Central Administration for Pharmaceutical Products
General Administration of Stability

Guideline

Guidelines On
Stability Testing Of Finished Pharmaceutical Products and Active Drug Substance

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TABLE OF CONTENTS

1 Introduction

This guideline provides recommendations on stability testing protocols including temperature, humidity and duration for climatic zone IVa for the submission of stability study dossier for the following purposes:

- Registration and re-registration of pharmaceutical products and biocides.
- Approval of stability studies represented to fulfill requirements of committee of variation for registered pharmaceutical products including pharmaceutical products and biocides. And also, to fulfill requirements of registration license.

2 Scope

Applicable on stability studies for locally manufactured, under license, imported products from reference and non -reference countries submitted to General Administration of Stability.

3 Definitions

Stability study

The study that reflects the effect of temperature and humidity on the stability of drug substance or drug product in its final packaging material during storage period to determine re-test period of an active pharmaceutical ingredient (API) or shelf-life of finished pharmaceutical product (FPP) and storage conditions (as defined by International Council for Harmonization). It is long-term and accelerated (and intermediate) studies performed on primary and/or commitment batches according to a prescribed stability protocol.

Pilot scale batch

A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. a pilot scale is generally, at a minimum, one-tenth that of a full production scale.

Accelerated testing

Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur

during shipping. Results from accelerated testing studies are not always predictive of physical changes.

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 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.

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.

Container closure system

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

Dosage form

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

Drug product

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

Drug substance

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

Excipient

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

Expiration date

The date placed on the container label of a product (API or FPP) 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. It is established for each batch by adding the shelf-life to the date of manufacture.

Intermediate testing

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

Long term testing

Experiments on the physical, chemical, biological 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 for labeling.

Production batch

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

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.

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.

Re-test date

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

Re-test period

The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be re-tested for compliance with the specification and then used immediately. A batch of drug substance can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification.

Impermeable containers

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

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 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.

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
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 IVa,** 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.

Commitment batches

First three production batches of a FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application when the primary submitted are pilot batches.

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.

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. Failure to meet the acceptance criterion for pH.

5. 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.

Stress testing (drug substance)

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

Stress testing (drug product)

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

Supporting 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.

Accuracy

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. This is sometimes termed trueness.

Repeatability

Expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision.

Intermediate precision

Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc.

Linearity

The linearity of an analytical procedure is its ability (within a given range) to obtain test

results which are directly proportional to the concentration (amount) of analyte in the sample.

Precision

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility. Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample it may be investigated using artificially prepared samples or a sample solution. The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements.

Specificity:

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically, these might include impurities, degradants, matrix, etc. Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s). This definition has the following implications: Identification: to ensure the identity of an analyte. Purity Tests: to ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, i.e. related substances test, heavy metals, residual solvents content, etc. Assay (content or potency): to provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample.

4 Procedures

4.1 For Active Drug Substance

4.1.1 Selection of batches:

-Stability study should be provided on three primary batches of the drug substance at the long-term storage condition for the required retest period.

-Stability study at the accelerated storage condition shall be provided.

-Data from the accelerated storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as during shipping)

-If results of accelerated stability study have significant change, stability study at the intermediate storage condition should be provided.

-If there is more than one supplier, the company should submit stability study for each supplier separately.

-If “protect from light” is stated in one of the officially-recognized pharmacopoeias for the

drug substance, it is sufficient to state "protect from light" on labeling, in lieu of photo stability studies, when the container-closure system is shown to be light protective.
- In case of availability of valid Certificate of suitability of the European Pharmacopoeia (CEP) stating retest period and container closure system:
Stability data will not be submitted if the CEP specifies a retest period that is the same as or longer than that proposed by the applicant, and storage conditions are the same or at a higher temperature and humidity than those proposed by the applicant
Stability data (with less requirements) should be submitted if container closure system is stated in the CEP, analytical procedure and validation of analytical procedure may be omitted.

4.1.2 Specifications:

The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes.

