GUIDELINES FOR STABILITY TESTING OF PHARMACEUTICAL PRODUCTS

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DRUGS ADVISORY BOARD

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Preface

This guideline is intended to provide requirements to applicants wishing to submit applications for registration of medicines in Botswana. It is an adaptation and adoption of the Southern African Development Community (SADC) Guidelines for Stability Studies as well as International Convention on Harmonization (ICH) Guidance on Bracketing and Matrixing designs for Stability Testing of Drug Substances and Drug Products (Q1D).

The Drugs Regulatory Unit may request additional information to establish the safety, quality and efficacy of the medicines in order to keep up with current knowledge at the time of submission. It will be of importance for applicants to adhere to the requirements of these guidelines and any other administrative requirements to avoid delays in processing and evaluation of the applications.

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PART B: WELL ESTABLISHED ACTIVE PHARMACEUTICAL INGREDIENTS AND RELATED FINISHED PRODUCTS

1. DEFINITIONS

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.

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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℃/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℃.

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 – 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, which 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.

2. INTRODUCTION

2.1. Objectives of the Guideline

The following guideline defines the stability data package for new active pharmaceutical ingredients (APIs) and medicinal products (Part A) and existing active pharmaceutical ingredients and medicinal products (Part B) that is sufficient for a registration application in Botswana.

2.2. Scope of the Guideline

The guideline addresses the information to be submitted in registration applications for new molecular entities and the medicinal products thereof as well as the existing molecules and the associated products. These guidelines will also apply to the stability of products used in clinical trials.

2.3. General Principles

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

Climatic conditions have been divided into four zones for stability testing as follows:

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

The climatic conditions in Botswana falls within Zone III and hence the design of stability testing programme should take into account those conditions and the shelf-life be established based on those.

To ensure both patient safety and the rational management of medicines supplied, it is important that the expiry date and storage conditions are indicated on the label. The storage conditions established by the manufacture should guarantee the maintenance of quality, efficacy and safety throughout the shelf-life of the product.

3. GUIDELINES

PART A: NEW CHEMICAL ENTITIES AND RELATED FINISHED PRODUCTS

3.1. Active Pharmaceutical Ingredient (API)

3.1.1. General

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

3.1.2. Stress Testing

Stress testing of the API 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 API and the type of the medicinal product involved.

Stress testing is likely to be carried out on two batches of the API. It should include the effect of temperatures (in 10℃ increments (e.g., 50℃, 60℃, etc.) above that for accelerated testing), humidity (e.g., 65% RH or greater), 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.

Results from these studies will form an integral part of the information provided for evaluation by the regulatory authority.

3.1.3. Selection of Batches

Stability data 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 the API placed on formal stability studies should be representative of the quality of the material to be made on a production scale.

3.1.4. Container Closure System

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

3.1.5. Specification

Stability studies should include testing of those parameters 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 parameters. 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.

3.1.6. Testing Frequency

For long term studies, frequency of testing should be sufficient to establish the stability profile of the API. For APIs 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.

3.1.7. Storage Conditions

In general, an API should be evaluated under storage conditions 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 DRU when they are available. Data from the accelerated 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 and accelerated storage conditions for APIs are detailed in the sections below. The general case applies if a subsequent section does not specifically cover the API.

3.1.7.1. *General case*

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

3.1.7.2. *APIs intended for storage in a refrigerator*

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

Data from refrigerated storage should be assessed according to the evaluation section of this guideline (section 2.1.9), 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 API for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test APIs through 6 months when a significant change has occurred within the first 3 months.

3.1.7.3. *APIs intended for storage in a freezer.*

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

For APIs 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℃ ± 3℃ or 25℃ ± 2℃) 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.

3.1.7.4. *APIs intended for storage below -20℃*
APIs intended for storage below -20℃ should be treated on a case-by-case basis.

3.1.8. 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.

3.1.9. 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 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 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 parameters.

3.1.10. Statements for Labeling

A storage statement should be established for the labeling based on the stability evaluation of the API. Where applicable, specific instructions should be provided, particularly for APIs 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.

3.2. Finished Product

3.2.1. General

The design of the formal stability studies for the medicinal product should be based on knowledge of the behavior and properties of the API and from stability studies on the API and on experience gained from clinical formulation studies. The likely changes on storage and the rationale for the selection of parameters to be tested in the formal stability studies should be stated.

3.2.2. Photostability Testing

Photostability testing should be conducted on at least two primary batches of the drug product if appropriate.

3.2.3. Selection of Batches

Data from stability studies should be provided on at least three primary batches of the medicinal product (two pilot and one production). The batches should be of the same formulation and packaged in the same container closure system as proposed for marketing and should provide product of the same quality and meeting the same specification as that intended for marketing.

Where possible, batches of the medicinal product should be manufactured by using different batches of the API.

Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied (Appendix 1).

3.2.4. 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.

3.2.5. Specification

Stability studies should include testing of those parameters 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 parameters, 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 medicinal 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.

3.2.6. 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.

Reduced designs, i.e., matrixing or bracketing (Appendix 1*),* where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied, if justified.

