Egyptian Guidelines for Stability testing of Imported Finished Pharmaceutical Products (FPPs)

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

Table of Contents

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194
Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

References.....

1. Introduction:

These guidelines are adapted from the World Health Organization (WHO) guidelines and International council of harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) on stability testing of finished pharmaceutical products.

1.1. Objectives of these guidelines

These guidelines seek to exemplify the core stability data package required for registration of finished pharmaceutical products (FPPs) in Egypt. However, alternative approaches can be used when they are scientifically justified. Further guidance can be found in International council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.
It is recommended that these guidelines should also be applied to products that are already being marketed, e.g. upon re-registration or upon re-evaluation.

1.2. Scope of these guidelines

These guidelines apply to new and existing APIs and address information to be submitted in original and subsequent applications for marketing authorization of their related FPP for human use.

1.3. General principles

The purpose of stability testing is to provide evidence of how the quality of FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability program also includes the study of product-related factors that influence its quality, for example, interaction of API with excipients, container closure systems and packaging materials. In fixed-dose combination FPPs (FDCs) the interaction between two or more APIs also has to be considered.
As a result of stability testing a shelf-life for the FPP can be established and storage conditions can be recommended.

2. Guidelines:

2.1. Finished Pharmaceutical Product (FPP)

2.1.1. General

The design of the stability studies for the FPP should be based on knowledge of the behavior and properties of the API, information from stability studies on the API and on experience gained from preformulation studies and investigational FPPs.

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

2.1.2. Selection of batches:

Fully imported products:

New registration

Case 1:

At the time of stability file submission, stability data on production batches is available.

Data to be submitted:

Stability data (long term and accelerated) on three production batches to cover the proposed shelf life.

Case 2:

At the time of stability file submission, stability data on production batches is not available or not yet completed as the product is newly registered in the reference country.

Data to be submitted:

- Stability data (long term and accelerated) on three primary batches (pilot-scale batches) to cover the proposed shelf life.
- Available ongoing stability data on the production batches (if applicable).

In case of Renewal registration:

- It is accepted to submit long term stability data to cover the registered shelf life on one batch.

Bulk Imported products (primary packager in Egypt):

New registration

Data to be submitted:

- Stability data on one bulk batch in the intended bulk container.
- Long term and accelerated stability data on three production batches from the primary packager in the reference country to cover the proposed shelf life of the product.
- Commitment from the primary packager in Egypt:
  1- To follow the same packaging materials specifications as the reference country.
  2- To submit long term stability data on three production batches to cover the proposed shelf life once available and in this case this condition will be stated in the stability approval.

Renewal

Data to be submitted:

- Stability data on one bulk batch in the intended bulk container.
- Long term stability data on one production batch from the primary packager in Egypt to cover the proposed shelf life of the product.

N.B:

- If the scale of batches (production / pilot / primary) is not stated in the CTD, scanned copy of signed and stamped declaration is needed to clarify the scale of the submitted batches.
- All stability data (long term and accelerated) to be submitted with manufacturing date of the stability batches to be within the last 10 years from the date of submission.
- In case of non-availability of any requested data, scanned copy of signed and stamped justification needs to be submitted to be evaluated by **Stability Committee**.

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

- Stability study should be performed on each individual strength, dosage form and for each container closure system type unless bracketing or matrixing is applied.

2.1.3. Container closure system

-Stability testing should be conducted on the dosage form packaged in the same container closure system proposed for marketing. Any available studies carried out on the FPP 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.

2.1.4. Specification

-Stability studies should include testing of stability-indicating attributes of the FPP 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 or antimicrobial preservative) and functionality tests (e.g. for a dose delivery system). Examples of testing parameters in the stability studies are listed in Appendix 1.

-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 of the pharmaceutical product with the product in its final formulation (except for preservative concentration) intended for marketing.

-A single primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf-life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

2.1.5. Testing frequency

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

-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 three months over the first year, every six months over the second year and annually thereafter throughout the proposed shelf-life (e.g., 0, 3, 6, 9, 12, 18, 24, 36 months).

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

-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 six-month study is recommended.

-Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, testing should be increased 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 and12 months), from a 12-month study is recommended.

