ASEAN GUIDELINE
ON STABILITY STUDY OF DRUG PRODUCT

Update revision : 22 February 2005.

9th ACCSQ-PPWG Meeting, Philippines, 21-24 Feb 2005

LIST OF CONTENTS

1. INTRODUCTION

1.1 The objective of a stability study is to determine the shelf-life, namely the time period of storage at a specified condition within which the drug product still meets its established specifications.

1.2 Stability is an essential factor of quality, safety and efficacy of a drug product. A drug product, which is not of a sufficient stability, can result in changes in physical (like hardness, dissolution rate, phase separation, etc.) as well as in chemical characteristics (formation of high risk decomposition substances). Microbiological instability of a sterile drug product could also be hazardous.

1.3 The stability study consists of a series of tests in order to obtain an assurance of stability of a drug product, namely maintenance of the specifications of the drug product packed in its specified packaging material and stored in the established storage condition within the determined time period.

2. OBJECTIVES

This guideline is intended to provide recommendations on the core stability study package required for 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 products being evaluated. This guideline can also be used to propose shelf-life based on the stability data generated from the study package.

3. SCOPES

This guideline addresses the information to be submitted in application for marketing authorization of drug products in ASEAN countries including examples of a protocol of stability study, a report format, reduced design and extrapolation of data, and examples of types, thickness and permeability coefficient which are covered in Annexes.
The drug products covered in this guideline include NCE, Generics and Variations (MaV and MiV) but exclude drug products containing vitamin and mineral preparations.

4. DESIGN

4.1. General

The design of the stability studies for the product should be based on knowledge of the behavior and properties of the drug substance and dosage form.

4.2. Photostability Testing

Photostability testing should be conducted on at least one primary batch of the drug product if appropriate. The standard conditions for photostability testing are described in ICH Q1B.

4.3. Selection of Batches

At the time of submission, stability data should be provided for batches of the same formulation and dosage form in the container closure system proposed for marketing.

- For NCE stability data should be provided on at least three primary batches of the drug products.
- For Generics and Variations the following will apply :
  - For conventional dosage forms (e.g., immediate release solid dosage forms, solutions) and when the drug substances are known to be stable, stability data on at least two pilot scale batches are acceptable.
  - For critical dosage forms (e.g., prolonged release forms) or when the drug substances are known to be unstable, stability data on three primary batches are to be provided. Two of the three batches should be at least of a pilot scale; the third batch may be smaller.
- The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing.
- Where possible, batches of the drug product should be manufactured by using 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 is applied.

Other supporting data can be provided.

4.4. Specification (Testing Parameter*)*

Specification is a list of tests, reference to analytical procedures, and proposed acceptance criteria, including the concept of different acceptance criteria for release and shelf-life specifications.

Stability studies should include testing of those attributes of the drug product 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, preservative content (e.g. antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). The analytical procedure should be fully validated and stability indicating according to ASEAN guideline on Analytical Validation. Whether and to what extent replication should be performed will depend on the results from validation studies.

The following list of parameters for each dosage form is presented as a guide for the types of tests to be included in a stability study. In general, appearance, assay and degradation products should be evaluated for all dosage forms. For generic products, degradation products should be limited to compendial requirements.

The list of tests presented for each dosage form is not intended to be exhaustive, nor is expected that every listed test be included in the design of a stability protocol for a particular drug product (for example, a test for odour should be performed only when necessary and with consideration for analyst safety).

Furthermore, it is not expected that every listed test be performed at each time point.
The storage orientation of the product, i.e., upright versus inverted, may need to be included in a protocol where there has been a change in the container/closure system..

1. Tablets

   Tablets should be evaluated for appearance, odour, colour, assay, degradation products, dissolution, moisture and hardness/friability.

2. Capsules

   Hard gelatin capsules should be evaluated for appearance (including brittleness), colour, and odour of content, assay, degradation products, dissolution, moisture and microbial content.
   Testing of soft gelatin capsules should include appearance, colour, and odour of content, assay, degradation products, dissolution, microbial content, pH, leakage, and pellicle formation. In addition, the fill medium should be examined for precipitation and cloudiness.

3. Emulsions

   An evaluation should include appearance (including phase separation), colour, odour, assay, degradation products, pH, viscosity, microbial limits, preservative content, and mean size and distribution of dispersed globules.

4. Oral Solutions and Suspensions

   The evaluation should include appearance (including formation of precipitate, clarity for solutions), colour, odour, assay, degradation products, pH, viscosity, preservative content and microbial limits.

   Additionally for suspensions, redispersibility, rheological properties and mean size and distribution of particles should be considered. After storage, sample of suspensions should be prepared for assay according to the recommended labeling (e.g. shake well before using).

5. Oral Powders for Reconstitution

   Oral powders should be evaluated for appearance, colour, odour, assay, degradation products, moisture and reconstitution time.

   Reconstituted products (solutions and suspensions) should be evaluated as described in Oral Solutions and Suspensions above, after preparation according to the recommended labeling, through the maximum intended use period.

6. Metered-dose Inhalations and Nasal Aerosols

   Metered-dose inhalation**s** and nasal aerosols should be evaluated for appearance (including content, container, valve, and its components), colour, taste, assay, degradation products, assay for co-solvent (if applicable), dose content uniformity, labeled number of medication actuations per container meeting dose content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate, microbial limits, valve delivery (shot weight) and extractables/leachables from plastic and elastomeric components. Samples should be stored in upright and inverted/on-the-side orientations.

   For suspension-type aerosols, the appearance of the valve components and container's contents should be evaluated microscopically for large particles and changes in morphology of the drug surface particles, extent of agglomerates, crystal growth, as well as foreign particulate matter.

   These particles lead to clogged valves or non-reproducible delivery of a dose. Corrosion of the inside of the container or deterioration of the gaskets may adversely affect the performance of the drug product.

7. Nasal Sprays : Solutions and Suspensions

   The stability evaluation of nasal solutions and suspensions equipped with a metering pump should include appearance, colour, clarity for solution, assay, degradation products, preservative and antioxidant content, microbial limits, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet and/or particle size distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign particulate matter and extractable/bleachable from plastic and elastomeric components of the container, closure and pump.

8. Topical, Ophthalmic and Otic Preparations

   Included in this broad category are ointments, creams, lotions, paste, gel, solutions and non-metered aerosols for application to the skin.