3.2.7. 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 DRU when available. Data from the accelerated 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 medicinal products are detailed in the sections below. The general case applies if the medicinal product is not specifically covered by a subsequent section.

3.2.7.1. *General case*

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

3.2.7.2. *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. However, stability must be established for when the container is opened under using the storage conditions in 2.2.7.1 above.

3.2.7.3. *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 condition	Minimum time period covered by data at submission
Long term	30℃ ± 2℃/65% RH ± 5% RH	12 months
Accelerated	40℃ ± 2℃/not more than (NMT) 25% RH	6 months

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 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℃, 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.

3.2.7.4. *Medicinal products intended for storage in a refrigerator*

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

If the 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 (2.2.9), 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.

3.2.7.5. *Medicinal 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 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.

3.2.7.6. *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.

3.2.8. 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.

3.2.9. 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 parameters 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 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 parameters. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performance.

3.2.10. Statements for Labeling

A storage statement should be established for the labeling in accordance with DRU requirements in the Registration Guidelines. The statement should be 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 be avoided.

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

PART B: WELL ESTABLISHED ACTIVE PHARMACEUTICAL INGREDIENTS AND RELATED FINISHED PRODUCTS

3.3 Active Pharmaceutical Ingredient (API)

3.3.1 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.

3.3.2 Stress Testing

Stress testing of the API 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 two batches of the active substance. It should include the effect of temperatures (in 10℃ increments (e.g., 50℃, 60℃, etc.) above that for accelerated testing), humidity (e.g., 75 % RH or greater), 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.

3.3.3 Selection of Batches

Two options are acceptable:

(i) Stability information from accelerated and long term testing is to be provided on at least three 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.

3.3.4 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.

3.3.5 Specification

Stability studies should include testing of those parameters 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 parameters. 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.

3.3.6 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.

3.3.7 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 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 can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).
Long term and accelerated 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.

3.3.7.1 General case

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

3.1.7.2 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
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 (2.3.9), 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.

3.3.7.3 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

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.

3.1.7.4 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.

3.3.8 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.

3.3.9 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 parameters.

3.3.10 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.

3.4 Finished Products

3.4.1 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.

3.4.2 Photostability Testing

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

3.4.3 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.
Stability data on at least three production batches are should be submitted.

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 (Appendix 2).

3.4.4 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.

3.4.5 Specification

Stability studies should include testing of those parameters 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 parameters, 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.

3.4.6 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.

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.

3.4.7 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 12 months' duration 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 DRU when available. Data from the accelerated 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 and accelerated 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.

3.4.7.1 General case

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

3.4.7.2 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. However, stability must be established for when the container is opened under using the storage conditions in 2.4.7.1 above.

3.4.7.3 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	30℃ ± 2℃ / 65% RH ± 5% RH	12 months
Accelerated	40℃ ± 2℃ / not more than (NMT) 25% RH	6 months

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℃, 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℃/ 25% RH	25℃ / 60% RH	1.9 = (100-25) : (100-60)
25℃ / 40% RH	25℃ / 60% RH	1.5 = (100-40) : (100-60)
40℃ / 25% RH	40℃ / 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.

3.4.7.4 Finished products intended for storage in a refrigerator

Study	Storage conditions	Minimum time period covered by data at submission
Long term	5℃ ± 3℃	12 months
Accelerated	25℃ ± 2℃/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 (2.4.9), 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.

3.4.7.5 Finished products intended for storage in a freezer

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

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℃ ± 3℃ or 25℃ ± 2℃) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition.

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

3.4.8 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.

3.4.9 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 parameters 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 parameters. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performance.

3.4.10 Statements for Labelling

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

4. REFERENCES

1. SADC Guidelines for Stability Studies, April 2007

2. International Convention on Harmonization (ICH) – Bracketing and Matrixing designs for Stability Testing of Drug Substances and Drug Products (Q1D), February 2002.

APPENDIX 1

Bracketing and Matrixing Designs for Stability Testing of Pharmaceutical Substances and Products

This section is intended to address recommendations on the application of bracketing and matrixing to stability studies conducted in accordance with DRU Guidelines for Stability Testing of Pharmaceutical Products (referred to as the parent guideline).

The parent guideline notes that the use of matrixing and bracketing can be applied, if justified, to the testing of new drug substances and products, and this document will provide further guidance on the subject by defining specific principles that can be applied.

STABILITY STUDY DESIGNS

There are two study designs that can be applied to stability testing of pharmaceutical products and those include:

1. A full study design

A full study design is one in which samples for every combination of all design factors are tested at all time points. It is the most commonly used study design and it is applicable for all types of pharmaceutical products.

2. A reduced study design

A reduced study 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.

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.

2.1 Bracketing

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.

2.1.1 Design Factors

Design factors are variables to be evaluated in a study design for their effect on product stability and include:

- **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., colorants, flavorings).

  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.

- **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.

2.1.2 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).

2.2 Matrixing

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.

2.2.1 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.

2.2.2 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.

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.

2.2.3 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.

DATA EVALUATION

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