National Consultation: ASEAN Traditional Medicines (TM) and Health Supplements (HS)

05 January 2015
AVR, 3rd Floor FDA Annex Building
Presentation Outline

A. Objectives
B. Introduction to ASEAN
C. Current Status
D. ASEAN Agreements on TM and HS
E. Annexes to the Agreement

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2. Annex II – ASEAN Guiding Principles for the Use of Additives and Excipients in Traditional Medicines and Health Supplements
Presentation Outline

3. Annex III – ASEAN Guidelines on Limits of Contaminants for Traditional Medicines and Health Supplements

4. Annex IV – ASEAN Guidelines for Minimising the Risk of Transmission of Transmissible Spongiform Encephalopathies in Traditional Medicines and Health Supplements
5. Annex V – ASEAN Guidelines on Stability and Shelf-Life of Traditional Medicines and Health Supplements

6. Annex VI – ASEAN Guiding Principles on Safety Substantiation for Traditional Medicines and Health Supplements
Presentation Outline


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Presentation Outline


10. Annex X – ASEAN General Principles for Establishing Maximum Levels of Vitamins and Minerals in Health Supplements
Objectives

- To provide information in preparation for the adoption and implementation of the ASEAN Guidelines for TM and HS
- To gather feedback/comments from various stakeholders for deliberation of the ASEAN TMHS PWG
The ASEAN
What is ASEAN?

- Member countries (Original)
  - Philippines
  - Indonesia
  - Singapore
  - Malaysia
  - Thailand
  1984
  - Brunei
  1995
  - Viet Nam
  1997
  - Laos
  - Myanmar
  1999
  - Cambodia

The Association of Southeast Asian Nations (1967)
Why the need for ASEAN Economic Integration?

10 ASEAN Member States have:

- Combined Market of **about 600 million** people
- Very Diverse Racial, Religious, Cultural, Social, Political, Economic & Geographical Background
Objectives:

1. To accelerate the economic growth, social progress, and cultural development
2. To promote regional peace and stability

1995 – ASEAN Leaders reaffirmed that:

“Cooperative peace and shared prosperity shall be the fundamental goals of ASEAN”
Objectives of ASEAN

Target of ASEAN
To create single market by the year 2015

Priority products
Agricultural, Fisheries, Wood, Rubber, Automotives, Textiles, Electronics, Tourism, Travel, Logistic, Healthcare, e-ASEAN

Harmonization of TMHS
Elimination of technical barriers to trade posed by regulations, without compromising the quality, efficacy and safety of TMHS products
## Organization of ASEAN

<table>
<thead>
<tr>
<th>Level</th>
<th>Function</th>
<th>Meeting, output</th>
</tr>
</thead>
<tbody>
<tr>
<td>President</td>
<td>Highest decision-making body</td>
<td>Annual meeting</td>
</tr>
<tr>
<td>Prime Minister</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minister of Economy, Trade, Foreign Affairs</td>
<td>Coordinate the work of Association</td>
<td>Joint Ministerial Meeting (JMM)</td>
</tr>
<tr>
<td>ASEAN Consultative Committee for Standards and</td>
<td>Facilitate the objectives of the Free Trade Area / Implement the mutual</td>
<td>Harmonized sectors: pharmaceutical,</td>
</tr>
<tr>
<td>Quality</td>
<td>recognition agreement</td>
<td>electrical, telecommunication,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cosmetics, foodstuff, TMHS</td>
</tr>
<tr>
<td>Traditional Medicine &amp; Health Supplement</td>
<td>Develop harmonization scheme of TMHS regulations</td>
<td>Harmonized guidelines, requirements,</td>
</tr>
<tr>
<td>Product Working Group</td>
<td></td>
<td>Glossary of Terms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Objectives
Eliminate technical barriers to trade posed by regulations, without compromising the quality, efficacy and safety of TMHS products

History of TMHS PWG

1992 ACCSQ was initiated

2004
• TMHS PWG form’n
• Conceptualization

2005 - 2014
• Harmonized key areas
• ACTR developed and finalized
• GMP Guide finalized
• Mapping of technical infrastructure and capacity building

2015 - 2020
• Signing of agreement
• Trial implementation
• Capacity Building
• SME Development

2021
• Full Implementation?
Current Status

- All the ten (10) Annexes have been already adopted and endorsed to the ASEAN TMHS PWG.
ASEAN Agreements on TM and HS
“Traditional Medicines” mean any medicinal product for human use consisting of active ingredients derived from natural sources (plants, animals and/or minerals) used in the system of traditional practice. It shall not include any sterile preparation, vaccines, any substance derived from human parts, any isolated and characterised chemical substances.

Article 2: Definition
“Health Supplements” mean any product that is used to supplement a diet and to maintain, enhance and improve the healthy function of human body and contains one or more, or a combination of the following:

Article 2: Definition
i. Vitamins, minerals, amino acids, fatty acids, enzymes, probiotics and other bioactive substances.

ii. Substances derived from natural sources, including animal, mineral and botanical materials in the forms of extracts, isolates, concentrates, metabolites.

iii. Synthetic sources of ingredients mentioned in (i) and (ii).