4.1.3 Container Closure System:

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

4.1.4 Testing Frequency:

-At the long-term storage conditions, the frequency of testing should normally be every3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed retest period.
-At the accelerated storage conditions, a minimum of three time points including the initial andfinal time points (e.g.: 0, 3, and 6 months) is recommended.
-At the intermediate storage conditions, a minimum of four time points including the initial andfinal time points (e.g.: 0, 6, 9, and 12 months) is recommended.

4.1.5 Storage Conditions:

-A drug substance should be evaluated under storage conditions that test its thermal stability and, if applicable, its sensitivity to moisture.

General case:

Study	**Storage conditions**	**Study period**
Long term	25ºC±2ºC/60%RH ±5%RH or 30ºC±2ºC/65%RH ±5%RH	For the required re-test period
Intermediate	30ºC±2ºC/65%RH ±5%RH	12 months
Accelerated	40ºC±2ºC/75%RH ±5%RH	6 months

- If 30ºC±2ºC/65%RH ±5%RH is the long-term storage condition, no studies at intermediate condition is required.
-If significant change occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria.
- "Significant change" for a drug substance is defined as failure to meet its specification.

Drug substance intended for storage in refrigerator:

Study	Storage conditions	Study period
Long term	5ºC±3ºC	For the required retest period
Accelerated	25ºC±2ºC/ 60%RH ±5%RH	6 months

Drug substance intended for storage in freezer:

Study	Storage condition	Study period
Long term	-20 ºC±5ºC	For the required retest period

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

4.2 For Finished Drug Product

4.2.1 Selection of batches:

Shall be comply with ministerial decrees , legal provisions and regulations a according to type of products.

4.2.2 Specifications:

-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 Annex 6.3.

-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 andpreservative effectiveness demonstrated during development of the pharmaceutical productwith 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.

4.2.3 Container Closure System:

-Stability testing of finished drug product 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).

-Description of pack in details should be submitted:

- Type of packaging material (in details).
- Appearance and color of the pack (opaque, transparent, amber, colorless).
- Complete description of the closure system including the cap liner and rubber (if applicable).
- Clarification of the container filling volume.

4.2.4 Testing Frequency:

- At the accelerated storage conditions, a minimum of three time points including the initial and final time points (e.g.: 0, 3, and 6 months) is recommended.

- 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.

- For long term stability study, it should normally be every 3 months over the first year, every6 months over the second year, and annually thereafter through the proposed shelf life.

- For ongoing stability study, initial time point, at 6 months, and annual time points to the end of the shelf-life period is sufficient.
- Stability study should start within one month from manufacturing date of the batch and duration of stability study determined from date of starting the study, not from manufacturing date of the batch. Otherwise, any delay in starting stability study should be justified.
- For biocide's stability study, at least three-time intervals is recommended.

4.2.5 Storage Conditions:

-A drug product should be evaluated under storage conditions that test its thermal stability and sensitivity to moisture, if applicable, its sensitivity to moisture.

-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, 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.

General case

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

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

*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 25º C ± 2º 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.

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

- A 5% change in assay from its initial value, or failure to meet the acceptance criteria for potency when using biological or immunological procedures.

-In case of herbal medicinal product containing herbal substance and/or herbal preparation with constituent(s) of known therapeutic activity, the variation in content during the proposed shelf-life should not exceed ±5% of the declared assay value ; in exceptional cases a widening to a maximum ±10% of the declared content value may be acceptable with sufficient justification.

- Any degradation product's exceeding its acceptance criteria.

- Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, re-suspendibility, 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.

- Failure to meet the acceptance criteria for pH.
- Failure to meet the acceptance criteria for dissolution for 12 dosage units.

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

-Softening of a suppository that is designed to melt at 37ºC, if the melting point is clearly demonstrated.

-Failure to meet acceptance criteria for dissolution for 12 units of gelatin capsule or gel-coated tablet if the failure can be unequivocally attributed to cross-linking.

a-Finished Drug products or active drug substance packaged in impermeable containers:

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity conditions.

b-Finished Drug products packaged in semi-permeable containers:

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

-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 30°C and the reference relative humidity of 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 3 months' storage at 40°C/NMT 25% RH.

