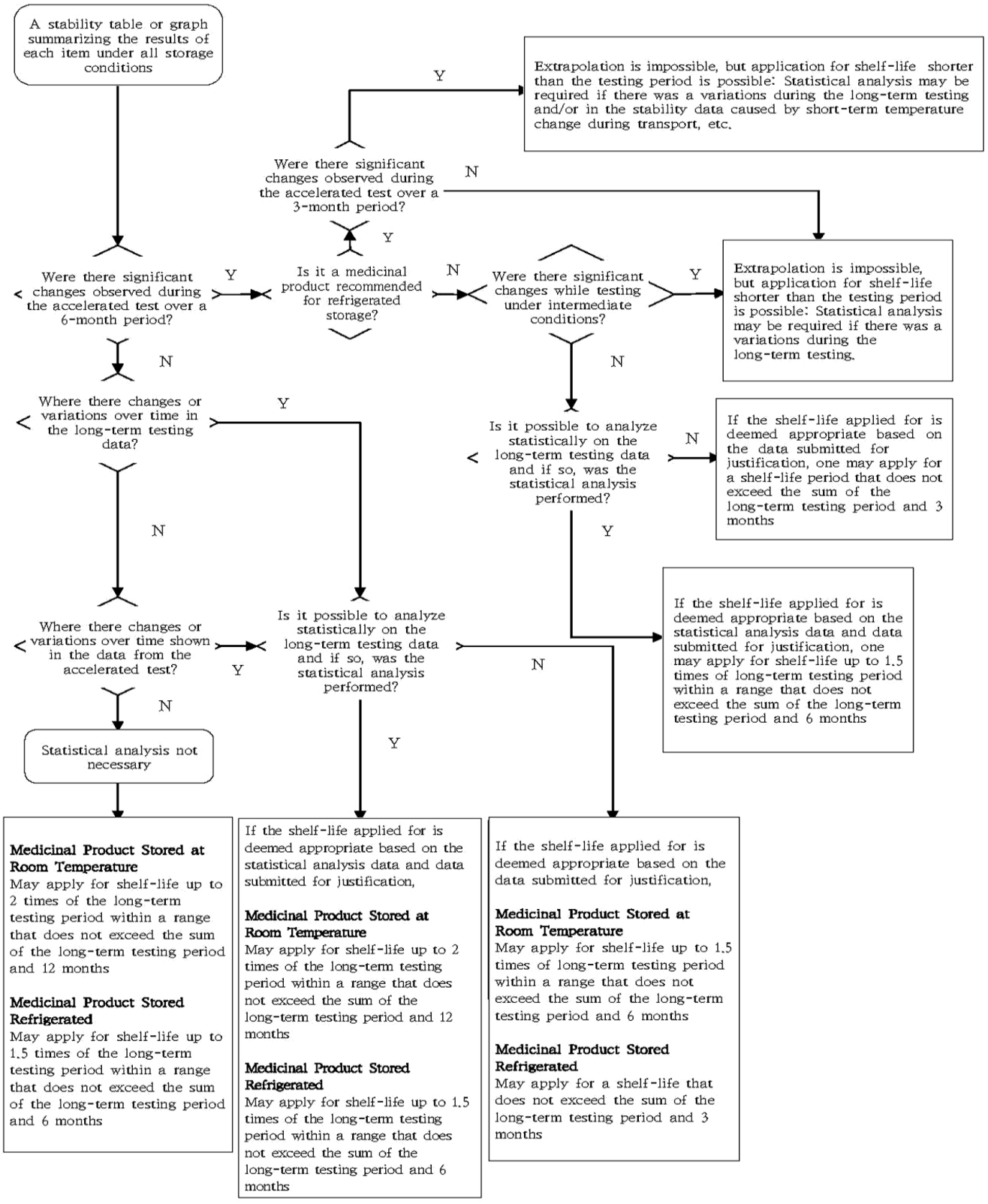
Example 2: One-third Reduction

Testing point (Months)			0	3	6	9	12	18	24	36
Strength*	Strength 1	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
	Strength 2	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

* Content: the amount of API in the unit dosage form

4. When using the matrix design, data justifying its utilization must be submitted. If there are large changes or variations over time, such data cannot be used. It must be thoroughly planned in the early stages of testing.

[Annex 3] Decision tree for Application of Shelf-life, etc.[1)]



1. Extrapolation for Application of Shelf-life, etc. for drugs stored at room temperature

a. In the following cases, one may apply for a shelf-life up to 2 times the long-term testing period within a range that does not exceed the sum of the long-term testing period and 12 months:

1) Changes deemed to be significant as per Article 3 Paragraph 5 were not observed in a 6-month accelerated testing period; changes and/or variations over time were not observed in a 6-month long-term testing period; and justifiable reason(s)[2)] are submitted;

2) Changes deemed to be significant as per Article 3 Paragraph 5 were not observed in a 6-month accelerated testing period; changes and/or variations over time are observed in a 12-month long-term testing period or 6-month accelerated testing period, and statistical analysis are performed for test items that can be analyzed statistically[3)]

b. In the following cases, one may apply for a shelf-life up to 1.5 times the long-term testing period within a range that does not exceed the sum of the long-term testing period and 6 months:

1) Changes deemed to be significant as per Article 3 Paragraph 5 were not observed in a 6-month accelerated testing period; changes and/or variations are observed over time in a 12-month long-term testing period or 6-month accelerated testing period but statistical analysis were not performed on test items that can be analyzed statistically, or supporting justification data[4)] were submitted when test items cannot be statistically analyzed;

2) Changes deemed to be significant as per Article 3 Paragraph 5 were observed in a 6-month accelerated testing period; but changes and/or variations were not observed under intermediate testing conditions for a 12-month period; and statistical analysis of test items that can be analyzed were performed

c. In the following case, one may apply for a shelf-life that does not exceed the sum of the long-term testing period and 3 months:

1) Changes deemed to be significant as per Article 3 Paragraph 5 were observed in a 6-month accelerated test period, but not under intermediate testing conditions for a 12-month period; and statistical analysis of test items that can be analyzed statistically were not performed, or supporting justification data were submitted when test items cannot be analyzed statistically

2. Extrapolation for the Extension of Shelf-life, etc. for refrigerated drugs

a. In the following cases, one may apply for a shelf-life up to 1.5 times the long-term testing period within a range that does not exceed the sum of the long-term testing period and 6 months:

1) Changes deemed to be significant as per Article 3 Paragraph 5 were not observed in a 6-month accelerated testing period; changes and/or variations were not observed over time in the long-term testing of over 12 months; and justifiable reason(s) were submitted;

2) Changes deemed to be significant as per Article 3 Paragraph 5 were not observed in a 6-month

accelerated testing period; changes and/or variations were observed over time in a 12-month long-term testing period or 6-month accelerated testing period; and statistical analysis of test items that can be analyzed were performed

b. In the following case, one may apply for a shelf-life that does not exceed the sum of the long-term testing period and 3 months:

1) Changes deemed to be significant as per Article 3 Paragraph 5 were not observed in a 6-month accelerated testing period, but changes and variations were observed in a 12-month long-term testing period or a 6-month accelerated testing period; and statistical analysis of test items that can be analyzed statistically were not performed, or supporting justification data were submitted when test items cannot be statistically analyzed

3. Statistical Analysis Method

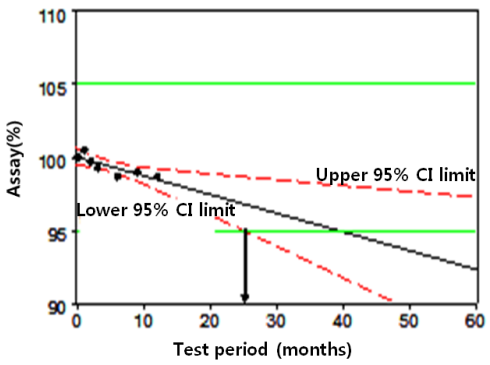
b. Extrapolation: Linear Regression Analysis

1) For test items that decrease over time (e.g., assay), a lower one-sided 95 percent confidence limit shall be performed to extrapolate shelf-life, etc. (However, for drugs stored in semi-permeable containers, assay may increase over due to loss of water. Thus, two-sided 95 percent confidence limit shall be performed to extrapolate shelf-life, etc.).

