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Review Article

# Regulatory aspects of drug stability studies

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**ABSTRACT**

The U.S. Pharmacopeia (USP) defines stability as the extent to which a product retains, within specified limits and throughout its period of storage and use (i.e., its shelf life), the same properties and characteristics that it possessed at the time of manufacture. Stability studies play a major role in determining shelf-life of the product, fixing storage conditions for the product. Stability studies in general are divided into long term, accelerated, stress testing. Long term stability studies are conducted at normal storage conditions of the pharmaceutical product. Accelerated studies are conducted at exaggerated storage conditions and useful in predicting the stability in normal storage conditions. Stress testing strictly cannot be considered as stability studies however, they are performed to identify degradation products, and thus provide insight into validation of analytical testing methods, that determines the stability of pharmaceutical products (e.g. photo-stability studies). Regulatory aspects of stability studies includes the selection of batches for performing stability studies, storage conditions for performing stability studies and their frequency, test to be performed to analyze the stability of the drug substance and drug product. Data generated from stability studies forms the basis for evaluating shelf-life and storage conditions for the pharmaceutical product. Thus, Stability studies ensures that right amount of drug is available to the patient throughout its shelf life, and it is the one of the important criterion to be satisfied for the registration/ obtaining license for marketing pharmaceuticals.

**Keywords:** Stability studies; Shelf-life; Drug substance; Drug product; Long term stability studies; Accelerated stability studies; Stress testing

## INTRODUCTION

Every drug product on the market requires the expiration date to be specified on the immediate container label. The International Conference on Harmonization (ICH) (US, EU, JAPAN are ICH member countries) requires that pharmaceutical companies present factual evidence supporting the shelf life for either existing or new products. The presence of the right amount of the active ingredients in a pharmaceutical formulation is extremely important for the drug product to be an effective medicament. A rigorous protocol is usually implemented to measure the amount of the active ingredient through time for a given drug product and the collected data are analyzed to estimate the shelf life, which leads to the calculation of the expiration date. Thus, the expiration date provides the consumer the confidence that the drug product will retain its identity, strength, quality, and purity throughout the expiration period.

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Long term and short term (accelerated) stability studies are performed to identify the shelf-life (for drug product) and re-test period (for drug substance). The long term stability studies are performed under the recommended storage conditions and packaging configuration to be used for marketing the drug product and during the shelf life period, which is displayed on the product label. Accelerated Studies are Studies designed to increase the rate of chemical degradation and/or physical change of a drug substance or drug product by using exaggerated storage conditions with the purpose of monitoring degradation reactions and predicting the shelf life under normal storage conditions.

Data from the accelerated and 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 that might occur during shipping. Thus, Stability tests provides evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity and light, and to establish a shelf life or retest period and recommended storage conditions for the drug substance or drug product, respectively.

**Table 1: Storage conditions for stability studies**

| Stability study type | Stability storage conditions | Minimum time period covered by data at submission |
|---|---|---|
| Marketed API intended for storage at room temperature (general case) | | |
| Long term* | 25 ° C ± 2 ° C, 60% RH ± 5% RH or 30 ° C ± 2 ° C, 65% RH ± 5% RH | 12 months |
| Intermediate | 30 ° C ± 2 ° C, 65% RH ± 5%RH | 6 months |
| Accelerated | 40 ° C ± 2 ° C, 75% RH ± 5% RH | 6 months |
| Marketed API intended for storage in refrigerator | | |
| Long term | 5 ° C ± 3 ° C | 12 months |
| Accelerated | 25 ° C ± 2 ° C, 60% RH ± 5%RH | 6 months |
| Marketed API intended for storage in freezer | | |
| Long term | − 20 ° C ± 5 ° C | 12 months |

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30$^{o}$C ± 2$^{o}$C/65% RH ± 5% RH

**I. STABILITY REQUIREMENTS FOR DRUG SUBSTANCE (APIs)**

Drug substance is the unformulated drug substance that may subsequently be formulated with Excipient to produce the dosage form.