Topical preparations should be evaluated for appearance, clarity, colour, homogenity, odour, pH, resuspendability (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible), assay, degradation products, preservative and antioxidant content (if present), microbial limits/sterility and weight loss (when appropriate).

Evaluation of ophthalmic or otic products (e.g., creams, ointments, solutions, and suspensions) should include the following additional attributes: sterility, particulate matter, and extractable.

Evaluation of non-metered topical aerosols should include: appearance, assay, degradation products, pressure, weight loss, net weight dispensed, delivery rate, microbial limits, spray pattern, water content, and particle size distribution (for suspensions).

9. Suppositories

Suppositories should be evaluated for appearance, colour, assay, degradation products, particle size, softening range, dissolution (at 37^{o}C) and microbial limits.

10. Small Volume Parenterals (SVPs)

SVPs include a wide range of injection products such as Drug Injection, Drug for Injection, Drug Injectable Suspension, Drug for Injectable Suspension, and Drug Injectable Emulsion.

Evaluation of Drug Injection products should include appearance, clarity, colour, assay, preservative content (if present), degradation products, particulate matter, pH, sterility and pyrogen/endotoxin.

Stability studies for Drug for Injection products should include monitoring for appearance, colour, reconstitution time and residual moisture content. The stability of Drug for Injection products should also be evaluated after reconstitution according to the recommended labeling. Specific parameters to be examined at appropriate intervals throughout the maximum intended use period of the reconstituted drug product, stored under condition(s) recommended in labeling, should include appearance, clarity, odour, colour, pH, assay (potency), preservative (if present), degradation products/ aggregates, sterility, pyrogen/endotoxin and particulate matter.

The stability studies for Drug Injectable Suspension and Drug for Injectable Suspension products should also include particle size distribution, redispersibility and rheological properties in addition to the parameters cited above for Drug Injection and Drug for Injection products.

The stability studies for Drug Injectable Emulsion products should include, in addition to the parameters cited above for Drug Injection, phase separation, viscosity, and mean size and distribution of dispersed phase globules.

11. Large Volume Parenterals (LVPs)

    Evaluation of LVPs should include appearance, colour, assay, preservative content (if present), degradation products, particulate matter, pH, sterility, pyrogen/endotoxin, clarity and volume.

12. Drug Admixture

    For any drug product or diluents that is intended for use as an additive to another drug product, the potential for incompatibility exists. In such cases, the drug product labeled to be administered by addition to another drug product (e.g. parenterals, inhalation solutions), should be evaluated for stability and compatibility in admixture with the other drug products or with diluents both in upright and in inverted/on-the side orientations, if warranted.

    A stability protocol should provide for appropriate tests to be conducted at 0-, 6- to 8- and 24-hour time points, or as appropriate over the intended use period at the recommended storage/use temperature(s). Tests should include appearance, colour, clarity, assay, degradation products, pH, particulate matter, interaction with the container/closure/device and sterility. Appropriate supporting data may be provided in lieu of an evaluation of photo degradation.

13. Transdermal Patches

    Stability studies for devices applied directly to the skin for the purpose of continuously infusing a drug substance into the dermis through the epidermis should be examined for appearance, assay, degradation products, in-vitro release rates, leakage, microbial limits/sterility, peel and adhesive forces, and the drug release rate.

14. Freeze-dried Products

    Appearance of both freeze-dried and its reconstituted product, assay, degradation products, pH, water content and rate of solution.

4.5. Testing Frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. 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 shelf-life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that 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 by including a fourth time point in the study design.

Reduced designs, i.e., matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied, if justified; see Annex 5.3.

Storage Condition	Products	Testing Frequency
Real Time	NCE , Generics, and Variations (MaV and MiV)	0, 3, 6, 9, 12, 18, 24 months and annually through the proposed shelf-life
Accelerated	NCE , Generics, and Variations (MaV and MiV)	0, 3 and 6 months
Alternatives to accelerated study	Generics and Variations (MaVand MiV)	0, 1 and 3 months

4.6. Storage Condition

General Case

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 (e.g., after reconstitution or dilution as recommended in the labeling).

- Stability testing of the finished 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 stability studies at initial and final time points and, if full shelf-life long term data will not be available before submission, at the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

- Stability study is conducted under storage condition:

TYPE OF CONTAINER/STUDY	STORAGE CONDITION
Products in primary containers permeable to water vapour	$30^{o}C \pm 2^{o}C/75\%$ RH ± 5% RH
Products in primary containers impermeable to water vapour	$30^{o}C \pm 2^{o}C$/RH not specified
Accelerated studies	$40^{o}C \pm 2^{o}C/75\%$ RH ± 5% RH
Stress studies*)	$40^{o}C \pm 2^{o}C/75\%$ RH ± 5% RH

*) Stress studies are necessary for analytical method validation, pharmaceutical formulation, identifying and monitoring potential degradants during stability testing.

The real time testing will be continued for a sufficient time beyond **12** months to cover shelf-life at appropriate test periods.
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).

- If submitted data is based on conditions that are less stressful (e.g. $30^{o}C/65\%$ RH) than those required, the data should be accompanied by appropriate complementary data which will permit to conduct a proper scientific evaluation. Factors to be taken into consideration will include:
  - Whether any instability is seen**;**
  - Whether data have also been provided under accelerated conditions**;**
  - Whether more protective packaging is provided/ required.

  During the transition period, National authorities may decide either not to allocate a shelf life and to require more data before the product is approved, or to allocate a shelf life based on technical judgement and to require a commitment that the applicant will generate data under the new guideline conditions ($30^{o}C/75\%$ RH, or $40^{o}C/75\%$ RH, or both) within a specified period.
  A suitable label recommendation such as "Store below $30^{o}C$ and protect from moisture" may also be applied.

- Additional data accumulated during the assessment period of the registration application should be submitted to the regulatory authorities if requested.

- Other storage conditions are allowable if justified, e.g., under the following circumstances :

- Heat sensitive drug products should be stored under an alternative lower temperature condition which will eventually become the designated long-term storage temperature.
    * Products containing less stable active ingredients and formulations not suitable for experimental studies on storage at elevated temperature (e.g., suppositories) will need more extensive real time stability studies.
- Special consideration may need to be given to products which change physically or even chemically at lower storage temperature conditions e.g., suspensions or emulsions which may sediment or cream, oils and semi-solid preparations which may show an increased viscosity.
    * Where a lower temperature condition is used, the 6 month accelerated testing should be carried out at a temperature at least 15°C above the expected actual storage temperature (together with appropriate relative humidity conditions for that temperature). For example, for a product to be stored long term under refrigerated conditions, accelerated testing should be conducted at 25°C ± 2ºC, 60% RH ± 5% RH. The designated real time testing conditions will be reflected in the labeling and shelf-life (expiration date).