2) For test items that increase over time (e.g., related substances in an impurity test), an upper one-sided 95 percent confidence limit shall be performed to extrapolate shelf-life, etc..

e.g.) In the case of a drug stored in a semi-permeable container with a acceptance criteria in assay of 95.0% ~ 105.0%, the assay may not only decrease but also increase due to loss of water over time. Thus, a regression line shall be analyzed by performing a two-sided test with a 95% confidence limit, and designate the time point (26 months) at which the assay is still within the acceptance criteria (95% ~ 105%) and crosses the regression line as the maximum allowable shelf-life, etc.

e.g.) Extrapolation for drugs in semi-permeable container with assay criteria of 95.0 % ~ 105.0 %



3) Determination Method

Perform the test on 3 or more batches. If there is a difference in the extrapolated results, use the shortest time period to justify shelf-life, etc.,

a. Poolability test

1) When extrapolations of test results on 3 or more batches produce different results due to a difference in the stability among batches, if there is no significant difference amongst batches through analysis of covariance, the common slope from the batches may be calculated to apply the poolability test for determining shelf-life, etc. In such case, analysis of covariance shall be performed with a significance level of 0.25 for one factor (e.g., dose of the same type or fill volume of the same type) and 0.05 for 2 or more factors (e.g., between different doses, between different fill volumes, etc.)

Footnote:

1) When establishing shelf-life, etc., based on the results of long-term testing and accelerated testing, long-term testing shall be performed up to the shelf-life period, and the data shall be retained by the manufacturer or importer. If the stability is observed to decrease during the testing period, the shelf-life, etc. shall be re-established based on the long-term testing results.

2) Justifiable reason refers to the review results of patterns of change in the drug substance, no change observed, appropriateness of accelerated test data, invariability between pre- and post-test mass, and other supporting data for justification, etc.

3) Statistical analysis is deemed possible for quantifiable test items (e.g., assay, related substance, preservative content, pH, dissolution, etc.), whereas it is deemed not possible for microbial limit test or tests of which results are unquantifiable.

4) Supporting justification data include stability test data on initial manufacture batch of API, stability test data on a batch for a research purpose as opposed to commercial purpose, similar formulations and those using a container closure system not intended for commercial use, information on test data for container closure system, etc.

[Annex 4] Stability Testing Standard for New Drugs

1. INTRODUCTION

1.1. Objectives of the Guideline

The following regulation aims the domestic application of the ICH Q1A guideline.

This regulation defines the stability data package for a new drug substance or drug product. The guideline 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.

1.2. Scope of the Guideline

The regulation addresses the information to be submitted in registration applications for new drugs. 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 can be found in Annex 5 "Stability Testing of New Dosage Forms for New Drugs", and on biological products can be found in the ICH Q5C guideline.

1.3. 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.

2. GUIDELINES

2.1. Drug Substance

2.1.1. General

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

2.1.2. 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 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 Annex 6 "Photostability Testing of New Drugs".

Examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures. However, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long term storage conditions.

Results from these studies will form an integral part of the information provided to regulatory authorities.

2.1.3. 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.

Other supporting data can be provided.

2.1.4. 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.

2.1.5. 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.

2.1.6. 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.

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.

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.

2.1.7. Storage Conditions

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

Long term, accelerated, and, where appropriate, intermediate storage conditions for drug substances are detailed in the sections below. The general case applies if the drug substance is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

2.1.7.1. 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.

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.

"Significant change" for a drug substance is defined as failure to meet its specification.

2.1.7.2. 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

Data from refrigerated storage should be assessed according to the evaluation section of this guideline, except where explicitly noted below.

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 real time data available at the long term storage

condition.

If significant change occurs within the first 3 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 drug substance for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug substance through 6 months when a significant change has occurred within the first 3 months.

2.1.7.3. 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

For drug substances intended for storage in a freezer, the re-test period should be based on the real time data obtained at the long term storage condition. In the absence of an accelerated storage condition for drug substances 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.

2.1.7.4. 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.

2.1.8. Stability Commitment

When 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.

Where the submission includes long term stability data on three production batches covering the proposed re-test period, 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 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.

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

2.1.9. 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.

2.1.10. 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 substance. Where applicable, specific instructions should be provided, particularly for drug substances that cannot tolerate freezing. 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.

2.2. Drug Product

2.2.1. 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.

2.2.2. 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.

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

Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied.

Other supporting data can be provided.

2.2.4. 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.

2.2.5. 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. 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.

Shelf life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during drug development on the product in its final formulation (except for preservative concentration) intended for marketing. A single primary stability batch of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

2.2.6. 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. 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.

Reduced designs, i.e., matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied, if justified.

2.2.7. 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).

Long term, accelerated, and, where appropriate, intermediate storage conditions for drug products

are detailed in the sections below. The general case applies if the drug product is not specifically covered by a subsequent section. Alternative storage conditions can be used, if justified.

2.2.7.1. 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.

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. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

In general, "significant change" for a drug product is defined as:

1. A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
2. Any degradation product's exceeding its acceptance criterion;
3. Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions;

and, as appropriate for the dosage form:

4. Failure to meet the acceptance criterion for pH; or
5. Failure to meet the acceptance criteria for dissolution for 12 dosage units.

2.2.7.2. 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.

2.2.7.3. Drug products packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately, it should be demonstrated that aqueous-based drug products stored in semi-permeable containers can withstand low relative humidity environments.

Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

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

*It is up to the applicant to decide whether long term stability studies are performed at 25 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 as described under the general case to evaluate the temperature effect at 30°C if significant change other than water loss occurs during the 6 months' testing at the accelerated storage condition. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate that the drug product will not have significant water loss throughout the proposed shelf life if stored at 25°C and the reference relative humidity of 40% RH.

A 5% loss in water from its initial value is considered a significant change for a product packaged

in a semi-permeable container after an equivalent of 3 months' storage at 40°C/NMT 25% RH. However, for small containers (1 mL or less) or unit- dose products, a water loss of 5% or more after an equivalent of 3 months' storage at 40°C/NMT 25% RH may be appropriate, if justified.

An alternative approach to studying at the reference relative humidity as recommended in the table above (for either long term or accelerated testing) is performing the stability studies under higher relative humidity and deriving the water loss at the reference relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worst case scenario (e.g., the most diluted of a series of concentrations) for the proposed drug product.