-The initial date of storage should be considered t0 and stability time points should be defined as a date with respect to t0. For example, if t0 is1 January 2020 then the one-month time point corresponds to either 1 February or 31 January 2020. For each time point, samples should be withdrawn and tested as per the protocol. Testing should be completed as soon as possible. Deviations from the protocol should be recorded and justified.

-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 **(refer to ICH Q1D).**

2.1.6. Storage conditions:

-In general an FPP should be evaluated under storage conditions with specified 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.
-Photo stability testing, which is an integral part of stress testing, should be conducted on at least one primary batch of the FPP if appropriate **"in case of new-registration**".
-The orientation of the product during storage, i.e. upright versus inverted, may need to be included in a protocol where 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.
-Storage condition tolerances are usually defined as the acceptable variations in temperature and relative humidity of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in these guidelines. The storage conditions should be monitored and recorded. Short-term environmental changes due to opening of the doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be assessed, 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 effects assessed.
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 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 storage and, intermediate storage conditions for FPPs are detailed in the sections below.

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

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

2.1.6.1. General case

Study	Storage condition	Study period
Long term*	30°C ± 2°C/ 65% RH ± 5% RH Or 25°C ± 2°C/ 60% RH ± 5% RH	Proposed shelf life
Intermediate**	30°C ± 2°C/ 65% RH ± 5% RH	12months
Accelerated	40°C ± 2°C/ 75% RH ± 5% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at (25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH).
**If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

-If long-term studies are conducted at 25° C ± 2° C/60% RH ± 5% RH and "significant change" occurs at any time during six months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. In this case the initial application should include a minimum of six months' data from a 12-month study at the intermediate storage condition.

In general "significant change" for an FPP is defined as:

• A change from the initial content of API(s) of 5% or more detected by assay, or failure to meet the acceptance criteria for potency when using biological or immunological procedures. (**Note**: Other values may be applied, if justified, to certain products, such as multivitamins and herbal preparations.)
• Any degradation product exceeding its acceptance criterion.
• Failure to meet the acceptance criteria for appearance, physical attribute and functionality test (e.g. color, phase separation, resuspendability, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams, and partial loss of adhesion for transdermal products) may be expected under accelerated conditions.
Also, as appropriate for the dosage form:
•Failure to meet the acceptance criterion for pH;
Or •Failure to meet the acceptance criteria for dissolution for 12 dosage units.

2.1.6.2. FPPs packaged in impermeable containers

-Parameters required to classify the packaging materials as permeable or impermeable depend on the characteristics of the packaging material, such as thickness and permeability coefficient. The suitability of

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

the packaging material used for a particular product is determined by its product characteristics. Containers generally considered to be moisture-impermeable include glass ampoules.

-Sensitivity to moisture or potential for solvent loss is not a concern for FPPs 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 relative humidity condition.

2.1.6.3. FPPs 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 FPPs stored in semi-permeable containers could withstand environments with low relative humidity.

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

Study	Storage condition	Study period
Long term*	30°C ± 2°C/ 35% RH ± 5% RH Or 25°C ± 2°C/ 40% RH ± 5% RH	Proposed shelf life
Intermediate**	30°C ± 2°C/ 35% RH ± 5% RH	12 months
Accelerated	40°C ± 2°C/ NMT* 25% RH	6 months

* **NMT**: not more than.

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH.

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

-For long-term studies conducted at (25°C ± 2°C/40% RH ± 5% RH), additional testing at the intermediate storage condition should be performed as described under the general case to evaluate the temperature effect at 30°C if significant change other than water loss occurs during the 6 months' testing at the accelerated storage condition. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate that the drug product will not have significant water loss throughout the proposed shelf life if stored at 25°C and the reference relative humidity of 40% RH.

-Products meeting either of the long-term storage conditions and the accelerated conditions, as specified in the table above, have demonstrated the integrity of the packaging in semi-permeable containers. When a significant change in water loss alone at the accelerated storage condition is observed, data should be

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

provided to demonstrate that the pharmaceutical product would not have significant water loss throughout the proposed shelf-life if stored at (30 °C/35% RH or 25 °C/40% RH).

-A 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of three months' storage at 40 °C not more than (NMT) 25% RH. However, for small containers (1 ml or less) or unit-dose products, a water loss of 5% or more after an equivalent of three months' storage at 40 °C/NMT 25% RH may be appropriate, if justified.