**A. Selection of batches**

Stability studies should be done on at least three primary batches. The batch size should be minimum of pilot scale (1,00,000 units or one tenth of commercial batch whichever is larger) by the same synthetic route and manufacturing process as the production batches. The quality of the API placed on a formal stability program should be similar to the quality of the material to be made on a commercial production scale.

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

**B. Storage conditions**

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

ICH provides information on storage conditions and testing frequency for APIs under four intended storage conditions.

1. General case.

2. Intended for storage in refrigerator.

3. Intended for storage in freezer.

4. Intended for storage below -20$^{o}$ C.

**1. Drugs intended for storage at room temperature (general case):** If long-term studies are conducted at 25$^{o}$C ± 2$^{o}$C/60% RH ± 5% RH and "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.

**2. Drugs intended for storage in refrigerator:** If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed re-test period should be based on the real time data available at the long term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipping or handling.

**3. Drugs intended for storage in freezer:** For drug substances intended for storage in a freezer, the re-test period should be based on the real time data obtained at the long term storage condition. In the absence of an accelerated storage condition for drug substances intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5$^{o}$C ± 3$^{o}$C or 25$^{o}$C ± 2$^{o}$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.

**4. Drugs intended for storage below -20$^{o}$C:** Drug substances intended for storage below -20$^{o}$C should be treated on a case-by-case basis.

**What is a significant change?**

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

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

b. Any degradation product exceeding its acceptance criterion.

c. Failure to meet the acceptance criteria for appearance and physical attributes (e.g. colour, phase separation, re-suspendibility, caking, hardness). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams, partial loss of adhe-

sion for transdermal products) may be expected under accelerated conditions.

d. Failure to meet the acceptance criterion for pH (for liquid preparation).

e. Failure to meet the acceptance criteria for dissolution for 12 dosage units (tablet and capsule). Significant change for an API means failure to meet its specification.

**C. Testing frequency**

**Table 2: Testing frequency for stability studies**

| Study type | Testing frequency |
|---|---|
| Long term | For Every 3 months over 1st year<br>For every 6 months over 2nd year<br>Annually thereafter |
| Accelerated | For 6 month studies a minimum of 3 time point is recommended (i.e.at 0, 3, 6 months) |
| Intermediate | For 12 months study, samples are tested at 0, 6, 9, 12 months |

**D. Stress studies and stability - indicating methods for analysis of API stability**

Appropriate physical, chemical, biological, and microbiological characters of the API that are likely to be susceptible to change during storage and are likely to influence the quality, safety, and efficacy should be tested. In order to develop stability – indicating method, it is necessary to conduct stress studies on an API. Stress testing is carried out on a single batch of the drug substance and the stresses can include acid and base hydrolysis, temperature (10°C increments above the accelerated stability storage temperature of 40°C, e.g. 50°C, 60°C), humidity (75% RH or greater), photolysis, and oxidation of the API.

The stress studies should demonstrate that impurities and degradants from the active ingredient do not interfere with the quantitation of the API. Stress testing of the API, in addition to validating the stability - indicating power of the analytical method, can also help establish the degradation pathways and the intrinsic stability of the molecule.

**E. Specifications**

Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.

**F. Stability Commitment**

When the submission includes long - term stability studies on three batches of API covering the proposed retest period, a post approval commitment is unnecessary.

1. If, at the time of approval long - term stability data for the primary batches do not cover the proposed retest period granted, a commitment should be made to continue the stability studies post approval to firmly establish the retest period(like shelf-life of drug product).
2. If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed retest period and to place additional production batches for a total of three and generate data through the proposed retest period.
3. If the submission does not include stability data on the production batches, a commitment should be made to place the first three production batches on long - term stability studies through the proposed retest period.