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

-An alternative approach to studying at the reference relative humidity as recommended in the table above (for either accelerated or intermediate 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 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.

c-Finished Drug products intended for storage in refrigerator:

Study	Storage conditions
Long term	5°C ± 3°C
Accelerated	25ºC±2ºC/ 60%RH ±5%RH

-The term "room temperature" or "ambient temperature" refers to the general customary environment and should not be used to state the storage conditions in which stability study was done or the storage conditions on the label.

d- Finished Drug products intended for storage in freezer:

Study	Storage condition
Long term	-20°C

-For drug product intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition, e.g., during shipping or handling.

e- Finished drug Products intended for storage below -20 °C

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

f- For biocides under registration

Temperature	Time
54°C ± 2°C	14 days
50°C ± 2°C	4 weeks
45°C ± 2°C	6 weeks
40°C ± 2°C	8 weeks

- There is no humidity specification.
- Each container should be weighted at the beginning of the test and at each of the test

4.2.6 Stability Commitment:

In case of imported pharmaceutical products and biocides from reference and non-reference countries, when available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the shelf life. Where the submission includes long term stability data from three production batches covering the proposed shelf life, a post approval commitment is considered unnecessary.

Otherwise, one of the following commitments should be made:

1. If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months.
2. If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months, and to place additional production batches, to a total of at least three, on long term stability studies through the proposed shelf life and on accelerated studies for 6 months.
3. If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long term stability studies through the proposed shelf life and on accelerated studies for 6 months.

4.2.7 In- Use Stability Testing:

4.2.7.1 The purpose of 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 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 drug product in practice, taking into consideration the filling volume of the container and any dilution or reconstitution before use. 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 drug product remaining in the container.

4.2.7.2 Selection of batches:

a-For Local Finished Pharmaceutical Products

The same batches submitted in stability study 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.

- The batch number, date of manufacture and size of each batch should be stated.
- The appropriate physical, chemical and microbiological properties of the product susceptible to change during storage should be determined over the period of the proposed in-use shelf life.

b-For Imported Finished Pharmaceutical Products from Reference and Non- Reference Products

-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.
-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.

General Case

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.

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

-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.

4.2.7.3 Testing Frequency:

Testing should be performed if possible at the beginning, 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.

4.3 Bracketing Designs for Stability Testing

-This design can be applied on samples on the extremes of certain design factors (e.g., strength, container size and/or fill)

- The use of a bracketing design would not be considered appropriate if it cannot be demonstrated that the strengths or container sizes and/or fills selected for testing are indeed the extremes.

-If, after starting the studies, one of the extremes is no longer expected to be marketed, the study design can be maintained to support the bracketed intermediates. A commitment should be provided to carry out stability studies on the marketed extremes post-approval.

-Design example

Strength		50 mg			75 mg			100 mg		
Batch		1	2	3	1	2	3	1	2	3
Container size	15 ml	T	T	T				T	T	T
	100 ml									
	500 ml	T	T	T				T	T	T

Key: T = Sample tested

4.4 Photostability 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.

-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 and 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.

-For substances, photostability testing should consist of two parts: forced degradation testing and confirmatory testing.

4.5 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.

-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 updatingto 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 therelevant 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.

