

Introduction

The following guidelines set out information on stability testing for registration application within the Arab Countries and other areas of the world, where applicable. The guidelines seek to exemplify the core stability data package appropriate for new products or new formulation of existing drug substances. It is not always necessary to follow these when there are scientifically justifiable reasons for using alternative approaches.

The guidelines provide a general indication of the information on product stability to be generated, but leave sufficient flexibility to encompass the variety of different practical situations required for specific scientific situations and characteristics of the materials being evaluated.

The principle is that information on stability generated in any of the Arab Countries would be mutually acceptable in the other countries, provided it conforms to the elements of these guideline and the labeling is in accord with national/regional requirements.

1. OBJECTIVES

The purpose of stability testing is to provide evidence on how the quality of drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light.

The evidence will form the basis for recommending storage conditions, suitable container and closure system and establishing shelf life for the finished products.

2. DEFINITIONS AND INFORMATION

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

Accelerated Stability Testing

Studies designed to increase the rate of chemical degradation and/or physical change(s) of a drug product by using exaggerated storage conditions with the purpose of monitoring degradation reactions, to evaluate the impact of short term excursions outside the labelled storage conditions such as might occur during shipping and predicting the shelf-life under normal storage conditions. The design of accelerated studies may include elevated temperature, high humidity and intense light, low temperature and freeze/thaw cycling, as appropriate.

Such test conditions are also applied to provide comparative evidence in short-term experiments of the equivalence of pharmaceutical products from various sources, such as those made by different manufacturers, processes, procedures, packaging, or where volumes and strengths of drug products are changed.

Batch (Lot)

A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity.

Note: It may be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

Bracketing

The design of a stability schedule so that at any time point only the samples on the extremes, for example, of container size and/or dosage strengths, are tested. The design assumes that the stability of the intermediate condition samples is represented by those at the extremes.

Where a range of dosage strengths is to be tested, bracketing designs may be particularly applicable if the strengths are very closely related in composition (e.g. for a tablet range made with different compression forces 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). Where a range of sizes of immediate containers is to be evaluated, bracketing designs may be applicable if the material of composition of the container and the type of closure are the same throughout the range.

Climatic Zones

The concept of dividing the world into four zones based on defining the prevalent annual climatic conditions. Four climatic zones can be distinguished for the purpose of worldwide stability testing :

Zone I: Temperate.

Zone II: Sub-tropical with possible high humidity.

Zone III: Hot / dry.

Zone IV: Hot / humid.

Climatic Zone	Calculated Data			Derived Storage Condition ¹ (for Real Time Studies)	
	[°C]	[°C MKT] ²	[%R.H.]	[°C]* ± 2°C	[%R.H.]± 5%
I	20.0	20.0	42	21	45
II	21.6	22.0	52	25	60
III	26.4	27.9	35	30	35
IV	26.7	27.4	76	30	60

Commitment

A signed statement accompanying an application for product registration to conduct or complete prescribed studies and obtain data on commercial production batches after approval of an application.

Commitment Batches

Production batches of a drug product for which the stability studies will be initiated or completed post approval through a commitment made in the registration application.

Container Closure System

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

Drug Substance

The unformulated drug substance which may be subsequently formulated with excipients to produce the drug product.

Dosage Form; Preparation

A pharmaceutical product type, for example tablet, capsule, solution, cream etc. that contains a drug ingredient generally, but not necessarily, in association with excipients.

Drug Product; Finished Product

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

Excipients

Any ingredient other than the drug substance in the dosage form.

¹ Grimm W. storage conditions for stability testing in the E.C., Japan and USA; the most important markets for drug products. *J. Drug Development and Industrial Pharmacy*, 19:2795-2830, 1993.

² Mean Kinetic Temperature.

Expiry/Expiration Date

The date placed on the container/labels of a drug product written in month/year designating the time during 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.

Formal Stability Studies

Long-term and accelerated (and intermediate) studies undertaken on primary and /or commitment batches according to a prescribed stability protocol to establish or confirm the retest period of a drug substance or the shelf life of a drug product.

Good Manufacturing Practice(GMP)

Is that part of Quality Assurance aimed at ensuring that products are consistently manufactured to the quality appropriate to their intended use and as required by marketing authorization. It is thus concerned with both production and quality control.

Impermeable Containers

Container which provide a permanent barrier to the passage of gases or solvents.

