

**The Saudi Food & Drug Authority (SFDA)**  
**Guidelines for Stability Testing of New**  
**Drug Substances and Products**

**Final Draft**

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## **(1) INTRODUCTION**

The following guideline defines the stability data package for a drug substance or drug product that is sufficient for registration within the Kingdom of Saudi Arabia (K.S.A). The guideline seeks to exemplify the core stability data package for drug substance or drug products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated. Alternative approaches may be used when there are scientifically justifiable reasons.

## **(2) OBJECTIVES**

This guideline is intended to provide recommendations on the core stability study package required for drug substance or drug products. The purpose of stability testing is to provide 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 for the drug substance or drug product and recommended storage conditions for the drug substance or drug product.

## **(3) SCOPE**

The guideline addresses the information to be submitted in registration applications for drug substance or drug products. The choice of test conditions defined in this guideline is based on analysis of the effects of climatic conditions in the areas of the K.S.A.

## **(4) GLOSSARY**

The definitions given below apply to the terms used in this guideline and provided to facilitate interpretation of the guideline.

### ***Accelerated Studies:***

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.

The design of accelerated studies may include elevated temperature, high humidity and intense light, low temperature and freezing/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.

Data for these studies, in addition to long-term stability studies, can be used to assess longer-term chemical effects at non-accelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

***Active Substance; Active Ingredient; Drug Substance; Medicinal Substance:***

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

***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 only the samples on the extremes, for example of container size and/or dosage strengths, are tested at all time points as in a full design. The design assumes that the stability of any intermediate samples are represented by those at the extremes tested.

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 weights of a similar basic granulation, or a capsule

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\* For more detailed information see ICH Q1D.

range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can also be applied to different container sizes or different fills in the same container closure system (See Appendix I).

***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.

<b>Zone I</b>	<b>Temperate</b>
<b>Zone II</b>	<b>Sub-tropical with possible high humidity</b>
<b>Zone III *</b>	<b>Hot/dry</b>
<b>Zone IV *</b>	<b>Hot/humid</b>

\* K.S.A is categorized in climatic zones III & IV.

***Commitment:***

A signed statement accompanying an application for product registration to complete prescribed studies and obtain data on commercial production batches after approval of an application. The commitment constitutes an agreement to:

- a) Complete the required studies to the end of the tentatively approved shelf life;
- b) Submit results periodically to regulatory authorities;
- c) Withdraw from the market any lots found to fall outside the approved specification for the drug product.

***Commitment Batches:***

Production batches of a drug substance or drug product for which the stability studies are initiated or completed postapproval 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 components if the

latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

***Dosage Form:***

A Pharmaceutical product type (e.g., tablet, capsule, solution, cream etc.) that contains a drug substance.

***Drug Product; Finished Product:***

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

***Drug Substance:***

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

***Excipient:***

Anything other than the drug substance in the dosage form.

***Expiry Date (Shelf Life):***

The date placed on the container label of a drug substance or drug product designating the time during which a batch of the drug substance or drug 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 studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the shelf life of a drug substance or drug product.

***Impermeable Containers:***

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

***Mass Balance:***

The process of adding together the assay value and levels of degradation products to see how closely these add up to 100 % of the initial value, with due consideration of the margin of analytical error.

***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. 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 closure system, and possibly in some cases, different container closure systems (See Appendix I).

***Mean Kinetic Temperature:***

A single derived temperature which if maintained over a defined period of time, would afford the same thermal challenge to a drug substance or drug product as would have been experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation (See Appendix II). When establishing the Mean Kinetic Temperature for a defined period, the formula of Haynes J. D. (1971) can be used.

***New Molecular Entity:***

An active pharmaceutical substance not previously contained in any drug substance or drug product registered with the national or regional authority concerned. A new salt, ester, or non covalent bond derivative of an approved drug substance is considered a new molecular entity for the purpose of stability testing under this guidance.

***On Going Real Time Stability:***

It is the study carried out by the manufacturer on production batches according to pre-determined schedule in order to confirm the projected shelf life or extend the shelf life of the drug substance or drug product.

***Pilot Scale Batch:***

A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms this is generally taken to be at a minimum scale of one tenth that of full production batch.

***Primary Batch:***

A batch of a drug substance or 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 of the drug substance or drug product. For registration purposes, at least three batches should be submitted. Two of the three batches should be at least pilot scale, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

***Production Batch:***

A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.

***Real Time (Long-Term) Studies:***

Studies designed to evaluate the physical, chemical, biological and microbiological characteristics of a drug substance or drug product, during the expected time of shelf life and storage of samples at expected storage conditions in the intended market. The results are used to establish shelf life, confirm projected shelf life and recommend storage conditions.

