

## ZAMBIA MEDICINES REGULATORY AUTHORITY

---



---

## APPLICATION FOR MARKETING AUTHORISATION OF A MEDICINE FOR HUMAN USE

---

### STABILITY GUIDELINE

Version 2 draft	June 2014
Version 2 released for pilot implementation and comment	June 2014
Deadline for comment	October 2014
Version 03 published for implementation	November 2014
Date of implementation	June 2015

## TABLE OF CONTENTS

<b>GLOSSARY .....</b>	<b>4</b>
STABILITY TESTS .....	7
<b>GUIDELINES FOR STABILITY STUDIES .....</b>	<b>8</b>
1. INTRODUCTION .....	8
1.1 Objective of the guideline.....	8
1.2 Scope of the Guideline.....	8
1.3 General Principles .....	8
2. GUIDELINES.....	9
2.1 ACTIVE PHARMACEUTICAL INGREDIENT (API) .....	9
2.1.1 General.....	9
2.1.2 Stress Testing .....	9
2.1.3 Selection of Batches .....	9
2.1.4 Container Closure System .....	10
2.1.5 Specification .....	10
2.1.6 Testing Frequency .....	10
2.1.7 Storage Conditions.....	10
2.1.7.1 General case.....	10
2.1.7.2 Active pharmaceutical ingredients (API's) intended for storage in a refrigerator	11
2.1.7.3 Active pharmaceutical ingredient intended for storage in a freezer.....	11
2.1.7.4 Active pharmaceutical ingredients intended for storage below –20°C .....	11
2.1.8 Stability Commitment .....	11
2.1.9 Evaluation.....	12
2.1.10 Statements for Labelling .....	13
2.1.11 Ongoing stability studies.....	13
2.2 FINISHED PRODUCTS .....	14
2.2.1 General.....	14
2.2.2 Photostability Testing .....	14
2.2.3 Selection of Batches .....	14
2.2.4 Container Closure System .....	14
2.2.5 Specification .....	14
2.2.6 Testing Frequency .....	15
2.2.7 Storage Conditions.....	15
2.2.7.1 General case.....	16
2.2.7.2 Medicinal products packaged in impermeable containers.....	16
2.2.7.3 Medicinal products packaged in semi-permeable containers.....	16
2.2.7.4 Testing at elevated temperature and/or extremes of humidity .....	17
2.2.7.5 Medicinal products intended for storage in a refrigerator .....	17
2.2.7.6 Medicinal products intended for storage in a freezer.....	18
2.2.7.7 Medicinal products intended for storage below –20°C .....	18
2.2.8 Stability Commitment .....	18
2.2.9 Evaluation.....	19
2.2.10 Statements for Labelling .....	20
2.2.11 In-use Stability.....	20
2.2.12 Variations .....	21
2.2.13 Ongoing Stability Studies .....	21
<b>3. REFERENCE .....</b>	<b>23</b>
<b>ANNEXES.....</b>	<b>23</b>
ANNEXURE I – STABILITY CONDITIONS FOR SADC MEMBER STATES .....	23
ANNEXURE 2 - EXAMPLES OF TESTING PARAMETERS .....	24
Section I for active pharmaceutical ingredients.....	24

Section II for finished pharmaceutical products.....24

*Tablets*..... 24

*Capsules* ..... 24

*Oral solutions, suspensions and emulsions*..... 24

*Powders and granules for oral solution or suspension* ..... 25

*Metered-dose inhalers and nasal aerosols* ..... 25

*Nasal sprays: solutions and suspensions* ..... 25

*Topical, ophthalmic and otic preparations* ..... 25

*Suppositories* ..... 25

*Small volume parenterals (SVPs)* ..... 25

*Large volume parenterals (LVPs)* ..... 26

*Transdermal patches* ..... 26

ANNEXURE 3 – RECOMMENDED LABELLING STATEMENTS.....27

## GLOSSARY

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

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

**Active pharmaceutical ingredient (API):** Any substance or mixture of substances used in the manufacture of a pharmaceutical dosage form, and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

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).

**Batch:** A defined quantity of starting material, packaging material or finished pharmaceutical product (FPP) processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

**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 (see Annexure I).

**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:** Any substance or compound, 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.

#### **Finished pharmaceutical product (FPP) or drug product**

A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling.

**Formal stability studies:** Long term and accelerated 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.

**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.

**Ongoing stability study:** The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected re-test period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP.