Long-Term (Real-Time) Stability Testing

Stability evaluation of the physical, chemical, biological and microbiological characteristics of a drug product covering the expected duration of the shelf life which is claimed in the submission and will appear on the labeling.

Matrixing

The statistical design of stability schedule so that only a fraction of the total number of samples is tested at any specified sampling point. At a subsequent sampling point, different sets of samples of the total number would be tested. The design assumes that the stability of the samples tested represents the stability of all samples. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container and closure and possibly, in some cases, different container/closure systems.

Matrixing can cover reduced testing when more than one variable is being evaluated. Thus the design of the matrix will be dictated by the factors needing to be covered and evaluated. This potential complexity precludes inclusion of specific details and examples, and it may be desirable to discuss design in advance with the regulatory authority, where this is possible. In every case, it is essential that all batches be tested initially and at the end of the long-term testing.

Mean Kinetic Temperature

A single derived temperature which if maintained over a defined period would afford the same thermal challenge to a drug product as would have been experienced over a range of both higher and lower temperature for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.

When establishing the mean kinetic temperature for a defined period, the formula of J.D. Haynes (*J. Pharma. Sci.*, 60:927-929, 1971) can be used.

On Going Stability Testing

It is the post-marketing stability testing carried out by the manufacturer on production batches according to pre-determined schedule in order to confirm the projected shelf life of the product.

Photostability

The intrinsic photostability characteristics of drug products should be evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable change(s). Normally, photostability testing is carried out on a single batch of material selected.

Pilot Scale

The manufacture of a drug product by a procedure fully representative of and simulating that to be applied on a production batch. For oral solid dosage forms this is generally taken to be at a minimum scale of one-tenth that of the full production scale.

Post Approval Changes

Those changes encountered after a drug application is approved, e.g. composition of the product, site of manufacture, scale-up/scale-down of manufacture and manufacturing process and equipment.

Primary batch

A batch of drug product used in a formal stability study, from which stability data are submitted in a Registration Application for the purpose of establishing a shelf life, respectively. Two of the primary batches should be at least pilot scale and the third may be smaller, but it may be a production batch.

Semi-permeable Containers

Containers which allow the passage of solvents, 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 or semi-rigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), LDPE ampules, bottles, and vials.

Shelf-life; Expiration Dating Period

The time interval that a drug product is expected to remain within the approved shelf-life specification provided that it is stored under the conditions defined on the label in the proposed container and closure.

Specification-Release

The combination of physical, chemical, biological and microbiological acceptance criteria and test requirements that determine a drug product is suitable for release at the time of its manufacture.

Specification- Shelf-life

The combination of physical, chemical, biological and microbiological acceptance criteria and test requirements that a drug product must meet throughout its shelf life.

Stability

The ability of a drug product to retain its properties within specified limits throughout its shelf life. The chemical, physical and microbiological aspects of stability are to be considered.

Stability Indicating Methods

Quantitative analytical methods that distinguish drug substance from its degradation products and related substances and interfering excipients in a drug product so that the drug substance content can be accurately measured.

Stability Study Protocol

The detailed plan applied to generate and analyze acceptable stability data in support of the expiration-dating period. It may also be used in developing similar data to support an extension to the expiration-dating period.

Stability Tests

Stability tests are a series of tests designed to obtain information on the stability of a drug substance or a drug product for the determination of its shelf life and utilization period under specified packaging and storage conditions.

Strength

The concentration of the drug substance (for example weight/weight, weight/volume, or unit dose/volume basis), and/or the potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory test or by adequately developed and controlled clinical data (expressed for example, in terms of units by reference to a standard).

Stress Testing

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

Supporting Stability Data

Supplementary data, such as stability data on small scale batches, related formulations or higher temperature, products presented in containers other than those proposed for marketing and other scientific rationale that support the analytical procedures, the proposed shelf-life and storage conditions.

Tentative Expiration Dating Period (Tentative Shelf Life)

A provisional expiration-dating period determined by extrapolating data from accelerated studies for the drug product to be marketed in the proposed container-closure.

Utilization Period

A period of time during which a reconstituted preparation or the preparation in an opened multidose container can be used.

Validation

The documented act of proving that any procedure, process, equipment, material, activity, or system actually consistently leads to expected results.

3. PURPOSE OF STABILITY TESTING

The main objectives of stability testing are shown in the table below.