4.6.1. For NCE Drug Products

Study	Storage Condition	Minimum Time Period Covered by Data at Submission	Number of Batches (Refer to "Selection of batches")
Real Time	30°C ± 2°C/75% RH ± 5% RH	12 months	Min. 3
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months	Min. 3

4.6.2. For Generics and Variation (MaV and MiV if appropriate) Products

Study	Storage Condition	Minimum Time Period Covered by Data at Submission	Number of Batches (Refer to Selection of batches")
Real Time	$30^{o}C \pm 2^{o}C/75\%$ RH $\pm$ 5% RH	12 months 12 months	Min. 2 For conventional dosage form and stable drug substances Min. 3 For critical dosage form or unstable drug substances
Accelerated	$40^{o}C \pm 2^{o}C/75\%$ RH $\pm$ 5% RH	6 months	Min. 2

4.6.3. Drug Products intended for storage in a refrigerator

Study	Storage Condition	Minimum time Period Covered by Data at Submission	Number of Batches (Refer to "selection of batches")
Real Time	$5^{o}C \pm 3^{o}C$	12 months	Min. 3
Accelerated	$25^{o}C \pm 2^{o}C/$ 60% RH $\pm$ 5%RH	6 months	Min. 3

If the drug product is packed in a semi-permeable container, appropriate information should be provided to assess the extent of water loss. Data from refrigerated storage should be assessed according to the evaluation section of this guideline, except where explicitly noted below.

If there is a "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 at the Real Time storage condition.
In general, "significant change" for a drug product is defined as :

1. A 5% change in assay from its initial value, or failure to meet the acceptance criteria;
2. Any degradation product exceeding the acceptance criterion;
3. Failure to meet the acceptance criteria for appearance, physical attributes, and functionality tests (e.g. colour, phase separation, resuspendability, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions and as appropriate for the dosage form.

4. Failure to meet the acceptance criteria for pH;
5. Failure to meet the acceptance criteria for dissolution for 12 dosage units (capsule or tablet).

If the "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 product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug product through 6 months when a "significant change" has occurred within the first 3 months.
This can be applied to products such as ointments, cream or suppositories that are impossible to test at accelerated condition whereas only real time testing is required.

4.6.4. Drug Products Intended for Storage in a Freezer

Study	Storage Condition	Minimum Time Period Covered by Data at Submission
Real time	$-20^{o}C \pm 5^{o}C$	12 months

For drug products intended for storage in a freezer, the shelf-life 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 products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. $5^{o}C \pm 3^{0}C$ or $25^{o}C \pm 2^{o}C$) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition.

4.6.5. Drug Products Intended for Storage Below $-20^{o}C$
Drug products intended for storage below $-20^{o}C$ should be treated on a case-by-case basis.

4.7. Container Closure System

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

When using moisture-permeable containers for packaging, due consideration should be given to the stability of the contents under high humidity conditions. Moisture may have an undesirable effect on chemical stability (e.g. some antibiotics may undergo hydrolysis) and physical stability (e.g. dissolution rate may change).

The issue of the different permeability of various packaging materials should be addressed. Therefore, it will be necessary to specify parameters, such as the material's thickness and permeability coefficient.

Generally considered moisture-impermeable containers include glass ampoules, aluminum/aluminum blisters, High Density Polyethylene (HDPE) or glass bottles fitted with metal or HDPE closures.

The effect of high humidity on solid dosage forms packaged in containers permeable to moisture should be supported by data. Examples of moisture-permeable containers include polyvinyl chloride (PVC) blisters, Low Density Polyethylene (LDPE) bottles, glass or HDPE bottles when fitted with polypropylene closures.

Parameters required to classify the packaging materials as permeable or impermeable depend on the packaging material characteristics such as thickness and permeability coefficient. The suitability of the packaging material used for a particular product is determined by its product characteristics. An Example of Types, Thickness and Permeability Coefficient of Packaging Material is provided in Annex 5.5.

4.8. 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 and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms).

The purpose of the stability study is to establish, based on testing a minimum of two or 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.

The basic concepts of stability data evaluation are the same for single-versus multi-factor studies and for full- versus reduced-design studies. Data evaluation from the stability studies and as appropriate, supporting data should be used to determine the critical quality attributes likely to influence the quality and performance of the drug product. Each attribute should be assessed separately and an overall assessment made of the findings for the purpose of proposing a shelf-life. The shelf-life proposed should not exceed that predicted for any single attribute.

In general, certain quantitative chemical attributes (e.g. assay, degradation products, preservative content) for a drug product can be assumed to follow zero-order kinetics during long-term storage. Data for these attributes are therefore amenable to linear regression and poolability testing. Although the kinetics of other quantitative attributes (e.g. pH, dissolution) is generally not known, the

same statistical analysis can be applied, if appropriate. Qualitative attributes and microbiological attributes are not amenable to this kind of statistical analysis.

Where the long-term data and accelerated data for an attribute show little or no change over time and little or no variability, it may be apparent that the drug product will remain well within its acceptance criterion for that attribute during the proposed shelf-life. Under these circumstances, it is normally considered unnecessary to go through a statistical analysis, but justification for the omission should be provided. Justification can include a discussion of the mechanisms of degradation or lack of degradation, relevance of the accelerated data, mass balance, and/or other supporting data.

Where applicable, an appropriate statistical method should be employed to analyze the long-term primary stability data in an original application. The purpose of this analysis is to establish, with a high degree of confidence, a shelf-life during which a quantitative attribute will remain within acceptance criteria for all future batches manufactured, packaged, and stored under similar circumstances. This same method could also be applied to commitment batches to verify or extend the originally approved shelf-life.

Regression analysis is considered an appropriate approach to evaluating the stability data for a quantitative attribute and establishing a shelf-life. The nature of the relationship between an attribute and time will determine whether data should be transformed for linear regression analysis. Usually, the relationship can be represented by a linear or non-linear function on an arithmetic or logarithmic scale. Sometimes a non-linear regression can be expected to better reflect the true relationship.

