Updating of regulating guideline for Stability Studies of Pharmaceutical Products

Objective of this guideline:

This Guideline provides recommendations on stability testing protocols including temperature, humidity and duration for climatic Zone IV A for the submission of stability study dossier for the following purposes:

- Registration or re-registration of human pharmaceutical products.
- Approval of accelerated and long term stability study of the first three production batches for human pharmaceutical products represented for establishing shelf life of the finished drug product and its storage conditions.
- Registration or re-registration of biological products.
- Approval of stability studies represented to fulfill requests of committee of biological variation for registered biological products
- Registration or re-registration of veterinary medicinal products.
- Registration or re-registration of Dietary Supplement and Herbal Medicine.
- Registration or re-registration of disinfectants and pesticides.
- Approval of stability studies represented to fulfill requests of committee of variation for registered pharmaceutical products

Scope of this guideline:

Applicable on stability studies for local, under license, imported products from non -reference countries submitted to stability study reception department in stability directorate in general directorate of registeration

-This regulating guideline is not applicable on stability studies for imported products from reference countries.

1-For Local Human Pharmaceutical Products under registration according to ministerial decrees (296/2009, 425 /2015):

1.1: For ministerial decree 296/2009:

Selection of batches:

* Follow the last update of the stability study regulating guidelines of human pharmaceutical product issued in 18/8/2015

*Formulation on which stability study was done should be identical to that attached with the transfer letter and should be displayed, assessed and approved first by committee members before assessing the stability study

1.2: For ministerial decree 425/2015:

Selection of batches:

*Stability study should be provided on one pilot batch of the finished pharmaceutical product at accelerated storage conditions **(according to ministerial decree 425/2015 article 7)**

*Formulation on which stability study was done should be identical to that used for manufacture of pilot batch and sent to stability directorate internally by general directorate of inspection. Then the formulation should be displayed, assessed and approved first by committee members

2-For Under License Human Pharmaceutical Products under registration according to ministerial decrees (296/2009, 425 /2015):

2.1: For ministerial decree 296/2009:

Selection of batches:

*The same as 1.1: For Local Human Pharmaceutical Products under registration according to ministerial decree 296/2009

*Formulation on which stability study was done should be identical to that attached with the transfer letter and should be displayed, assessed and approved first by committee members before assessing the stability study.

2.2: For ministerial decree 425/2015:

Selection of batches:

*The same as 1.2: For Local Human Pharmaceutical Products under registration according to ministerial decree 425/2015

3-For Export only Human Pharmaceutical Products under registration according to ministerial decrees (296/2009, 425 /2015):

3.1: For ministerial decree 296/2009: (according to article 6 and technical committee decision in 6/4/2017)

Selection of batches:

*The same as 1.1: For Local Human Pharmaceutical Products under registration according to ministerial decree 296/2009

*Formulation on which stability study was done should be displayed, assessed and approved first by committee members before assessing the stability study

3.2: For ministerial decree 425/2015: (according to article 7)

Selection of batches:

*Stability study should be provided on three R&D batches of the finished pharmaceutical product at accelerated or long term storage conditions

*Formulation on which stability study was done should be identical to that used for manufacture of R&D batch which then should be displayed, assessed and approved first by committee members

4-For Imported from non-reference countries Human Pharmaceutical Products under registration according to ministerial decrees (296/2009 "article 8", 425 /2015 "article 7"):

Selection of batches:

*Stability study should be provided on three productions batches of the finished pharmaceutical product at accelerated or long term storage conditions.