Objective	Type of study	For use in
* To select adequate (from the view-point of stability) formulations and container-closure systems	Accelerated	Development of product
* To determine shelf-life and storage conditions	Accelerated and/or long term	Development of product and registration dossier
* To substantiate the claimed shelf-life	Long term	Registration dossier
* To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product	Accelerated and/or long term	Post approval changes and quality assurance in general, including quality control

3.1 In The Development Phase

Accelerated stability tests are carried out to compare alternative formulations, packaging materials, and/or the manufacturing process in short-term experiments. As soon as the final formulation and manufacturing process have been established, the manufacturer will carry out a series of accelerated studies which will permit prediction of the stability, and predetermine the tentative shelf-life and storage conditions of the drug product. Long term studies have to be started for confirmation. Suitable measures should be taken for the establishment of the utilization period for preparation in multidose containers, if appropriate.

3.2 For The Registration Dossier

The drug regulatory authority will require the manufacturer to submit information on the stability of the product derived from tests on the final dosage form in its final container and packaging. The data submitted are obtained from both accelerated and Long term studies. Published and/or recently obtained experimental supporting stability data may also be submitted, e.g. on the stability of drug substances and related formulations.

With the approval of the drug regulatory authority, a tentative shelf life is often established on the condition that additional information from first three production batches will be submitted after registration.

3.3 In The Post-Registration Period

The manufacturer will carry out on-going stability studies to substantiate the expiry date and the previously projected storage conditions. Stability data have to be submitted by the applicant and may be required at any time by the national health authorities. In the course of good manufacturing practice (GMP) inspection, their availability and validity are normally verified. To ensure the quality and safety of products with particular reference to degradation, national health authorities will monitor the stability and quality of preparations in the market through a follow-up inspection and testing programme.

Once the product has been registered, additional stability studies are required whenever major modifications are made to e.g. formulation, manufacturing process, packaging or method of preparation and site of manufacture (change in manufacturing site to different campus). These results should/must be communicated to the respective drug regulatory authorities.

4. DRUG PRODUCTS STABILITY STUDY PROTOCOL

The pharmaceutical industry is urged to adopt study protocols for accelerated, long term and on-going stability testing taking into account the followings:

- A.** The design of stability studies for the drug product should be based on the knowledge of properties and stability characteristics of drug substance(s).
- B.** The design of the stability testing programme needs to take into consideration the intended market and the climatic conditions of the area in which the drug product will be used.

A stability study is based on varying degrees of temperature, time, humidity, light intensity and partial vapour pressure, and their effects on the product in question. It should be pointed out that the effective or mean kinetic temperature reflects the actual situation more precisely than measured mean temperature, i.e. there is a difference between a product being kept for one month at 20°C and one month at 40°C, or two months at 30°C. Moreover, storage conditions often represent a higher temperature than the average meteorological data indicated for a country.

For some dosage forms, especially liquid and semi-solid dosage forms, the study design may also need to consider low temperatures, e.g. below zero (freezer, -10°C to -20°C), freeze-thaw cycles and temperatures between 2°C - 8°C (refrigerator). For certain preparations it is important to observe effects caused by their exposure to light.

4.1 Selection of Batches

- 4.1.1** For registration purposes, stability information from accelerated and long term studies is to be provided for three batches of the same formulation and dosage form in the containers and closure proposed for marketing. Two of the three batches should be at least pilot scale; the third batch may be smaller. The manufacturing process to be used should meaningfully simulate one which would be applied to large-scale batches for marketing. The process should provide a product of the same quality intended for marketing and meeting the same specifications as to be applied for the drug product to be released (release specifications). Where possible, batches of the finished product should be manufactured using identifiably different batches of drug substance. Photostability testing should be conducted on at least one batch of the product if appropriate.
- 4.1.2** For on-going studies, batches from current production should be sampled in accordance with a predetermined schedule. The following approach may be suggested :
- *one batch every other year may be tested for formulations considered to be stable (otherwise one batch per year); unless a major product change has been made, e.g. the formulation or the method of manufacture.*

4.2 Storage Conditions

Storage conditions are determined by the intended climatic zone in which the drug product will be distributed and used, as well as by the type of dosage form.

Stability of the drug product after reconstitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, 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 primary batches as part of the formal stability studies at initial and final time points and, if full shelf life long term data will not be available before submission, at 12 months or the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

The long term testing should cover a minimum of 6 months duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life.