**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.

**Provisional shelf-life:** A provisional expiry date which is based on acceptable accelerated and available long-term data for the FPP to be marketed in the proposed container closure system.

**Re-test date:** The date after which an active API should be examined to ensure that the material is still in compliance with the specification and thus is still 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.

**Significant change:** In general “significant change” for an FPP is defined as:

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

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

**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.

#### **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.

**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.

## **GUIDELINES FOR STABILITY STUDIES**

### **1. INTRODUCTION**

#### **1.1 Objective of the guideline**

The following guideline defines the stability data package for active pharmaceutical ingredients (API's) and medicinal products 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 existing APIs, and associated medicinal products.

#### **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 and Mediterranean, with possible high humidity.
- Zone III: Hot/dry.
- Zone IVA: Hot/humid.
- Zone IVB: Hot/very humid

The stability testing recommendations in this guideline cover the long-term storage condition for Climatic Zones IVA/IVB

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.

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

### 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. Potential attributes to be tested on an API during stability testing are listed in the examples of testing parameters (Annexure 2).

The re-test period or shelf-life assigned to the API by the API manufacturer should be derived from stability testing data.

#### 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.

For an existing API the following approaches may be used:

- when available, it is acceptable to provide the relevant data published in the scientific literature to support the identified degradation products and pathways;
- when no data are available, stress testing should be performed.

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.

For existing active substances that are known to be stable, data from at least two primary batches should 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*

The minimum data required at the time of submitting the dossier (in the general case)

<b>Storage temperature (°C)</b>	<b>Relative humidity (%)</b>	<b>Minimum time period (months)</b>
Accelerated 40 ±2	75 ± 5	6

Intermediate *	*	*
Long term 30±2	65 ± 5 or 75 ± 5	12

Where long-term conditions are 30°C±2°C/65%± 5%RH or 30°C ± 2°C/75%±5%RH, there is no intermediate condition.

#### 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 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.

### 2.1.9 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 APIs that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” should not be used.

The recommended labelling statements for use if supported by the stability studies are provided in Annexure 3.

A re-test period should be derived from the stability information, and a retest date should be displayed on the container label if appropriate.

#### 2.1.11 Ongoing stability studies

The stability of the API should be monitored according to a continuous and appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products). The purpose of the ongoing stability programme is to monitor the API and to determine that the API remains, and can be expected to remain, within specifications under the storage conditions indicated on the label, within the re-test period in all future batches.

The ongoing stability programme should be described in a written protocol and the results presented in a formal report.

The protocol for an ongoing stability programme should extend to the end of the re-test period and shelf-life and should include, but not be limited to, the following parameters:

- number of batch(es) and different batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test methods;
- acceptance criteria;
- reference to test methods;
- description of the container closure system(s);
- testing frequency;
- description of the conditions of storage (standardized conditions for long term testing as described in these guidelines, and consistent with the API labelling, should be used); and
- other applicable parameters specific to the API.

At least one production batch per year of API (unless none is produced during that year) should be added to the stability-monitoring programme and tested at least annually to confirm the stability. In certain situations additional batches should be included in the ongoing stability programme. For example, an ongoing stability study should be conducted after any significant change or significant deviation to the synthetic route, process or container closure system, which may have an impact upon the stability of the API.

Out-of-specification results or significant atypical trends should be investigated. Any confirmed significant change, out-of-specification result, or significant atypical trend should be reported immediately to the relevant finished product manufacturer. The possible impact on batches on the market should be considered in consultation with the relevant finished product manufacturers and the competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

## **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**

To establish the shelf-life, data should be provided on at least three production batches conducted through the proposed shelf life. If not available, not less than two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP with written commitment to provide stability data on the required three commercial batches. The pilot batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

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

Unless otherwise justified, the minimum data required at the time of submitting the dossier (in the general case):

Storage temperature (°C)	Relative humidity (%)	Minimum time period (months)
Accelerated 40 ± 2	75 ± 5	6
Long term 30 ± 2	75 ± 5	12

Applicants should consult the respective NMRA on acceptability of six month long term stability data at the time of submission. In any case, minimum of 12 month long term stability data should be available at the time of registration. Applicants should consult the respect NMRA on acceptability of the stability conditions, other than the general case as stated in this guideline.