-An alternative approach to studies at the low relative humidity as recommended in the table above (For either long-term or accelerated testing) is to perform the stability studies under higher relative humidity and deriving the water loss at the low 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 FPP.

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 rate of water loss at the low relative humidity is to multiply the rate of water loss 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.

Low humidity testing condition	Alternative testing condition	Ratio of water loss rates	Calculation
25°C / 40% RH	25°C / 60% RH	1.5	(100-40) / (100-60)
30°C / 35% RH	30°C / 65% RH	1.9	(100-35) / (100-65)
30°C / 35% RH	30°C / 75% RH	2.6	(100-35) / (100-75)
40°C / NMT* 25% RH	40°C / 75% RH	3.0	(100-25) / (100-75)

* NMT: not more than.

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

2.1.6.4. FPPs intended for storage in a refrigerator

Study	Storage condition	Study period
Long term	5° C ± 3° C	Proposed shelf life
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

-If the FPP is packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss.

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

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

-If significant change occurs between three and six months' testing at the accelerated storage condition, the proposed shelf-life should be based on the data available from the long-term storage condition.

-If significant change occurs within the first three 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 FPP for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test a product throughout six months when a significant change has occurred within the first three months of accelerated studies at the specific condition chosen in accordance with the risk analysis.

2.1.6.5. FPPs intended for storage in a freezer

Study	Storage condition	Study period
Long term	-20^{o} C ± 5^{o} C	Proposed shelf life

-For FPPs intended for storage in a freezer, the shelf-life should be based on the long-term data obtained at the long-term storage condition. In the absence of an accelerated storage condition for FPPs 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 or 30 °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.

2.1.6.6. FPPs intended for storage below -20 °C

-FPPs intended for storage at temperatures below -20 °C should be treated on a case-by-case basis.

2.1.7. Evaluation

-A systematic approach should be adopted to 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 number of batches of the FPP, a shelf-life and label storage instructions applicable to all future batches of the FPP manufactured 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.

2.1.8. Extrapolation

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

-For products that are marketed in the country of origin for less than one year, or when complete long term stability data covering the proposed shelf life is not available and clearly justified by statistical analysis.

-Accelerated stability data for 6 months and available long term stability data should be submitted, and the Extrapolation could be applied as follow:

- Shelf life estimation for drug products at room temperature storage

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

-Extrapolation of the shelf life beyond the period covered by the submitted long-term data can be proposed to be up to twice the period covered by the submitted long-term data, but extrapolation period of shelf life should not be more than 12 months beyond, the period covered by long-term data (satisfying the requirements stated in appendix 4).

- Shelf life estimation for drug products intended for storage at below room temperature (refrigerator)

-When long term and accelerated data showing little change over time and little variability

-Extrapolation of the shelf life beyond the period covered by the submitted long-term data can be proposed to be up to one-and-a-half times the period covered by the submitted long-term data, but extrapolation period of shelf life should not be more than 6 months beyond, the period covered by long-term data.

N.B:

-In case of applying the extrapolation a commitment of submitting the complete long term stability study is required and the stability approval will be conditioned on that submission.

2.1.9. Statements and labeling

-A storage statement should be established for the label in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the FPP. Where applicable, specific instructions should be provided particularly for FPPs that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” should be avoided.There should be a direct link between the storage statement on the label and the demonstrated stability of the FPP. An expiry date should be displayed on the container label.

-The labeling statements recommended for use, if supported by the stability studies, are provided in Appendix 2. Information on the interpretation and conversion of storage statements for products approved in zone II when the products are to be distributed in zone IV is provided in Appendix 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 labeling statements could be used in cases where the results of the stability testing demonstrate limiting factors (see Appendix 2).

2.1.10. Photo-stability testing

-The intrinsic photo-stability characteristics of new drug products should be evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable change.

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

-Normally, photo-stability testing is carried out on a single primary batch. Under some circumstances these studies should be repeated if certain variations and changes are made to the product (e.g., formulation, packaging). Whether these studies should be repeated depends on the photo-stability characteristics determined at the time of initial filing and the type of variation and/or change made.

-A systematic approach to photo-stability testing is recommended covering, as appropriate, studies such as:
i) Tests on the exposed drug product outside of the immediate pack; and if necessary;
ii) Tests on the drug product in the immediate pack; and if necessary;
iii) Tests on the drug product in the marketing pack.