Long term, accelerated and where appropriate intermediate storage conditions for drug products are detailed in the section below, alternative storage conditions are allowable if justified. If not covered by a subsequent section, a drug product should be considered as belonging to the general case.

4.2.1 General Case

Study	Storage Conditions	Minimum Time Period at Submission
Long term	25 ± 2°C / 60% RH ± 5% Zone I,II.	6 Months *
	30 ± 2°C / 35% RH ± 5% Zone III.	6 Months *
	30 ± 2°C / 60% RH ± 5% Zone IV.	6 Months *
Intermediate	30 ± 2°C / 60% RH ± 5%	6 Months**
Accelerated	40 ± 2°C / 75 % RH ± 5%	6 Months

* *This is only for generic drug products , while 12 months data for new drug products is to be submitted.*

** *This is applicable for zone I and II.*

Since there are few countries in zone I, the manufacturer would be well advised to apply climatic zone II conditions if he intends to market in temperate climates. For countries where certain regions are situated in zones III or IV, and also with the view to the global market, it is recommended that the stability-testing programme be based on conditions corresponding to climatic zone IV.

Where significant change(s) occur(s) in the course of accelerated studies, additional tests at intermediate conditions should be conducted. The initial registration application should then include a minimum of 6 months data from a 1-year study at the intermediate conditions, and 12 months from long-term stability data.

In general, ‘significant change’ is defined as:

1. A 5 percent change in assay from the initial value;
2. Any degradation product exceeding its acceptance criterion;
3. Failure to meet acceptance criteria for appearance, physical attributes, and functionality test (e.g., color , phase separation, resuspendability, delivery per actuation, caking, hardness, etc.); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams, suspension sedimentation, viscosity changes of suspension and emulsion, phase separation) may be expected under accelerated conditions; and as appropriate for the dosage form.
4. Failure to meet the acceptance criteria for pH; or
5. Failure to meet the acceptance criteria for dissolution for 12 dosage units.

If any parameter fails “significant change” during the accelerated stability study, testing of all parameters during the intermediate stability study should be performed.

If stability samples have been put into the intermediate conditions, but have not been tested, testing these samples may begin as soon as the accelerated study shows significant change in the drug product. Alternatively, the study at the intermediate condition would be started from the initial time point.

4.2.2 Products packed in impermeable containers.

Stability studies for drug products packed in impermeable containers may be conducted under any relative humidity. However, the same range of temperatures should be applied e.g. semisolids in sealed aluminium tubes and solutions in sealed glass ampules.

4.2.3 Products packed 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 humidity¹. Ultimately, it should be demonstrated that aqueous-based drug products stored in semi-permeable containers can withstand low relative humidity environments.

Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Study	Storage Conditions	Minimum Time Period at Submission
Long term	25 ± 2°C / 40% RH ± 5% zone I,II	6 Months *
Long term	30 ± 2 °C/ 60% RH ± 5% zone III,IV	6 Months *
Intermediate	30 ± 2°C / 60% RH ± 5%	6 Months
Accelerated	40 ± 2°C / NMT 25% RH	6 Months

* This is only for generic drug products, while 12 months data for new drug products is to be submitted.

4.2.4 Products intended for storage in a Refrigerator

Study	Storage Conditions	Minimum Time Period at Submission
Long term	5 ± 3°C	6 Months*
Accelerated	25 ± 2°C / 60% RH ± 5%	6 Months*

* This is only for generic drug products, while 12 months data for new drug products is to be submitted.

If significant change occurs between 3 and 6 months testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from 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 conditions, e.g., during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug product

¹ ICH Guideline on Stability Testing of New Drug Substances And Products. Recommended for Adoption under Step 4 of the ICH Process on 8 November 2000 by the ICH Steering Committee.

for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when an obvious significant change has occurred within the first 3 months.

4.2.5 Products intended for storage in a freezer

Study	Storage Conditions	Minimum Time Period at Submission
Long term	-20 ± 5°C	12 Months

For drug products intended for storage in a freezer, the shelf life should be based on the real time data presented at the long-term storage condition. In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, data from elevated temperature (e.g. 5°C ± 3°C or 25°C ± 2°C), on a single batch should be conducted to support use of the drug product outside of the proposed label storage condition.

4.2.6 Products intended for storage below -20°C

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

4.3 Commitment

When the available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, the studies should be continued post approval in order to firmly establish the shelf life.