#### 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*	30°C ± 2°C/35% RH ± 5% RH	12 months
Intermediate**	NA	NA
Accelerated	40°C ± 2°C/not more than (NMT) 25% RH	6 months

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 3months' 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 30°C/80% RH to cover extremely high humidity conditions.

Stability testing at a high humidity condition, e.g., 30°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 IVb. 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 or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 months

\*Whether accelerated stability studies are performed at 25 ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to the storage condition at 25 °C/60% RH or 30 °C/65% RH.

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.

### 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. However, a provisional shelf-life of 24 months may be established provided the following conditions are satisfied:

- The API is known to be stable (not easily degradable).
- Stability studies have been performed and no significant changes have been observed.
- Supporting data indicate that similar formulations have been assigned a shelf-life of 24 months or more.
- The manufacturer will continue to conduct long-term studies until the proposed shelf-life has been covered, and the results obtained will be submitted to the national medicines regulatory authority.

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.

The recommended labelling statements for use, if supported by the stability studies, are provided in Annexure 3.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Additional labelling statements could be used in cases where the results of the stability testing demonstrate limiting factors (see also Annexure 3).

#### **2.2.11 In-use Stability**

The purpose of in-use stability testing is to provide information for the labelling on the preparation, storage conditions and utilization period of multidose products after opening, reconstitution or dilution of a solution, e.g. an antibiotic injection supplied as a powder for reconstitution.

As far as possible the test should be designed to simulate the use of the FPP in practice, taking into consideration the filling volume of the container and any dilution or reconstitution before use. At intervals comparable to those, which occur in practice, appropriate quantities should be removed by the withdrawal methods normally used and described in the product literature.

The physical, chemical and microbial properties of the FPP susceptible to change during storage should be determined over the period of the proposed in-use shelf-life. If possible, testing should be performed at intermediate time points and at the end of the proposed in-use shelf-life on the final amount of the FPP remaining in the container. Specific parameters, e.g. for liquids and semi-solids, preservatives, per content and effectiveness, need to be studied.

A minimum of two batches, at least pilot-scale batches, should be subjected to the test. At least one of these batches should be chosen towards the end of its shelf-life. If such

results are not available, one batch should be tested at the final point of the submitted stability studies.

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

In general this testing need not be repeated on commitment batches

#### **2.2.12 Variations**

Once the FPP has been registered, additional stability studies are required whenever variations that may affect the stability of the API or FPP are made, such as major variations.

The following are examples of such changes:

- change in the manufacturing process;
- change in the composition of the FPP;
- change of the immediate packaging;
- change in the manufacturing process of an API.

In all cases of variations, the applicant should investigate whether the intended change will or will not have an impact on the quality characteristics of APIs and/or FPPs and consequently on their stability.

The scope and design of the stability studies for variations and changes are based on the knowledge and experience acquired on APIs and FPPs.

The results of these stability studies should be communicated to the regulatory authorities concerned

#### **2.2.13 Ongoing Stability Studies**

After a marketing authorization has been granted, the stability of the FPP should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of impurities or dissolution profile) associated with the formulation in the container closure system in which it is marketed. The purpose of the ongoing stability programme is to monitor the product over its shelf-life and to determine that the product remains, and can be expected to remain, within specifications under the storage conditions on the label.

This mainly applies to the FPP in the container closure system in which it is supplied, but consideration should also be given to inclusion in the programme of bulk products. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied. Generally this would form part of development studies, but where this need has not been foreseen, inclusion of a one-off study in the ongoing stability programme could provide the necessary data. Similar considerations could apply to intermediates that are stored and used over prolonged periods.

The ongoing stability programme should be described in a written protocol and results formalized as a report.

The protocol for an ongoing stability programme should extend to the end of the shelf-life period and should include, but not be limited to, the following parameters:

- number of batch(es) per strength and different batch sizes, if applicable. The batch size should be recorded, if different batch sizes are employed;
- relevant physical, chemical, microbiological and biological test methods;
- acceptance criteria;
- reference to test methods;
- description of the container closure system(s);
- testing frequency;
- description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines, and consistent with the product labelling, should be used); and
- other applicable parameters specific to the FPP.

The protocol for the ongoing stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorization dossier provided that this is justified and documented in the protocol (for example, the frequency of testing, or when updating to meet revised recommendations).

The number of batches and frequency of testing should provide sufficient data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none is produced during that year). The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.