-The extent of drug product testing should be established by assessing whether or not acceptable change has occurred at the end of the light exposure testing. Acceptable change is change within limits justified by the applicant.

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

-Normally, only one batch of drug product is tested during the development phase, and then the photo-stability characteristics should be confirmed on a single primary batch if the product is clearly photo-stable or photo-labile. If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted.

-For some products where it has been demonstrated that the immediate pack is completely impenetrable to light, such as aluminum tubes or cans, testing should normally only be conducted on directly exposed drug product.
-It may be appropriate to test certain products such as infusion liquids, dermal creams, etc., to support their photo-stability in-use. The extent of this testing should depend on and relate to the directions for use, and is left to the applicant's discretion.

The analytical procedures used should be suitably validated.

2.1.11. In-use stability testing

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

-The registration for a multi-dose product should include either the in-use stability data on which the in-use shelf-life is based or a justification why no in-use shelf-life is established. This justification can also be based on experimental results.

-In case of manufacturing site change or addition (variation) of a multi dose product, in use stability study is required from the new manufacturer. (If it is not available, it should be justified).

a. Selection of batches

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

-A minimum of two batches, at least pilot scale batches, should be subjected to the test. At least one of the 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.

-The batch number, date of manufacture and size of each batch should be stated. The container and closure of the product and, if present, the medicinal device should be equivalent to that proposed for marketing.

-If the product is to be supplied in more than one container size or in different strengths, the in-use stability test should be applied to the product which presents the greatest susceptibility to change. The choice of the tested product should always be justified.

b. Test design

-As far as possible the test should be designed to simulate the use of the product in practice taking into consideration the filling volume of the container and any dilution/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. Sampling should take place under normal environmental conditions of use.

-The appropriate physical, chemical and microbial properties of the product 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 remaining amount of the product in the container. Specific parameters, e.g. for liquids and semi-solids, preservatives, per content and effectiveness, need to be studied.

c. Test storage conditions

The product should be stored under the conditions as recommended in the product literature (SPC and PIL) throughout the in-use stability test period. Any other storage conditions should be justified.

d. Test parameters

The appropriate physical, chemical and microbial properties of the product susceptible to change during use should be monitored. The tests used must be appropriate to individual dosage forms, however, examples of parameter types which may need to be studied are given below:

- Physical: color, clarity, closure integrity, particulate matter, particle size
- Chemical: active substance assay(s), antimicrobial preservative and antioxidant content(s), degradation product level(s), pH
- Microbial: Total viable count, sterility

e. Analytical procedures

The analytical procedures used in the study should be described and fully validated. Stability indicating assays should be employed.

f. Presentation of the results

The results should be summarized and tabulated. If relevant, the results should be presented graphically.

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

g. Evaluation

-Conclusions reached based on the data provided should be stated. In the case of anomalous results these should be explained.

-Where applicable and justified an in-use shelf life specification should be given. In-use stability data should be used to determine whether or not a declaration of an in-use shelf life and additional storage conditions are necessary.

h. Labeling of the primary container

The in-use shelf life should be stated on the label. In addition (if space allows) there should be a space for the user to write the date of opening or the "use-by" date.

i. SPC, leaflet and labeling of the secondary container

-Because it is difficult to predict all the possible conditions, under which the product will be opened, diluted reconstituted and stored, etc., the user is responsible for maintaining the quality of the product that is administered to the patient.

--In order to help the user in this responsibility, the applicant should provide the relevant information about in-use shelf life and in-use storage recommendations in the User Information Texts, (e.g. SPC, Package insert, labels) as the following examples:

Ex.: For unpreserved sterile products:

- General

-Chemical and physical in-use stability has been demonstrated for x hours/days at y ^{o}C.
-From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

- Specific text for Preparations for Infusion or Injection

-Chemical and physical in-use stability has been demonstrated for x hours/days at y ^{o}C.
-From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ^{o}C, unless reconstitution/dilution (etc.) has taken place in controlled and validated aseptic conditions.