*formulations on which the stability study was done should be identical to the formulation illustrated in the certificate of pharmaceutical product which then should be displayed, assessed and approved first by committee members

5-For Human Pharmaceutical Products either local, under license, or imported from non-reference countries submitted for the purpose of re-registration according to ministerial decrees (296/2009, 425 /2015):

5.1: For ministerial decree 296/2009: (according to article 9)

Selection of batches:

*Ongoing stability study should be provided on at least one production batch so that the finished drug product is monitored over its shelf life and is confirmed to remain within specifications under the storage conditions on the label

*Formulation on which stability study was done should be identical to that attached with the transfer letter

5.2: For ministerial decree 425/2015: (according to article 8)

Selection of batches:

*Ongoing stability study should be provided on at least one production batch so that the finished pharmaceutical product is monitored over its shelf life and is confirmed to remain within specifications under the storage conditions on the label

*Formulation on which stability study was done should be either attached with registration license or with variation committee approval in case of changing formulation after issuing registration license or checked by National Organization for Drug Control and Research (NODCAR), otherwise if the formulation is not attached and is not inferred by NODCAR, it should be displayed, assessed and approved first by committee members before assessing the stability study (according to technical committee decision in 15/6/2017)

6-For Human Pharmaceutical Products either local or under license submitted for the purpose of representing accelerated and long term stability studies for commitment batches according to ministerial decrees (296/2009, 425 /2015)

Selection of batches:

*Commitment batches are the first three batches produced in production scale after issuing tentative license (for finished pharmaceutical products following ministerial decrees 296/2009) or final license (for finished pharmaceutical products following ministerial decrees 425/2015)

*Both accelerated and long term stability studies should be provided for commitment batches to establish shelf life of the finished pharmaceutical product and its storage conditions (according to article 6 in ministerial decree 296/2009 and article 11 in ministerial decree 425/2015)

*Formulation on which stability study was done should be identical to that attached with registration license or with variation committee approval in case of changing formulation after issuing registration license

7- For Biological Products under registration either local, under license or imported from non-reference countries according to ministerial decrees (297/2009).

Selection of batches:

*Stability study should be provided on three pilot scale batches of the finished product at long term storage conditions followed by long term stability study on three production batches after registration license .

*Formulation on which stability study was done should be identical to that attached with the transfer letter and should be displayed, assessed and approved first by committee members before assessing the stability study.

8- For Biological Products either local, under license, or imported from non-reference countries submitted for the purpose of re-registration according to ministerial decrees (297/2009):

Selection of batches:

*Ongoing stability study should be provided on three production batches so that the finished product is monitored over its shelf life and is confirmed to remain within specifications under the storage conditions on the label.

*Formulation on which stability study was done should be identical to that attached with the transfer letter

9-For Biological Products either local, under license, or imported from non-reference countries submitted for the purpose of fulfilling requests of committee of biological variation for registered biological products:

Selection of batches:

*Number and type of batches on which stability study should be done in addition to duration and type of stability study (whether accelerated or long term) is determined by committee of variation for registered biological products according to the type of change requested.

10 -For veterinary medicinal products under registration either local or under license

Selection of batches:

* Follow the last update of the stability study regulating guidelines of veterinary medicinal products issued in 18/8/2015

*Formulation on which stability study was done should be displayed, assessed and approved first by committee members

11-For Imported veterinary medicinal products from non-reference countries under registration

Selection of batches:

*Stability study should be provided on three productions batches of the veterinary medicinal products at accelerated or long term storage conditions.

*formulations on which the stability study was done should be identical to the formulation illustrated in the certificate of pharmaceutical product which then should be displayed, assessed and approved first by committee members

12-For veterinary medicinal products either local, under license, or imported from non-reference countries submitted for the purpose of re-registration

Selection of batches:

*Ongoing stability study should be provided on at least one production batch so that the veterinary medicinal products is monitored over its shelf life and is confirmed to remain within specifications under the storage conditions on the label

*Formulation on which stability study was done should be identical to that attached with the transfer letter

13 -For Dietary Supplement and Herbal Medicine under registration either local or under license

Selection of batches:

* Follow the last update of the stability study regulating guidelines of Dietary Supplement and Herbal Medicine issued in 18/8/2015

*Formulation on which stability study was done should be identical to the composition attached to the transfer letter or identical to NODCAR composition which then should be displayed, assessed and approved first by committee members

14-For Dietary Supplement and Herbal Medicine either local and under license submitted for the purpose of re-registration

Selection of batches:

*Ongoing stability study should be provided on at least one production batch so that Dietary Supplement and Herbal Medicine is monitored over its shelf life and is confirmed to remain within specifications under the storage conditions on the label.