Example of an approach for determining water loss:

For a product in a given container closure system, container size, and fill, 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 shown in the table below. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

For example, at a given temperature, e.g., 40°C, the calculated water loss rate during storage at NMT 25% RH is the water loss rate measured at 75% RH multiplied by 3.0, the corresponding water loss rate ratio.

Alternative relative humidity	Reference relative humidity	Ratio of water loss rates at a given temperature
60% RH	25% RH	1.9
60% RH	40% RH	1.5
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 also be used.

2.2.7.4. Drug products intended for storage in a refrigerator

Study	Storage condition	Minimum time period

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 assess the extent of water loss.

Data from refrigerated storage should be assessed according to the evaluation section of this guideline, except where explicitly noted below.

If significant 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 term storage condition.

If significant change occurs within the first 3 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 shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

2.2.7.5. Drug products 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

For drug products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long term storage condition. In the absence of an accelerated storage condition for drug 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.

2.2.7.6. Drug products intended for storage below -20°C

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

2.2.8. Stability Commitment

When available long term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the shelf life.

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.

2.2.9. Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms).

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.

Limited extrapolation of the real time data from the long term storage condition beyond the observed range to extend the shelf life can be undertaken at approval time, if justified. This justification should be based on what is known about the mechanisms 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 consider not only the assay but also the degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performance.

2.2.10. 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.

3. GLOSSARY

The following definitions are provided to facilitate interpretation of the guideline.

Accelerated testing

Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Bracketing

The design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, 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. 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.

Climatic zones

The four zones in the world that are distinguished by their characteristic prevalent annual climatic conditions. This is based on the concept described by W. Grimm (*Drugs Made in Germany*, 28:196-202, 1985 and 29:39-47, 1986).

Commitment batches

Production batches of a drug substance or drug product for which the stability studies are initiated or completed post approval through a commitment made in the registration application.

Container closure system

The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container

closure system.

Dosage form

A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Drug product

The dosage form in the final immediate packaging intended for marketing.

Drug substance

The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

Excipient

Anything other than the drug substance in the dosage form.

Expiration date

The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification if stored under defined conditions, and after which it must not be used.

Formal stability studies

Long term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or the shelf life of a drug product.

Impermeable containers

Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions.

Intermediate testing

Studies conducted at 30°C/65% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long term at 25°C.

Long term testing

Stability studies under the recommended storage condition for the re-test period or shelf life proposed

(or approved) for labeling.

Mass balance

The process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical error.

Matrixing

The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is 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.

Mean kinetic temperature

A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.

When establishing the mean kinetic temperature for a defined period, the formula of J. D. Haynes (J. Pharm. Sci., 60:927-929, 1971) can be used.

New molecular entity

An active pharmaceutical substance not previously contained in any drug product registered with the national or regional authority concerned. A new salt, ester, or non-covalent-bond derivative of an approved drug substance is considered a new molecular entity for the purpose of stability testing under this guidance.

Pilot scale batch

A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger.

Primary batch

A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf life, respectively. A primary batch of a drug substance should be at least a pilot scale batch. For a drug product, two of the three batches should be at least pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

Production batch

A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.

Re-test date

The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given drug product.

Re-test period

The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be re-tested for compliance with the specification and then used immediately. A batch of drug substance can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a re-test period. The same may be true for certain antibiotics.

Semi-permeable containers

Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient. Examples of semi- permeable containers include plastic bags and semi-rigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles, and vials.

Shelf life (also referred to as expiration dating period)

The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Specification

See ICH Q6A and ICH Q6B.

Specification – Release

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

Specification - Shelf life

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its re-test period, or that a drug product should meet throughout its shelf life.

Storage condition tolerances

The acceptable variations in temperature and relative humidity of storage facilities for formal stability studies. The equipment should be capable of controlling the storage condition within the ranges defined in this guideline. The actual temperature and humidity (when controlled) should be monitored during stability storage. Short term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed, and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effect assessed.

Stress testing (drug substance)

Studies undertaken to elucidate the intrinsic stability of the drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (drug product)

Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing (see ICH Q1B) and specific testing on certain products, (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Supporting data

Data, other than those from formal stability studies, that support the analytical procedures, the proposed re-test period or shelf life, and the label storage statements. Such data include (1) stability data on early synthetic route batches of drug substance, small scale batches of materials,

investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing; (2) information regarding test results on containers; and (3) other scientific rationales.”

[Annex 5] Stability Testing of New Dosage Forms for New Drugs

1. GENERAL

This regulation is an annex to Annex 4 "Stability Testing Standard for New Drugs", 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.

2. 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 Annex 4 "Stability Testing Standard for New Drugs" 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.

[Annex 6] Photostability Testing of New Drugs

1. GENERAL

According to Annex 4 "Stability Testing Standard for New Drugs", photostability testing is a part of stress testing. This regulation is an annex to Annex 4 "Stability Testing Standard for New Drugs", and addresses matters regarding photostability testing.

A. Preamble

The intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable change. Normally, photostability testing is carried out on a single batch of material selected as described under Selection of Batches in the Parent Guideline. Under some circumstances these studies should be repeated if certain variations and changes are made to the product (e.g., formulation, packaging). Whether these studies should be repeated depends on the photostability characteristics determined at the time of initial filing and the type of variation and/or change made.

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:

i) Tests on the drug substance;

ii) Tests on the exposed drug product outside of the immediate pack; and if necessary ;

iii) Tests on the drug product in the immediate pack; and if necessary ;

iv) Tests on the drug product in the marketing pack.

The extent of drug product testing should be established by assessing whether or not acceptable change has occurred at the end of the light exposure testing as described in the Decision Flow Chart for Photostability Testing of Drug Products. Acceptable change is change within limits justified by the applicant.

The formal labeling requirements for photolabile drug substances and drug products are established by national/regional requirements.