An appropriate approach to shelf-life estimation is to analyze a quantitative attribute by determining the earliest time at which the 95 percent confidence limit for the mean around the regression curve intersects the proposed acceptance criterion.

For an attribute known to decrease with time, the lower one-sided 95 percent confidence limit should be compared to the acceptance criterion. For an attribute known to increase with time, the upper one-sided 95 percent confidence limit should be compared to the criterion. For an attribute which can either increase or decrease, or whose direction of change is not known, two-sided 95 percent confidence limits should be calculated and compared to the upper and lower acceptance criteria.

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 levels of significant 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 can be expected to remain within acceptance criteria.
Any evaluation should consider not only the assay, but also the degradation products and other appropriate attributes. Where appropriate, attention should be

paid to reviewing the adequacy of the mass balance and different stability and degradation performance.

The statistical method used for data analysis should take into account the stability study design to provide a valid statistical inference for the estimated shelf-life. The approach described above can be used to estimate the shelf-life for a single batch or for multiple batches when combined after an appropriate statistical test.

4.9. Stability Commitment

4.9.1. When available Real Time stability data on primary batches do not cover the proposed shelf-life granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the shelf-life.

4.9.2. Where the submission includes Real Time Stability data on at least the minimum number of production batches required covering the proposed shelf-life, a post approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

a. If the submission includes data from stability studies on at least the minimum number of production batches required, a commitment should be made to continue the long-term studies through the proposed shelf-life and the accelerated studies for 6 months.

b. If the submission includes data from stability studies on fewer than 3 production batches, a commitment should be made to continue the Real Time studies through the proposed shelf-life and the accelerated studies for 6 months, and to place additional production batches, to a total of at least the minimum number of production batches required, on Real Time stability studies through the proposed shelf-life and on accelerated studies for 6 months.

c. If the submission does not include stability data on production batches, a commitment should be made to place the first 3 production batches on Real Time stability studies through the proposed shelf-life and on accelerated studies for 6 months.

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

4.9.3. Applicant must submit commitment and protocol on post approval stability study if stability study submitted has been conducted under different conditions and it cannot be demonstrated that the drug product will remain within its acceptance criteria stated in this guideline. In such cases, the following options should be considered: (1) a reduced shelf-life (2) a more protective container closure system, or (3) additional cautionary statements in the labeling.

4.9.4. Post approval stability can be conducted in any ASEAN member country, country of origin, or any country that can meet the required storage condition.

4.10. 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 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 link between the label statement and the demonstrated stability characteristics of the drug product.

The storage conditions (temperature, light, humidity) indicated should refer to the relevant national/regional requirements or following the recommendations below. The range should be based on the stability evaluation of the drug product.

The following recommendations as to storage conditions can be prominently indicated on the label:

1. Storage temperature must be stated in figures rather than in words, e.g.:
   - Store below 30^{o}C or do not store above 30^{o}C (normal storage condition)
   - Store below 25^{o}C or do not store above 25^{o}C (under controlled air-conditioning)
   - Store between 2^{o} and 8^{o}C (under refrigeration, no freezing)
   - Store below 8^{o}C (under refrigeration)
   - Store between -5^{o} and 0^{o}C (in a freezer)
   - Store below -18^{o}C (in a deep freezer)
2. The use of terms such as "ambient conditions" or "room temperature" is unacceptable.
3. General precautionary statements, such as "Protect from light" and / or "Store in a dry place", may be included, but should not be used to conceal stability problems.
4. If applicable, recommendations should also be made as to the utilization period and storage conditions after opening and dilution or reconstitution of a solution, e.g., an antibiotic injection or suspension supplied as a powder for reconstitution.
5. Where applicable specific requirements should be stated particularly for drug products that cannot tolerate freezing.

5. ANNEXES

5.1 Protocol of Stability Study (example)

5.1.1 PARACETAMOL TABLET 500 MG PACKED IN PVC BLISTER

1. Purpose

To evaluate stability of product due to the scaling up from the Research and Development to the Manufacturing Site.

2. Test Design

The product is packed in PVC blister and will be stored according to storage condition or mentioned in manufacturing instruction

2.1. Test Material

- Push-through foil
  Alufoil of 20 micron thickness, heat-seal lacquered, PVC layered (8 g/m^2), hard temper, bright side finish silver-tinted.
  Forming foil
  PVC foil of 250 micron thickness.

Batch No.	Packaging type	Storage Condition/Period
001	PVC Blister	Real Time (60 months); Accelerated (6 months)
002	PVC Blister	Real Time (60 months); Accelerated (6 months)
003	PVC Blister	Real Time (60 months); Accelerated (6 months)

2.2 Testing Plan

2.2.1 Storage condition and sampling intervals

Paracetamol tablet is filled and sealed in PVC blister, 10 blisters are packed in carton folding box and stored at the following storage condition:

Storage Condition	Sampling Intervals
Real Time storage 30°C/75% RH	0, 3, 6, 9, 12, 18, 24, 36, 48, 60 months
Accelerated 40°C/75% RH	0, 1, 3, 6 months

The detail schedule is attached.

2.2.2 Testing and Test Criteria

QA/QC Dept. is responsible for storing and testing the sample in accordance with the storage condition and the valid test method.
The samples are taken out of the storage prior to the planned testing date, and kept at 5°C until the time for analysis.
The analytical work should be concluded not later than 4 weeks after the samples have been out of storage.
The testing procedure is: No. XXXX.and the parameters to be tested are as follows:

a. Physical test
   - appearance
   - average weight
   - dissolution
   - disintegration time
   - hardness
   - friability
   - water content
b. Content : Paracetamol
c. Degradation Product : p-aminophenol

3. Number of Samples (of one batch / storage condition)

3.1. Accelerated Test

- Appearance	:	0*	tablets	number of testing : 4 times
- water content	:	10	tablets	Quantity needed
- disintegration	:	6	tablets	= 4 x 100 tablets
- dissolution	:	6	tablets	= 400 tablets
- content & impurity	:	10	tablets	= 40 blisters of 10 tablets
- hardness	:	10	tablets	= 4 boxes
- friability	:	50	tablets	
	→	= 92	tablets ~	rounded to 100 tablets

3.2. Real Time Stability Study

- Appearance	:	0*	tablets	number of testing : 9 times
- water content	:	10	tablets	quantity needed
- disintegration	:	6	tablets	= 9 x 100 tablets
- dissolution	:	6	tablets	= 900 tablets
- content & impurity	:	10	tablets	= 90 blisters of 10 tablets
- hardness	:	10	tablets	= 9 boxes
- friability	:	50	tablets	
	→	= 92	tablets ~	rounded to100 tablets
			Total	= 13 boxes of 10 blisters