Ex.: For aqueous preserved sterile products (including antimicrobial preservatives or intrinsically self-preserving), Non-aqueous (e.g. Oily) preparations:

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

-Chemical and physical in-use stability has been demonstrated for x hours/days at y ^{o}C.
-From a microbiological point of view, once opened, the product may be stored for a maximum of z days at t ^{o}C. Other in-use storage times and conditions are the responsibility of the user.
-The applicant should justify the values of z and t on a case by case basis; z should not normally be greater than 28 days.

2.1.12. Variations

-Once the FPP has been registered, additional stability studies are required whenever variations that may affect the stability FPP are made.

-The following are examples of such changes:
- Change in the manufacturing process;
- Change in the composition of the FPP;
- Change or addition of the immediate packaging;
- Change or adding the manufacturing site.
- Extension of shelf life.
- Change in storage conditions.

-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 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 FPPs.
-The results of these stability studies should be communicated to the regulatory authorities concerned.
For further information see EMA:

Guideline on stability testing for application for variations to a marketing authorization.

2.1.13. Ongoing stability studies

-After a marketing authorization has been granted, the stability of the FPP should be monitored according to a continuous appropriate program 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 program 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 program 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 program could provide the necessary data. Similar considerations could apply to intermediates that are stored and used over prolonged periods.

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

-The ongoing stability program should be described in a written protocol and results formalized as a report. The protocol for an ongoing stability program 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 labeling, should be used); and other applicable parameters specific to the FPP. The protocol for the ongoing stability program 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 program (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 program. For example, an ongoing stability study should be conducted after any significant change or significant deviation to the processor 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 program, should be should be written and maintained. This summary should be subjected to periodic review.

2.1.14. Stability Commitment

When available long term stability data on production 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

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

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.

Appendix 1: Examples of testing parameters
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 can also apply to sterility

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

testing, which may be conducted for most sterile products at least at the beginning and at the end of the stability test period.

A validated container-closure integrity test may be used in lieu of sterility testing. Tests for pyrogens and bacterial end toxins 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 at least 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. Weight loss from plastic containers should be reported over the shelf life.

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 odor should be performed only when necessary and with due consideration for the analysts 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 (e.g. liquids or semisolids), or where there has been a change in the container closure system.

1. Tablets

Dissolution, disintegration, water content and hardness/friability. Dispersible tablets should additionally be tested for disintegration (with a limit of not more than 3 minutes) and fineness of dispersion.

2. 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.

In case of hard gelatin or soft gelatin capsule, declaration BSE/ TSE free Products policy is required:

- TSE (transmissible Spongiform Encephalopathies)

- BSE (Bovine Spongiform Encephalopathies)

3. Oral solutions, suspensions and emulsions

-Formation of precipitate, clarity (for solutions), pH, viscosity, extractable, 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.

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

4. 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 labeling, through the maximum intended use period.

5. Metered-dose inhalers and nasal aerosols

-Dose content uniformity, labeled 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), extractable/leachables from plastic and elastomeric components, weight loss, pump delivery, foreign particulate matter and extractable/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.

6. 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.

7. 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, suspend ability (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).

8. Suppositories

Disintegration and dissolution (at 37 °C) and as appropriate for the type, net filled content, rupture time, melting and solidification, liquefaction/softening time, leakage, pellicles and pH.

9. Small volume Parenterals (SVPs)

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

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

-Stability studies for powders for injection solution should include monitoring for color, 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, color, 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, specific gravity, re-suspendability, rheological properties and dissolution (when applicable). Content uniformity may be considered a stability indicating parameter for the primary stability studies of a depot injection such as depomedroxyprogesterone acetate (DMPA) (refer to the WHO Prequalification Team-medicines (PQTm) DMPA guidance document published on the PQTm website)

-The stability studies for emulsion for injection should include, in addition, phase separation, viscosity, mean size and distribution of dispersed phase globules.

10. Large volume parenterals (LVPs)

Color, clarity, particulate matter, pH, osmolality test, sterility, pyrogen/endotoxin and volume.