***Semipermeable Containers:***

Containers that allow the passage of solvent, usually water, while preventing solute loss.

The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial pressure gradient. Examples of semi-permeable containers include plastic bags and semirigid low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles and vials.

***Shelf Life:***

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

***Specifications:***

A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. “Conformance to specifications” means that the drug substance or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.

***Specification-Release:***

The combination of physical, chemical, biological and microbiological tests and acceptance criteria that determine the suitability of a drug substance or drug product at the time of its release.

***Specification-Shelf Life:***

The combination of physical, chemical, biological and microbiological tests and acceptance criteria that determine the suitability of a drug substance or drug product should meet throughout its shelf life.

***Stability:***

The ability of a drug substance or drug product to retain its chemical, physical, microbiological and biological properties within specified limits throughout its shelf life.



***Stability Indicating Methods:***

Validated quantitative analytical methods that can detect the changes with time in the chemical, physical or microbiological properties of the drug substance or drug product, and that are specific so that the contents of active ingredient, degradation products, and other components of interest can be accurately measured without interference.

***Stability Study Protocol:***

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

***Stability Tests:***

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

***Strength:***

A quantitative measure of an active ingredient(s) content as well as other ingredients requiring quantification such as alcohol and preservatives.

***Storage Conditions Tolerances:***

The acceptable variations in temperature and relative humidity of storage facilities for formal stability studies. The equipment should be capable of controlling the storage condition within the ranges defined in this guidance. The actual temperature and humidity should be monitored during stability storage. Short-term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed by the applicant and reported if judged to impact stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their impact assessed.

***Stress Testing (Drug Substance):***

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

***Stress Testing (Drug Product):***

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

***Supporting Stability Data:***

Supplementary data, such as stability data on small scale batches, related formulations, 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 which is based on acceptable accelerated data and available long-term data for the drug product to be marketed in the proposed container-closure system.

***Utilization Period:***

A period of time during which a reconstituted preparation or the finished dosage form in an opened multi-dose container can be used.

***Validation:***

A documented program providing a high degree of assurance that a specific process, methods, equipment or system will consistently produce results meeting predetermined acceptance criteria.

## **(5) PURPOSE OF STABILITY TESTING**

### **I. Drug Substance**

#### ***1. General***

Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation.

#### ***2. Stress Testing***

Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance.

Stress testing is likely to be carried out on a single batch of the drug substance. The testing should include the effect of temperatures (in 10° C increments (e.g., 50° C, 60° C) above that for accelerated testing), humidity (e.g., 75 percent relative humidity or greater) where appropriate, oxidation, and photolysis on the drug substance. The testing should also evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension. Photostability testing\* should be an integral part of stress testing.

Examining degradation products under stress conditions is useful in establishing degradation pathways, in developing and validating suitable analytical procedures. However, such examination may not be necessary for certain degradation products if it has been demonstrated that they are not formed under accelerated or long-term storage conditions.

Results from these studies will form an integral part of the information provided to regulatory authorities.

#### ***3. Selection of Batches***

Data from formal stability studies should be provided on at least three primary batches of the drug substance. The batches should be manufactured to a minimum of pilot scale by the same synthetic route as production batches and using a method of manufacture and

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\* For more detailed information see ICH Q1B.

procedure that simulates the final process to be used for production batches. The overall quality of the batches of drug substance placed on formal stability studies should be representative of the quality of the material to be made on a production scale.

#### ***4. Container Closure System***

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.

#### ***5. Specification***

Specifications, which are a list of tests, references to analytical procedures, and proposed acceptance criteria, are addressed in ICH Guidance documents Q3A, Q6A and Q6B.

Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes. Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed should depend on the results from validation studies.

#### ***6. Testing Frequency***

Frequency of testing should be sufficient to establish the stability profile of the drug substance. The frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed retest period.

At the accelerated storage condition for a 6-month study a minimum of three time points is recommended including the initial and final time points (e.g., 0, 3, and 6 months). Where an expectation (based on development experience) exists that the results from accelerated studies are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or including a fourth time point in the study design.

## 7. Storage Conditions

In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

The long-term testing should cover a minimum of 12 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 retest period. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term and accelerated storage conditions for drug substances are detailed in the sections below. The general storage conditions should apply if the drug substance is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

### a. General Storage Conditions

Study	Storage condition	Minimum time period covered by data at submission
Long-term	30°C ± 2°C / 65% RH ± 5% RH	12 months
Accelerated	40°C ± 2°C / 75% RH ± 5% RH	6 months

If it cannot be demonstrated that the drug substance will remain within its acceptance criteria when stored at 30°C ± 2°C / 65% RH ± 5% RH for the duration of the proposed shelf life, the following options should be considered:

- Ø A reduced retest period,
- Ø A more protective container closure system,
- Ø Additional cautionary statements in the labeling.

