



SADC GUIDELINE FOR STABILITY TESTING

2004

This guideline is intended to provide requirements to applicants wishing to submit applications for the registration of medicines. It represents SADC current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Member States reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. Member States are committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

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GUIDELINES FOR STABILITY STUDIES

1. INTRODUCTION

1.1 Objective of the guideline

The following guideline defines the stability data package for new active pharmaceutical ingredients (API's) and medicinal products (Part A) and existing active pharmaceutical ingredients and products (Part B) that is sufficient for a registration application within SADC. Alternative approaches can be used when there are scientifically justifiable reasons.

1.2 Scope of the Guideline

The guideline addresses the information to be submitted in registration applications for new molecular entities and associated medicinal products as well as existing active pharmaceutical ingredients and associated products. This guideline does not currently seek to cover the information to be submitted for abbreviated or abridged applications, variations, clinical trial applications, etc.

1.3 General Principles

The purpose of stability testing is to provide evidence on how the quality of an active pharmaceutical ingredient or medicinal 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 active pharmaceutical ingredient or a shelf life for the medicinal product and recommended storage conditions.

The design of the stability-testing programme should take into account the intended market and the climatic conditions in the area in which the medicinal products will be used.

Four climatic zones can be distinguished for the purpose of worldwide stability testing, as follows:

- Zone I: temperate.
- Zone II: subtropical, with possible high humidity.
- Zone III: hot/dry.
- Zone IV: hot/humid.

The stability testing recommendations in this guideline cover the long-term storage condition for all Climatic Zones, i.e. I – IV.

The shelf life should be established with due regard to the climatic zone(s) in which the products are to be marketed. For certain preparations, the shelf-life can be guaranteed only if specific storage instructions are complied with.

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To ensure both patient safety and the rational management of medicines supplies, it is important that the expiry date and, when necessary, the storage conditions are indicated on the label.

The storage conditions recommended by manufacturers on the basis of stability studies should guarantee the maintenance of quality, safety, and efficacy throughout the shelf-life of a product. The effect on products of the extremely adverse climatic conditions existing in certain countries to which they may be exported calls for special consideration.

Once the product has been registered, additional stability studies are required whenever major modifications are made to the formulation, manufacturing process, packaging or method of preparation. The results of these studies must be communicated to the competent drug regulatory authorities.

2. GUIDELINES

PART A: NEW CHEMICAL ENTITIES AND RELATED FINISHED PRODUCTS

2.1 ACTIVE PHARMACEUTICAL INGREDIENT (API)

2.1.1 General

Information on the stability of the active pharmaceutical ingredient is an integral part of the systematic approach to stability evaluation.

2.1.2 Stress Testing

Stress testing of the active pharmaceutical ingredient 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 active pharmaceutical ingredient and the type of medicinal product involved.

Stress testing is likely to be carried out on single batch of the active pharmaceutical ingredient. It should include the effect of temperature (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 API. The testing should also evaluate the susceptibility of the API to hydrolysis across a wide range of pH values when in solution or suspension. Photostability testing should be an integral part of stress testing.

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 on stability from accelerated and long-term studies should be provided on at least three primary batches of the API.

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 API 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 API packaged in a container closure system that is the same as the packaging proposed for storage and distribution.

2.1.5 Specification

Stability studies should include testing of those attributes of the API 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 API. For API's with a proposed re-test period of at least 12month, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 month 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-months study is recommended.

2.1.7 Storage Conditions

In general, an API should be evaluated under storage conditions (with appropriate tolerance) 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 API's are detailed in the sections below. The general case applies if a subsequent section does not specifically cover the API. Alternative storage conditions can be used if justified.

2.1.7.1 General case

Study	Storage conditions	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°C ± 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 an API is defined as failure to meet its specification.

2.1.7.2 Active pharmaceutical ingredients (API's) intended for storage in a refrigerator

Study	Storage conditions	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.

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 API for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test API's e through 6 months when a significant change has occurred within the first 3 months.

2.1.7.3 Active pharmaceutical ingredient intended for storage in a freezer

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

For API's 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 API's 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 Active pharmaceutical ingredients intended for storage below – 20°C

API's 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:

- i) 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.