Article 2: Definition
A Health Supplement is presented in dosage forms (to be administered) in small unit doses such as capsules, tablets, powder, liquids and it shall not include any sterile preparations (i.e. injectables, eye drops).

Article 2: Definition
ANNEX I – ASEAN Guiding Principles for Inclusion into or Exclusion from the Negative List of Substances for TM and HS
- List the active substances that are prohibited from being used in or being part of the composition of TM/HS

- Prepared from the following guidelines established to govern the acceptance of active substances to the list based on scientific rationale
1. A substance must carry a scientifically demonstrated/proven safety concern that its inclusion into a TM/HS product will be harmful to human health.
2. A substance that qualify for inclusion into the list should **carry the following details but not limited to**:
   a. Identity of the substance
   b. Source of the substance
   c. Rationale for inclusion
   d. References
Guiding Principles

3. The negative list should only include substances that are prohibited for use in a TM/HS product.
4. This negative list should not include:
   a. Substances in the ASEAN List of Restricted Additives and Excipients for TM/HS.
   b. Nutrients with established ASEAN maximum levels
   c. Naturally occurring toxic contaminants that are within established limits
   d. Substances which are prohibited under existing wildlife protection laws of ASEAN Member States
5. Prohibited substances in the national regulations of ASEAN Member States, where applicable, are prohibited in TM/HS. **Member States are recommended to propose relevant substances of herbal origin from their national legislation** for inclusion into the ASEAN Negative List for TM/HS; as long as their inclusion meets the criteria set in this guideline.
6. Proposal for inclusion or exclusion of substances into the ASEAN Negative List for TM/HS should be based on scientific rationale pertaining to human safety concerns and not upon majority rule or the commonality of a particular substance in the existing national negative list of each Member State.
Negative List of Substances

For TM – 39
For HS – 77

Information on the reason and supporting references, including pictures, is available as a compendium of the negative list.
### Negative List of Substances

<table>
<thead>
<tr>
<th>Scientific Name &amp; Photos</th>
<th>Common name(s)</th>
<th>Harmful Animal/Plant Part(s)</th>
<th>Name of Harmful Compound or Compound Class</th>
<th>Ban Status in TM</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Adonis vernalis</em> L.</td>
<td>Pheasant's eye</td>
<td>Whole plant</td>
<td>Adonitoxin</td>
<td>Banned</td>
</tr>
<tr>
<td><em>Aristolochia</em> spp. (all species) containing aristolochic acid</td>
<td>Birthwort, Pelican flower, Sangree root, Sangrel, Serpentaria, Snakeroot, Snakeweed</td>
<td>Whole plant</td>
<td>Aristolochic acid</td>
<td>Banned</td>
</tr>
<tr>
<td><em>Aspidosperma quebracho-blanco</em> Schidl.</td>
<td>Quebracho</td>
<td>Bark</td>
<td>Aspidospermine</td>
<td>Banned</td>
</tr>
<tr>
<td><em>Atropa belladonna</em> L.</td>
<td>Deadly Nightshade</td>
<td>Whole plant</td>
<td>Scopolamine, Hyoscyamine, Atropine</td>
<td>Banned</td>
</tr>
</tbody>
</table>
# Negative List of Substances

<table>
<thead>
<tr>
<th>Scientific Name &amp; Photos</th>
<th>Common name(s)</th>
<th>Harmful Animal/Plant Part(s)</th>
<th>Name of Harmful Compound or Compound Class</th>
<th>Ban Status in HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aconitum spp. (all species) containing aconite alkaloids</td>
<td>Monkshood, Aconite</td>
<td>Whole plant</td>
<td>Aconite alkaloids</td>
<td>Banned</td>
</tr>
<tr>
<td>Adonis vernalis L.</td>
<td>Pheasant's eye</td>
<td>Whole plant</td>
<td>Adonitoxin</td>
<td>Banned</td>
</tr>
<tr>
<td>Animals parts containing hormones (all species)</td>
<td>-</td>
<td>Parts that may contain hormones: Pituitary gland, Thyroid gland, Parathyroid glands, Adrenal glands, Pancreas, Thymus gland, Ovary, Testes, Placenta</td>
<td>Growth hormone, prolactin, adrenocortico-tropic hormone, Thyroid-stimulating hormone, Follicle-stimulating hormone, luteinizing hormone, oxytocin, antidiuretic hormone, thyroid hormone, calcitonin, parathyroid hormone, mineralocorti-coids, glucocorti-coids, sex hormones, insulin, glucagon, thymosin, estrogens, progesterone, testosterone</td>
<td>Banned</td>
</tr>
</tbody>
</table>
ANNEX II – ASEAN Guiding Principles for the use of Additives and Excipients in TM and HS
- Applies to restricted and prohibited additives and excipients intended for use in TH and HS in order to assist ASEAN Member States in the application of agreed requirements, to protect the consumer, and to facilitate fair trade.
Guiding Principles

Justification for the use of Additive and Excipients
1. When such use has an advantage
2. Does not present appreciable health risk
3. Does not mislead the consumer
4. Serves the technological functions set out by Codex and/or International References
Justification for the use of Additive and Excipients

Objectives cannot be achieved by other means that are economically and technologically practicable:

a. To preserve the quality
b. To enhance quality or stability or to improve its organoleptic properties
c. To provide aids in the manufacture, processing, preparation, treatment, packing, transport or storage
Additives and Excipients Safety
- Must not pose hazards or unacceptable risk to consumer’s health
- Quantity is at or below the maximum use level and is the lowest level necessary to achieve the intended technical effect.