B. 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.

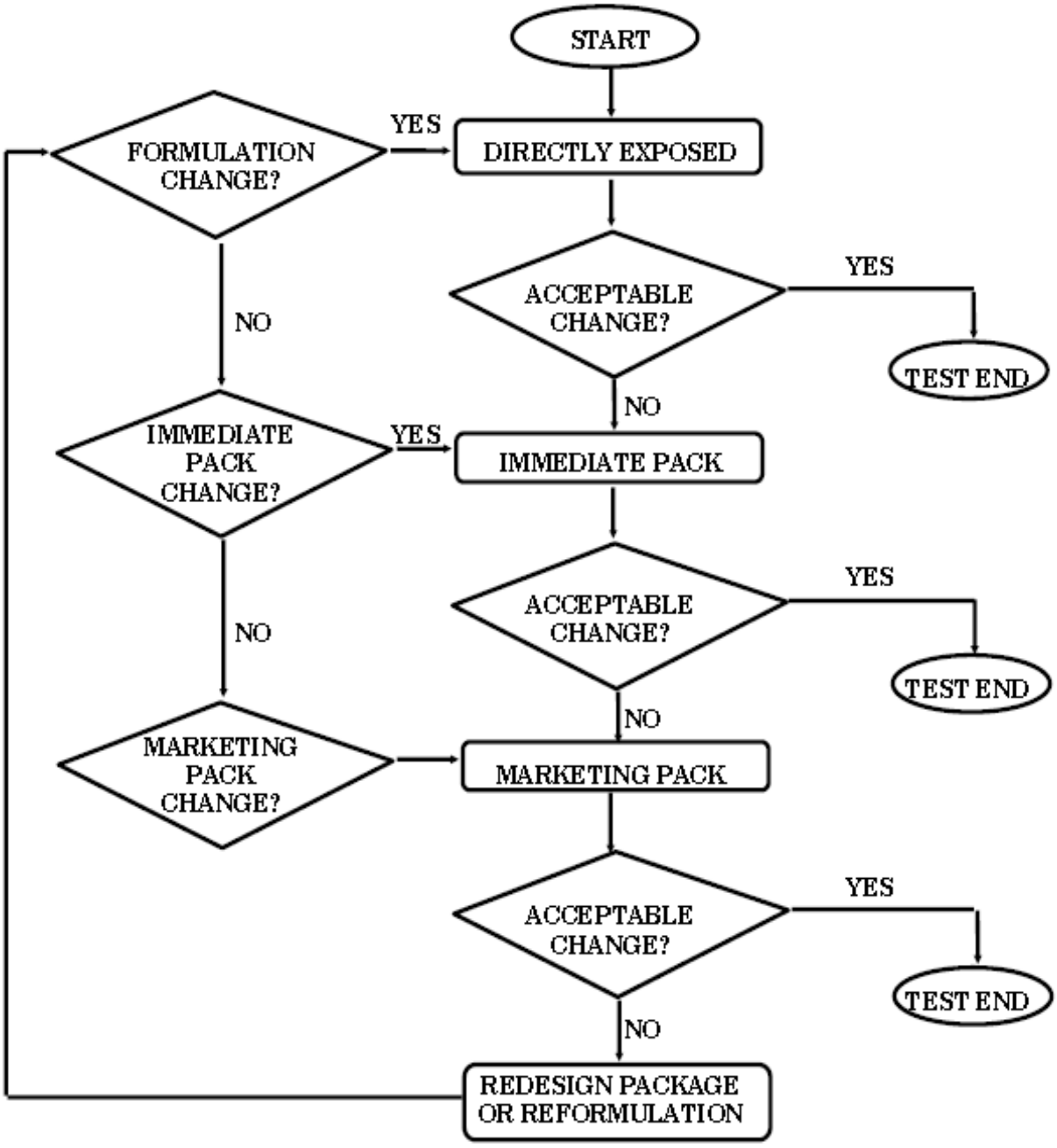
C. Procedure

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



2. 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.

Under forcing conditions, decomposition products may be observed that are unlikely to be formed under the conditions used for confirmatory studies. This information may be useful in developing and validating suitable analytical methods. If in practice it has been demonstrated they are not formed in the confirmatory studies, these degradation products need not be further examined.

Confirmatory studies should then be undertaken to provide the information necessary for handling, packaging, and labeling (see section I.C., Procedure, and II.A., Presentation, for information on the design of these studies).

Normally, only one batch of drug substance is tested during the development phase, and then the photostability characteristics should be confirmed on a single batch selected as described in Annex 4 "Stability Testing Standard for New Drugs" if the drug is clearly photostable or photolabile. If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted. Samples should be selected as described in the Parent Guideline.

A. 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.

B. 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.

C. Judgement of Results

The forced degradation studies should be designed to provide suitable information to develop and validate test methods for the confirmatory studies. These test methods should be capable of resolving and detecting photolytic degradants that appear during the confirmatory studies. When evaluating the results of these studies, it is important to recognize that they form part of the stress testing and are not therefore designed to establish qualitative or quantitative limits for change.

The confirmatory studies should identify precautionary measures needed in manufacturing or in formulation of the drug product, and if light resistant packaging is needed. When evaluating the results of confirmatory studies to determine whether change due to exposure to light is acceptable, it is important to consider the results from other formal stability studies in order to assure that the drug will be within justified limits at time of use (see the relevant ICH Stability and Impurity Guidelines).

3. DRUG PRODUCT

Normally, the studies on drug products should be carried out in a sequential manner starting with testing the fully exposed product then progressing as necessary to the product in the immediate pack and then in the marketing pack. Testing should progress until the results demonstrate that the drug product is adequately protected from exposure to light. The drug product should be exposed to the light conditions described under the procedure in section I.C.

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.

A. Presentation of Samples

Care should be taken to ensure that the physical characteristics of the samples under test are taken into account and efforts, such as cooling and/or placing the samples in sealed containers, should be made to ensure that the effects of the changes in physical states are minimized, such as sublimation, evaporation, or melting. All such precautions should be chosen to provide a minimal interference with the irradiation 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.

Where practicable when testing samples of the drug product outside of the primary pack, these should be presented in a way similar to the conditions mentioned for the drug substance. The samples should be positioned to provide maximum area of exposure to the light source. For example, tablets, capsules, etc., should be spread in a single layer.

If direct exposure is not practical (e.g., due to oxidation of a product), the sample should be placed in a suitable protective inert transparent container (e.g., quartz).

If testing of the drug product in the immediate container or as marketed is needed, the samples should be placed horizontally or transversely with respect to the light source, whichever provides for the most uniform exposure of the samples. Some adjustment of testing conditions may have to be made when testing large volume containers (e.g., dispensing packs).

B. 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, dissolution/disintegration for dosage forms such as capsules, etc.) and for assay and degradants by a method suitably validated for products likely to arise from photochemical degradation processes.

When powder samples are involved, sampling should ensure that a representative portion is used in individual tests. For solid oral dosage form products, testing should be conducted on an appropriately sized composite of, for example, 20 tablets or capsules. Similar sampling considerations, such as homogenization or solubilization of the entire sample, apply to other materials that may not be homogeneous after exposure (e.g., creams, ointments, suspensions, etc.). 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.

C. Judgement of Results

Depending on the extent of change special labeling or packaging may be needed to mitigate exposure to light. When evaluating the results of photostability studies to determine whether change due to exposure to light is acceptable, it is important to consider the results obtained from other formal stability studies in order to assure that the product will be within proposed specifications during the shelf life (see the relevant ICH Stability and Impurity Guidelines).

4. ANNEX

A. Quinine Chemical Actinometry

The following provides details of an actinometric procedure for monitoring exposure to a near UV fluorescent lamp (based on FDA/National Institute of Standards and Technology study). For other light sources/actinometric systems, the same approach may be used, but each actinometric system should be calibrated for the light source used.

Prepare a sufficient quantity of a 2 per cent weight/volume aqueous solution of quinine monohydrochloride dihydrate (if necessary, dissolve by heating).