*Formulation on which stability study was done should be identical to that attached with the transfer letter

15 -For disinfectant products under registration either local or under license

Selection of batches:

* Follow the last update of the stability study regulating guideline for **disinfectant and pesticides** issued in 18/8/2015

*Formulation on which stability study was done should be identical to that attached with the transfer letter

16-For Imported disinfectant products under registration from non-reference countries

Selection of batches:

*Stability study should be provided on three productions batches of the disinfectant and pesticides at accelerated or long term storage conditions.

*Formulation on which stability study was done should be identical to that attached with the transfer letter

17-For disinfectant and pesticides products either local, under license, or imported from non-reference countries submitted for the purpose of re-registration

Selection of batches:

*Ongoing stability study should be provided on at least one production batch so that the disinfectant and pesticides is monitored over its shelf life and is confirmed to remain within specifications under the storage conditions on the label

*Formulation on which stability study was done should be identical to that attached with the transfer letter

18- For Human Pharmaceutical Products, Veterinary medicinal products, Dietary Supplement and Herbal Medicine, Disinfectants and pesticides either local, under license, or imported from non-reference countries submitted for the purpose of fulfilling requests of committee of variation for registered pharmaceutical products

Selection of batches:

*Number and type of batches on which stability study should be done in addition to duration and type of stability study (whether accelerated or long term) is determined by committee of variation for registered pharmaceutical products according to the type of change requested.

*For some changes to finished pharmaceutical products such as: changes to shelf life, in-use period, and storage conditions, results of stability studies should be submitted directly to stability directorate without being displayed on committee of variation for registered pharmaceutical products.

In case of requesting extension of shelf life or in-use period or changing storage conditions, long term stability study on three production batches should be provided for the proposed shelf life and/or in-use period and at the proposed storage conditions.

18- Specification:

The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), impurities and related substance), and functionality tests (e.g., for a dose delivery system) .

19- Container Closure System:

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label)
Reference pack should be submitted if there is a change in the submitted pack justification should be submitted.

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.

20- 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.

*At the intermediate storage conditions, a minimum of four time points including the initial and final time points (e.g.: 0, 6, 9, and 12 months) is recommended.

*For long term stability study, it should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

*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.

21- Storage Conditions: .

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

General case:

Study	Storage conditions
Long term	25ºC±2ºC/60%RH ±5%RH or 30ºC±2ºC/65%RH ±5%RH
Accelerated	40ºC±2ºC/75%RH ±5%RH
Intermediate	30ºC±2ºC/65%RH ±5%RH

RH: Relative Humidity

*Storage conditions at 25ºC±2ºC/60%RH ±5%RH should be justified**.**

*If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

*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.

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

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

ii-Any degradation product's exceeding its acceptance criterion.

iii-Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness, dose delivery per actuation), however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions.

and, as appropriate for the dosage form:

iv-Failure to meet the acceptance criterion for pH.

v-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:

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

ii-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.

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 drug products stored in semi-permeable containers can withstand low relative humidity environments

Study	Storage conditions
Long term	25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH

Accelerated	40ºC±2ºC/ not more than (NMT) 25%RH ±5%RH
Intermediate	30ºC±2ºC/35%RH ±5%RH

*If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate 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 30°C and the reference relative humidity of 35% 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 drug product.

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

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.

22-In- Use Stability

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.

Selection of batches

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

23- Evaluation:

*Stability information, which 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) should be tabulated.

