Guideline for Stability Study of Imported Drug Substance and Drug Product for human and biological products submitted according to ministerial decree 820/2016 (CTD)

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Objective of the Guideline:

The purpose of stability testing is to provide evidence on how the quality of a drug substance and drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf life to be established.

Scope of the Guideline:

The guideline primarily addresses the information required to be submitted in registration applications for molecular entities and associated drug products

Applicable on:

Stability studies represented for imported drug products from:

1- Reference countries which are not approved from FDA and/or EMA

2- Non reference countries whether approved or not approved from FDA and/or EMA

Not Applicable on:

Stability studies represented for imported drug products from reference countries which are approved from FDA and/or EMA

1- For drug substance:

1.1: Selection of batches:

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

-Stability study at the accelerated storage condition can 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 photostability studies, when the container-closure system is shown to be light protective.

1.2: 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.

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

1.4: Testing Frequency:

-At the long term storage conditions, the frequency of testing should normally be every 3 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 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.

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.

1.4.1: 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 retest period
Intermediate	30ºC±2ºC/65%RH ±5%RH	12 months
Accelerated	40ºC±2ºC/75%RH ±5%RH	6 months

RH: Relative Humidity

-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.

1.4.2: 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

1.4.3: Drug substance intended for storage in freezer:

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

1.4.4: Drug substance intended for storage below -20°C:

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

2-For Drug Product:

2.1: Selection of batches:

-Stability study should be provided on three production batches of the drug product at the long term storage condition for the required shelf-life including composition on which stability study was done.

-Stability study at the accelerated storage condition can 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.

-Photostability testing should be conducted on at least one batch of the drug product if applicable.

-If "protect from light" is stated in one of the officially-recognized pharmacopoeias for the drug product, it is sufficient to state "protect from light" on labelling, in lieu of photostability studies, when the container-closure system is shown to be light protective.

-Stability studies should be performed on each individual strength and container size of the drug product unless bracketing is applied.

-Stability testing of the drug product after reconstitution or dilution or opening, if applicable, should be conducted to provide storage condition, and in-use period of the reconstituted or diluted product. This testing should be performed on the reconstituted or diluted product through the proposed in-use period on three batches as part of the stability studies at initial and final time points.
-The shelf life proposed by the company should be the same as that presented in Certificate of pharmaceutical product(CPP) .
-In case of changing shelf life and storage conditions of the drug product from that mentioned in CPP or in case of absence of shelf life and storage conditions of the drug product in CPP, the company should submit legalized clarification letter from the license holder stating shelf life and storage conditions for the drug product
-Batches on which stability study was done should be manufactured within the last 10 years from the date of submission

2.2: 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).
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.

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

2.4: Testing Frequency:

-At the long term storage conditions, the frequency of testing should normally be every 3 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 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.

2.5: Storage Conditions: .

A drug product should be evaluated under storage conditions that test its thermal stability and, if applicable, its sensitivity to moisture.
2.5.1: 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 shelf life
Intermediate	30ºC±2ºC/65%RH ±5%RH	12 months
Accelerated	40ºC±2ºC/75%RH ±5%RH	6 months

RH: Relative Humidity

-If 30ºC±2ºC/65%RH ±5%RH is the long term storage condition, no studies at intermediate condition is required.

-Studies performed at 25ºC±2ºC/60%RH ±5%RH should be justified**.**
-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.
2.5.2: Drug products 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.
2.5.3: 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**	**Study period**
Long term	25ºC±2ºC/40%RH ±5%RH or 30ºC±2ºC/35%RH ±5%RH	For the required shelf life
Intermediate	30ºC±2ºC/35%RH ±5%RH	12 months
Accelerated	40ºC±2ºC/ not more than (NMT) 25%RH ±5%RH	6 months

-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 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 long term or accelerated testing) is performing the stability studies under higher relative humidity and deriving the water loss at the reference relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or 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.

2.5.4: Drug product intended for storage in refrigerator:

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

2.5.5: Drug product intended for storage in freezer:

Study	**Storage condition**	**Study period**
Long term	-20 ºC±5ºC	For the required shelf life

2.5.6: Drug product intended for storage below -20°C:

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

3-Analytical Procedure:

-Analytical procedure for the assay of the major component(s) in the drug substance and the assay for the active or other selected component(s) (e.g.: preservatives, antioxidants, and related substances) in the drug product should be provided.