* = observation made on tablets allocated for other tests

4. Report Content :

1. Responsibility
2. Summary
3. Objective
4. Test Material
5. Composition
6. Packaging
7. Storage condition and testing materials (Schedule)
8. Analytical Procedures
9. Reference Standard
10. Results
    - 10.1. Physical Stability
    - 10.2. Chemical Stability
        - 10.2.1. Stability under real time storage condition
        - 10.2.2. Stability under accelerated storage condition
11. Discussion/Conclusion
12. Test result in tabular form

Approved by : Checked by: Prepared by :

5.1.2. Schedule for Stability Study
Paracetamol Tablet 500 mg

Dated:
02.07.1997

Storage		Schedule		
		Batch No.	Batch No.	Batch No.
Period	**Condition**	**001**	**002**	**003**
Initial	Accelerated	July 02, 1997	July 09, 1997	July 16, 1997
	Real Time	July 04, 1997	July 12, 1997	July 18, 1997
1 Month	Accelerated	Aug 02, 1997	Aug 09, 1997	Aug 16, 1997
3 Months	Accelerated	Oct 02, 1997	Oct 09, 1997	Oct 16, 1997
	Real Time	Oct 04, 1997	Oct 12, 1997	Oct 18, 1997
6 Months	Accelerated	Jan 02, 1998	Jan 09, 1998	Jan 16, 1998
	Real Time	Jan 04, 1998	Jan 12, 1998	Jan 18, 1998
9 Months	Real Time	Apr 04, 1998	Apr 12, 1998	Apr 18, 1998
12 Months	Real Time	Jul 04, 1998	Jul 12, 1998	Jul 18, 1998
18 Months	Real Time	Jan 02, 1999	Jan 12, 1999	Jan 18, 1999
24 Months	Real Time	Jul 04, 1999	Jul 12, 1999	Jul 18, 1999
36 Months	Real Time	Jul 04, 2000	Jul 12, 2000	Jul 18, 2000
48 Months	Real Time	Jul 04, 2001	Jul 12, 2001	Jul18, 2001
60 Months	Real Time	Jul 04, 2002	Jul 12, 2002	Jul 18, 2002

Remarks :

Accelerated : $40^{o}C \pm 2°C/75\%$ RH $\pm$ 5% RH
Real Time : $30°C \pm 2°C/75\%$ RH $\pm$ 5% RH

Approved by: Checked by: Prepared by :

5.2. Report Format (example)

DRUG PRODUCT: **PARACETAMOL TABLET**

STRENGTH:	500 mg	Date: 23/07/02
Doc. No.:	XXXX.	Page 20 of 1

Study Type:	Pre- and post-market Stability
Objective:	Stability profile of the drug product for storage under real time and accelerated conditions
Period of Investigation:	60 Months
Packaging:	PVC Blister
Originating Site :	MMM Ltd Jakarta - Indonesia

Stability Study Unit :	R&D Dept. John Doe
Quality Assurance :	Tom Smith

---

1. RESPONSIBILITY

Persons in Charge	Site / Department	Responsibility
John Doe	R&D	Physical and chemical tests
John Doe	R&D	Microbiological tests

2. SUMMARY

This report presents the stability data on Paracetamol tablet 500 mg stored up to 60 months in the primary packaging used for marketing.

Any storage-related changes occuring in the finished product were monitored by means of stability-specified control tests. The test design was based on the stability profile of the drug substance paracetamol and on the specific requirements of the dosage form.

Shelf-life:
The product has a shelf-life of five years

Storage Directions:
The finished product is not labelled with any storage directions.

3. OBJECTIVE

The objective of the present study on Paracetamol tablet 500 mg is the assessment of the stability profile for storage under real time and accelerated conditions. The samples were in inverted position to ensure contact with the container closure system.

4. TEST MATERIAL

The batches under stability testing are listed in the following table with further details:

Dosage	Batch No.	Manufacturing		Scale	Batch Size (Pack)	Drug Substance Batch No.
		Date	Site			
500 mg/tab	001	July 02, 1997	Jakarta	Production	2800	004
500 mg/tab	002	July 09, 1997	Jakarta	Production	2800	005
500 mg/tab	003	July 16, 1997	Jakarta	Production	2800	006

5. COMPOSITION

1 tablet of Paracetamol contains :

Composition	Weight [mg]
Paracetamol	500.00
Lactose $1H_2O$	79.00
Maize Starch	65.50
Pregelatinized Maize Starch	5.00
Talc	3.00
Colloidal Anhydrous Silica (Aerosil 200)	2.00
Magnesium Stearate	0.50
Total	655.00

6. PACKAGING

The stability tests on the batches listed above are performed in the following primary packaging:

The product is packed in PVC blister consisting of:

- Push trough foil : Alufoil of 20 micron thickness, heat-seal lacquered, PVC layered (8 g/m^2), hard temper, bright side finish silver-tinted.
- Forming foil : PVC foil of 250 micron thickness.

7. STORAGE CONDITIONS AND TESTING INTERVALS

The various samples of the packaged drug product have been / will be tested according to the following schedule:

Storage Condition											
	0	1	3	6	9	12	18	24	36	48	60
30°C ± 2°C/75% RH ± 5% RH	X	-	X	X	X	X	X	X	X	X	X
40°C ± 2°C/75% RH ± 5% RH	X	X	X	X	-	-	-	-	-	-	-

8. ANALYTICAL PROCEDURES

The stability tests on Paracetamol were performed according to the control tests of USP.
In the course of the stability testing the main emphasis was put on the stability-relevant test items as listed below:

Test Item	Control Test No.	Specification
Hardness	USP	≥ 70 N
Friability	USP	≤ 2%
Degradation Product • p-aminophenol	USP	≤ 0.005%
Microbial Contamination	USP	Total count ≤ 10^2 CFU E.coli : absent
Content (LC)	USP	95.0 – 105.0 %

Note: As mentioned in 2.1.2, 3.1 and 3.2, Disintegration Time and Dissolution should be added.

9. REFERENCE STANDARD

Standard Paracetamol USP, 99.5%, was used.

10. RESULTS

The test results of the study are presented in the tables attached.