**II. Stability requirements for drug products**

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the drug product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

**Table 3: General test that are done at regular intervals for generating stability data**

| Test | Description |
|---|---|
| Description | A qualitative description of the dosage form should be provided (e.g., size, shape, and color). If any of these characteristics change during manufacture or storage, this change should be investigated and appropriate action taken. |
| Identification | Identification testing should establish the identity of the new drug substance(s) in the new drug product and should be able to discriminate between compounds of closely related structure which are likely to be present. Examples of test include IR-spectroscopy, HPLC, HPLC/MS are generally acceptable. |
| Assay | A specific, stability-indicating assay to determine strength (content) should be included for all new drug substances. |
| Impurities | Include identification of organic and inorganic impurities and residual solvents are included in this category. |

**Table 4: Specific tests for generating stability data**

| Test | Description |
|---|---|
| Physico-chemical properties | They include properties like pH of an aqueous solution, melting point / range, and refractive index. The tests performed in this category should be determined by the physical nature of the new drug substance and by its intended use. |
| Particle size | For some new drug substances intended for use in solid or suspension drug products, particle size can have a significant effect on dissolution rates, bioavailability, and / or stability. In such instances, testing for particle size distribution should be carried out using an appropriate procedure, and acceptance criteria should be provided. |
| Polymorphic forms | Some new drug substances exist in different crystalline forms which differ in their physical properties. Polymorphism may also include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. Differences in these forms could, in some cases, affect the quality or performance of the new drug products. Examples of procedures are: melting point (including hot-stage microscopy), solid state IR, X-ray powder diffraction, thermal analysis procedures (like DSC, TGA and DTA), Raman spectroscopy, optical microscopy, and solid state NMR. |
| Tests for chiral new drug substance | Includes identification particular enantiomer. |
| Water content | This test is important in cases where the new drug substance is known to be hygroscopic or degraded by moisture or when the drug substance is known to be a stoichiometric hydrate. |
| Inorganic impurities | Are identified by procedures such as atomic absorption spectroscopy |
| Microbial limits | There may be a need to specify the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., Staphylococcus aureus, Escherichia coli, Salmonella, Pseudomonas aeruginosa). The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the drug product. |

**A. Selection of batches**

Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing.

**B. Bracketing and matrixing**

During the design of stability studies, bracketing and matrixing may be used to achieve reduced testing while at the same time generating enough stability data for evaluation of shelf-life. In bracketing, the design may include reduction in storage and sampling of dosage strengths or container closure configuration. Eg: In a three – batch stability study with dosage strengths of 50, 75, and 100 mg in 15 ml , 100 ml , and 150 ml high - density polyethylene (HDPE) containers, testing for 50 mg and 100 mg strengths in 15 ml and 150 ml container sizes may be adequate with no testing proposed for the 75 mg strength.

**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.

**Matrixing Designs**

**1. One half reduction**

In one-half design only half the number of batches is selected for full study at a point, and another half of the batches will be selected for full study in the next point and so on.

**2. One third reduction**

In one-third design removes one in every three batches (2 in 6) for full study at a point, and another half of the batches will be selected for full study in the next point.

**Table 5: Bracketing design of stability study**

| Dose strength | | 50mg | | | 75mg | | | 100mg | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Batch | | $B_1$ | $B_2$ | $B_3$ | $B_4$ | $B_5$ | $B_6$ | $B_7$ | $B_8$ | $B_9$ |
| Container size | 15 ml | T | T | T | | | | T | T | T |
| | 100 ml | | | | | | | | | |
| | 150 ml | T | T | T | | | | T | T | T |

T=Sample tested

**Table 6: One-half reduction matrixing design of stability study**

| Time point (months) | | | 0 | 3 | 6 | 9 | 12 | 18 | 24 | 36 |
|---|---|---|---|---|---|---|---|---|---|---|
| STRENGTH | $S_1$ | Batch 1 | T | T | | T | T | | T | T |
| | | Batch 2 | T | T | | T | T | T | | T |
| | | Batch 3 | T | | T | | T | T | | T |
| | $S_2$ | Batch 1 | T | | T | | T | | T | T |
| | | Batch 2 | T | T | | T | T | T | | T |
| | | Batch 3 | T | | T | | T | | T | T |