### b. Drug Substances Intended for Storage in a Refrigerator

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

Data from refrigerated storage should be assessed according to the evaluation section of this guidance, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed retest 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). This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug substance through 6 months when a significant change has occurred within the first 3 months.

### c. Drug Substances Intended for Storage in a Freezer

<b>Study</b>	<b>Storage condition</b>	<b>Minimum time period covered by data at submission</b>
<b>Long-term</b>	-20° C ± 5° C	12 months

For drug substances intended for storage in a freezer, the retest 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° C ± 3° C or 25° C ± 2° C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition (e.g., during shipping or handling).

#### **d. Drug Substances Intended for Storage below -20° C**

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

#### **8. Stability Commitment**

When available long-term stability data on primary batches do not cover the proposed retest period granted at the time of approval, a commitment should be made to continue the stability studies postapproval to firmly establish the retest period.

Where the submission includes long-term stability data on three production batches covering the proposed retest period, a postapproval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

- Ø If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue these studies through the proposed retest period.
- Ø 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, to a total of at least three, on long-term stability studies through the proposed retest period.
- Ø 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 retest period.

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

#### **9. Evaluation**

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug substance and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological, and microbiological tests), a retest period applicable to all future batches of the drug substance manufactured under similar circumstances.

The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned retest period. The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested retest period will be granted. Under these circumstances, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95 percent, one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches.

If it is inappropriate to combine data from several batches, the overall retest period should be based on the minimum time a batch can be expected to remain within acceptance criteria.

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

Limited extrapolation of the real time data from the long-term storage condition beyond the observed range to extend the retest period can be undertaken at approval time if justified. This justification should be based, for example, on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, and/or existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should cover not only the assay, but also the levels of degradation products and other appropriate attributes.



### ***10. Statements/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 substance. Where applicable, specific instructions should be provided, particularly for drug substances that cannot tolerate freezing. Terms such as "*ambient conditions*" or "*room temperature*" should be avoided.

A retest period should be derived from the stability information, and a retest date should be displayed on the container label.

## **II. Drug Product**

### ***1. In the Developing 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 shelf life and storage conditions of the drug product. Real-time studies must be started at the same time for confirmation purposes. Suitable measures should be taken for the establishment of the utilization period for preparations in multi-dose containers.

### ***2. For the Registration Dossier***

The SFDA will require the manufacturer to submit information on the stability of the product derived from tests made on the final dosage form in its final container and packaging. The data submitted should be from both accelerated and real-time studies. Published and/or experimental supporting stability data may be submitted, e.g. on stability of active ingredients and related formulations or packaging.

Where the product is to be diluted or reconstituted before being administered to the patient (e.g. a powder for injection or a concentrate for oral suspension), "in use" stability data must be submitted to support the recommended storage time and conditions for those dosage forms.

With the approval of the SFDA, a tentative shelf life is often established on the condition that additional stability data from first production batches will be submitted after registration.

### ***3. In the Post-Registration Period***

The manufacturer must carry out on-going real-time 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 SFDA. 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, SFDA will monitor the stability and quality of preparations on the market through a follow-up inspection and testing program.

Once the product has been registered, additional stability studies are required whenever major modifications are made to the formulation, manufacturing process, packaging or method of preparation. These results must be communicated to the SFDA.

#### ***4. Stability Study***

##### **A. Design of Stability Testing**

The design of stability studies for the drug product should be based on the knowledge of properties and stability characteristics of drug substance(s).

The design of the stability testing program needs to take into consideration the intended market and the climatic conditions of the area in which the drug products will be used. For K.S.A 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 program be based on conditions corresponding to climatic zones III and IV.

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 -10° C to -20° C (freezer), freeze thaw cycles and temperatures between 2° C to 8° C (refrigerator). For certain preparations it is important to observe effects caused by their exposure to light.

Photostability testing\* should be an essential part of the stability design. Photostability testing should be conducted on at least one primary batch of the drug product if appropriate.

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\* For more detailed information see ICH Q1B.

## **B. Selection of Batches**

For registration purposes, stability information from accelerated and long-term studies should be provided for three primary batches of the same formulation and dosage form in the containers and closure system 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 production 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 drug product should be manufactured using identifiably different batches of the drug substance.

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

## **C. Stability Commitment**

When available long-term stability data on primary batches do not cover the tentative shelf life granted at the time of approval, a commitment should be made to continue the stability studies post approval to firmly establish the shelf life.

