

# A REVIEW ON STABILITY TESTING OF FINISHED PHARMACEUTICAL PRODUCTS

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**Abstract:** For FPPs intended for storage in a freezer, the shelf life should be based on the long-term data obtained at the long-term storage condition. In the absence of an accelerated storage condition for FPPs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g.  $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$  or  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  or  $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ ) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition. Stability is defined as the extent to which a product retains within specified limit and throughout its period of storage and use (i.e. throughout its shelf life), the same properties and characteristics (i.e. chemical, physical and microbiological) that it possessed at the time of its manufacture.

The stability of the finished pharmaceutical product depends on several factors like environmental factors which include ambient temperature, humidity and light, product related factors such as the chemical and physical properties of the active substance and pharmaceutical excipients, the dosage forms and its composition, the manufacturing process, the nature of the container- closure system and the properties of the packaging material.

**Keywords:** Stability Studies, Finished pharmaceutical product, Shelf Life, Storage Conditions, in-use and hold time stability.

## STABILITY

The term drug stability can be defined as an extent to which a drug substance or product maintains the same properties and characteristics that it possessed at the time of its manufacture, within specified limits and throughout its period of storage and use. Stability is generally classified into chemical, physical, microbiological, therapeutic, and toxicological. [Anissa W. Wong 2005]

## FINISHED PHARMACEUTICAL PRODUCT

“Finished pharmaceutical product (FPP) is a product that has endured all the stages of production, comprising packaging in its final container and labeling.”

One or more active pharmaceutical ingredients may be contained by a finished pharmaceutical product.

Actually the design of the stability studies for the FPP should be depend on familiarity of the behaviour and properties of the API, information from stability studies on the API and on evidence gained from preformulation studies, similar marketed formulations and investigational FPPs. The likely changes during storage and the rationale for the selection of attributes to be tested in the stability studies should be stated.

## STRESS TESTING

Stress testing (of the finished pharmaceutical product (FPP)): Studies undertaken to assess the effect of severe conditions on the FPP. Alike studies include photo stability testing and specific testing on certain products (e.g. refrigerated aqueous liquid products metered-dose inhalers, creams, emulsions,)

Photo stability testing, which is an integral part of stress testing, should be conducted on at least one primary batch of the FPP if appropriate. Further stress testing of specific types of dosage forms may be apt, e.g. freeze–thaw studies for liquid products or cyclic studies for semi-solid products.

## SELECTION OF BATCHES

For FPPs containing new APIs, data from stability studies should be provided on at least three primary batches of each proposed strength of the FPP. Two of the three batches should be at least pilot-scale batches and the third batch can be smaller, if justified. Unless bracketing or matrixing is applied Stability studies should be performed on each individual strength, dosage form and container type and size of the FPP.

## CONTAINER-CLOSURE SYSTEM

The dosage form packaged in the primary container-closure systems proposed for marketing should be tested for stability. If the secondary container-closure system has protective properties, and labeling clearly indicates that the product is to be stored in the primary and secondary packaging (e.g. “tablets should be stored in blisters in the issued cartons”), or if the product is packaged in a semi-permeable container where components from the secondary packaging can wander into the product, the secondary packaging may also form part of the Packaging system for stability samples.

## SPECIFICATION

Stability studies should include testing of stability-indicating aspects of the FPP, i.e. those that are vulnerable to change during storage and are likely to affect quality, safety and/or efficacy. The testing should cover the physical, chemical, biological and microbiological aspects, preservative content and functionality tests.

Analytical procedures should be fully validated and should indicate the stability. The results of validation studies decide whether and to what extent replication should be performed.

Consideration of all available stability information derives the Shelf-life acceptance criteria. It may be relevant to have admissible differences between the shelf-life and release acceptance criteria based on the stability evaluation and the deviations observed on storage. Deviation between shelf-life acceptance criteria and the release for antimicrobial preservative content should be assisted by a validated correlation of preservative effectiveness and chemical content demonstrated during development of the pharmaceutical product with the product in its final intended for marketing. For effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf life for verification purposes, A single primary stability batch of the FPP should be tested, despite of the difference between the release and shelf-life acceptance criteria for preservative content.

## TESTING FREQUENCY

For long-term studies, to establish the stability profile of the FPP, frequency of testing should be sufficient. The frequency of testing at the long-term storage condition should normally be conducted every three months over the first year, every six months over the second year and annually thereafter throughout the proposed shelf life for products with a proposed shelf life of at least 12 months. A least possible of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six-month study is commended for the accelerated storage condition. An assumption results from accelerated testing are likely to access significant change criteria, testing should be increased either by including a fourth time point in the study design or by compute samples at the final time point.