S1 and S2 are two different strengths; T= samples tested

**Table 7: One- third reduction matrixing design of stability study**

| **Time point (months)** | | | **0** | **3** | **6** | **9** | **12** | **18** | **24** | **36** |
|---|---|---|---|---|---|---|---|---|---|---|
| STRENGTH | $S_1$ | Batch 1 | T | T | | T | T | | T | T |
| | | Batch 2 | T | T | T | | T | T | | T |
| | | Batch 3 | T | | T | T | T | T | T | T |
| | $S_2$ | Batch 1 | T | | T | T | T | T | T | T |
| | | Batch 2 | T | T | | T | T | | T | T |
| | | Batch 3 | T | T | T | | T | T | | T |

S1 and S2 are two different strengths; T= samples tested

**Table 8: Storage conditions for drug product**

| **Stability study type** | **Stability storage conditions** | **Minimum time period covered by data at submission(months)** |
|---|---|---|
| Marketed drug product intended for storage at room temperature | | |
| Long term | 25 ° C ± 2 ° C, 60% RH ± 5%RH or 30 ° C ± 2 ° C, 65% RH ± 5% RH | 12 |
| Intermediate | 30 ° C ± 2 ° C, 65% RH ± 5% RH | 6 |
| Accelerated | 40 ° C ± 2 ° C, 75% RH ± 5% RH | 6 |
| Marketed drug products packaged in semi permeable containers | | |
| Long term | 25 ° C ± 2 ° C, 40% RH ± 5% RH or 30 ° C ± 2 ° C, 35% RH ± 5% RH | 12 |
| Intermediate | 30 ° C ± 2 ° C, 65% RH ± 5% RH | 6 |
| Accelerated | 40 ° C ± 2 ° C, no more than 25% RH | 6 |
| Marketed drug products intended for storage in refrigerator | | |
| Long term | 5 ° C ± 3 ° C | 12 |
| Accelerated | 25 ° C ± 2 ° C, 60% RH ± 5% RH | 6 |
| Marketed API intended for storage in freezer | | |
| Long term | − 20 ° C ± 5 ° C | 12 |

**C. Storage conditions**

The ICH guidance document (Q1A) (R2) provides information on storage conditions and testing frequency for the drug products under six intended storage conditions:

**1.** General case (room temperature)

**2.** Drug products packaged in impermeable containers.

**3.** Drug products packaged in semi permeable containers.

**4.** Drug products intended for storage in refrigerator.

**5.** Drug products intended for storage in freezer.

**6.** Drug products intended for storage below -20$^{o}$C.

1. **Drug Products Packaged in Impermeable Containers:** For drug products packaged in impermeable containers that provide a permanent barrier, moisture or solvent loss is not a concern and for such products stability studies can be conducted under any controlled or ambient humidity conditions.

2. **Drug Products Packaged in Semipermeable Containers:** Stability studies for aqueous - based drug products packaged in semipermeable containers (containers that allow the passage of solvent, usually water, while preventing solute loss) should be conducted under conditions of low relative humidity and temperatures. Stability attributes such as potential water loss and physical, chemical, biological, and microbiological stability should be evaluated. If long - term storage studies are conducted at 25 ° C ± 2 ° C, 40% RH ± 5% RH and a significant change other than water loss occurs during the six months testing at the accelerated storage condition (40 ° C ± 2 ° C, 75% RH ± 5% RH),

testing for established stability specifications at the intermediate storage condition (30 ° C ± 2 ° C, 65% RH ± 5% RH) should be conducted to evaluate the effect of 30 ° C. While a significant change in water loss (5% water loss from initial value) alone under accelerated storage conditions need not prompt testing of samples under the intermediate storage condition, water loss through the proposed shelf life should be monitored to ensure that the drug product has no significant water loss during long -term storage at 25 ° C ± 2 ° C, 40% RH ± 5% RH.

3. **Drugs intended for storage in refrigerator:** For a drug product intended for storage in a refrigerator, if a significant change occurs between three and six months testing at the accelerated storage condition of 25$^{o}$C ± 2$^{o}$C, 60% RH ± 5% RH, the proposed retest period should be based on the real - time data available at the long-term storage condition of 5$^{o}$C±3$^{o}$C.