11. Transdermal patches

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

Appendix 2: Recommended labeling statements

-The statements that should be used if supported by the stability studies for finished pharmaceutical products (FPPs) are listed in Table below

Testing condition under which the stability of the FPP has been demonstrated	Recommended labeling statement [a]

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

25◦ C/60% RH (long-term) 40◦ C/75% RH (accelerated)	Don't store above 25◦C
25◦ C/60% RH (long-term) 30◦ C/65% RH (intermediate, failure of accelerated)	Don't store above 25◦C[b]
30◦ C/65% RH (long-term) 40◦ C/75% RH (accelerated)	Don't store above 30◦C[b]
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

-During storage, shipment and distribution of the FPP, the current good distribution practices (GDP) for Pharmaceutical products are to be observed (3). Details on storage and labeling requirements can be found in **WHO guide** to good storage practices for pharmaceuticals (2).
b "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 labeling statements that could be used in cases where the result of the stability testing demonstrates limiting factors are listed in Table below.

Limiting factors	Additional labeling statements, where relevant
FPPs that cannot tolerate refrigeration	"Do not refrigerate or freeze"
FPPs that cannot tolerate freezing	"Do not freeze"
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"
Packaging (with the packaging format specified in the statement, e.g. bottle blister)	"Store in the original package" "Keep the container in the outer carton" "Keep the container tightly closed in order to protect from light and moisture"

a 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.

Appendix 3: Interpretation of storage statements for products approved in climatic zone II when the products are to be distributed in Egypt

-In order to ensure the safe use of medicines in recipient countries, the wording on labeling storage statements must be considered in the context of both the region in and for which the stability studies were

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

conducted and the region (s) in which the products are intended to be distributed. For example, for products approved in a zone II region the stability testing has usually been conducted at accelerated conditions and at zone II long-term conditions. Demonstrated stability at zone II conditions may result in a label storage statement of "Store between 15 and 30 °C" in line with the convention of some zone II regions. A product with such a statement, received in Egypt, would be expected to have demonstrated stability at zone IVa long-term stability conditions. However, when the stability was demonstrated at zone II long-term conditions, the appropriate statement for distribution in a **zone IVa** region would be "Do not store above 25 °C". Typical examples of the storage statements for products approved in zone II, with examples of the stability data on which the statements are based and the corresponding recommended storage statement for distribution in Egypt are provided in Table below.

-Examples of stability data and storage statements for products approved in climatic Zone II and the recommended storage statements (for distribution in Egypt) based on the Same data