If testing at the intermediate storage condition is termed for as a result of important change at the accelerated storage condition, a least possible of four time points, including the initial and final time points (e.g. 0, 6, 9 and 12 months), from a 12-month study is commended.

The commencing date of storage should be considered  $t_0$  and stability time points should be defined as a date with respect to  $t_0$ . For example, if  $t_0$  is 1 January 2020 then the one-month time point corresponds to either 1 February or 31 January 2020. Samples should be withdrawn and tested as per the protocol for each time point. Testing should be finished as soon as possible. Differences from the protocol should be recorded and justified.

## STORAGE CONDITIONS

In the target countries Stability data must demonstrate stability of the medicinal product in every part of its intended shelf life under the climatic conditions. Only applying the same requirements apt to other markets could potentially result into substandard products if stability studies are conducted at the storage conditions for countries in Climatic Zone I/II when the products are supplied in countries in Climatic Zones III and IV. Above all an FPP should be assessed under storage conditions with specified forbearances that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The lengths of studies chosen and the storage conditions should be sufficient to cover storage, shipment and consequent use with expected concern to the climatic conditions in which the product is planned to be marketed.

Storage condition tolerances are defined as the acceptable deviations in RH and temperature of storage facilities for stability studies. The equipment used should be capable of regulating the storage conditions inner the ranges given in these guidelines. The storage conditions should be checked and documented. Short-term environmental changes due to opening of the doors of the storage facility are accepted as impending. The effect of excursions due to equipment failure should be figured, addressed and noted if judged to affect stability results. Jaunt that exceeds the defined tolerances for more than 24 hours should be described in the report study and their effects evaluated. At the time of submission, the long-term testing should cover a minimum of six months for FPPs containing existing APIs or 12 months for FPPs containing new should be continued for a period of time sufficient to cover the recommended shelf life. Long-term, accelerated and, where apt, intermediate storage conditions for FPPs are detailed in the sections below. The general case applies if the FPP is not specifically covered by a subsequent section. Radical storage conditions can be used if justified.

Table no.1: storage conditions

Study	Storage condition	Minimum time period covered by data at submission
Long-term <sup>a</sup>	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12 months or 6 months
Intermediate <sup>b</sup>	30 °C ± 2 °C/65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

a. Whether long-term stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is determined by the climatic zone in which the FPP is intended to be marketed. Testing at a more severe long-term condition can be an alternative to storage at 25 °C/60% RH or

30 °C/65% RH.

b. If 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are operated at 25 °C ± 2 °C/60% RH ± 5% RH and “eloquent change” occurs at any time during 6 months’ testing at the accelerated storage condition, further testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The commencing application should include a minimum of six months’ data from a 12-month study at the intermediate storage condition.

In general, “eloquent change” for an FPP is defined as:

- A deviation from the initial content of API(s) of 5% or more detected by assay, or inadequacy to meet the compliance criteria for potency when using biological or immunological procedures;
- Any degradation product exceeding its acceptance criterion; Inability to meet the acceptance criteria for appearance, physical attribute and functionality test (e.g. color, phase separation, resuspendability, caking, hardness, and dose delivery per actuation). Anyhow, some changes in physical attributes may be expected under accelerated conditions. Also, as appropriate for the dosage form.
- Inadequacy to meet the acceptance criterion for pH; or
- Inadequacy to meet the acceptance criteria for dissolution for 12 dosage units.

#### FPPS PACKAGED IN IMPERMEABLE CONTAINERS

Criterion needed for the classification of the packaging materials as permeable or impermeable solely depend on the characteristics of the packaging material, such as thickness, sealing and permeability coefficient. The propriety of the packaging material used for a particular product is determined by its product characteristics. Containers which are considered to be moisture-impermeable include glass ampoules. Sensitivity to moisture or potential for solvent loss is not a concern for FPPs packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus stability studies for impermeable containers containing product can be conducted under any controlled or ambient RH condition.

#### FPPS PACKAGED IN SEMI-PERMEABLE CONTAINERS

Aqueous-based products packed in semi-permeable containers should be assessed for potential water loss in addition to physical, chemical, biological and microbiological stability. This evaluation can be executed under conditions of low RH. Conclusively it should be demonstrated that aqueous based FPPs stored in semi-permeable containers could withstand environments with low RH. Other comparable accesses can be developed and reported for non aqueous, Solvent-based products.