*Quantitative results should be presented numerically and not in general terms such as: complies or meet the limits

24- 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

* If there is no reference to analytical procedure used for the assay of related substance, one of the following methods should be applied:

1-Identify related substance from the drug master file of the active ingredient provided by supplier of active ingredient then determine in finished pharmaceutical product

2-Undergo forced degradation of active ingredient and separate degradation substances then determine in finished pharmaceutical product

Documentation needed before proceeding in application of one of the methods mentioned above:

- **In-house method of analysis developed for assay of related and degradation substances and its validation**
- **Certificate of analysis for active ingredient from its supplier**
- **List of related substances from the drug master file of the active ingredient provided by supplier of active ingredient (if available)**

All these documents should be first displayed on scientific specialized committee for assessing stability studies for approval before being implemented in stability study

*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.
*Acceptance criteria for retention time variation:
-On using the same instrument, the percentage of RSD of retention times should be calculated and must be $\leq 1\%$,
-If it is more than 1% specificity and peak identification should be repeated.
*On using different instruments, the method should be verified by repeating accuracy, precision, specificity and last time interval of the drug.

25- 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.

26- General requirements:

*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.
*In case of performing stability study in a place other than manufacturer and license holder, contract between site where stability study was done and applicant or license holder should be submitted, then the contract should be documented by the legal counselor of the Central Administration for Pharmaceutical Affairs (CAPA)
*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
*For imported drug products, if proposed shelf life, proposed in-use period (if applicable), proposed storage conditions and pack are not illustrated in the certificate of pharmaceutical product (CPP)

27- Outer label and additional label

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)

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

28- 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 (or disintegration, if justified) -Water content (if the specification stated that) -Hardness / Friability (for uncoated tablet)
2- Hard gelatin capsules	-Average weight (of whole capsule and capsule content) -Dissolution (or disintegration, if justified) -Water content (if the specification stated that)
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
4-Emulsions	-Phase separation -Viscosity
5-Oral Solutions	-Clarity -pH -Viscosity (if the specification stated that)
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
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
9-Nasal Sprays: Solutions and Suspensions	-Clarity (for solutions) -pH -Weight loss
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). -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) -Evaluation of cutaneous sprays should include: -Weight loss -Net weight dispensed

	-Water content
11-Suppositories	-Softening time or disintegration time -Dissolution (at 37^0C)
12-Small Volume Parenteral (SVPs)	-Color -Clarity (for solutions) -Particulate matter -pH
13-Powders for solution for injection	-Monitoring for color -Reconstitution time -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 in labeling should include: -Clarity -Color -pH -Sterility -Pyrogen /endotoxin (at the release only) -Particulate matter The stability studies for suspensions for injection should include, in addition: -Dispersibility -Rheological properties (viscosity and specific gravity)(if applicable) The stability studies for emulsions for injection should include, in addition: -Phase separation -Viscosity
14-Large Volume Parenterals (LVPs)	-Color -Clarity -Particulate matter -pH -Sterility -Pyrogen /endotoxin -Volume

15-Transdermal Patches	-In vitro release rates -Leakage

GLOSSARY

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 or shelf-life and storage conditions (as defined by International Council for Harmonization)

Pilot scale batch
A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger

Accelerated testing
Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes

Bracketing
The design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all-time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system

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

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

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

Drug substance

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

Excipient

Anything other than the drug substance in the dosage form.

Expiration date

The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification if stored under defined conditions, and after which it must not be used

Impermeable containers

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

Intermediate testing

Studies conducted at 30°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

Stability studies under the recommended storage condition for the re-test period or shelf life proposed (or approved) 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.

Re-test date

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

Re-test period

The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be re-tested for compliance with the specification and then used immediately. A batch of drug substance can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a re-test period. The same may be true for certain antibiotics

Semi-permeable containers

Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the

bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient. Examples of semi-permeable containers include plastic bags and semi-rigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles, and vials.

Shelf life (also referred to as expiration dating period)

The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Stress testing (drug substance)

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

Stress testing (drug product)

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

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

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.

REFERENCES

ICH Q1B: "Photostability Testing of New Drug Substances and Products"

ICH Q1C: "Stability Testing of New Dosage Forms"

ICH Q5C: Stability Testing of biotechnological/biological products

ICH Q1E: Evaluation of stability data

ICH Q3A: "Impurities in New Drug Substances"
ICH Q1A stability testing of new drug substance and products
ICH Q2R1validation of analytical procedure text and methodology
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