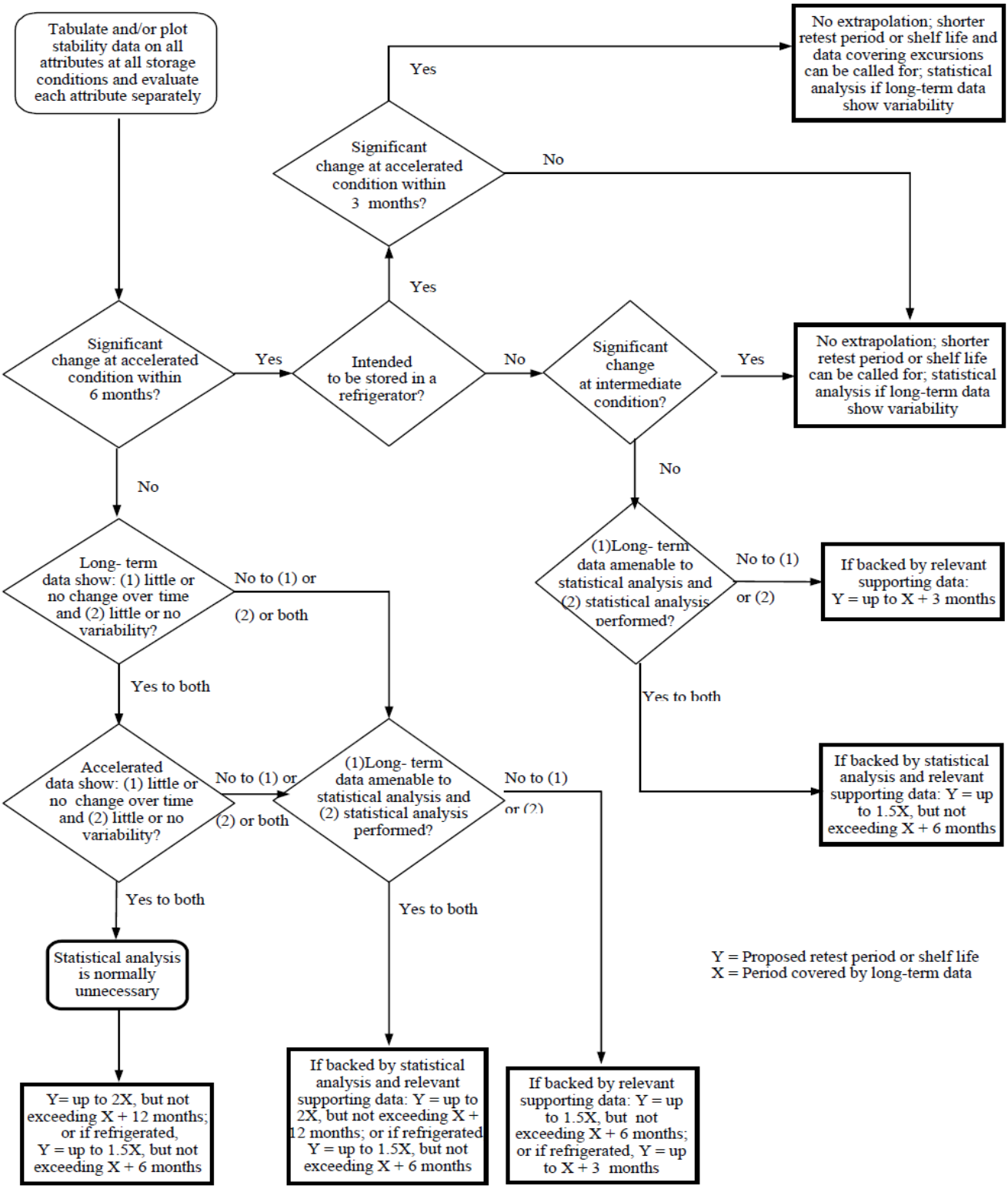
Storage statement for products approved in zone II	Examples of stability data on which the statements are based	Recommended storage statement for products to be distributed in Egypt
This medicinal product does not require any special storage conditions (or similar, i.e. no temperature mentioned)	Zone II + accelerated (finished pharmaceutical product (FPP) is stable at long-term conditions, with no significant change at accelerated conditions	"Do not store above 25 °C. Protect from moisture"
This medicinal product does not require any special storage conditions	Zone II + Zone IVb + Accelerated (FPP is stable at long-term conditions (zones II and IVb), with no significant change at accelerated conditions)	"Do not store above 30 °C"
Do not store above 30 °C	Zone IVa + accelerated (FPP is stable at long term conditions, with significant change at accelerated conditions)	"Do not store above 30 °C, Avoid excursions. Protect from moisture"
Store at 15 °C to 30 °C **OR** Store at 25 °C; excursions permitted to 15 °C to 30 °C **OR** Store at controlled room temperature (15–30 °C).	Zone II + accelerated (FPP is stable at long term conditions, with no significant change at accelerated conditions)	"Do not store above 25 °C. Protect from moisture"

Note: Zone II is 25 °C/60% RH, zone IVa is 30 °C/65% RH and zone IVb is 30 °C/75% RH.
Note: IVa may be acceptable in lieu of IVb when humidity is not an issue, for example, for storage in glass container.

Appendix 4 (ICH-Q1E): Decision Tree for Data Evaluation for Shelf Life Estimation for Drug Products (excluding Frozen Products)

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg



Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

Glossary:

The definitions given below apply to the terms used in this guideline and provided to facilitate interpretation of the guidelines.

Accelerated testing

Studies designed to increase the rate of chemical degradation and physical change of an API or FPP by using exaggerated storage conditions as part of the stability testing program. The data thus obtained, in addition to those derived from long-term stability studies, may be used to assess longer-term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes.

Active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be 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.

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 stability schedule such that only samples at the extremes of certain design factors, e.g. strength and 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 zone

The zones into which the world is divided based on the prevailing annual climatic conditions.

Climatic zone	Definition	Long term testing
I	Temperate climate	21^0C / 45% RH
II	Subtropical and Mediterranean climate	25^0C / 60% RH
III	Hot/dry climate	30^0C / 35% RH

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

IV a	Hot/humid climate	30^0C / 65% RH
IV b	Hot/very humid climate	30^0C / 75% RH

N.B:
Egypt is categorized in **climatic zone (IV a),** However studies performed at 25^0C / 60% RH would be accepted by submitting commitment for taking the responsibility of protecting the product under this condition in the **below cases**:
- If 25^0C storage condition is mentioned in the CPP.
- Legalized declaration form the company of 25^0C storage condition in case of the mentioned storage conditions in Smpc (summary of pharmaceutical product) as "it doesn't require any specialized conditions".