- ii) 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 a least three, on long term stability studies through the proposed re-test period.
- iii) 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 API 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 API 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 analysing 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 for any degradation relationship will determine whether or not 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 for Labelling

A storage statement should be established based on the stability evaluation of the API. Where applicable, specific instructions should be provided, particularly for API's that cannot tolerate freezing. Terms such as "ambient conditions" or "room temperature" should not be used.

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 FINISHED PRODUCTS

2.2.1 General

The design of the formal stability studies for the medicinal product should be based on knowledge of the behaviour and properties of the API 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 medicinal product if appropriate.

2.2.3 Selection of Batches

Data from stability testing should be provided on at least three primary batches of the medicinal 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 medicinal product should be manufactured by using different batches of the medicinal substance.

Stability studies should be performed on each individual strength and container size of the medicinal 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 medicinal 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

Stability studies should include testing of those attributes of the medicinal 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, anti-microbial 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 difference 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 anti-microbial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during medicine development on the product in its final formulation (except for preservative concentration) intended for marketing. A single primary stability batch of the medicinal product should be tested for anti-microbial preservative effectiveness (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is 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 medicinal 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, e.g., 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 medicinal 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 medicinal product after constitution or dilution, if applicable, should be conducted to provide information for the labelling 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 not be available. In general, this testing need not to 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 conditions and, if appropriate, from the intermediate storage conditions 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 medicinal products are detailed in the sections below. The general case applies if a subsequent section does not specifically cover the medicinal product. Alternative storage conditions can be used, if justified.

2.2.7.1 General case

Study	Storage conditions	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°C ± 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 medicinal product is defined as:

- (i) A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
- (ii) Any degradation product's exceeding its acceptance criterion;
- (iii) Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g. colour, 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:

- (i) Failure to meet the acceptance criterion for pH; or
- (ii) Failure to meet the acceptance criteria for dissolution for 12 dosage units.

2.2.7.2. Medicinal products packaged in impermeable containers

Sensitivity to moisture or potential for solvent loss is not a concern for medicinal 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 Medicinal 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 medicinal 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 conditions	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/40% RH ± 5%RH or 30°C ± 2°C/35% RH ± 5% RH	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°C ± 2°C/40% RH ± 5% RH or 30°C ± 2° C/35% RH ± 5% RH.

**If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

For long-term studies conducted at 25°C ± 2°C/40% R H ± 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 medicinal 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 (1ml 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 medicinal 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 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 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 Testing at elevated temperature and/or extremes of humidity

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

Stability testing at a high humidity condition, e.g., 25°C/80% RH, is recommended for solid dosage forms in water-vapour permeable packaging, e.g., tablets in PVC/aluminium blisters, intended to be marketed in territories with extremely high humidity conditions in Zone IV. However, for solid dosage forms in primary containers designed to provide a barrier to water vapour, e.g. aluminium/aluminium blisters, stability testing at a storage condition of extremely high humidity is not considered necessary.

2.2.7.5 Medicinal products intended for storage in a refrigerator

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

If the medicinal 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 medicinal 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.

2.2.7.6 Medicinal products intended for storage in a freezer

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

For medicinal 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 medicinal 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.

2.2.7.7 Medicinal products intended for storage below –20°C

Medicinal 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 data from stability studies on at least three production batches a post approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

- (i) 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.
- (ii) 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.
- (iii) 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 medicinal product, a shelf life and label storage instructions applicable to all future batches of the medicinal 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 analysing data of a quantitative attribute that is expected to change with time is to determine the time at which the 95 one-side 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 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 for Labelling

A storage statement should be established based on the stability evaluation of the medicinal product. Where applicable, specific instruction should be provided, particularly for medicinal products that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” should not be used.

There should be a direct link between the label storage statement and the demonstrated stability of the medicinal product. An expiry date should be displayed on the container label.

PART B WELL ESTABLISHED ACTIVE PHARMACEUTICAL INGREDIENTS AND RELATED FINISHED PRODUCTS**2.3 ACTIVE PHARMACEUTICAL INGREDIENTS (API'S)****2.3.1 General**

Information on the stability of the active pharmaceutical ingredient is an integral part of the systematic approach to stability evaluation.