Where the submission includes long-term storage data from three production batches covering the proposed shelf life, no post approval commitment is necessary. Otherwise the appropriate alternatives from those shown below should be followed:

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

4.4 Specifications

Shelf life acceptance criteria should relate to the release limits (where applicable) and should be derived from consideration of all available stability information. The shelf life specification could allow acceptable and justifiable deviation from the release specification based on the stability evaluation and the changes observed on storage. It will need to include specific upper limits for degradation products, the justification for which should be influenced by the levels observed in material used in preclinical studies and clinical trials if applicable. The justification for the limits proposed for certain other tests such as particle size and/or dissolution rate will require reference to the results observed for batch(s) used in bioavailability, bioequivalence and/or clinical studies. Any differences between the release and shelf life specification for antimicrobial preservatives should be supported by preservative efficacy testing.

4.5 Frequency of Testing

Schedules for the withdrawal of samples for analysis must be determined on the basis of prior knowledge and experience of the physicochemical stability properties of the active drug substance as evidenced by its time degradation profile. Hence, determination of the sampling schedule must be done so as to assure that significant measurements are not missed. Failing to do so would result in poor characterization of the drug's stability profile.

In the development phase and for studies in support of an application for registration, a reasonable frequency of testing is considered to be a time period of:

- For accelerated (storage conditions) studies 0 , 1 , 2 , 3 and 6 months;
- For intermediate (storage conditions) studies 0 , 3 , 6 , 9 , and 12 months;
- For long term (storage conditions) studies 0 ,3, 6 , 9,12 ,18 ,24 months and beyond that once a year (the use of matrixing or bracketing can be applied if justified).
- For on-going studies samples may be tested less frequently, e.g. at six-month intervals for the confirmation of provisional shelf life, or every 12 months for well established products.
- Highly stable formulation may be tested after the first 12 months and at the end of the shelf life.

4.6 Container Closure System

The stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing. Additional testing of unprotected drug product can form a useful part of the stress testing and pack evaluation, as can studies carried out in other related packaging materials in supporting the definitive pack(s).

4.7 Microbial Testing

4.7.1 Sterility

Sterile dosage forms in sealed glass ampoules:

The stability studies for this dosage form should include data from a sterility test of each batch at the beginning of the test period. For long-term (real-time) stability studies it is recommended to perform the sterility test at the end of shelf life.

Other Sterile drug products:

1. The accelerated stability studies for these products should include data from a sterility test of each batch at the beginning and at the end of the test period.
2. For long-term (real-time) stability studies, the sterility test should be performed initially and at the expiry, and it is recommended to do the test annually.

4.7.2 Preservative Effectiveness:

Both sterile and nonsterile drug products may contain preservative(s) or preservative system(s) to control bacteria and fungi that may be inadvertently introduced during manufacturing.

1. For accelerated stability study, data should include results from microbial challenge test conducted initially and at the end of study.
2. For long-term stability study, data from microbial challenge test should be included initially and at the expiry and at appropriate intervals during the stability period.
3. Chemical assays of preservative content should be performed at appropriate intervals.

4.7.3 Microbiological Limits for Nonsterile Drug Products.

Nonsterile drug products that have specified microbial limits for drug product release should be tested for conformance to the specified limits.

1. Accelerated stability studies should include data from a microbial limit test conducted initially, one month, 3 months and at the end of the study.
2. Long-term stability studies should include data from a microbial limit test conducted initially, annually, and at the expiry date.

4.7.4 Pyrogens and Bacterial Endotoxins

Drug products with specified limits for pyrogens and bacterial endotoxins should be tested for conformance to the specified limits.

Sterile dosage form in sealed glass ampoules:

The stability studies for this dosage form should include data from the test for pyrogens and/or bacterial endotoxins of each batch at the beginning of the test period. For long-term (real-time) stability studies it is recommended to perform the pyrogens test at the end of shelf life.

Other drug products:

1. The stability studies for these products should include data from the test for pyrogens and/or bacterial endotoxins of each batch at the beginning of the test period.
2. For long-term stability studies, conduct the test at the beginning and the end of the stability period.

4.8 Test Procedure and Test Criteria.

The testing should cover those features susceptible to change during storage and likely to influence quality, safety and / or efficacy. Analytical test procedures should be fully validated and the assays should be stability-indicating . The need for the extent of replication will depend on the results of validation studies.