Commitment batches
Production batches of a FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.

Container closure system
The sum of packaging components that together contains and protects the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the FPP. A packaging system is equivalent to a container closure system.

Dosage form
The form of the FPP, e.g. tablet, capsule, elixir or suppository.

Excipient
A substance or compound, other than the API and packaging materials, that is intended or designated to be used in the manufacture of a FPP.

Expiry date
The date given on the individual container (usually on the label) of a product up to and including which the API and FPP are expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf-life to the date of manufacture.

Finished pharmaceutical product (FPP)
A product that has undergone all stages of production, including packaging in its final container and labeling. An FPP may contain one or more APIs.

Impermeable containers
Containers that provide a permanent barrier to the passage of gases or solvents e.g. sealed aluminium tubes for semisolids, sealed glass ampoules for solutions and aluminum/aluminum blisters for solid dosage forms.

Long-term stability studies
Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of an API or FPP, during and beyond the expected shelf-life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the re-test period or the shelf-life, to confirm the projected re-test period and shelf-life, and to recommend storage conditions.

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

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 FPP 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.

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 shelf-life of the FPP.

Pilot-scale batch
A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, 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; unless otherwise adequately justified.

Primary batch
A batch of an API or FPP used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf-life, as the case may be. A primary batch of an API should be at least a pilot-scale batch. For an FPP, two of the three batches should be at least pilot-scale batches, 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 FPP 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.

Release specification
The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of an API or FPP at the time of its release.

Semi-permeable containers
Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by adsorption into one container surface, diffusion through the bulk of the container

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

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
The period of time during which FPP, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the FPP. The shelf-life is used to establish the expiry date of each batch.

Shelf-life specification
The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that an FPP should meet throughout its shelf-life.

Significant change
In general "significant change" for an FPP is defined as:
1. A 5% or more change in assay from its initial content of API(s), or failure to meet the acceptance criteria for potency when using biological or immunological procedures. (*Note*: other values may be applied, if justified, to certain products, such as multivitamins and herbal preparations.)
2. Any degradation product exceeding its acceptance criterion.
3. Failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g. color, phase separation, re-suspendability, caking, hardness, and dose delivery per actuation). However, some changes in physical attributes (e.g. softening suppositories, melting of creams or partial loss of adhesion for transdermal products) may be expected under accelerated conditions.
4. Also, as appropriate for the dosage form:
5. Failure to meet the acceptance criterion for pH; or
6. Failure to meet the acceptance criteria for dissolution for 12 dosage units.

Specification
A list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges or other criteria for the tests described. It establishes the set of criteria to which a FPP should conform to be considered acceptable for its intended use.

Stability indicating methods
Validated analytical procedures that can detect the changes with time in the chemical, physical or microbiological properties of the API or FPP, and that are specific so that the content of the API, degradation products, and other components of interest can be accurately measured without interference.

Stability studies (stability testing)
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 (or shelf-life) of an API or the shelf-life of an FPP.

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg

Stress testing (of the FPP)

Studies undertaken to assess the effect of severe conditions on the FPP. Such studies include photo stability testing and specific testing on certain products
(E.g. metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Supporting stability data

Supplementary data, such as stability data on small-scale batches, related formulations, and products presented in containers not necessarily the same as those proposed for marketing, and scientific rationales that support the analytical procedures, the proposed re-test period or the shelf-life and storage conditions.

References:

-ICH Harmonized tripartite guideline: stability testing of new drugs substances and products Q1A (R2).

-ICH Harmonized tripartite guideline: stability testing of new drugs substances and products Q1B.

-WHO (World Health Organization) annex 10: stability testing of active pharmaceutical ingredients and finished pharmaceutical products.

-EMA (European Medicine Agency) guidelines on stability testing: stability testing of existing active substance and related finished products.

- Decisions of the internal committee of the stability of imported drugs from reference countries department.

Tel.: +202 – 23684288 +202 – 23648769 +202 – 25354100 Ext.:1204 Fax: +202 - 23684194

Website: www edaegypt.gov.eg Email: stabilityimported@edaegypt.gov.eg