10.1. Physical Stability

The physical stability of Paracetamol tablet 500 mg proved to be unchanged after storage up to 60 months at 30°C/75% RH and after 6 months under accelerated conditions at 40°C/75% RH.
The result obtained for the test item's "appearance" was not changed significantly.

10.2. Chemical Stability

10.2.1. Stability under Real time Conditions

Storage for up to 60 months at 30°C/75% RH had no significant effect on the chemical stability of the drug product. With regard to test item "Organic Impurity" only slight changes were observed. The p-aminophenol concentration was below 0.005%.

The content of paracetamol did not change significantly after storage under real time conditions compared to initial assay of the batches.

10.2.2. Stability under Accelerated Conditions

Storage under accelerated conditions for 6 months did not effect the chemical stability.

The content of paracetamol was not significantly changed compared to the initial value of the batches.

11. DISCUSSION / CONCLUSIONS

Storage under real time testing conditions causes insignificant change of assay results of paracetamol. Significant changes in physical and chemical stabilities were not observed. Since the long-term data and accelerated data show little or no change over time and little variability, a statistical analysis is considered unneecessary.

Shelf-life:
Based on the result data the shelf-life has been established for five years.

Storage Directions:
The product can be labelled with "Store below 30°C"

Summary of Stability Study Result

Table 1

Drug Product : Paracetamol
Dosage : 500 mg/tablet
Packaging : PVC Blister
Batch No. : 001

Storage		Appearance	Hardness [N]	Friability [%]	Content : Paracetamol 500 mg	Degradation Product	Microbial Contamination
Time [Months]	Conditions					p-aminophenol [%]	
Specifications		White, round-flat tablet	≥ 70 N	≤ 2 %	95.0 – 105.0%	≤ 0.005%	Total count ≤ 10^2 CFU **E.coli: absent**
Initial	-	Complies	80	1	98.8	0.001	Complies
3	30°C ± 2°C/ 75% RH ± 5%RH	Complies	80	1	101.4	0.002	Complies
6		Complies	85	0.5	98.3	0.004	Complies
9		Complies	90	0.5	99.6	0.001	Complies
12		Complies	85	1	98.9	0.003	Complies
18		Complies	97	1	99.0	0.003	Complies
24		Complies	94	0.5	98.9	0.004	Complies
36		Complies	87	1	99.1	0.002	Complies
48		Complies	98	1	99.5	0.001	Complies
60		Complies	93	0.5	99.3	0.001	Complies
3	+40°C ± 2°/75% RH ± 5%RH	Complies	96	0.5	100.5	0.004	Complies
6		Complies	80	0.5	99.6	0.004	Complies

Note: - More data on disintegration time or dissolution are required for each batch.
- For batch number 002 and 003, study results are provided in the same format as batch number 001.

5.3 Reduced Design (Bracketing and Matrixing)

A full study design is one in which samples for every combination of all design factors are tested at all time points. A reduced design is one in which samples for every factor combination are not all tested at all time points. A reduced design can be a suitable alternative to a full design when multiple design factors are involved. Any reduced design should have the ability to adequately predict the shelf-life. Before a reduced design is considered, certain assumptions should be assessed and justified. The potential risk should be considered of establishing a shorter shelf-life than could be derived from a full design due to the reduced amount of data collected.

During the course of a reduced design study, a change to full testing or to a less reduced design can be considered if a justification is provided and the principles of full designs and reduced designs are followed. However, proper adjustments should be made to the statistical analysis, where applicable, to account for the increase in sample size as a result of the change. Once the design is changed, full testing or less reduced testing should be carried out through the remaining time points of the stability study.

Applicability of Reduced Designs
Reduced designs can be applied to the stability study of most types of drug products, although additional justification should be provided for certain complex drug delivery systems where there are a large number of potential drug-device interactions.

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.

Design Example
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 combinations 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 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.

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

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

Design Examples

Examples of matrixing designs on time points for a product in two strengths (S1 and S2) are shown in Table 2. The terms "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, final, and 12-month time points. 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: Examples of Matrixing Designs on Time Points for a Product with Strengths

"One-Half Reduction"

Time point (months)			0	3	6	9	12	18	24	36
STRENGTH	S1	Batch 1	T	T		T	T		T	T
		Batch2	T	T		T	T	T		T
		Batch3	T		T		T	T		T
	S2	Batch 1	T		T		T		T	T
		Batch2	T	T		T	T	T		T
		Batch3	T		T		T		T	T

Key: T = Sample tested

"One-Third Reduction"

Time point (months)			0	3	6	9	12	18	24	36
STRENGTH	S1	Batch 1	T	T		T	T		T	T
		Batch2	T	T	T		T	T		T
		Batch3	T		T	T	T	T	T	T
	S2	Batch 1	T		T	T	T	T	T	T
		Batch2	T	T		T	T		T	T
		Batch3	T	T	T		T	T		T

Key: T = Sample tested

More details are described in ICH Q1D.

5.4 Extrapolation of Data

Limited extrapolation to extend the retest period or shelf-life beyond the observed range of available long-term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition. Any extrapolation should take into consideration the possible worst-case situation at the time of batch release.

Extrapolation is the practice of using a known data set to infer information about future data sets. An extrapolation of stability data assumes that the same change pattern will continue to apply beyond the observed range of available long-term data. Hence, the use of extrapolation should be justified in terms of, for example, what is known about the mechanisms of degradation, the goodness of fit of any mathematical model, and the existence of relevant supporting data.

The correctness of the assumed change pattern is crucial if extrapolation beyond the available long-term data is contemplated. For example, when estimating a regression line or curve within the available 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 available beyond the length of observed data. Thus, 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 extrapolated shelf-life.

