Association of South East Asian Nations (ASEAN)

ANNEX V
ASEAN GUIDELINES ON STABILITY STUDY AND SHELF-LIFE OF TRADITIONAL MEDICINES

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This document is provided for information purpose only and subject to changes, pending the finalisation of the ASEAN Agreement on Regulatory Framework for Traditional Medicines. Official references to this document can only be made once the said Agreement has been finalised.

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DOCUMENT INFORMATION

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INTRODUCTION

Stability is an essential factor of quality in traditional medicines (TM). It is determined by a series of tests conducted, namely to ensure maintenance of the specifications of the finished product when packed in its specified packaging material and stored in the established storage condition within the determined shelf-life.

The aim of conducting a stability study on TM is to determine its shelf-life as a finished product in its container closure system under the recommended storage condition, within which the finished product still meets its established physical, microbiological and/or chemical specifications.

OBJECTIVE

This guideline is intended to provide recommendations on the core stability study required for products; nevertheless it 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.

DESIGN

1. GENERAL

The design of a stability study for the product should be based on the nature of the product. It should take into account of the following:

- Selection of batches;
- Specifications/Testing parameters;
- Testing frequency;
- Storage condition.
- Container closure system

2. SELECTION OF BATCHES

Stability data should be provided for batches of the same formulation and dosage form in the container closure system intended for marketing.

- Stability data from at least two batches would be required, derived either from pilot scale, primary scale, production scale or their combination.
- The manufacturing process of batches used in stability studies should simulate that of production batches and should be of the same quality as well as meet the same specification as those batches intended for marketing.
- Stability studies should be performed on individual strengths of the product and/or type of container closure system in which the finished product is packed unless bracketing/matrixing is applied as in Appendix 1.

3. SPECIFICATION / TESTING PARAMETERS

A stability study should cover the testing of the physical, chemical, and microbiological properties of a finished product that are susceptible to change during storage and are likely to influence quality when changed.

The list of testing parameters is presented as a guide for the types of tests to be included in a stability study as in Appendix 2.

The list of tests for each product is not intended to be exhaustive, nor is it expected that every listed test to be included in the design of the stability study protocol for a particular finished product.

For a product containing ingredients without known marker(s), physical parameters may be used as surrogate indicators during storage, when the use of such parameters can be justified. The physical parameters of the finished product can be checked by at least one of the following test methods:

I. Gross organoleptic analysis; Examination by general impression
II. Other scientifically valid criteria.

For a combination product containing multiple active ingredients, although it may not be necessary to assay all the active ingredients, it may be appropriate to assay one, and in some cases, more than one active ingredient, or a surrogate marker that is known to be susceptible to change during storage and is likely to influence the quality of the combination product. A valid justification shall be submitted.

4. TESTING FREQUENCY

For accelerated and real time stability studies, frequency of testing should be sufficient to establish the stability profile of the finished product. At the accelerated storage condition,

a minimum of three time points, including the initial and final time points, for example, 0, 3, and 6 months for a 6-month study, is recommended.

The frequency of testing at real time storage conditions 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. A typical testing frequency is as shown in Table 1 below.

Table 1 A typical testing frequency

Storage Condition	Testing Frequency
Real Time	0, 3, 6, 9, 12, 18, 24 months and annually there after through the proposed shelf-life
Accelerated	0, 3 and 6 months

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, as in Appendix 1.

Where an expectation (based on development experience) exists that outcomes from accelerated studies are likely to approach significant change criteria, i.e. parameters tested are out of the specifications set, it is advised an 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.

If the "significant change" occurs within the first 3 months' testing at the accelerated storage condition, a justification should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipping or handling. This justification can be supported, if appropriate, by further testing on a single batch of the product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through the remaining months when a "significant change" has occurred within the first 3 months, and as such the shelf-life shall be based on real time data. This can be applied to products such as ointments, cream, or suppositories that are impossible to test at accelerated condition where by only real time testing shall be required.

If "significant change" occurs between 3 and 6 months' testing at the accelerated storage condition, shelf-life shall be based on real time data.

5. STORAGE CONDITION

In general, TM as a finished product should be evaluated under its storage conditions (with appropriate tolerances) that test its thermal stability under recommended storage conditions 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, for example, after reconstitution or dilution as recommended in the labelling.

Specific recommended temperature and relative humidity conditions for storage applied to stability studies and types of container closure system are based on the nature of the products and the type of primary container used, in accordance with recommended storage condition on product label. Common storage conditions are shown in Table 2 below.