4.6 Analytical Procedures

- Analytical procedure for the assay of the active ingredient and other selected component(s) (e.g.: preservatives, antioxidants, and related substances) in the drug product should be provided.
- Validated stability-indicating analytical procedures should be applied.
- The assay of preservatives and antioxidant should be done at least at the initial and final time points.
- In case of accelerated and intermediate stability study, the assay of impurities and related substances should be done at least at the initial and final time points.
- In case of long-term stability study, the assay of impurities and related substances should be done at least at the initial and final time points in addition to being done annually throughout the proposed shelf life.
- Reference to analytical procedure used for the assay of related substance should be provided so that the analytical procedure is identical to that mentioned in the pharmacopoeia monograph for the active ingredient.
- Original chromatograms of HPLC with peaks labeled (containing injection date, injection time, injection volume, drug substance name, drug product name, and its concentration, peak area, retention time, peak height) or equivalent data if other analytical procedures are used should be submitted.
- Chromatograms for assay at each time interval should be included.
- Regression equation used for calculation should be submitted.
- During microbiological analysis of a product that has antimicrobial or antifungal property, a neutralization step must be done to neutralize this property to recover viable microorganisms before performing the microbiological analysis. This neutralization may be achieved by one of the following, chemical neutralization (by neutralizing agents), dilution below their minimum inhibitory concentration and membrane filtration (by using membrane filters having a nominal pore size not greater than 0.45 μm) or by any combination of these methods.
- Some tests such as content uniformity, residual solvents and bacterial endotoxins may be limited to the time of release only. This can also apply to sterility testing, which may be conducted for most sterile products at least at the beginning and at the end of the stability test period.
- Particulate matter test in Injectable solutions, including solutions constituted from sterile solids intended for parenteral use, is indefinitely postponed for products for veterinary use.

4.6.1 Validation of Analytical Procedure:

- The main objective of validation of an analytical procedure is to demonstrate that the procedure is suitable for its intended purpose.
- Validation of analytical procedure should be provided for the following:
  - Assay for active ingredient in drug product.
  - Assay for other selected component(s) (e.g.: preservatives, antioxidants, and related substances) in the drug product.
  - Assay for impurities' content

-If analytical procedure for the assay is non-official, full validation is required which include: Linearity and range, Accuracy, Precision, Specificity, Intermediate Precision (Ruggedness), Robustness.

- Detailed results coupled with chromatograms should be submitted.
- A table for each parameter with calculated %RSD should be submitted.
- In case of absence of degradation product, forced degradation should be submitted under the following conditions:
  - Acid degradation: by treating API with HCl on cold, then with heating.
  - Alkaline degradation: by treating API with NaOH on cold, then with heating.
  - Oxidative degradation: by treating API with H_2O_2 on cold, then with heating.
  - Thermal degradation: performed when the previously mentioned degradation methods failed.
  - Photolytic degradation: subjecting API to U.V lamp (specification reported if applicable).
- Degradation product if present should be eluted at different retention time from active pharmaceutical ingredient.
- In case of presence of two or more active pharmaceutical ingredients, specificity of each active pharmaceutical ingredient should be done separately, then the Overlay chromatograms and their degradation product (If present) of all active pharmaceutical ingredients should be submitted together.
- Detailed results coupled with chromatograms including placebo and blank charts should be submitted.
- Precision should be assessed using a minimum of 9 determinations covering the specified range for the procedure (e.g.,3 concentrations/ 3 replicates each) or a minimum of 6 determinations at 100% of the test concentration.

4.7 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.

4.8 General Considerations

- In case of synthetic or semisynthetic antibiotics, the shelf life of drug product is not related to re test period of drug substance

- In case of antibiotic prepared by fermentation, the shelf life of drug product must be the same as re test period of drug substance.

- If there is more than one supplier of active ingredient, the applicant should submit stability study for finished drug product manufactured from each supplier separately.

-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.

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

5 References

1. ICH Topic Q 1 A (R2) “Stability testing of new drug substance and products”. ICH Topic Q 1 A (R2) Step 4 version dated 6 February 2003, “Stability testing of new drug substance and products”.
2. ICH Topic Q1B: Step 4 version dated 6 November 1996, “Photostability Testing of New Drug Substances and Products”.
3. ICH Topic Q1C: Step 4 version dated 6 November 1996, “Stability Testing: Requirements for New Dosage Forms”.
4. ICH Topic Q1D: Step 4 version dated 7 February 2002, “Bracketing and matrixing designs for Stability Testing of Drug Substances and Drug Product”.
5. ICH Topic Q1E: Step 4 version dated 6 February 2003, “Evaluation of Stability Data”.
6. ICH Topic Q2(R1): Step 4 version dated 1 November 2005, “Validation of analytical procedure text and methodology”.
7. ICH Topic Q3A: Step 4 version dated 25 October 2006 “Impurities in New Drug Substances”.
8. EMA, CPMP/QWP/848/96, EMEA/CVMP/598/99, 2001, "Note for guidance on process validation".
9. EMA, EMA/CVMP/QWP/709423/2022, 8 December 2022, "guidelines on stability testing: stability testing of existing active substance and related finished products".
10. WHO Technical Report Series, No. 1010, 2018. Annex 10 "Stability testing of active pharmaceutical ingredients and finished pharmaceutical products".
11. WHO Technical Report Series No. 986, 2014, Annex 6 "Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part".
12. WHO Technical Report No. 953, 2009, "WHO expert committee on specifications for pharmaceutical preparations".
13. USP 44, General chapter. <1225> "Validation of compendial procedures".
14. USP 44, General chapter, <788> "Particulate matter in injections".
15. USP 44, General chapter, <71> "Sterility Tests".
16. USP 44, General chapter, <61> "Microbiological examination of nonsterile products: microbial enumeration tests".
17. USP 44, General chapter, <62> "Microbiological examination of nonsterile