Where the submission includes long-term stability data from three production batches covering the proposed shelf life, a post approval commitment is considered unnecessary.

Otherwise, one of the following commitments should be made:

- Ø If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life.
- Ø If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue the long-term studies through 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.
- Ø 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.

#### **D. Packaging /Containers**

The 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). Additional testing of unprotected drug product, outside its immediate container, can form a useful part of stress testing and packaging evaluation, as studies carried out in other related packaging materials in supporting the definitive package(s).

#### **E. Storage Conditions**

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Stability testing of the drug product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted 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 12 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. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term and accelerated storage conditions for drug products are detailed in the sections below. The general storage conditions should apply if the drug product is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

### (1) General Storage Conditions

Study	Storage condition	Minimum time period covered by data at submission
Long-term	30° C ± 2° C/ 65% RH ± 5% RH	12 months
Accelerated	40° C ± 2° C/ 75% RH ± 5% RH	6 months

If it cannot be demonstrated that the drug product will remain within its acceptance criteria when stored at 30° C ± 2° C/ 65% RH ± 5% RH for the duration of the proposed shelf life, the following options should be considered:

- Ø A reduced shelf life,
- Ø A more protective container closure system,
- Ø Additional cautionary statements in the labeling.

### (2) Drug Products Stored in Impermeable Containers

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent, e.g. semi-solids in sealed aluminum tubes, and solutions in sealed glass ampoules. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

### (3) Drug Products Packaged in Semipermeable Containers

Aqueous-based products packaged in semipermeable containers (such as large volume parenterals (LVPs), small volume parenterals (SVPs), ophthalmics, otics and nasal drops packaged in semipermeable plastic bags, semi-rigid plastic container, sealed plastic ampoules, vials and any containers which may be susceptible to water loss) should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity as discussed below. Other comparable approaches may be developed and reported, for nonaqueous solvent-based products.

Ultimately, the shelf life for aqueous based drug products stored in semipermeable containers should justify storage in low relative humidity environments.

Study	Storage condition	Minimum time period covered by data at submission
Long-term	30° C ± 2° C/ 35% RH ± 5% RH	12 months
Accelerated	40° C ± 2° C/ NMT* 25% RH	6 months

\* NMT: not more than.

A 5 % loss in water from its initial value is considered a significant change for a product packaged in a semipermeable container after an equivalent of 3 months' storage at 40° C/ NMT 25% RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5% or more may be appropriate if justified.

An alternative approach to studying at the reference relative humidity as recommended in the above table is performing the stability studies under higher relative humidity and deriving the water loss at the reference relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for container closure system can be experimentally determined by using the worst case scenario (e.g., the most diluted of a series of concentrations) for the proposed drug product.

**Example of an approach for determining water loss:**

For a product in a given container closure system, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio shown in the next table. The ratio of water loss rates at a given temperature is calculated by the general formula:

$$\frac{100 - \text{reference \% RH}}{100 - \text{relative \% RH}}$$

A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

For example, at a given temperature (e.g., 40° C), the calculated water loss rate during storage at NMT 25 % RH is the water loss rate measured at 75 percent RH multiplied by 3.0, the corresponding water loss rate ratio.

<b>Alternative Relative humidity</b>	<b>Reference relative humidity</b>	<b>Ratio of water loss rates at a given temperature</b>
60% RH	25% RH	1.9
60% RH	40% RH	1.5
65% RH	35% RH	1.9
75% RH	25% RH	3.0

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

#### **(4) Drug Products Intended for Storage in a Refrigerator**

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

Data from refrigerated storage should be assessed according to the evaluation section of this guideline except where explicitly noted below.

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, data should be supplied to cover the effect of short-term excursions outside of the label storage condition (e.g., during shipping and handling). This can be done by further testing on a single batch of the drug product for a period shorter than 3 months but with more frequent testing than usual. It is not necessary to continue to test a product to 6 months when an obvious significant change has occurred within the first 3 months.



### **(5) Drug Products Intended for Storage in a Freezer**

<b>Study</b>	<b>Storage condition</b>	<b>Minimum time period covered by data at submission</b>
<b>Long-term</b>	-20° C ± 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 for an appropriate time period to address the effect of short-term excursions outside of the proposed label storage condition.

### **(6) Drug Products Intended for Storage below -20° C**

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

### **(7) Tests at Elevated Temperature and/or Extremes of Humidity\***

Transportation and climatic conditions outside the storage conditions recommended in this guidance should be supported by additional data. For example, these data can be obtained from studies on one batch of drug product conducted for up to 3 months at 50° C/ambient humidity to cover extremely hot and dry conditions and at 25° C/ 80 % RH to cover extremely high humidity conditions (Grimm 1985 and 1986).