In certain situations additional batches should be included in the ongoing stability programme. For example, an ongoing stability study should be conducted after any significant change or significant deviation to the process or container closure system. Any reworking, reprocessing or recovery operation should also be considered for inclusion.

Out-of-specification results or significant atypical trends should be investigated. Any confirmed significant change, out-of-specification result, or significant atypical trend should be reported immediately to the relevant competent authorities. The possible impact on batches on the market should be considered in consultation with the relevant competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

### 3. REFERENCE

International Conference on Harmonisation. ICH Q1A (R2): Stability testing of new drug substances and products (<http://www.ich.org/LOB/media/MEDIA419.pdf>)

Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report. Geneva, World Health Organization, 2009, Annex 2 (WHO Technical Report Series, No. 953).

## ANNEXES

### Annexure I – Stability conditions for SADC Member States

Member State	Stability conditions (confirmed long-term testing conditions) <sup>a</sup>
Angola	30 °C/65% RH
Botswana	30 °C/50% RH
Democratic Republic of Congo	30 °C/65% RH
Lesotho	30 °C/75% RH
Madagascar	30 °C/65% RH
Malawi	25 °C/60% RH
Mauritius	30 °C/65% RH
Mozambique	30 °C/75% RH
Namibia	30 °C/65% RH
Seychelles	30 °C/65% RH
South Africa	25 °C/60% RH
Swaziland	25 °C/60% RH
United Republic of Tanzania	30 °C/75% RH
Zambia	30 °C/65% RH
Zimbabwe	30 °C/75% RH

<sup>a</sup>Information on climatic zones was from the Annex 2 to WHO Technical Report Series, No. 953: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products, Table 2 - updated 1 February 2013

## Annexure 2 - Examples of testing parameters

### Section I for active pharmaceutical ingredients

In general, appearance, assay and degradation products should be evaluated for all active pharmaceutical ingredients (APIs). Other API parameters that may be susceptible to change should also be studied where applicable.

### Section II for finished pharmaceutical products

The following list of parameters for each dosage form is presented as a guide to the types of tests to be included in a stability study. In general, appearance, assay and degradation products should be evaluated for all dosage forms, as well as the preservative and antioxidant content if applicable.

The microbial quality of multiple-dose sterile and non-sterile dosage forms should be controlled. Challenge tests should be carried out at least at the beginning and at the end of the shelf-life. Such tests would normally be performed as part of the development programme, for example, within primary stability studies. They need not be repeated for subsequent stability studies unless a change has been made which has a potential impact on microbiological status.

It is not expected that every test listed be performed at each time point. This applies in particular to sterility testing, which may be conducted for most sterile products at the beginning and at the end of the stability test period. Tests for pyrogens and bacterial endotoxins may be limited to the time of release. Sterile dosage forms containing dry materials (powder filled or lyophilized products) and solutions packaged in sealed glass ampoules may need no additional microbiological testing beyond the initial time point. The level of microbiological contamination in liquids packed in glass containers with flexible seals or in plastic containers should be tested no less than at the beginning and at the end of the stability test period; if the long-term data provided to the regulatory authorities for marketing authorization registration do not cover the full shelf-life period, the level of microbial contamination at the last time point should also be provided.

The list of tests presented for each dosage form is not intended to be exhaustive, nor is it expected that every test listed be included in the design of a stability protocol for a particular finished pharmaceutical product (FPP) (for example, a test for odour should be performed only when necessary and with consideration for the analyst's safety).

The storage orientation of the product, i.e. upright versus inverted, may need to be included in a protocol when contact of the product with the closure system may be expected to affect the stability of the products contained, or where there has been a change in the container closure system.

#### *Tablets*

Dissolution (or disintegration, if justified), water content and hardness/ friability.

#### *Capsules*

- Hard gelatin capsules: brittleness, dissolution (or disintegration, if justified), water content and level of microbial contamination.
- Soft gelatin capsules: dissolution (or disintegration, if justified), level of microbial contamination, pH, leakage, and pellicle formation.

#### *Oral solutions, suspensions and emulsions*

Formation of precipitate, clarity (for solutions), pH, viscosity, extractables, level of microbial contamination.

Additionally for suspensions, dispersibility, rheological properties, mean size and distribution of particles should be considered. Also polymorphic conversion may be examined, if applicable.



Additionally for emulsions, phase separation, mean size and distribution of dispersed globules should be evaluated.