The range of testing should cover not only chemical and biological stability but also loss of preservative, physical properties and characteristics, organoleptic properties and where required, microbiological attributes. Preservative efficacy and assay testing of stored sample should be carried out to determine the content and efficacy of antimicrobial preservatives.

4.9 Evaluation of Stability Data

The design of the stability study aims at establishing, based on testing a minimum of three batches of the drug product, a shelf-life and label storage instructions applicable to all future batches of the dosage form manufactured and packed under similar circumstances. A systematic approach should be adopted in the presentation and evaluation of the stability information which should cover as necessary physical, chemical, biological, and microbiological quality characteristics, including particular properties of the dosage form, e.g. dissolution rate for oral solid dosage forms.

Generally, an expiration dating is confirmed based on statistical analysis of observed long-term data. And any evaluation should consider not only the assay, but the levels of degradation products and appropriate attributes. Where appropriate, attention should be paid to review the adequacy of the mass balance, different stability and degradation performance. Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf-life will be granted, it is normally unnecessary to go through the formal statistical analysis but only to provide a justification for the omission. The method recommended in the following section can be used to establish with a high degree of confidence an expiration-dating period during which average drug product attributes of the batch will remain within specifications.

4.9.1 Expiration Dating Period for an individual batch:

The time during which a batch may be expected to remain within specifications depends not only on the rate of physical, chemical or microbiological changes, but also on the initial average testing value for the batch. Thus, information on the initial value for the batch is relevant to the determination of the allowable expiration dating period and should be included in the stability study report. Percentage from label claim, not percentage from initial average value, is the variable of interest.

An acceptable approach for analyzing an attribute that is expected to decrease with time is to determine the time at which the 95 percent one-sided lower confidence limit -also known as the 95 percent lower confidence bound- for the estimated curve intercepts the acceptable lower specification limit.

4.9.2 Expiration Dating Period for all batches:

If batch-to-batch variability is small, that is, the relationship between the parameter of interest such as assay or degradation products and time is essentially the same from batch to batch, stability data should be combined into one overall estimate. Combining the data should be supported by preliminary testing of batch similarity.

The similarity of the estimated curves among the batches tested should be assessed by applying statistical tests of the equality of slopes and of zero time intercepts. The level of significance of the tests, expressed in the *p-value*, should be chosen so that the decision to combine the data is made only if there is strong evidence in favor of combining. A *p-value* of 0.25 for preliminary statistical tests is recommended. If the tests for equality of slopes and for equality of intercepts do not result in rejection at a level of significance of 0.25, the data from the batches could be pooled. If these tests resulted in *p-values* less than 0.25, a judgment should be made as to whether pooling could be permitted.

The nature of the degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be presented by a linear, quadratic or cubic function, on an arithmetic or cubic function, on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches, and combined batches (where appropriate to the assumed degradation line or curve).

If it is inappropriate to combine data from several batches, the overall expiration-dating period will depend on the minimum time within which a batch may be expected to remain within acceptable limits.

Where applicable limited extrapolation of the real-time data beyond the observed range, may be undertaken to extend expiration dating at approval time, particularly where the accelerated data supports this. However, this assumes that the same degradation relationship will continue to apply beyond the observed data, and hence the use of extrapolation must be justified in each application in terms of what is known about the mechanisms of degradation, the goodness of fit of any mathematical model, batch size, existence of supportive data, etc.

The stability of the drug products, after reconstituting or diluting according to labeling, should be addressed to provide appropriate and supportive information.

4.9.3 Extension of Expiration Dating Period:

An extension of the expiration dating period based on full long-term stability data obtained from three production batches may be done if the criteria set forth are met in obtaining and analyzing data, including statistical analysis, if appropriate.

4.10 Stability Report

A stability report must be established for internal use, registration purposes ...etc. detailing the design and the concept of the study, as well as results, data analysis and conclusions. The results should be presented as a table and a graph if applicable. For each batch, results of testing should be given both at the time of manufacture and at different period during storage. A standard form should be prepared containing a summary of the results for each pharmaceutical preparation. A form is given in Annex 1, as one possible example. The stability of a given product, therefore the proposed shelf life and storage conditions must be determined on the basis of these results.

4.11 Shelf-Life

Shelf life should always be determined in relation to storage conditions. A tentative shelf life of up to 24 or 36 months, at the labeled storage condition¹, may be established based on satisfactory accelerated stability data (with no significant change), carried out on three batches selected as mentioned under (4.1), and tested as described under (4.2). The adequate accelerated stability results combined with available long-term data are used at the registration time- as the basis for the proposed tentative expiration-dating period. Other supportive data related to the drug product or the drug substance stability, may also be submitted.