Stability testing at a high humidity condition (e.g., 25° C/ 80 % RH) is recommended for solid dosage forms in water-vapor permeable packaging (e.g., tablets in PVC/aluminum blisters) intended to be marketed in territories with extremely high humidity conditions in zone IV. However, for solid dosage forms in primary containers designed to provide a barrier to water vapor (e.g., aluminum/aluminum blisters), stability testing at a storage condition of extremely high humidity is not considered necessary.

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\* Optional additional test.

## **F. Test Attributes, Test Procedures and Acceptance Criteria\***

The testing should cover those attributes 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 range of testing should cover as appropriate chemical and/or biological stability, loss of preservative, physical properties, characteristics, functionality (e.g., metered dose inhaler) and microbiological attributes.

Acceptance criteria should relate to the release limits to be derived from consideration of all the available stability information. The shelf life specification could allow acceptable and justifiable differences from the release specification based on the stability evaluation and the changes observed on storage. It should include specific upper limits for degradation products. The justification for the limits proposed for certain other tests such as particle size and/or dissolution rate should reference to the results observed for batch(es) used in bioavailability and/or clinical studies. Any differences between the release and shelf life specifications for anti-microbial preservatives should be supported by preservative efficacy testing, in addition to the chemical content.

## **G. Testing Frequency**

Frequency of testing should be sufficient to establish the stability attributes of the drug products. Stability testing for long-term studies generally should be performed at three-month intervals during the first year, six-month intervals during the second year, and yearly thereafter (e.g., 0, 3, 6, 9, 12, 18, 24, 36 months).

For the accelerated storage conditions, a minimum of three test points including the initial and final time points (e.g., 0, 3 and 6 months) is recommended. Where an expectation (based on development experience) exists that results from accelerated storage are likely to approach significant change criteria, increased testing should be conducted either by testing additional samples at other time points in the protocol (e.g., 0, 1, 2, 3 and 6 months).

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\* For more detailed information see ICH Q6A.

## **H. Microbial Testing**

The microbial quality of multiple dose sterile and non-sterile pharmaceutical preparations should be controlled in order to prevent microbial hazard and instability. However, to achieve this, the following measures should be taken:

1. Safe and suitable preservative system should be used.
2. A chemical assay for the preservative must be carried out (see analytical methods).
3. Preparations containing preservatives must be tested (challenge test) in the final container as described by the compendia or any other validated method. If the shelf life specifications for anti-microbial preservatives are different from the release specifications, challenge tests should be carried out at least at the beginning and at the end of the shelf life.

## **I. Bacterial Endotoxins and Pyrogen Testing**

Drug products with specified limits for pyrogens or bacterial endotoxins should be tested at the time of release and at appropriate intervals during the stability period. For most parenteral products, testing at the beginning and at the end of the stability test period may be adequate. Sterile dosage forms containing dry materials (powder filled or lyophilized products) and solutions packaged in sealed glass ampoules may need no additional testing beyond the initial time point. Products containing liquids in glass containers with flexible seals or in plastic containers should be tested no less than at the beginning and at the end of the stability test period.

## **J. Analytical Methods**

All product characteristics likely to be affected by the storage including assay value or potency, content of products of decomposition and physicochemical properties should be evaluated. Therefore, tests such as hardness, disintegration, dissolution, particle size, particulate matter, etc. should be carried out as appropriate for the dosage form under stability study.

Analytical test procedures should be validated, and the assay methods should be stability-indicating. Tests for related compounds or products of decomposition should be validated to demonstrate that they are specific to the product being examined and are of adequate sensitivity.

Test methods to demonstrate the efficacy of additives, such as anti-microbial agents, should be used to determine whether such additives remain effective and unchanged throughout the projected shelf life.

## **K. Evaluation**

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including particular attributes of the dosage form (e.g., dissolution rate for solid oral dosage forms).

The purpose of the stability study is to establish, 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 drug product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

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. However, justification for the omission should be sufficient and included.

An approach for analyzing data of a quantitative attribute that is expected to change with time is to determine the time at which the 95 percent one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch may be expected to remain within acceptance criteria.

The nature of the degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic 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.

Limited extrapolation to extend the shelf life beyond the period covered by long-term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition. Whether extrapolation of stability data is appropriate depends on the extent of knowledge about the change pattern, the goodness of fit of any mathematical model, and the existence of relevant supporting data. Any extrapolation should be performed in such a way that the extended shelf life will be valid for a future batch released with test results within the release acceptance criteria.