Table 2 Common storage conditions

TYPE OF CONTAINER CLOSURE SYSTEM / STUDY	STORAGE CONDITION
Products in primary containers permeable to water vapour	30°C ± 2°C/75% RH ± 5% RH
Products in primary containers impermeable to water vapour	30°C ± 2°C
Accelerated studies	40°C ± 2°C/75% RH ± 5% RH

If submitted data is based on conditions that are less stressful (e.g. 30°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;
- The type of container closure system

Other storage conditions are allowable, if justified. Examples would include:

- Heat sensitive products which should be stored under lower temperature condition which will eventually become the designated long term storage temperature.

- Products containing less stable active ingredients and formulations not suitable for storage at elevated temperature (e.g., suppositories) will need real time stability studies.
- 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 ± 2°C, 60% RH ± 5% RH. The designated real time testing conditions will be reflected in the labelling and shelf-life (expiration date). Typical storage conditions recommended for stability studies on products intended for storage in a refrigerator as shown in Table 3 below

Table 3 Typical storage conditions recommended for products intended in a refrigerator

STUDY	STORAGE CONDITION
Real Time	5°C ± 3°C
Accelerated	25°C ± 2°C/60% RH ± 5% RH

- 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.

Data from the accelerated stability studies can be used to evaluate the effect of short-term excursions outside the label storage conditions such as during shipping. The data from accelerated study and ongoing real time stability study can be used to justify an interim extrapolated shelf-life. However, the actual shelf-life should be based ultimately on the real time stability data at the recommended storage conditions.

6. CONTAINER CLOSURE SYSTEM

Stability testing should be conducted on the product packaged in the primary container closure system proposed for marketing including, as appropriate, any secondary packaging.

Finished products packed in moisture-impermeable primary containers are not required to be tested under high humidity conditions. Generally considered moisture- impermeable

containers include aluminum/aluminum blisters, High Density Polyethylene (HDPE) or glass bottles fitted with metal or HDPE closures .

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 and physical stability of a finished product.

The issue of the different permeability of various packaging materials should be addressed e.g. the effect of high humidity on solid dosage forms packaged in containers permeable to moisture should be supported by data and an indication, like "keep in a dry place or protect from moisture" should be added to the label. Examples of moisture permeable containers include polyvinyl chloride (PVC) blisters, low density polyethylene (LDPE) bottles, glass or HDPE bottles when fitted with polypropylene closures.

7. 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. Any evaluation should consider not only the assay, but also other appropriate test attributes. A recommended presentation of the summary table of stability results appears as in Appendix 3.

8. LABELLING

The storage conditions that include temperature, light and humidity indicated on the label should be based on the stability evaluation of the product. 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 of the finished product. Specific instruction on storage condition should be provided. Terms such as `ambient conditions' or 'room temperature' should be avoided.

GLOSSARY

Assay

A test procedure for measuring or determining the quantity of active ingredient or marker in a finished product.

Batch

A quantity of the finished product produced during a given cycle of manufacture and from a specific formulation order, that is uniform in character and quality [the essence of a manufacturing batch is its homogeneity]

Pilot Scale Batch

A batch of substances or product manufactured by procedure fully representative of and simulating that to be applied to a full production scale batch. A pilot scale is generally, at minimum, one tenth that of a full production scale.

Primary Scale Batch

A batch of product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. A primary scale may comprise ten to one hundred percent of a full production scale.

Production Scale Batch

A batch of product manufactured at production scale by using production equipment in a production facility as specified in the 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 finished product. A packaging system is equivalent to a container closure system.

Disintegration

The rate that tablets or capsules disintegrate within the prescribed time when placed in a liquid medium and under the experimental conditions as prescribed in references such as official pharmacopoeia.

Dissolution

The quantity of active substance dissolved in a specified time, expressed as a percentage of the content stated on the product label.

Expiry Date

The date placed on the container label of a finished 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.

Hardness/friability

Is the resistance to crushing of tablets, measured by the force needed to disrupt it by crushing.

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.

Water content

A measure of free water content of product when surrounded by air at a specified relative humidity and temperature.

Microbial content

Is the amount of microorganisms including bacteria, yeast and mold present in the product.

pH

The pH value of an aqueous solution is a number describing its acidity or alkalinity. A pH is the negative logarithm (base 10) of the concentration of hydrogen ions (equivalent per liter). The pH value of a neutral solution is 7. An acidic solution has a pH less than 7, while a basic solution has a pH greater than 7, up to 14.

Shelf-life (also referred to as expiration date period)

The time period during which a product is expected to remain within the approved specification provided 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 substance, 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 substance and 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).

Stability Study Protocol

A document describing rationale, goals, methodology, and statistical methods of the stability study which specifies the terms and conditions under which the stability study must be conducted and managed.

Stability Studies

Real time and accelerated studies/testing undertaken on primary batches according to a prescribed stability protocol to establish or confirm the re-test period of a substance or shelf-life of a finished product.