*Powders and granules for oral solution or suspension*

Water content and reconstitution time.

Reconstituted products (solutions and suspensions) should be evaluated as described above under "Oral solutions suspensions and emulsions", after preparation according to the recommended labelling, through the maximum intended use period.

*Metered-dose inhalers and nasal aerosols*

Dose content uniformity, labelled number of medication actuations per container meeting dose content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate, level of microbial contamination, valve delivery (shot weight), extractables/ leachables from plastic and elastomeric components, weight loss, pump delivery, foreign particulate matter and extractables/leachables from plastic and elastomeric components of the container, closure and pump. Samples should be stored in upright and inverted/on-the-side orientations.

For suspension-type aerosols, microscopic examination of appearance of the valve components and container's contents for large particles, changes in morphology of the API particles, extent of agglomerates, crystal growth, foreign particulate matter, corrosion of the inside of the container or deterioration of the gaskets.

*Nasal sprays: solutions and suspensions*

Clarity (for solution), level of microbial contamination, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet and/ or particle size distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign particulate matter and extractables/ leachables from plastic and elastomeric components of the container, closure and pump.

*Topical, ophthalmic and otic preparations*

Included in this broad category are ointments, creams, lotions, paste, gel, solutions, eye drops and cutaneous sprays.

- Topical preparations should be evaluated for clarity, homogeneity, pH, suspendability (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible), level of microbial contamination/sterility and weight loss (when appropriate).
- Evaluation of ophthalmic or otic products (e.g. creams, ointments, solutions and suspensions) should include the following additional attributes: sterility, particulate matter and extractable volume.
- Evaluation of cutaneous sprays should include: pressure, weight loss, net weight dispensed, delivery rate, level of microbial contamination, spray pattern, water content and particle size distribution (for suspensions).

*Suppositories*

Softening range, disintegration and dissolution (at 37 °C).

*Small volume parenterals (SVPs)*

Colour, clarity (for solutions), particulate matter, pH, sterility, endotoxins.

Stability studies for powders for injection solution should include monitoring for colour, reconstitution time and water content. Specific parameters to be examined at appropriate intervals throughout the maximum intended use period of the reconstituted drug product, stored under condition(s) recommended on the label, should include clarity, colour, pH, sterility, pyrogen/endotoxin and particulate matter. It may be appropriate to consider monitoring of sterility after reconstitution into a product, e.g. dual-chamber syringe, where it is claimed that reconstitution can be performed without compromising sterility.

- The stability studies for Suspension for injection should include, in addition, particle size distribution, dispersibility and rheological properties.
- The stability studies for Emulsion for injection should include, in addition, phase separation, viscosity, mean size and distribution of dispersed phase globules.

*Large volume parenterals (LVPs)*

Colour, clarity, particulate matter, pH, sterility, pyrogen/endotoxin and volume.

*Transdermal patches*

In vitro release rates, leakage, level of microbial contamination/sterility, peel and adhesive forces.

### Annexure 3 – Recommended labelling statements

The statements that should be used if supported by the stability studies for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) are listed in Table 1

**Table 1: Recommended labeling statements**

Testing condition under which the stability of the API/FPP has been demonstrated	Recommended labelling statement
30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"*
30 °C/75% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
5 °C ± 3 °C	"Store in a refrigerator (2 °C to 8 °C)"
-20 °C ± 5 °C	"Store in freezer"

\*"Protect from moisture" should be added as applicable.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Additional labelling statements that could be used in cases where the result of the stability testing demonstrates limiting factors are listed in Table 2.

**Table 2: Additional labelling statements for use where the result of the stability testing demonstrates limiting factors**

Limiting factors	Additional labelling statement, where relevant
FPPs that cannot tolerate refrigeration	"Do not refrigerate or freeze" <sup>a</sup>
FPPs that cannot tolerate freezing	"Do not freeze" <sup>a</sup>
Light-sensitive FPPs	"Protect from light"
FPPs that cannot tolerate excessive heat, e.g. suppositories	"Store and transport not above 30 °C"
Hygroscopic FPPs	"Store in dry condition"

<sup>a</sup> Depending on the pharmaceutical form and the properties of the FPP, there may be a risk of deterioration due to physical changes if subjected to low temperatures, e.g. liquids and semi-solids. Low temperatures may also have an effect on the packaging in certain cases. An additional statement may be necessary to take account of this possibility.