Table no.2: fpps packaged in semi-permeable containers

Study	Storage condition	Minimum time period covered by data at submission
Long-term <sup>a</sup>	25 °C ± 2 °C/40% RH ± 5% RH or 30 °C ± 2 °C/35% RH ± 5% RH	12 months or 6 months
Intermediate <sup>b</sup>	30 °C ± 2 °C/35% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/not more than (NMT) 25% RH	6 months

a. Whether long-term stability studies are performed at 25 °C ± 2 °C/40% RH ± 5% RH or 30 °C ± 2 °C/35% RH ± 5% RH is determined by the climatic condition under which the FPP is intended to be marketed. Testing at 30 °C/35% RH can be an alternative to the storage condition at 25 °C/40% RH.

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

#### FPPS INTENDED FOR STORAGE IN A REFRIGERATOR

Table no.3: fpps intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5 °C ± 3 °C	12 months or 6 months
Accelerated <sup>a</sup>	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 months

a. Whether accelerated stability studies are performed at  $25\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$  or  $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$  or  $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$  is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to the storage condition at  $25\text{ }^{\circ}\text{C}/60\% \text{ RH}$  or  $30\text{ }^{\circ}\text{C}/65\% \text{ RH}$ .

#### FPPS INTENDED FOR STORAGE IN A FREEZER

Table no.4: fpps intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long-term	$-20\text{ }^{\circ}\text{C} \pm 5\text{ }^{\circ}\text{C}$	12 months or 6 months

#### FPPS INTENDED FOR STORAGE BELOW $-20\text{ }^{\circ}\text{C}$

FPPs intended for storage at temperatures below  $-20\text{ }^{\circ}\text{C}$  should be treated on a case-by-case basis.

#### STABILITY COMMITMENTS

One or more of the following devours should be made.

- A commitment should be made to continue the stability studies post approval throughout the proposed shelf life when the available long-term stability data on primary batches do not cover the proposed shelf life acknowledged at the time of approval. This is the primary batch stability commitment.
- A commitment should be made to place the next production batches, up to a total of at least three, on long-term stability studies throughout the proposed shelf life and on accelerated studies for six months. If the submission comprise data from stability studies on less than three production batches. This is the production batch stability commitment.
- An ongoing stability programme is needed to monitor the product over its shelf life and to determine that the product remains and can be expected to remain within specifications under the storage conditions on the label for each product. This is the ongoing stability commitment.

The stability protocol used for studies on commitment batches should be the same as for the primary batches, unless otherwise scientifically justified.

#### EVALUATION

The primary stability programme should be reported in a written protocol and the outcomes presented in a formal report. An organized way should be endorsed to the presentation and evaluation of the stability data, which should comprise, as appropriate, results from the chemical, physical, microbiological and biological tests, including particular attributes of the dosage form.

#### STATEMENTS AND LABELLING

A storage description should be vested for the label based on the stability evaluation of the FPP. Where suitable, specific instructions should be provided, particularly for FPPs that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” should be averting. There should be unambiguous storage statement on the label and the demonstrated stability of the FPP. The container label should have a expiry date.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for deficient or menial packaging. Further labeling statements could be used in cases where the results of the stability testing demonstrate limiting factors.

#### IN-USE AND HOLD TIME 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. Examples include an antibiotic injection supplied as a powder for reconstitution, or a moisture-sensitive or hygroscopic solid oral FPP in a large format multidose container (e.g. high density polyethylene (HDPE) bottle of 500 tablets). In general, a month in-use period is normally considered acceptable without any further supporting data.

The physical, chemical and microbial properties of the FPP that are 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 FPP remaining in the container. Specific parameters, e.g. for liquids and semisolids: the content and effectiveness of preservatives need to be studied.

#### Variations

Once the FPP has been registered, additional stability studies are required whenever variations are made that may affect the stability of the API or FPP. The applicant should investigate whether or not the intended change will have an impact on the quality characteristics of APIs and/or FPPs and consequently on their stability. The scope and design of the stability studies for variations are based on the knowledge and experience acquired on APIs and FPPs.

The results of these stability studies should be communicated to the regulatory authorities concerned, following the applicable requirements stipulated in the variation guidelines for the region.



## ONGOING STABILITY STUDIES

After a marketing authorization has been granted, the stability of the FPP should be appropriately monitored according to a continuous programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products or dissolution profile) associated with the formulation in the container closure system in which it is marketed. The aim of the ongoing stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the storage requirements on the label.

## CONCLUSION

The purpose of stability testing is to provide evidence of how the quality of finished pharmaceutical products (FPP) varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability testing program also includes the study of product-related factors that influence its quality, for packaging materials. The purpose of the stability study is to establish, based on testing a minimum number of batches of the FPP, a shelf life and label storage instructions applicable to all future batches of the FPP manufactured and packaged under similar circumstances. The degree of deviations of individual batches affects the certainty that a future production batch will remain within specification all through its shelf life. As a result of stability testing, a shelf life for the FPP can be established and storage conditions can be recommended and hence stability testing is a very important parameter.

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