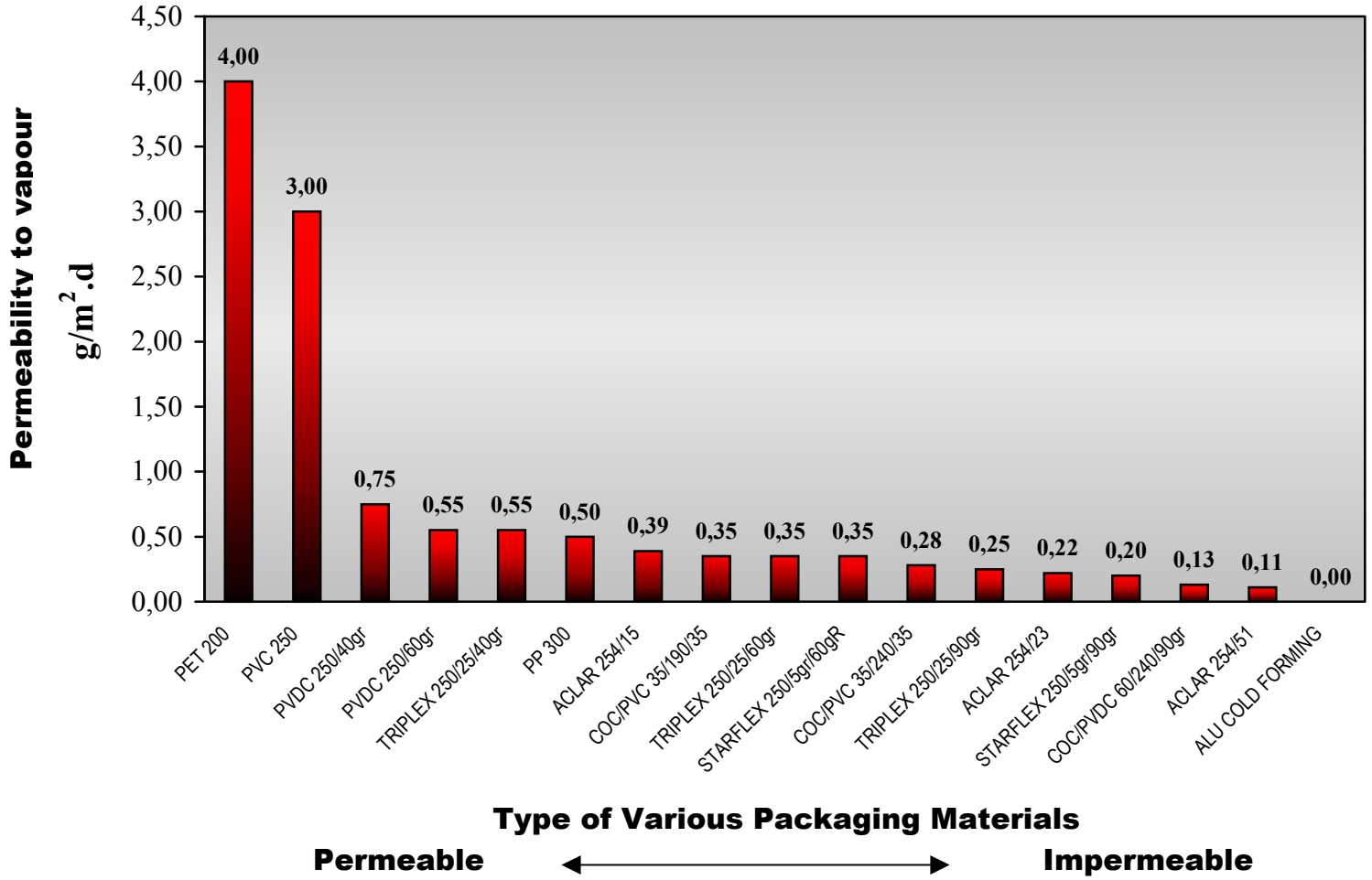
If the real time data are supported by results from accelerated studies, the shelf-life may be extended beyond the end of real time studies. The extrapolated shelf-life may be up to twice, but should not be more than 12 months beyond, the period covered by real time data, depending on the change over time, variability of data observed, proposed storage conditions and extent of statistical analyses performed.

5.5 Example of Types, Thickness and Permeability Coefficient of Packaging Materials can be seen in Table-1 and Permeability to Vapour of Various Packaging Materials can be seen in Figure-1.

Table-1 : Example of Types, Thickness and Permeability Coefficient of Packaging Materials

No.	Material	Thickness	Thickness Commonly Used (µm)	SPECIFICATION PERMEABLITY		Thermo-formability
				At 23°C / 85%RH (g/m².d)	At 38°C / 90%RH (g/m².d)	
1	**PVC** (Polyvinyl Chloride)	250 µm	200 - 250 µm	1,6 - 1,8	3,0 - 3,2	Good
2	**Duplex (PVC + PVDC)**		270 µm			Good / Excellent
	PVC (Polyvinyl Chloride)	200 – 250 µm				
	PVDC (Polyvinylidene Chloride)	5 µm for spread of 10 g/m² (40 - 60 - 80 g/m²)	40g/m²	0,15	0,6	
			60g/m²	0,1	0,4	
			80g/m²	0,05	0,3	
3	**Triplex (PVC + PE + PVDC)**		300 µm			Good/Excellent (according to thickness)
	PVC (Polyvinyl Chloride)	200 – 250 µm				
	PE (Polyethylene)	25 µm				
	PVDC (Polyvinylidene Chloride)	5 µm for spread of 10 g/m² (40 - 60 - 90 g/m²)	40g/m²	0,12	0,55	
			60g/m²	0,06	0,35	
			90g/m²	0,02	0,2	
4	**Starflex (PVC + TE + PVDC)**		Max. 300 µm			Good/Excellent (according to thickness)
	PVC (Polyvinyl Chloride)	200 - 250 µm				
	TE (Thermolast)	Spreading TE (coating) 5 g/m²				
	PVDC (Polyvinylidene Chloride)	5 µm for spread of 10 g/m² (60 - 90 - 120 g/m²)	60g/m²	0,06	0,35	
			90g/m²	0,03	0,2	
			120g/m²	0,01	0,15	
5	**PVC + ACLAR**		270 µm			Excellent
	PVC (Polyvinyl Chloride)	200 - 250 µm				
	ACLAR (Polyfluor Carbonat)	15-23-51 µm	15g/m²	-	0,39	
			23g/m²	-	0,22	
			51g/m²	-	0,11	
6	**PVC/PE/ACLAR**		280 µm			Excellent
	PVC (Polyvinyl Chloride)	200- 250 µm				
	PE (Polyester)	25 µm				
	ACLAR (pfc)	15 - 51 µm	15 µm	-	< 0.32	
			51µm	-	< 0.11	
7	**Aluminum Cold Forming**		130 µm	-	0	Excellent
	Aluminum	40 µm - 45 µm		-	-	
	PVC rigid	60 µm		-	-	
	OPA	25 µm		-	-	
8	**Aluminum Foil Hard Temper (Lidding Foil)**		20 µm	-	-	
	Alublister for PVC Foil			-	-	
	- Aluminum	20 µm		-	-	
	- PVC	min. 7 g/m²		-	-	
	Alublister for PVC - PVDC Foil		30 µm	-	-	
	- Aluminum	20 µm		-	-	
	- PVDC	15 g/m²		-	-	
9	**Aluminum Foil for Soft Temper**		40 µm	-	-	
	- Aluminum	30 µm				
	- PVDC	15 g/m²				

Figure 1 Permeability to Vapour of Various Packaging Materials (Method ASTM F1249, 38°C/90%RH)



6. GLOSSARY

Accelerated Testing

Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies.(Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated condition 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**;** see also Stability and related terms)

Bracketing

The design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all time points as in a full design.
(The design assumes that the stability of any intermediate level is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition [e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weight of the same basic composition into different size capsule shell]. Bracketing can be applied to different container sizes or different fills in the same container closure system).