- Accelerated Stability Studies

Studies designed to increase the rate of chemical degradation or physical change of a finished 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).

- Real Time Stability Studies

Stability studies under the recommended storage condition for the re-test period or shelf-life proposed (or approved) for labeling.

Storage Condition

Condition for intended storage of a finished product defined on the container label based on the stability study.

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.

Viscosity

The tendency of a fluid to resist flowing because of molecular attraction (cohesion). Is a property of liquid that is closely related to its resistance to flow.

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APPENDICES

APPENDIX 1 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 whereas 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 when establishing a shorter shelf-life using a reduced design should be considered due to the reduced amount of data collected compared to data derived from a full design.

During the course of a reduced design study, a change to full testing or to a less reduced design can be considered if justification is provided and the principles of full designs and reduced design studies 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.

Bracketing

Bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors, for example, 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 Appendix Table 1 below. This example is based on a product available in three strengths and three container sizes. In this example, it 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.

Appendix 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 finished 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 finished 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 (SI and S2) are shown in Appendix Table 2 below. 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 Appendix Table 2, the reductions are less than 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 as shown in Appendix Table 2.

Appendix Table 2: Example of Matrixing Design on Time Points for a Product with Strengths "One-Half Reduction"

Time point (months)			0	3	6	9	12	18	24	36
Strength	S1SI	Batch1	T	T		T	T		T	T
		Batch2	T		T		T	T		T
	S2S2	Batch1	T		T		T		T	T
		Batch2	T	T		T	T	T		T
				At least 6 out of 12 time points				At least 4 out of 8 time points		

Examples of Matrixing Designs on Time Points for a Product with Strengths "One-Third Reduction"

Time point (months)			0	3	6	9	12	18	24	36
Strength	S1SI	Batch1	T	T		T	T	T	T	T
		Batch2	T	T	T		T	T		T
	S2S2	Batch1	T		T	T	T	T	T	T
		Batch2	T	T		T	T		T	T
				At least 8 out of 12 time points				At least 6 out of 8 time points		

Time point (months)			0	3	6	9	12	18	24	36
Strength	S1S1	Batch1	T	T		T	T	T	T	T
		Batch2	T	T	T		T	T		T
	S2S2	Batch1	T		T	T	T	T		T
		Batch2	T	T		T	T		T	T
	S3S3	Batch1	T		T	T	T	T	T	T
		Batch2	T	T		T	T		T	T
				At least 12 out of 18 time points				At least 8 out of 12 time points		

Key: T = Sample tested

APPENDIX 2 TABULATED LIST OF STABILITY INDICATING PARAMETERS FOR TRADITIONAL MEDICINE

The tabulated list of parameters for each dosage form is presented as a guide for the following types of tests to be included in a stability study.

TM Dosage Form

Testing Parameters / TM Dosage Form	Organoleptic characteristics	Assay	Hardness/ friability	Dissolution /Disintegration	Water content	Viscosity	pH	Microbial content	Granules/Particle Size variation	Resuspendability	Adhesiveness
Oral powder	√	√			√			√			
Hard capsule	√	√		√	√			√			
Soft capsule	√	√		√				√			
Coated and Uncoated Tablet	√	√	√	√	√			√			
Coated and Uncoated Pill/Pellet	√	√		√	√			√			
Suspension	√	√				√	√	√	√	√	
Solution	√	√				√	√	√			
Emulsion	√	√				√	√	√			
Semi Solid Preparations (Ointment/Cream/Gel/Lotion/Paste)	√	√				√	√	√			
Plaster	√	√						√			√
Granules	√	√			√			√	√		

Testing Parameters / TM Dosage Form	Organoleptic characteristics	Assay	Hardness/ friability	Dissolution /Disintegration	Water content	Viscosity	pH	Microbial content	Granules/Particle Size variation	Resuspendability	Adhesiveness
Herbal Infusion Bag /Herbal Tea Bag	√	√			√			√			
Pastilles	√	√			√			√			

APPENDIX 3 RECOMMENDED PRESENTATION OF THE SUMMARY TABLE OF STABILITY RESULTS

Product Name	:		Storage Conditions	:	
Dosage Form	:		Batch No.	:	
Strength	:		Manufacturing Date	:	
Container	:		Date of Report	:	
Pack Size	:		Period of the study	:	

Testing Parameters (as applicable)	Permissible Level /Acceptance Criteria	Testing Frequency (Months)							
		0	3	6	9	12	18	24	
Organoleptic characteristics									
Assay									
Hardness/Friability									
Dissolution/Disintegration									
Water content									
Viscosity									
pH									
Microbial content									
Granules/Particle size variation									
Resuspendability									
Adhesiveness									

Conclusion:

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