   If a significant change occurs within three months at the accelerated storage condition, the effect of short - term excursions outside the label storage condition during shipping or handling should be discussed.

4. **Marketed Drug Products Intended for Storage in Freezer:** For a drug product with intended storage in a freezer, the retest period should be based on the real – time data available at the long - term storage condition of – 20$^{o}$C ± 5$^{o}$C. Since no accelerated storage condition for a freezer - stored API is proposed, storage and testing of a single batch at elevated temperatures of 5$^{o}$C ± 3$^{o}$C or 25$^{o}$C ± 2$^{o}$C for an appropriate time period should be considered to understand the effect of short - term excursions outside the label storage condition during shipping or handling

**D. Testing Frequency**

**Table 9: Testing frequency for drug product**

| Study type | Testing frequency |
|---|---|
| Long term | For Every 3 months over 1$^{st}$ year<br>For every 6 months over 2$^{nd}$ year<br>Annually thereafter |
| Accelerated | For 6 month studies a minimum of 3 time point is recommended (i.e. at 0, 3, 6 months) |
| Intermediate | For 12 months study, samples are tested at 0, 6, 9, 12 months |

**E. Stress studies and stability - indicating methods for analysis of drug product stability:**

Appropriate physical, chemical, biological, and microbiological attributes, antimicrobial preservative and antioxidant content, and dosage functionality test (eg: dose delivery system) of the drug product that are likely to be susceptible to change during storage and are likely to influence quality, safety, and efficacy should be tested. The analytical testing performed to evaluate the stability of the drug product should be validated and stability indicating. Impurities and degradants of the active ingredient and drug product excipients should not interfere with the quantitation of the active ingredient in the drug product.

**F. Stability commitment for drug product**

1. If, at the time of approval long - term stability data for the primary batches do not cover the proposed shelf life, a commitment should be made to continue the stability studies post approval to firmly establish shelf-life of drug product and 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 these studies through the proposed shelf life and the accelerated studies for 6 months and to place additional production batches for a total of three and generate data through the proposed shelf life period.

3. If the submission does not include stability data on the 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.

**G. Specification (testing parameters)**

**1. General tests for new drug products**

a. Description

b. Identification

c. Assay

d. Impurities

**2. Specific tests for some common drug products**

**H. Storage statement and labeling**

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug product. There should be a direct link between the label statement and the demonstrated stability characteristics of the drug product.

General precautionary statement may be included, but should not be used for the purpose to cover stability problem.

**Table 10: Specific test for some common drug products**

| Dosage form | Tests |
|---|---|
| Tablet (coated and uncoated), hard gelatin capsules, small gelatin capsules (few tests are applicable) | Dissolution, disintegration, hardness, friability, uniformity of dosage units, water content, microbial limits |
| Soft gelatin capsules | Dissolution (or disintegration, if justified), microbial bioburden, pH, leakage, and pellicle formation. |
| Emulsions | Phase separation, pH, viscosity, microbial bioburden, mean size and distribution of dispersed globules. |
| Oral liquids and suspensions | pH, microbial limits, antimicrobial preservative content, antioxidant preservative content, extractables, alcohol content for alcohol containing preparations, particle size distribution and dissolution for oral suspensions and dry powder products for resuspension and also redispersibility. |
| Parenteral drug products | pH, sterility, endotoxins, particulate matter, water content, antimicrobial preservative content, antioxidant properties, extractables, osmolarity, particle size distribution and re-dispersibility and reconstitution time for injectable suspensions. |
| Suppositories | Softening range, dissolution at 37 ° C. |
| Transdermal patches | *In vitro* release rates, leakage, microbial bioburden/ sterility, and peel and adhesive forces. |
| Metered dose inhalers and nasal aerosols. | Content uniformity, aerodynamic<br>particle size distribution, microscopic evaluation, water content, leak rate,<br>microbial bioburden, valve delivery, extractables, leachables from plastic and elastomeric components. |