Option 1

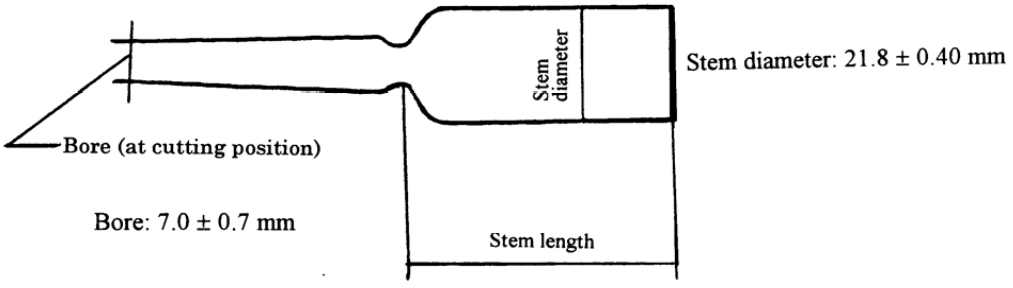
Put 10 milliliters (ml) of the solution into a 20 ml colorless ampoule seal it hermetically, and use this as the sample. Separately, put 10 ml of the solution into a 20 ml colourless ampoule (see note 1), seal it hermetically, wrap in aluminum foil to protect completely from light, and use this as the control. Expose the sample and control to the light source for an appropriate number of hours. After exposure determine the absorbances of the sample (AT) and the control (Ao) at 400 nm using a 1 centimeter (cm) path length. Calculate the change in absorbance, A = AT - Ao. The length of exposure should be sufficient to ensure a change in absorbance of at least 0.9.

Option 2

Fill a 1 cm quartz cell and use this as the sample. Separately fill a 1 cm quartz cell, wrap in aluminum foil to protect completely from light, and use this as the control. Expose the sample and control to the light source for an appropriate number of hours. After exposure determine the absorbances of the sample (AT) and the control (Ao) at 400 nm. Calculate the change in absorbance, A = AT - Ao. The length of exposure should be sufficient to ensure a change in absorbance of at least 0.5.

Alternative packaging configurations may be used if appropriately validated. Alternative validated chemical actinometers may be used.

Note 1: Shape and Dimensions (See Japanese Industry Standard (JIS) R3512 (1974) for ampoule specifications)



Stem length: 80.0 ± 1.2 mm

5. GLOSSARY

Immediate (primary) pack is that constituent of the packaging that is in direct contact with the drug substance or drug product, and includes any appropriate label.

Marketing pack is the combination of immediate pack and other secondary packaging such as a carton.

Forced degradation testing studies are those undertaken to degrade the sample deliberately. These studies, which may be undertaken in the development phase normally on the drug substances, are used to evaluate the overall photosensitivity of the material for method development purposes and/or degradation pathway elucidation.

Confirmatory studies are those undertaken to establish photostability characteristics under standardized conditions. These studies are used to identify precautionary measures needed in manufacturing or formulation and whether light resistant packaging and/or special labeling is needed to mitigate exposure to light. For the confirmatory studies, the batch(es) should be selected according to batch selection for long-term and accelerated testings which is described Annex 4 "Stability Testing Standard for New Drugs".

[Annex 7] Bracketing and Matrixing Designs for New Drugs

1.1 Objectives of the Guideline

This regulation intends to address matters on the application of bracketing and matrixing designs to stability studies conducted in accordance with Annex 4 "Stability Testing Standard for New Drugs".

1.2 Background

Annex 4 "Stability Testing Standard for New Drugs" addresses the use of matrixing and bracketing can be applied, if justified, to the stability testing of new drug substances and products, but provides no further guidance on the subject.

1.3 Scope of the Guideline

This document provides guidance on bracketing and matrixing study designs. Specific principles are defined in this guideline for situations in which bracketing or matrixing can be applied. Sample designs are provided for illustrative purposes, and should not be considered the only, or the most appropriate, designs in all cases.

2. GUIDELINES

2.1 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. Once the design is changed, full testing or less reduced testing should be carried out through the remaining time points of the stability study.

2.2 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.

2.3 Bracketing

As defined in the glossary of Annex 4 "Stability Testing Standard for New Drugs", 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.

2.3.1 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.

2.3.1.1 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.

In cases where different excipients are used among strengths, bracketing generally should not be

applied.

2.3.1.2 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.

With justification, bracketing can be applied to studies for the same container when the closure varies. Justification could include a discussion of the relative permeation rates of the bracketed container closure systems.

2.3.2 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).

2.3.3 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.

Table 1: 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

2.4 Matrixing

As defined in the glossary of Annex 4 "Stability Testing Standard for New Drugs", 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.

2.4.1 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.

2.4.2 Design Considerations

A matrixing design should be balanced as far as possible so that each combination of factors is tested to the same extent over the intended duration of the study and through the last time point prior to submission. However, due to the recommended full testing at certain time points, as discussed below,

it may be difficult to achieve a complete balance in a design where time points are matrixed.

In a design where time points are matrixed, all selected factor combinations should be tested at the initial and final time points, while only certain fractions of the designated combinations should be tested at each intermediate time point. If full long-term data for the proposed shelf life will not be available for review before approval, all selected combinations of batch, strength, container size, and fill, among other things, should also be tested at 12 months or at the last time point prior to submission. In addition, data from at least three time points, including initial, should be available for each selected combination through the first 12 months of the study. For matrixing at an accelerated or intermediate storage condition, care should be taken to ensure testing occurs at a minimum of three time points, including initial and final, for each selected combination of factors.

When a matrix on design factors is applied, if one strength or container size and/or fill is no longer intended for marketing, stability testing of that strength or container size and/or fill can be continued to support the other strengths or container sizes and/or fills in the design.

2.4.3 Design Examples

Examples of matrixing designs on time points for a product in two strengths (S1 and S2) are shown in Table 2. 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 2, 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 as discussed in section 2.4.2. 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.

Table 2: 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

Additional examples of matrixing designs for a product with three strengths and three container sizes are given in Tables 3a and 3b. Table 3a shows a design with matrixing on time points only and Table 3b depicts a design with matrixing on time points and factors. In Table 3a, all combinations of batch, strength, and container size are tested, while in Table 3b, certain combinations of batch, strength and container size are not tested.

Tables 3a and 3b: Examples of Matrixing Designs for a Product with Three Strengths and Three Container Sizes

3a. Matrixing on Time Points

Strength	S			S			S		
Container size	A	B	C	A	B	C	A	B	C
Batch 1	T1	T2	T3	T2	T3	T1	T3	T1	T2
Batch 2	T2	T3	T1	T3	T1	T2	T1	T2	T3
Batch 3	T3	T1	T2	T1	T2	T3	T2	T3	T1

3b. Matrixing on Time Points and Factors

Strength	S			S			S		
Container size	A	B	C	A	B	C	A	B	C
Batch 1	T1	T2		T2		T1		T1	T2
Batch 2		T3	T1	T3	T1		T1		T3
Batch 3	T3		T2		T2	T3	T2	T3	

Key : S1, S2, and S3 are different strengths. A, B, and C are different container sizes.

T = Sample tested

Time-point	0	3	6	9	12	18	24	36
T1	T		T	T	T	T	T	T
T2	T	T		T	T		T	T
T3	T	T	T		T	T		T

2.4.4 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/or
- number of factor combinations in the study

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. However, where the supporting data exhibit moderate variability, a matrixing design should be statistically justified. If the supportive data show large variability, a matrixing design should not be applied.

A statistical justification could be based on an evaluation of the proposed matrixing design with respect to its power to detect differences among factors in the degradation rates or its precision in shelf life estimation.

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.

2.4.5 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.

2.5 Data Evaluation

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

[Annex 8] Evaluation of Stability Data

1. INTRODUCTION

1.1 Objectives of the Guideline

This regulation is intended to provide recommendations on how to use stability data generated in accordance with the principles detailed in Annex 4 "Stability Testing Standard for New Drugs" in establishing shelf life in a registration application. This regulation 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 “stability data of long-term storage condition” (hereafter referred to as long-term data).