An extrapolation of stability data assumes that the same change pattern will continue to apply beyond the period covered by long-term data. The correctness of the assumed change pattern is critical when extrapolation is considered. When estimating a regression line or curve to fit the long-term data, the data themselves provide a check on the correctness of the assumed change pattern, and statistical methods can be applied to test the goodness of fit of the data to the assumed line or curve. No such internal check is possible beyond the period covered by long-term data. Thus, a shelf life granted on the basis of extrapolation should always be verified by additional long-term stability data as soon as these data become available. Care should be taken to include in the protocol for commitment batches a time point that corresponds to the end of the extrapolated shelf life.

Any evaluation should consider not only the assay, but the levels of degradation products and appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performance.

#### **L. Statements/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. Where applicable, specific instruction should be provided, particularly for drug products that cannot tolerate freezing. Terms such as "*ambient conditions*" or "*room temperature*" should be avoided.

There should be a direct linkage between the label storage statement and the demonstrated stability of the drug product. An expiration date should be displayed on the container label.

### **M. Shelf Life**

Shelf life is always determined in relation to storage conditions. If batches of a product demonstrate different stability profiles, the shelf life proposed should be based on the stability of the least stable.

A tentative shelf life of 24 months may be established. However, the proposed shelf life could be 12 months longer than the period covered by long-term data. This should be based on the duration and evaluation of the data submitted and provided the following conditions are satisfied:

- 1- The active ingredient is considered to be stable (not easily degradable).
- 2- Stability studies as previously outlined have been performed with no significant changes.
- 3- Supporting data indicated that similar formulations in the same packaging container and closer system have been assigned a shelf life of 24 months or more.
- 4- The manufacturer will continue to perform the real-time studies until the proposed shelf life is covered, and the results, as received will be submitted to the SFDA.

### **N. Stability Report**

A stability report must be established for internal use and registration purposes, detailing the protocol design and the concept of the study, as well as results and conclusions.

The results should be presented as a table and a graph. For each batch, results of testing should be given both at the time of manufacture and at different times during storage.

A standard form should be prepared containing a summary of the results for each pharmaceutical preparation (See Appendix III).

The stability of a given product, and therefore the proposed shelf life and storage conditions, must be determined on the basis of these results.

### O. Recommended Description of Labeled Storage Conditions

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

<b>Storage conditions</b>	<b>Storage statement The label should state:</b>
<b>Room temperature</b>	"Store up to 30° C" or "Store up to 25° C" if deemed essential in some cases.
<b>Refrigerator</b>	"Store in refrigerator, between 2° C and 8° C".
<b>Freezer</b>	"Store in freezer between - 5° C and - 20° C".

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

<b>Stability problem</b>	<b>Precautionary statement The label should state:</b>
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	"Protect from light"
For drug products sensitive to humidity	"Store in a dry place"

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.

## **Appendices**



# Appendix I

## Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products

### Bracketing

Bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g. strength, container size and/or fill) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

Bracketing design is applicable to most types of drug products, including oral solids, liquids, semi-solids, and injectables. Certain types of drug products, such as metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and transdermal delivery systems (TDSs), may not be amenable to bracketing design due to the potential of drug-device interactions.

Bracketing can be applied to studies with multiple strengths of identical or closely related formulations. Examples include but not limited to (1) capsules of different strengths made with different fill plug sizes from the same powder blend, (2) tablets of different strengths manufactured by compressing varying amounts of the same granulation, and (3) oral solutions of different strengths with formulations that differ only in minor excipients (e.g., colorants, flavorings).

In cases where different excipients are used among strengths, bracketing should not be applied.

Bracketing can be applied to studies of the same container closure system where either container size or fill varies while the other remains constant.

An example of a bracketing design is given in Table 1. This example is based on a product available in three strengths and three container sizes. In this example, it should be demonstrated that the 15 ml and 500 ml high-density polyethylene container sizes truly represent the extremes. The batches for each selected combination should be tested at each time point as in a full design.

**Table 1: Example of a Bracketing Design**

Strength		50 mg			75 mg			100 mg		
Batch		1	2	3	1	2	3	1	2	3
Container Size	15 ml	T	T	T				T	T	T
	100 ml									
	500 ml	T	T	T				T	T	T

Key: T = Sample tested

### Matrixing

Matrixing is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point. At a subsequent time point, another subset of samples for all factor combination would be tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time points. 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 closure system, and possibly, in some cases, different container closure systems.

When a secondary packaging system contributes to the stability of the drug product, matrixing can be performed across the packaging systems.

Matrixing design is applicable to most types of drug products, including oral solids, liquids, semi-solids, and injectables. Certain types of drug products, such as metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and transdermal delivery systems (TDSs), may not be amenable to matrixing design due to the potential of drug-device interactions.

Matrixing design can be applied to batches, strengths with identical or closely related formulations, container sizes, fill sizes and intermediate time points.