Climatic Zones
The four zones into which the world is classified based on the prevailing annual climatic conditions, i.e.:
Zone I : temperate
Zone II : sub-tropical, with possible high humidity
Zone III : hot and dry
Zone IV : hot and humid

Commitment batches
Production batches of a drug substance or drug product for which the stability studies are 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 components, if latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Dosage Form
A pharmaceutical product type (e.g.**,** tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Drug Product/Pharmaceutical Product
Any preparation for human use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

Drug Substance
The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.(See also Active Pharmaceutical Ingredient in the Glossary of Term of ACTD Quality)

Excipient
An ingredient, added intentionally to the drug substance, which should not have pharmacological properties in the quantity used.

Expiry Date
The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf-life specification if stored under defined conditions. (After the expiry date, there is no guarantee that the product will remain within the approved specifications and, therefore, it may be unsuitable for use and should not be used).

Major Variation (MaV)
Variation to authorized pharmaceutical product affecting one or more of the following aspects :

- route of administration
- strength, posology
- indication, or
- or that does not fall within the definition of mi**n**or variation

(Applications for major variations usually require the submission of data necessary to establish quality, safety and efficacy of the new formulation resulting from the variation).

Impermeable Containers
Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions.

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 factors 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).

Minor Variation (MiV)
Variation to authorized pharmaceutical product not affecting one or more of the following aspects :

- route of administration
- strength, posology
- indications, and
- active ingredient(s)

(Applications for minor variations usually require the submission of data necessary to establish quality of the new formulation resulting from the variations**).**

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, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger unless otherwise justified).

Primary Batch
A batch of a drug substance or drug product used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf-life, respectively. (A primary batch of a drug substance should be at least a pilot scale batch. For a drug product, two of the three batches should be at least pilot scale batch, 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 Testing
Stability studies under the recommended storage condition for the re-test period or shelf life proposed (or approved) for labeling.

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

Shelf-life(also referred to as expiration dating period)
The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the condition defined on the container label.

Specification
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, drug product or material at other stages of its manufacture should conform to be considered acceptable for its intended use. "Conformance to specification" means that the drug substance and drug product, when tested according to the

listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval).

Specifications – Release
The specifications that determine the suitability of a drug product at the time of its release. (See also Specification)

Specification – Shelf-life
The specifications that determine the suitability of a drug substance throughout its re-test period, or that a drug product should meet throughout its shelf-life.

Stability
The ability of an active ingredient or a drug product to retain its properties within specified limits throughout its shelf-life. (The chemical, physical, microbiological and biopharmaceutical aspects of stability must be considered).

Stability Studies
Real time and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or shelf life of a drug product.

Storage Condition 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 the current relevant guidelines. The actual temperature and humidity - when controlled - 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, and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effect assessed).

Stress Testing (Drug Product)
Studies undertaken to assess the effect of severe condition on the drug product. (Such studies include photo-stability testing; - see ICH Q1B - and specific testing on certain products, e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

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.

Supporting Data
Data, other than those from formal stability studies, that support the analytical procedures, the proposed re-test period or shelf-life, and the label storage statements. (Such data include (1) stability data on early synthetic route batches of drug substance, small scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing; (2) information regarding test results on containers; and (3) other scientific rationales).

REFERENCES

1. Note for Guidance on Stability Testing of Existing Active Substance and Related Finished Product (Draft), February 2002, The European Agency for The Evaluation of Medicinal Product (EMEA)
2. ICH Q1A (R2) Guideline on Stability Testing of New Drug Substances and Product, February 2003 and its annexes (Q1B Photostability Testing of New Drug Substances and Producsts, Q1C Stability Testing : Requirements for New Dosage Forms, Q1D Bracetting and Matrixing Designs for Stability Testing of New Drug Substances and Products, Q1E Evaluation for Stability Data, Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV).
3. Guidelines for Stability Testing of Pharmaceutical Products Containing Well Established Drug Substances in Conventional Dosage Form, WHO Technical Report Series No. 863, 1996.
4. ASEAN Operational Manual of Good Manufacturing Practice, 2000.
5. Carstensen, J.T., "Stability and Dating of Solid Dosage Forms," *Pharmaceutics of Solids and Solid Dosage Forms*, Wiley-Interscience, 182-185, 1977.
6. Ruberg, S.J. and Stegeman, J.W., "Pooling Data for Stability Studies: Testing the Equality of Batch Degradation Slopes," *Biometrics*, 47:1059-1069, 1991.
7. Ruberg, S.J. and Hsu, J.C, "Multiple Comparison Procedures for Pooling Batches in Stability Studies," *Technometrics*, 34:465-472, 1992.
8. Shao, J. and Chow, S.C., "Statistical Inference in Stability Analysis," *Biometrics*, 50:753-763, 1994.
9. Murphy, J.R. and Weisman, D., "Using Random Slopes for Estimating Shelf-life," *Proceedings of American Statistical Association of the Biopharmaceutical Section*, 196-200, 1990.
10. Yoshioka, S., Aso, Y, and Kojima, S., "Assessment of Shelf-life Equivalence of Pharmaceutical Products," *Chem. Pharm. Bull.*, 49:1482-1484, 1997.
11. Chen, J.J., Ahn, H., and Tsong, Y., "Shelf-life Estimation for Multifactor Stability Studies," *Drug Inf. Journal*, 31:573-587, 1997.
12. Fairweather, W., Lin, T.D., and Kelly, R., "Regulatory, Design, and Analysis Aspects of Complex Stability Studies," *J. Pharm. Sci*., 84 (11):1322-1326, 1995.