The application should include a commitment from the manufacturer to conduct long term stability testing on the first three production batches and annual batches until the tentative expiration dating period is verified, or appropriate expiration dating period is determined. Based on what had been mentioned under (4.10), data evaluation should be done at the end of the long term testing (covering the tentative shelf life), to confirm the shelf life of all future batches with a high degree of confidence.

Products with less stable drug substances and formulations that do not tolerate storage for testing at elevated temperatures (e.g. suppositories) will need more extensive real-time stability studies. The proposed shelf life in this case should not exceed twice the time period covered by real-time studies. The computation of the shelf life (expiration dating) of the drug product should generally not exceed 30 days from the production date, regardless of the packaging date.

4.12 Statements/ Labeling for Recommended Storage Conditions

A storage temperature range may be used based on the stability evaluation of the drug product. There should be a direct linkage between the label statement and the demonstrated stability characteristics of the drug product. The use of terms such as ambient conditions or room temperature is unacceptable.

Where applicable a single set of uniform storage statements is recommended to avoid different labeling:

Room temperature storage statements:

The label should state “store up to 30°C” or “store up to 25°C” if appropriate.

Refrigerator storage statement:

Store in a refrigerator, between 2 - 8°C.

Freezer storage statement:

Store in a freezer between -20°C and -10°C.

Specific requirements may be stated, but should not be used for the purpose to cover stability problems:

For drug products that cannot tolerate refrigerating “Do not refrigerate”.

For drug products that cannot tolerate freezing: “Do not freeze”.

¹ Grimm W. *Extension of the International Conference on Harmonization Tripartite Guideline for Stability Testing of New Drug Substances and Products to Countries of Climatic Zones III and IV J. Drug Development and Industrial Pharmacy*, 24,313-325, 1998.

For light sensitive drug products: “Protect from light”.

For drug products sensitive to humidity: “Store in a dry place”.

Certain recommendations may also be given regarding the utilization period after opening and dilution, or reconstitution of the powders.

REFERENCES

1. The Arab Good Manufacturing Practice Guidelines "GMP" 1995 by The Arab Union of the Manufacturers of Pharmaceuticals & Medical Appliances (**AUPAM**).
2. Guidance for Industry (Stability testing of drug substances and drug products). June 1998.
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4. Stability Testing of New Drug Substances and Products.ICH Harmonised Tripartite Guidelines in October 1999.
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6. Grimm W. storage conditions for stability testing in the E.C., Japan and USA; the most important markets for drug products. J. Drug Development and Industrial Pharmacy, 19:2795-2830, 1993.
7. Grimm W. Extension of the International Conference on Harmonization Tripartite Guideline for Stability Testing of New Drug Substances and Products to Countries of Climatic Zones III and IV J. Drug Development and Industrial Pharmacy, 24,313-325, 1998.
8. ICH Guidline on Stability Testing of New Drug Substances And Products.Recommended for Adoption under Step 4 of the ICH Process on 8 November 2000 by the ICH Steering Committee.

STABILITY REPORT
Summary sheet
Accelerated/real-time studies

Name of drug product and dosage form
 Manufacturer /site Packaging site.....
 Address
 Drug substance (INN)*
 Strength
 Packaging

*Fill one summary sheet for each ingredient for which a study was conducted.

<u>Batch number</u>	<u>Batch size</u>	<u>Date of manufacture</u>	<u>Expiry date</u>	<u>Type of batch**</u>	<u>Packaging material</u>
1/...../...../...../.....
2/...../...../...../.....
3/...../...../...../.....

** (experimental, pilot, production)

Proposed shelf-lifeyear(s)month(s)
 Samples tested (per batch)

Storage conditions:

Temperature°C Humidity%
 Duration Month(s) Lightcd PressureBar

TEST CONDITIONS

Test methodology used for each test (attach a copy)

Results

- 1) Chemical results
- 2) Physical findings
- 3) Microbiological and biological findings
- 4) Data evaluation
- 5) Conclusions

Responsible officer **Date** / /

Approved by **Date** / /

The first edition of this guidelines have been developed in 1995 by a team of pharmaceutical experts working in collaboration with AUPAM.

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