For API's not described in an official pharmacopoeial monograph (British Pharmacopoeia, European Pharmacopoeia or the United States Pharmacopoeia) stability studies are required.

For API's described in an official pharmacopoeial monograph (British Pharmacopoeia, European Pharmacopoeia or the United States Pharmacopoeia), which covers the degradation products and for which suitable limits have been set but a re-test period is not defined, two options are acceptable:

- (i) The applicant should specify that the API comply with the pharmacopoeial monograph immediately prior to manufacture of the finished product. In this case no stability studies are required on condition that the suitability of the pharmacopoeial monograph has been demonstrated for the particular named source;
- (ii) Need to make a statement on non-pharmacopoeial pharmaceutical ingredients
- (iii) The applicant should fix a re-test period based on the results of long term testing stability studies.

2.3.2 Stress Testing

Stress testing of the active pharmaceutical ingredient 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.

For an active pharmaceutical ingredient the following approaches may be used:

- (i) When an active pharmaceutical ingredient is described in an official pharmacopoeial monograph (British Pharmacopoeia, European Pharmacopoeia or the United States Pharmacopoeia) and fully meets its requirements no data are required on the degradation products if they are named under the headings "purity test" and / or "section on impurities".
- (ii) For active pharmaceutical ingredients not described in an official pharmacopoeial monograph, there are two options:

- (a) When available, it is acceptable to provide the relevant data published in the literature to support the proposed degradation pathways;
- (b) When no data are available in the scientific literature, including official pharmacopoeias, stress testing should be performed. Results from these studies will form an integral part of the information provided to regulatory authorities.

Stress testing is likely to be carried out on a single batch of the active 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 active substance. The testing should also evaluate the susceptibility of the active 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.

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 conditions.

2.3.3 Selection of Batches

Two options are acceptable:

- (i) Stability information from accelerated and long term testing is to be provided on at least two production scale batches manufactured by the same manufacturing (synthetic) route and procedure. The long term testing and accelerated testing should cover a minimum of 6 months duration at the time of submission

or

- (ii) Stability information from accelerated and long term testing is to be provided on at least three pilot scale batches manufactured by the same manufacturing (synthetic) route. The long term testing and accelerated testing should cover a minimum of 6 months duration at the time of submission.

2.3.4 Container Closure System

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

2.3.5 Specification

Stability studies should include testing of those attributes of the active 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.

Acceptance criteria are numerical limits; ranges and other criteria for the specific tests described and should include individual and total upper limits for impurities and degradation products. The justification of individual and total upper limits for degradation products should be based on safety and/or efficacy considerations. For active substances described in an official pharmacopoeial monograph (British Pharmacopoeia, European Pharmacopoeia or the United States Pharmacopoeia) the testing should be performed in accordance with the monograph or by using a test that has been cross-validated against the compendial test and the justification should be given that all potential impurities (process impurities and degradation products) from the actual manufacturing (synthetic) route are adequately controlled.

2.3.6 Testing Frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the active substance. 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 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.

2.3.7 Storage Conditions

In general, an active 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 for both options (a) and (b) should cover a minimum of 6 months' duration 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 active substances are detailed in the sections below. The general case applies if a subsequent section does not specifically cover the active substance. Alternative storage conditions can be used if justified.

2.3.7.1 General case

Study	Storage Conditions	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	6 months (option a and b)
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. In the latter case, no additional data under intermediate conditions will have to be generated.

When "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 an active substance is defined as failure to meet its specification.

2.1.7.2 Active pharmaceutical ingredients intended for storage in a refrigerator

Study	Storage conditions	Minimum time period covered by data at submission
Long term	5°C ± 3°C	6 months (option a and b)
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 active substance for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test an active substance through 6 months when a significant change has occurred within the first 3 months.

2.3.7.3 Active pharmaceutical ingredients intended for storage in a freezer

Study	Storage conditions	Minimum time period covered by data at submission
Long term	-20°C ± 5°C	6 months (option a and b)

For active 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 active 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. Such a study will address the effect of short term excursions outside the proposed label storage condition, e.g., during shipping or handling.

2.1.7.4 Active pharmaceutical ingredients intended for storage below -20°C

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

2.3.8 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:

- (i) 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.
- (ii) 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.
- (iii) 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.