products: tests for specified microorganisms".

6 Annexes

6.1 Outer label and Additional Label

6.1.1 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 Annex 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 Annex 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 Annex 2).

Testing condition under which the stability of the drug product has been demonstrated	Recommended labeling Statement
25 °C/60% RH (long-term) 40 °C/75% RH (accelerated)	Store at temperature not exceeding 25°C
25 °C/60% RH (long-term) 30 °C/65% RH (intermediate, failure of accelerated)	Store at temperature not exceeding 25°C
30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	Store at temperature not exceeding 30°C
30 °C/75% RH (long-term) 40 °C/75% RH (accelerated)	Store at temperature not exceeding 30°C
5 °C ± 3 °C	Store in a refrigerator (2°C to 8°C)
-20°C	Store in freezer

Limiting factors	Additional labeling statement, where relevant
Drug product that cannot tolerate refrigeration	Do not refrigerate or freeze
Drug product that cannot tolerate freezing	Do not freeze
Light-sensitive drug product	Protect from light
Drug product that cannot tolerate excessive heat, e.g. suppositories	Store and transport at temperature not exceeding 30°C
Hygroscopic drug product	Store in dry place

6.1.2 Interpretation of Storage Statements for Products approved in Climatic Zone II When the Products are to be distributed in Egypt (For Imported Pharmaceutical Products):

-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 whichthe stability studies were conducted and the region (s) in which the products are intended tobe 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 "Storebetween 15 and 30 °C" in line with the convention of some zone II regions. A product withsuch a statement, received in Egypt, would be expected to have demonstrated stability atzone IVa long-term stability conditions. However, when the stability was demonstrated atzone II long-term conditions, the appropriate statement for distribution in a zone IVa regionwould 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.

6.1.3 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 not require any Special storage conditions (or similar,	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 or similar,	Zone II + Zone IVb + Accelerated (FPP is stable at long-term conditions (zone 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.

6.2 Examples of Testing Parameters for Finished Drug Products:

In general, physical characters (including: description in details "color, shape, coating, markings as: score, ink, or embossing"), chemical analysis (including: assay and degradation products), microbiological analysis (including: total count of aerobic microorganisms, total count of yeasts and mold, sterility, and pathogen/endotoxin) and biological analysis (including: skin sensitivity test, and eye irritation test only in ophthalmic and topical preparations) should be evaluated for all dosage forms as well as preservative and antioxidant content if applicable.

Dosage Form	Tests to be done
1-Tablets	- Average weight. - Dissolution and disintegration (or one of them if justified). -Water content (if the specification stated that). -Hardness / Friability (for uncoated tablet). - Dispersible tablets should additionally be tested for disintegration (with a limit of not more than 3 minutes) and fineness of dispersion.
2- Hard gelatin capsules	-Average weight (of whole capsule and capsule content). -Dissolution (or disintegration, if justified). -Water content (if the specification stated that). - Brittleness. - Level of microbial contamination.
3- Soft gelatin capsules	- Physical characters (appearance and color of the shell & content). -Average weight (of whole capsule and capsule content). -Dissolution (or disintegration, if justified). -Leakage. -pH - Level of microbial contamination. - Pellicle formation.
4-Emulsions	-Phase separation. -Viscosity. -Formation of precipitate. - pH - Extractable, level of microbial contamination. -mean size and distribution of dispersed globules should be