1.2 Background

The guidance on the evaluation and statistical analysis of stability data provided in Annex 4 "Stability Testing Standard for New Drugs" is brief in nature and limited in scope. Annex 4 "Stability Testing Standard for New Drugs" states that regression analysis is an appropriate approach to analyzing quantitative stability data for retest period or shelf life estimation and recommends that a statistical test for batch poolability be performed using a level of significance of 0.25. However, Annex 4 "Stability Testing Standard for New Drugs" includes few details and does not cover situations where multiple factors are involved in a full- or reduced-design study.

This regulation is an expansion of the guidance presented in the Evaluation sections of Annex 4 "Stability Testing Standard for New Drugs".

1.3 Scope of the Guideline

This guideline addresses the evaluation of stability data that should be submitted in registration applications for new molecular entities and associated drug products. The guideline provides recommendations on establishing retest periods and shelf lives for drug substances and drug products intended for storage at or below “room temperature”*. It covers stability studies using single- or multi-factor designs and full or reduced designs.

*__Note__: The term “room temperature” refers to the general customary environment and should not be inferred to be the storage statement for labeling.

ICH Q6A and Q6B should be consulted for recommendations on the setting and justification of acceptance criteria, and Annex 7 “Bracketing and Matrixing Designs for New Drugs” should be referenced for recommendations on the use of full- versus reduced-design studies.

2. GUIDELINES

2.1 General Principles

The design and execution of formal stability studies should follow the principles outlined in Annex 4 "Stability Testing Standard for New Drugs". 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.

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 support the registration application are higher than 100 percent of label claim 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 adequacy of the mass balance should be assessed. Factors that can cause an apparent lack of mass balance should be considered, including, for example, the mechanisms of degradation and the stability-indicating capability and inherent variability of the analytical procedures.

The basic concepts of stability data evaluation are the same for single- versus multi- factor 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.

The decision tree in Annex 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. Annex 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 Annex 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.

The recommendations on statistical approaches in this guideline are not intended to imply that use of statistical evaluation is preferred when it can be justified to be unnecessary. However, statistical analysis can be useful in supporting the extrapolation of retest periods or shelf lives in certain situations and can be called for to verify the proposed retest periods or shelf lives in other cases.

2.2 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.

2.3 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. 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. No such internal check is possible beyond the period covered by long-term data. 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.

2.4 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 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. The circumstances are delineated under which extrapolation of retest period or shelf life beyond the period covered by long-term data can be appropriate. A decision tree is provided in Annex A as an aid.

2.4.1 No significant change at accelerated condition

Where 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.

2.4.1.1 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. 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.

2.4.1.2 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). A discussion should be provided to address the cause for the differences and the overall significance

of such differences on the product. 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*

Where 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.

- *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.

2.4.2 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.

***Note**: The following physical changes can be expected to occur at the accelerated condition and would not be considered significant change that calls for intermediate testing if there is no other significant change:

- 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.

2.4.2.1 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*

When 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.

2.4.2.2 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.

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

2.5.1 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 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 Annex A can be used as an aid.

2.5.1.1 No significant change at accelerated condition

Where 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 outlined in Section 2.4.1, 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.

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 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.

2.5.1.2 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.

2.5.2 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).

2.5.3 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.

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.

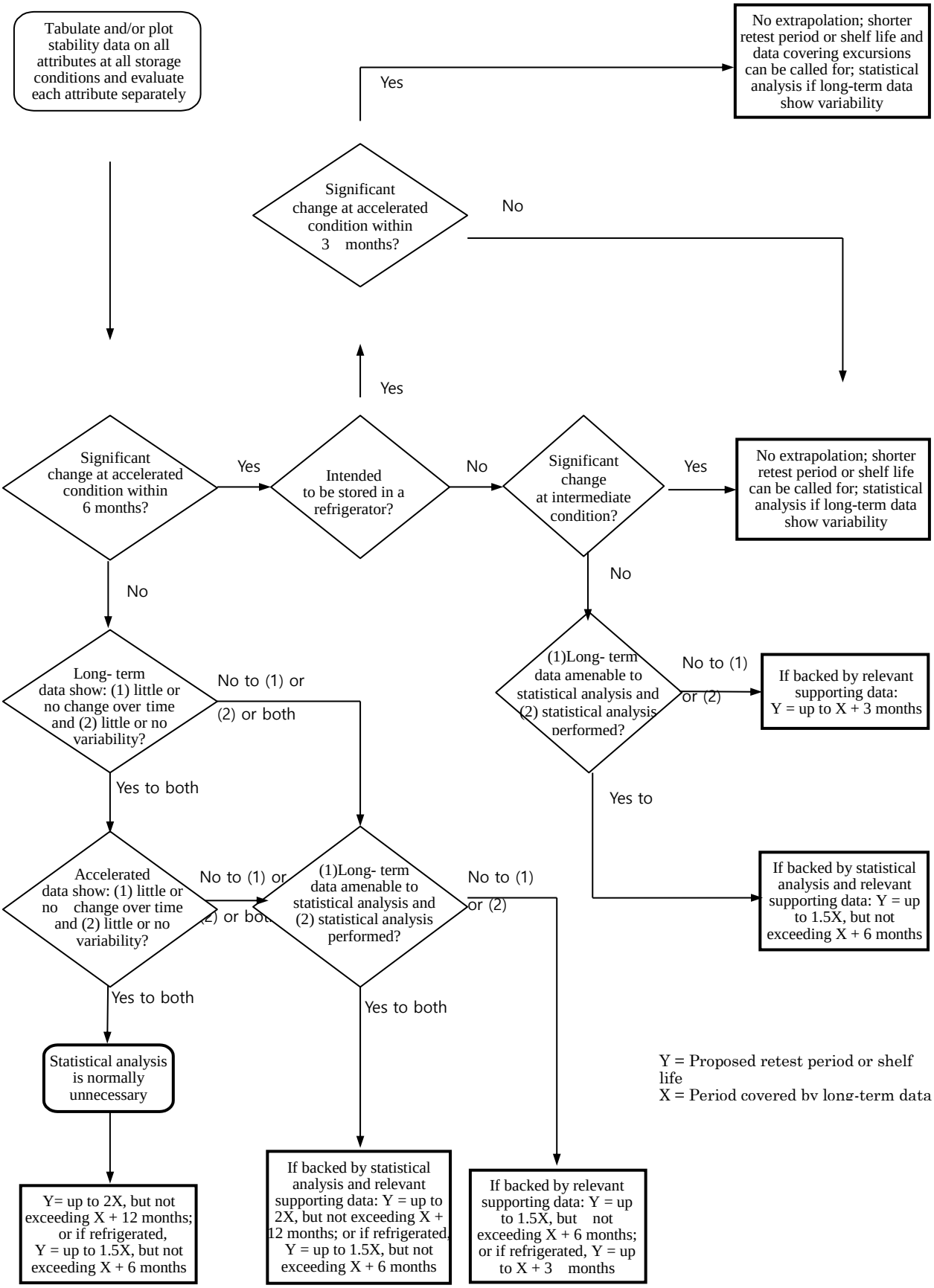
An appropriate approach to retest period or shelf life estimation is to analyze a quantitative attribute (e.g., assay, degradation products) by determining the earliest time at which the 95 percent confidence limit for the mean intersects the proposed acceptance criterion.