-The assay of preservatives and antioxidant should be done at least initial and final time interval.

-A specific stability indicating assay should be provided. (e.g.: HPLC)

-In case of biological product there is no single stability-indicating assay or parameter that profiles the stability characteristics of abiological product. Consequently, the manufacturer should propose a stability-indicating profile that provides assurance that changes in the identity, purity and potency of the product will be detected.

-Original chromatograms of HPLC containing injection date, injection time, injection volume, drug substance name, drug product name, and its concentration, peak area, retention time, peak height 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 ≤ 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.
-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.

4-Validation of analytical procedure:

-Validation of analytical procedure for the assay of the major component(s) in the drug substance and the assay for the active component in drug product should be provided.
-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 &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.

5-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 ,the company must submit covering letter(legalized) declare the relation between site of stability and (license holder and manufacturer)

6-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)"
-20 °C ± 5 °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 FPPs	Protect from light
drug product that cannot tolerate excessive heat, e.g. suppositories	Store and transport at temperature not exceeding 30 °C

Appendix

In general physical character including appearance, chemical including (assay and degradation products) ,microbiological & biological analysis including skin sensitivity test eye irritation test only in ophthalmic and topical preparation) should be evaluated for all dosage forms as well as preservative and antioxidant content

Dosage Form	**Tests to be done**
1-Tablets	- Physical characters (appearance and color of capsule shell &content) - Average weight - Dissolution (or disintegration, if justified) -Water content (if the specification stated that) -Hardness / Friability (for un coating tablet) -Level of microbial contamination.

2- Hard gelatin capsules	- Physical characters (appearance and color) -Average weight (of whole capsule and capsule content) -Dissolution (or disintegration, if justified) -Water content(if the specification stated that) - 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) -Level of microbial contamination -Leakage
4-Emulsions	-Physical characters (appearance and color) -Phase separation - Viscosity -Level of microbial contamination
5-Oral Solutions	- Physical characters (appearance and color) -Clarity for solutions -pH -Viscosity (if the specification stated that) -Level of microbial contamination.
6-Suspensions	Physical characters (appearance and color) -pH -Viscosity(if the specification stated that) -Level of microbial contamination. -Additionally for suspensions: -redispersibility -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 & Granules for Oral Solutions or Suspensions	- Physical characters (appearance and color) - Water content - Reconstitution time. - Reconstituted products (solutions & suspensions) should be evaluated as described in “Oral solutions & Suspensions” above, after preparation according to the recommended labeling, through the maximum intended use period.
8-Metered-dose inhalers & Nasal Aerosols	-Dose content uniformity -Labeled number of medication actuations per container meeting

	dose content uniformity, -Water content -Leak rate -Level of microbial contamination -Samples should be stored in upright & inverted/on-the-side orientations.
9-Nasal Sprays: Solutions & Suspensions	-Clarity (for solutions) -level of microbial contamination -pH -Weight loss
10-Topical, Ophthalmic & Otic preparations	- Included in this broad category: Ointments, creams, lotions, pastes, gels, solutions, Eye drops, & cutaneous sprays. -Topical preparations should be evaluated for: - Physical characters (appearance and color) -Clarity -Homogeneity -pH -Viscosity -Level of microbial contamination /sterility - Weight loss (when appropriate). - Evaluation of ophthalmic or otic products (e.g. creams, ointments, solutions & 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 -Level of microbial contamination -Water content
11-Suppositories	Physical character(color &average weight) -Softening range or disintegration time -Dissolution (at 370C)
12-Small Volume Parenteral (SVPs)	- Color -Clarity (for solutions) -Particulate matter -pH -Sterility(at the beginning and at the end)

	-Endotoxins.
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 or/ bacterial endotoxin (at the release only) -Particulate matter -The stability studies for suspensions for injection should include, in addition: -dispersibility -Rheological properties (viscosity & specific gravity)(if applicable) -The stability studies for emulsion 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 -Level of microbial contamination/ sterility

GLOSSARY

Stability study: is 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)

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 Q3A: "Impurities in New Drug Substances"
ICH Q1A stability testing of new drug substance and products
ICH Q2R1validation of analytical procedure text and methodology
ICH Q5C stability testing of biotechnological/biological products
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002913.pdf
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