	evaluated.
5-Oral Solutions	-Clarity. -pH -Viscosity (if the specification stated that). -Formation of precipitate, clarity (for solutions), extractable, level of microbial contamination.
6-Suspensions	-pH -Viscosity (if the specification stated that) -Dispersibility -Rheological properties for the viscous suspension -Mean size (if applicable) -Distribution of particles should be considered -Anti microbial preservative effectiveness at zero & at the end -Formation of precipitate, - extractable, level of microbial contamination. -Additionally, polymorphic conversion may be examined, if applicable.

7-Powders and Granules for Oral Solutions or Suspensions	- Water content. - Reconstitution time. - Reconstituted products (solutions and suspensions) should be evaluated as described in “Oral Solutions and Suspensions” above, after preparation according to the recommended labelling, through the maximum intended use period.

8-Metered-dose Inhalers and Nasal Aerosols	-Dose content uniformity. -Labelled number of medication actuations per container meeting dose content uniformity. -Water content. -Leak rate. -Samples should be stored in upright and inverted/on-the-side orientations. -Aerodynamic particle size distribution. -Microscopic evaluation. - Level of microbial contamination. -Valve delivery (shot weight). -Extractable/leachable from plastic and elastomeric components, -weight loss. - pump delivery. -Foreign particulate matter and extractable/leachable from plastic and elastomeric components of the container, closure and pump. **-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.

9-Nasal Sprays: Solutions and Suspensions	-Clarity (for solutions). -pH . -Weight loss. - Level of microbial contamination, - 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 extractable/leachable from plastic and elastomeric components of the container, closure and pump.

10-Topical, Ophthalmic and Otic Preparations	- Included in this broad category: Ointments, creams, lotions, pastes, gels, solutions, eye drops, and cutaneous sprays. Topical preparations should be evaluated for: -Clarity. -Homogeneity. -pH . -Viscosity. -Weight loss (when appropriate). - Suspend ability (for lotions). -Consistency. -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 (in case of otic products if antibiotics are present only). - Particulate matter and extractable volume. **Evaluation of cutaneous sprays should include:** -Weight loss. -Net weight dispensed. -Water content. - Pressure, delivery rate, level of microbial contamination, spray pattern, water content and particle size distribution (for suspensions).
11-Suppositories	-Softening time or disintegration time. - Disintegration and Dissolution (at 37^0C). - Net filled content, rupture time, melting and solidification, - Liquefaction/softening time, - Leakage. -Pellicles. -pH

12-Small Volume Parenteral (SVPs)	-Color. -Clarity (for solutions). -Particulate matter. -pH -Sterility. - Bacterial endotoxins.
13-Powders for solution for injection	-Monitoring for color. -Reconstitution time. -Water content. - Pyrogen /endotoxin (at the release only). -Sterility. Specific parameters to be examined at appropriate intervals throughout the maximum intended use period of the reconstituted drug product, stored under condition(s) recommended in labeling should include: -Clarity. -Color. -pH -Sterility. -Pyrogen /endotoxin (at the release only). -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 suspensions for injection should include, in addition: -Dispersibility. -Rheological properties (viscosity and specific gravity) (if applicable) -Particle size distribution. - Specific gravity, re-suspendability. - Content uniformity may be considered a stability indicating parameter for the primary stability studies of a depot injection such as depomedroxy progesterone acetate (DMPA) (refer to the WHO Prequalification Team-medicines (PQTm) DMPA guidance document published on the PQTm website) The stability studies for emulsions for injection should include, in addition: -Phase separation. -Viscosity. -Mean size and distribution of dispersed phase globules.
14-Large Volume Parenteral (LVPs)	-Color. -Clarity. -Particulate matter. -pH -Sterility. -Pyrogen /endotoxin. -Volume. -Osmolality test.

15-Transdermal Patches	-In vitro release rates. -Leakage. -Level of microbial contamination/sterility. -Peel and adhesive forces.