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. Examples of statistical approaches to the analysis of stability data from single or multi-factor, full- or reduced-design studies are included in Annex B. References to current literature sources can be found in Annex B.6.

3. APPENDICES

Annex A: Decision Tree for Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products (excluding Frozen Products)



Annex B: Examples of Statistical Approaches to Stability Data Analysis

Linear regression, poolability tests, and statistical modeling, described below, are examples of statistical methods and procedures that can be used in the analysis of stability data that are amenable to statistical analysis for a quantitative attribute for which there is a proposed acceptance criterion.

B.1 Data Analysis for a Single Batch

In general, the relationship between certain quantitative attributes and time is assumed to be linear[1]. Figure 1 shows the regression line for assay of a drug product with upper and lower acceptance criteria of 105 percent and 95 percent of label claim, respectively, with 12 months of long-term data and a proposed shelf life of 24 months. In this example, two-sided 95 percent confidence limits for the mean are applied because it is not known ahead of time whether the assay would increase or decrease with time (e.g., in the case of an aqueous-based product packaged in a semi-permeable container). The lower confidence limit intersects the lower acceptance criterion at 30 months, while the upper confidence limit does not intersect with the upper acceptance criterion until later. Therefore, the proposed shelf life of 24 months can be supported by the statistical analysis of the assay, provided the recommendations in Sections 2.4 and 2.5 are followed.

When data for an attribute with only an upper or a lower acceptance criterion are analyzed, the corresponding one-sided 95 percent confidence limit for the mean is recommended. Figure 2 shows the regression line for a degradation product in a drug product with 12 months of long-term data and a proposed shelf life of 24 months, where the acceptance criterion is not more than 1.4 percent. The upper one-sided 95 percent confidence limit for the mean intersects the acceptance criterion at 31 months. Therefore, the proposed shelf life of 24 months can be supported by statistical analysis of the degradation product data, provided the recommendations in Sections 2.4 and 2.5 are followed.

If the above approach is used, the mean value of the quantitative attribute (e.g., assay, degradation products) can be expected to remain within the acceptance criteria through the end of the retest period or shelf life at a confidence level of 95 percent.

The approach described above can be used to estimate the retest period or shelf life for a single batch, individual batches, or multiple batches when combined after appropriate statistical tests described in Sections B.2 through B.5.

B.2 Data Analysis for One-Factor, Full-Design Studies

For a drug substance or for a drug product available in a single strength and a single container size and/or fill, the retest period or shelf life is generally estimated based on the stability data from a minimum of three batches. When analyzing data from such one-factor, batch-only, full-design studies, two statistical approaches can be considered.

- The objective of the first approach is to determine whether the data from all batches support the

proposed retest period or shelf life.

- The objective of the second approach, testing for poolability, is to determine whether the data from different batches can be combined for an overall estimate of a single retest period or shelf life.

B.2.1 Evaluating whether all batches support the proposed retest period or shelf life

The objective of this approach is to evaluate whether the estimated retest periods or shelf lives from all batches are longer than the one proposed. Retest periods or shelf lives for individual batches should first be estimated using the procedure described in Section B.1 with individual intercepts, individual slopes, and the pooled mean square error calculated from all batches. If each batch has an estimated retest period or shelf life longer than that proposed, the proposed retest period or shelf life will generally be considered appropriate, as long as the guidance for extrapolation in Sections 2.4 and 2.5 is followed. There is generally no need to perform poolability tests or identify the most reduced model. If, however, one or more of the estimated retest periods or shelf lives are shorter than that proposed, poolability tests can be performed to determine whether the batches can be combined to estimate a longer retest period or shelf life.

Alternatively, the above approach can be taken during the pooling process described in Section B.2.2. If the regression lines for the batches are found to have a common slope and the estimated retest periods or shelf lives based on the common slope and individual intercepts are all longer than the proposed retest period or shelf life, there is generally no need to continue to test the intercepts for poolability.

B.2.2 Testing for poolability of batches

B.2.2.1 Analysis of covariance

Before pooling the data from several batches to estimate a retest period or shelf life, a preliminary statistical test should be performed to determine whether the regression lines from different batches have a common slope and a common time-zero intercept. Analysis of covariance (ANCOVA) can be employed, where time is considered the covariate, to test the differences in slopes and intercepts of the regression lines among batches. Each of these tests should be conducted using a significance level of 0.25 to compensate for the expected low power of the design due to the relatively limited sample size in a typical formal stability study.

If the test rejects the hypothesis of equality of slopes (i.e., if there is a significant difference in slopes among batches), it is not considered appropriate to combine the data from all batches. The retest periods or shelf lives for individual batches in the stability study can be estimated by applying the approach described in Section B.1 using individual intercepts and individual slopes and the pooled mean square error calculated from all batches. The shortest estimate among the batches should be chosen as the retest period or shelf life for all batches.

If the test rejects the hypothesis of equality of intercepts but fails to reject that the slopes are equal (i.e., if there is a significant difference in intercepts but no significant difference in slopes among the

batches), the data can be combined for the purpose of estimating the common slope. The retest periods or shelf lives for individual batches in the stability study should be estimated by applying the approach described in Section B.1, using the common slope and individual intercepts. The shortest estimate among the batches should be chosen as the retest period or shelf life for all batches.

If the tests for equality of slopes and equality of intercepts do not result in rejection at a level of significance of 0.25 (i.e., if there is no significant difference in slope and intercepts among the batches), the data from all batches can be combined. A single retest period or shelf life can be estimated from the combined data by using the approach described in Section B.1 and applied to all batches. The estimated retest period or shelf life from the combined data is usually longer than that from individual batches because the width of the confidence limit(s) for the mean will become narrower as the amount of data increases when batches are combined.

The pooling tests described above should be performed in a proper order such that the slope terms are tested before the intercept terms. The most reduced model (i.e., individual slopes, common slope with individual intercepts, or common slope with common intercept, as appropriate) can be selected for retest period or shelf life estimation.

B.2.2.2 Other methods

Statistical procedures[2-6] other than those described above can be used in retest period or shelf life estimation. For example, if it is possible to decide in advance the acceptable difference in slope or in mean retest period or shelf life among batches, an appropriate procedure for assessing the equivalence in slope or in mean retest period or shelf life can be used to determine the data poolability. However, such a procedure should be prospectively defined, evaluated, and justified and, where appropriate, discussed with the regulatory authority. A simulation study can be useful, if applicable, to demonstrate that the statistical properties of the alternative procedure selected are appropriate[7].

B.3 Data Analysis for Multi-Factor, Full-Design Studies

The stability of the drug product could differ to a certain degree among different factor combinations in a multi-factor, full-design study. Two approaches can be considered when analyzing such data.

- The objective of the first approach is to determine whether the data from all factor combinations support the proposed shelf life.
- The objective of the second approach, testing for poolability, is to determine whether the data from different factor combinations can be combined for an overall estimate of a single shelf life.

B.3.1 Evaluating whether all factor combinations support the proposed shelf life

The objective of this approach is to evaluate whether the estimated shelf lives from all factor combinations are longer than the one proposed. A statistical model that includes all appropriate factors

and factor combinations should be constructed as described in Section B.3.2.2.1, and the shelf life should be estimated for each level of each factor and factor combination.