2.3.9 Evaluation

The purpose of the stability study is to establish, based on testing a minimum of two or three batches of the active 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 active 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 analysing 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 retest 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 or not 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 (see annex II), 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.

2.3.10 Statements for Labelling

The storage conditions (temperature, light, humidity) indicated should be based on the stability evaluation of the active pharmaceutical ingredient.

The use of terms such as "ambient conditions" or "room temperature" is unacceptable.

2.4 FINISHED PRODUCTS

2.4.1 General

The design of the formal stability studies for the finished product should be based on knowledge of the behaviour and properties of the active substance and the dosage form.

2.4.2 Photostability Testing

Photostability testing should be conducted on at least one primary batch of the finished product if appropriate.

2.4.3 Selection of Batches

At the time of submission data from stability studies should be provided for batches of the same formulation and dosage form in the container closure system proposed for marketing.

Two options are acceptable:

- (i) For conventional dosage forms (e.g. immediate release solid dosage forms, solutions) and when the active substances are known to be stable, stability data on at least two pilot scale batches are acceptable.
- (ii) For critical dosage forms or when the active substances are known to be unstable, stability data on three primary batches are to be provided. Two of the three batches should be of at least pilot scale, the third batch may be smaller.

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. Where possible, batches of the finished product should be manufactured by using different batches of the active substance.

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

Other supporting data can be provided.

2.4.4 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 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.

2.4.5 Specification

Stability studies should include testing of those attributes of the finished 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 development on the product in its final formulation (except for preservative concentration) intended for marketing. A single primary stability batch of the finished 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.

2.4.6 Testing Frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the finished product. 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 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.

2.4.7 Storage Conditions

In general, a finished 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 finished product after constitution or dilution, if applicable, should be conducted to provide information for the labelling 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 six 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 6 months' duration (option a) or 12 months' duration (option b) 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 finished products are detailed in the sections below. The general case applies if a subsequent section does not specifically cover the finished product. Alternative storage conditions can be used, if justified.

2.4.7.1 General case

Study	Storage Conditions	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	6 months (option a) 12 months (option b)
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. In the latter case, no additional data under intermediate conditions will have to be generated.

When a "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 finished product is defined as:

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

And, as appropriate for the dosage form:

- (i) Failure to meet the acceptance criterion for pH; or
- (ii) Failure to meet the acceptance criteria for dissolution for 12 dosage units.

2.4.7.2 Finished products packaged in impermeable containers

Sensitivity to moisture or potential for solvent loss is not a concern for finished 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.

2.4.7.3 Finished 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 finished products stored in semi-permeable containers could withstand low relative humidity environments. Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Study	Storage Conditions	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	6 months (option a) 12 months (option b)
Intermediate	30°C ± 2°C / 65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C / not more than (NMT) 25% RH	6 months

When a significant change other than water loss occurs during the 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be performed as described under the general case to evaluate the temperature effect at 30°C. 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 finished 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 finished 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.

Reference relative humidity	General testing conditions at the same temperature	Ratio of loss rates at a given temperature
25°C / 25% RH	25°C / 60% RH	1.9 = (100-25) : (100-60)
25°C / 40% RH	25°C / 60% RH	1.5 = (100-40) : (100-60)
40°C / 25% RH	40°C / 75% RH	3.0 = (100-25) : (100-75)

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

2.4.7.4 Finished products intended for storage in a refrigerator

Study	Storage conditions	Minimum time period covered by data at submission
Long term	5°C ± 3°C	6 months (option a) 12 months (option b)
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

If the finished 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 finished 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.

2.4.7.5 Finished products intended for storage in a freezer

Study	Storage conditions	Minimum time period covered by data at submission
Long term	-20°C ± 5°C	6 months (option a) 12 months (option b)

For finished 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 finished 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.

2.4.7.6 Finished products intended for storage below -20°C

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

2.4.8 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 on two production batches covering the proposed shelf life, a post approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

- (i) If the submission includes data from stability studies on at least two production batches, a commitment should be made to continue the long-term studies through the proposed shelf life.
- (ii) If the submission includes data from stability studies on fewer than two production batches, a commitment should be made to continue the long term studies through the proposed shelf life, 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.
- (iii) If the submission does not include stability data on production batches, a commitment should be made to place the first two 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.