**Table 11: Storage statement and labelling**

| Storage condition | Storage statement |
|---|---|
| Room temperature | "Store below $30^0$ C" or "Store below $25^0$ C" if deemed essential in some cases. |
| Refrigerator | "Store in refrigerator, between $2^0$C and $8^0$ C". |
| Freezer | "Store in freezer between – $5^0$ C and – $20^0$C". |

**Table 12: General precaution statement for storing drug product**

| Stability problem | Precautionary statement<br>The label should state: |
|---|---|
| For drug products that cannot tolerate refrigerating | "Do not refrigerate" |
| For drug products that cannot tolerate freezing | "Do not freeze" |
| For light sensitive drug products | "Store in original pack to protect from light" |
| For drug products sensitive to humidity | "Store in a dry place |

**Table 13: Climatic zones and their corresponding long term storing conditions**

| Climatic zone | Definition | Mean annual temperature | Long term testing condition[ temperature ($^0$ C) and RH] |
|---|---|---|---|
| I | Temperate climate | ≤ 15 ° C | > 21 ° C, 45% RH |
| II | Subtropical and Mediterranean climate | > 15 – 22 ° C | > 25 ° C, 60% RH |
| III | Hot and dry climate | > 22 ° C | > 30 ° C, 35% RH |
| IVA | Hot and humid climate | > 22 ° C | > 30 ° C, 65% RH |
| IVB | Hot and very humid climate | > 22 ° C | > 30 ° C, 75% RH |

If applicable, recommendations should also be made as to the utilization period and storage conditions after opening and dilution or reconstitution of a solution, for example an antibiotic injection supplied as a powder for reconstitution.

**III. Assignment of climatic zones and recommended storage conditions**

As per ICH QIF guidance the long -term storage condition for climatic zones I and II is 25$^o$C ± 2$^o$C, 60% RH ± 5% RH, and the intermediate storage condition for climatic zones I and II is 30$^o$C ± 2$^o$C, 65% RH ± 5% RH. It

also stated that the storage condition of 30°C ± 2°C, 65% RH ± 5% can also be a suitable alternative for the long - term storage condition of 25°C ± 2°C, 60% RH ± 5% RH for climatic zones I and II, in which case no intermediate condition is required. For climatic zones III and IV, the Q1F guidance suggested using 30°C ± 2°C, 65% RH ± 5% (for products intended to be stored at room temperature; general case stated in the guidance) as the long - term storage condition (12 months) with accelerated storage at 40°C ± 2°C, 75% RH ± 5% (6 months), and further no intermediate storage condition was recommended for climatic zones III and IV.

## CONCLUSION

Studies on the stability of pharmaceutical products provide information on how the quality of APIs, and drug products varies with time under the influence of various environmental factors such as temperature, humidity, and light which helps to determine shelf life and recommended storage conditions for the life cycle of products.

Good manufacturing practice regulations require that stability studies on pharmaceutical products be conducted and shelf life be determined based on the results from stability studies. Accelerated stability studies at elevated temperature and humidity and long - term stability studies at more moderate temperature and humidity conditions are performed during drug development and approval process to predict the shelf life of pharmaceutical products. The proposed shelf life is then confirmed by performing long - term studies for the duration of the shelf life or longer. Stress studies using acid, base, temperature, oxidation, and light stresses are conducted to predict the degradation products that may be formed during the accelerated and/or long - term studies and to develop stability – indicating methods required for stability evaluation. Photo-stability and temperature studies also help determine the packaging configuration as well as make recommendations for storage conditions during the shelf life. For a realistic assessment of shelf life in diverse climates that exist around the world, five climatic zones are identified and the long - term storage condition for shelf life determination in these climatic zones is based on humidity and temperature conditions likely to prevail in those climatic zones. Quality parameters for evaluation of stability of pharmaceutical products depend on the chemical nature of the active ingredient being studied as well as the type of dosage form of the drug product.

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