If all shelf lives estimated by the original model are longer than the proposed shelf life, further model building is considered unnecessary and the proposed shelf life will generally be appropriate as long as the guidance in Sections 2.4 and 2.5 is followed. If one or more of the estimated shelf lives fall short of the proposed shelf life, model building as described in Section B.3.2.2.1 can be employed. However, it is considered unnecessary to identify the final model before evaluating whether the data support the proposed shelf life. Shelf lives can be estimated at each stage of the model building process, and if all shelf lives at any stage are longer than the one proposed, further attempts to reduce the model are considered unnecessary.

This approach can simplify the data analysis of a complicated multi-factor stability study compared to the data analysis described in Section B.3.2.2.1.

B.3.2 Testing for poolability

The stability data from different combinations of factors should not be combined unless supported by statistical tests for poolability.

B.3.2.1 Testing for poolability of batch factor only

If each factor combination is considered separately, the stability data can be tested for poolability of batches only, and the shelf life for each non-batch factor combination can be estimated separately by applying the procedure described in Section B.2. For example, for a drug product available in two strengths and four container sizes, eight sets of data from the 2x4 strength-size combinations can be analyzed and eight separate shelf lives should be estimated accordingly. If a single shelf life is desired, the shortest estimated shelf life among all factor combinations should become the shelf life for the product. However, this approach does not take advantage of the available data from all factor combinations, thus generally resulting in shorter shelf lives than does the approach in Section B.3.2.2.

B.3.2.2 Testing for poolability of all factors and factor combinations

If the stability data are tested for poolability of all factors and factor combinations and the results show that the data can be combined, a single shelf life longer than that estimated based on individual factor combinations is generally obtainable. The shelf life is longer because the width of the confidence limit(s) for the mean will become narrower as the amount of data increases when batches, strengths, container sizes and/or fills, etc. are combined.

B.3.2.2.1 Analysis of covariance

Analysis of covariance can be employed to test the difference in slopes and intercepts of the regression lines among factors and factor combinations[7, 8]. The purpose of the procedure is to determine whether

data from multiple factor combinations can be combined for the estimation of a single shelf life.

The full statistical model should include the intercept and slope terms of all main effects and interaction effects and a term reflecting the random error of measurement. If it can be justified that the higher order interactions are very small, there is generally no need to include these terms in the model. In cases where the analytical results at the initial time point are obtained from the finished dosage form prior to its packaging, the container intercept term can be excluded from the full model because the results are common among the different container sizes and/or fills.

The tests for poolability should be specified to determine whether there are statistically significant differences among factors and factor combinations. Generally, the pooling tests should be performed in a proper order such that the slope terms are tested before the intercept terms and the interaction effects are tested before the main effects. For example, the tests can start with the slope and then the intercept terms of the highest order interaction, and proceed to the slope and then the intercept terms of the simple main effects. The most reduced model, obtained when all remaining terms are found to be statistically significant, can be used to estimate the shelf lives.

All tests should be conducted using appropriate levels of significance. It is recommended that a significance level of 0.25 be used for batch-related terms, and a significance level of 0.05 be used for non-batch-related terms. If the tests for poolability show that the data from different factor combinations can be combined, the shelf life can be estimated according to the procedure described in Section B.1 using the combined data.

If the tests for poolability show that the data from certain factors or factor combinations should not be combined, either of two alternatives can be applied: (1) a separate shelf life can be estimated for each level of the factors and of the factor combinations remaining in the model; or (2) a single shelf life can be estimated based on the shortest estimated shelf life among all levels of factors and factor combinations remaining in the model.

B.3.2.2.2 Other methods

Alternative statistical procedures[2-6] to those described above can be applied. For example, an appropriate procedure for assessing the equivalence in slope or in mean shelf life can be used to determine the data poolability. However, such a procedure should be prospectively defined, evaluated, properly justified, and, where appropriate, discussed with the regulatory authority. A simulation study can be useful, if applicable, to demonstrate that the statistical properties of the alternative procedure selected are appropriate[7].

B.4 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.

B.5 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.

Where bracketing and matrixing are combined in one design, the statistical procedure described in Section B.3 can be applied.

B.7 Figures

Figure 1

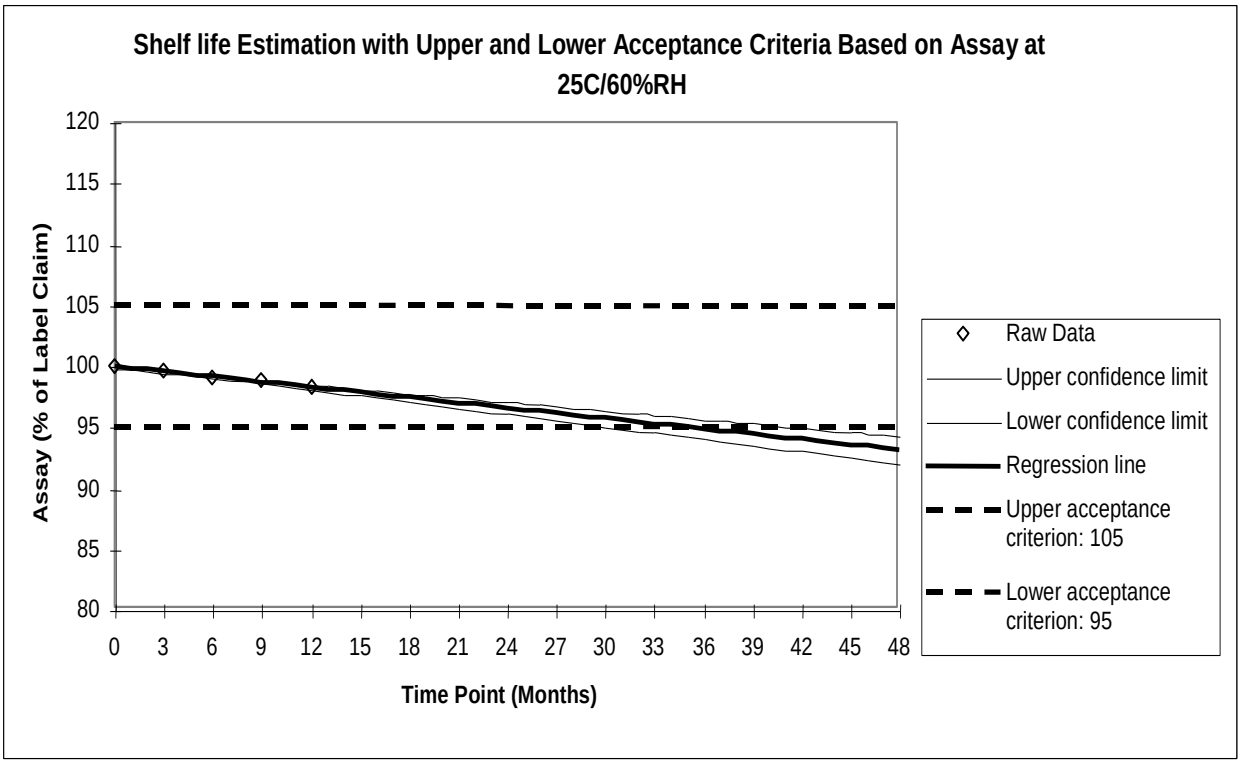


Figure 2