2.4.9 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 two or three batches of the finished product, a shelf life and label storage instructions applicable to all future batches of the finished 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 analysing 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 shelf life 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 shelf life can be undertaken at approval time (see annex II), 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.

2.4.10 Statements/Labelling

The use of terms such as "ambient conditions" or "room temperature" is unacceptable.

3. REFERENCE

- 3.1 ICHQ1AR – STABILITY TESTING GUIDELINE:
STABILITY TESTING OF NEW ACTIVE PHARMACEUTICAL
INGREDIENTS AND PRODUCTS.
- 3.2 STABILITY GUIDELINE – SOUTH AFRICA
- 3.3 MARKETING AUTHORIZATION OF PHARMACEUTICAL PRODUCTS
WITH SPECIAL REFERENCE TO MULTISOURCE (GENERIC)
PRODUCTS – A MANUAL FOR A MEDICINES REGULATORY
AUTHORITY ANNEX II (WHO)

GLOSSARY

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

Active pharmaceutical ingredient (API): The unformulated medicinal substance that may subsequently be formulated with excipients to produce the dosage form.

An active substance is considered as stable if it is within the defined/regulatory specifications when stored at 25°C / 60 % RH (2 years) and 40°C / 75 % RH (6 months).

Accelerated testing: Studies designed to increase the rate of chemical degradation or physical change of a medicinal substance or medicinal 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.

Commitment batches: Production batches of a medicinal substance or medicinal 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 medicinal product. A packaging system is equivalent to a container closure system.

Dosage form: A pharmaceutical product type (e.g. tablets, capsule, solution, cream) that contains an active pharmaceutical ingredient generally, but not necessarily, in association with excipients.

Excipient: Anything other than the active pharmaceutical ingredient in the dosage form.

Expiration date: The date placed on the container label of a medicinal 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.

Extrapolation of data: If real time data are supported by results from accelerated studies the re-test period/shelf life may be extended beyond the end of real time studies. Normally extrapolation to twice the length of the real time studies can be accepted. However, the maximum re-test period/shelf life justified by extrapolation should not exceed 3 years.

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 an API or the shelf life of a medicinal product.

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

Intermediate testing: Studies conducted at 30°C/60%RH and designed to moderately increase the rate of chemical degradation or physical changes for a medicinal substance or medicinal product intended to be stored long term at 25(°)C/60%RH and designed to moderately increase the rate of chemical degradation or physical changes for a medicinal substance or medicinal 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 labelling.

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 medicinal product should be identified as, for example, covering different batches, different strengths, 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 defined period of time, affords the same thermal challenge to an API or medicinal 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.

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

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

Pilot scale batch: A batch of an API or medicinal 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 an API or medicinal 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 an API should be at least a pilot scale batch. For a medicinal 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 an API or medicinal 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 API 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 medicinal product.

Re-test period: The period of time after which samples of the API is expected to remain within its specification and, therefore, can be used in the manufacture of a given medicinal product, provided that the API has been stored under the defined conditions. After this period, a batch of API destined for use in the manufacture of a medicinal product should be re-tested for compliance with the specification and

then used immediately. A batch of Api 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 medicinal product is expected to remain within the approved shelf life specification provided that it is stored under the conditions defined on the container label.

Stability tests

A series of tests designed to obtain information on the stability of a pharmaceutical product in order to define its shelf-life and utilization period under specified packaging and storage conditions.

Specification – Release: The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a medicinal 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 medicinal substance throughout its re-test period, or that a medicinal 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 interruptions due to equipment failure should be addressed, and reported if judged to affect stability results. Excursions that exceed the defined tolerance for more than 24 hours described in the study report and their effect should be assessed.

Stress testing (medicinal substance): Studies undertaken to elucidate the intrinsic stability of the medicinal 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 (medicinal product): Studies undertaken to assess the effect of severe conditions on the medicinal product. Such studies include photostability testing 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 API, 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.

Utilization period: The period of time during which a reconstituted preparation or the finished dosage form in an opened multi-dose container can be used.