Each storage condition should be treated separately under its own matrixing design. Matrixing should not be performed across test attributes. However, alternative matrixing design for different test attributes can be applied if justified.

In a design where time points are matrixed, all selected factor combinations should be tested at the initial and final time points, while only certain factions of the designated combinations should be tested at each intermediate time point. If full long-term data for

the proposed shelf life will not be available for review before approval, all selected combination for batch, strength, container size, and fill, among other things, should be tested at 12 months or at the last time point prior to submission. In addition, data from at least three time points, including initial, should be available for each selected combination through the first 12 months of the study.

For matrixing at an accelerated storage conditions, care should be taken to ensure testing occurs at a minimum of three time points, including initial and final, for each selected combination of factors.

Examples of matrixing design on time points for a product in two strengths (S1 and S2) are shown in Table 2. The term “*one-half reduction*” and “*one-third reduction*” refer to the reduction strategy initially applied to the full study design. For example, a “one-half reduction” initially eliminates one in every two time points from the full study design and a “one-third reduction” initially removes one in every three. In the examples shown in Table 2, the reductions are less than one-half and one-third due to the inclusion of full testing of all factor combinations at some time points. These examples include full testing at the initial, 12-month time points, and final. The ultimate reduction is therefore less than one-half (24/48) or one-third (16/48), and is actually 15/48 or 10/48, respectively.

**Table 2: Example of Matrixing Designs on Time Points for a Product with Two Strengths**

**“Less Than One-Half Reduction”**

Time point (months)			0	3	6	9	12	18	24	36
<b>S T R E N G T H</b>	<b>S1</b>	<b>Batch 1</b>	T	T		T	T		T	T
		<b>Batch 2</b>	T	T		T	T	T		T
		<b>Batch 3</b>	T		T		T	T		T
	<b>S2</b>	<b>Batch 1</b>	T		T		T		T	T
		<b>Batch 2</b>	T	T		T	T	T		T
		<b>Batch 3</b>	T		T		T		T	T

Key: T = Sample tested

**“Less Than One-Third Reduction”**

Time point (months)			0	3	6	9	12	18	24	36
<b>S T R E N G T H</b>	<b>S1</b>	<b>Batch 1</b>	T	T		T	T		T	T
		<b>Batch 2</b>	T	T	T		T	T		T
		<b>Batch 3</b>	T		T	T	T	T	T	T
	<b>S2</b>	<b>Batch 1</b>	T		T	T	T	T	T	T
		<b>Batch 2</b>	T	T		T	T		T	T
		<b>Batch 3</b>	T	T	T		T	T		T

Key: T = Sample tested

Additional examples of matrixing designs for a product with three strengths and three container sizes are given in Tables 3a and 3b. Table 3a shows a design with matrixing on time points only and Table 3b depicts a design with matrixing on time points and factors. In Table 3a, all combinations of batch, strength, and container size are tested, while in Table 3b, certain combinations of batch, strength and container size are not tested.

**Tables 3a and 3b: Examples of Matrixing Designs for a Product With Three Strengths and Three Container Sizes**

**3a Matrixing on Time Points**

Strength	S1			S2			S3		
Container size	A	B	C	A	B	C	A	B	C
Batch 1	T1	T2	T3	T2	T3	T1	T3	T1	T2
Batch 2	T2	T3	T1	T3	T1	T2	T1	T2	T3
Batch 3	T3	T1	T2	T1	T2	T3	T2	T3	T1

**3b Matrixing on Time Points and Factors**

Strength	S1			S2			S3		
Container size	A	B	C	A	B	C	A	B	C
Batch 1	T1	T2		T2		T1		T1	T2
Batch 2		T3	T1	T3	T1		T1		T3
Batch 3	T3		T2		T2	T3	T2	T3	

Key:

Time-point (months)	0	3	6	9	12	18	24	36
T1	T		T	T	T	T	T	T
T2	T	T		T	T		T	T
T3	T	T	T		T	T		T

S1, S2, S3 are different strengths.

A, B, and C are different container sizes.

T = Sample tested.

Another example (Table 4) illustrates how bracketing (of one factor) and matrixing (with three-fourths time points) can be combined in one protocol for a capsule dosage form which is available in 3 strengths of a common granulation and packaged in 3 container/closure systems and /or sizes: A, HDPE bottle, 30 counts; B, HDPE bottle,

100 counts; and C, HDPE bottle, 200 counts. A 36-month expiration dating period is proposed. The overall size of this design is  $\frac{1}{2}$  of that of a full testing protocol.

**Table 4: Bracketing (of one factor) and Matrixing (with three-fourths time points)**

Batch		1									2									3								
Strength		100 mg			200 mg			300 mg			100 mg			200 mg			300 mg			100 mg			200 mg			300 mg		
Container/ Closure		A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
Schedule		T1	T2	T3				T3	T1	T2	T2	T3	T1				T1	T2	T3	T3	T1	T2				T2	T3	T1
Time Points (Months)	0	x	x	x				x	x	x	x	x	x				x	x	x	x	x	x				x	x	x
	3	x	x						x	x	x		x				x	x			x	x				x		x
	6		x	x				x		x	x	x						x	x	x		x				x	x	
	9	x		x				x	x			x	x				x		x	x	x						x	x
	12	x	x	x				x	x	x	x	x	x				x	x	x	x	x	x				x	x	x
	18	x							x				x				x				x							x
	24		x	x				x		x	x	x						x	x	x		x				x	x	
	36	x	x	x				x	x	x	x	x	x				x	x	x	x	x	x				x	x	x

## Appendix II

### Mean Kinetic Temperature

Mean kinetic temperature (MKT) is defined as a single derived temperature which, if maintained over a defined period, would afford the same thermal challenge to a drug substance or drug product as would have been experienced over a range of both higher and lower temperatures for an equivalent period. In other words, MKT is a calculated fixed temperature that simulates the effects of temperature variations over a period of time. It expresses the cumulative thermal stress experienced by a product at varying temperature during storage and distribution.

Good warehousing and distribution practice requires that warehouse temperatures are controlled and monitored and that appropriate action is taken if temperatures exceed the storage conditions stated on product labels. It is not unusual to find that warehouse temperatures exceed the recommended maximum storage temperature of 25° C occasionally during summer months, even in those warehouses, which have sophisticated building management systems.

The concept of MKT may be applied in order to provide assurance that the actual storage conditions will not affect adversely the stability and shelf life of the products.

Mean kinetic temperature expresses the cumulative thermal stress experienced by a product at varying temperatures, during storage and distribution. It differs from other means (such as simple numerical average or arithmetic mean) in that higher temperatures are given greater weight in computing the average, thus, recognizing the accelerated rate of thermal degradation of materials at higher temperatures.

The formula for calculation of MKT is based on the Arrhenius equation:

$$T_K = \frac{-\Delta H/R}{\left\{ \frac{\sum_1^n \exp\left[\frac{-\Delta H}{RT_n}\right]}{n} \right\}}$$

Where  $T_K$  is the MKT in degrees Kelvin K (i.e. °C + 273.1),  $\Delta H$  is the activation energy,  $R$  is the universal gas constant (0.0083144 kJ/molK),  $T$  is the temperature in degrees K,  $n$  is the total number of (equal) time periods over which data are collected and  $\exp$  is the natural log base.



The practical application of this equation is less complex than it first appears.  $\Delta H/R$  is a constant (9982.68)  $T_1$  is the average temperature recorded over the first time period and  $T_n$  is the average temperature recorded over the nth time period. A simple way to apply MKT is to calculate the mean of the measured maximum and minimum daily temperatures for seven days (the time period) - this average temperature, plus 273.1°, becomes  $T_1$  in the equation. The mean over the next seven days becomes  $T_2$  and so on. If MKT is to be calculated over a four-week period, n is 4.

In order for MKT to be meaningful, there should be an appropriate number of temperature/time sampling points. Temperature monitoring should be carried out daily and MKT calculated on at least a monthly basis to provide the necessary assurance of temperature control.

MKT should not be used to compensate for poor control of storage facilities. It may be applied in situations where control is relatively good, but where occasional excursions may be encountered.

# Appendix III

## Stability Testing:

### Summary Sheet

An example of a form in which the results of stability testing can be presented is shown below. A separate form should be completed for each pharmaceutical preparation tested.

A separate form should be completed for each storage conditions.

Accelerated studies

Real-time studies

Name of drug product .....

Manufacturer .....

Address .....

Active ingredient .....

Dosage form.....

Packaging.....

Batch number	Date of manufacture	Expiry date
--------------	---------------------	-------------

1- .....	.....	.....
----------	-------	-------

2- .....	.....	.....
----------	-------	-------

3- .....	.....	.....
----------	-------	-------

Shelf life ..... Month(s)

Batch size	Type of batch (experimental, pilot plant, production)
------------	---

1- .....	.....
----------	-------

2- .....	.....
----------	-------

3- .....	.....
----------	-------

Samples tested (per batch).....

Storage / test conditions:

Temperature ..... °C

Humidity ..... %

Light ..... cd

Results:

1- Chemical findings.....

2- Microbiological and biological findings .....

3- Physical findings .....

4- Conclusions .....

Responsible officer ..... Date ... / ... / 20...

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