Guiding Principles
Guiding Principles

Specifications for the Identity and Purity of Additives and Excipients

- Food or Pharmaceutical Grade Quality
- Conform with the applicable specifications of Identity and Purity recommended by the Codex Alimentarius Commission or the official pharmacopoeias, or those developed by responsible national or international bodies.
Good Manufacturing Practice

1. The quantity shall be limited to the lowest possible level necessary to accomplish its desired effect.

2. The quantity that becomes a component of TM/HS as a result of its use in the manufacturing and which is not intended to accomplish any physical or other technical effect in the product is reduced to the extent reasonably possible.

Guiding Principles
3. The additive or excipient is of appropriate **food or pharmaceutical grade quality**, and is **prepared and handled in the same way** as food or pharmaceutical ingredient.
Lists of Restricted Additives and Excipients

- The list goes together with their maximum use levels. The maximum use level of zero means that additive or excipient is prohibited for use.
- International references can be used to substantiate the inclusion of an additive/excipient into the list of restricted additives/excipients.
- Codex General Standard for Food Additives (GFSA) online database
- Handbook of Pharmaceutical Excipients
- All Official Pharmacopoeiaeas
  - USP/NF
  - BP
  - Ph. Eur.
  - JP
  - Pharmacopoeia of China
  - Pharmacopoeia of India
  - Philippine Pharmacopoeia (PP)
Procedure for Determination of the Use of Additives and Excipients

On the List of Restricted Additives and Excipients

Yes → Refers to the List of Restricted Use and Prohibited Use of additives and excipients

No → Used according to the references

Refer to the latest version of Codex General Standard for Food Additives Provisions for Food Supplements (13.6) or Handbook of Pharmaceutical Excipients or Official Pharmacopoeias as specified in section 4

Safety Assessment shall be done
Procedure for Determination of the Use of Additives and Excipients

Yes

Used according to the references

No

New Additives/Excipients

Yes

Safety Assessment shall be done and approved for use by appointed scientific body. The national control/regulatory authority can act as an assessor and give input to the appointed scientific body application.

Refer to the latest version of Codex General Standard for Food Additives Provisions for Food Supplements (13.6) or Handbook of Pharmaceutical Excipients or Official Pharmacopoeias as specified in section 4
List of Restricted Additives and Excipients for TM and HS

Coloring agents – 15
Sweeteners – 7
Preservatives – 7
Antioxidants – 7
Excipients (Anticaking, Emusifier, Glazing agent, Stabilizer, Solvent, etc.) – 12
List of Restricted Additives and Excipients for TM and HS

The guideline does not include flavoring agents.

- No restriction/prohibition on any substance used as flavor, as long as their use can be supported by international references.
# List of Restricted Additives and Excipients for TM and HS

<table>
<thead>
<tr>
<th>Item</th>
<th>Common name</th>
<th>INS No./CAS No.</th>
<th>Synonym(s)</th>
<th>Limit (mg/kg product)</th>
<th>Reference (Scientific rational and/or technical reference)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Allura Red AC</td>
<td>129</td>
<td>- CI (1975) No.16035</td>
<td>300</td>
<td>Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Brilliant Blue FCF</td>
<td>133</td>
<td>- CI (1975) No. 42900</td>
<td>300</td>
<td>Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Caramel III – Ammonia process</td>
<td>150c</td>
<td>- Ammonia caramel</td>
<td>20,000</td>
<td>Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Caramel IV - Sulphite Ammonia Process</td>
<td>150d</td>
<td>- Sulfite ammonia caramel</td>
<td>20,000</td>
<td>Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)</td>
<td></td>
</tr>
</tbody>
</table>
ANNEX III – ASEAN Guidelines on Limits of Contaminants for TM and HS
- Developed taking into consideration the safety and quality requirements of TM/HS
- Other limits may be reviewed and included as deemed necessary.

Introduction
- Provide specifications on the limits of heavy metals and microbial contaminants.
- Provide guidance notes on control of pesticides
## Limit on Heavy Metals

<table>
<thead>
<tr>
<th>Heavy Metal</th>
<th>Limit¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>NMT 10.0ppm</td>
</tr>
<tr>
<td>Arsenic</td>
<td>NMT 5.0ppm²</td>
</tr>
<tr>
<td>Mercury</td>
<td>NMT 0.5ppm</td>
</tr>
<tr>
<td>Cadmium</td>
<td>NMT 0.3ppm</td>
</tr>
</tbody>
</table>

NMT – Not more than

¹Parts per million (ppm) can be expressed as mg/kg or mg/L

²Due to special circumstances such as national regulatory requirement, the limits of arsenic in the Philippines is 0.3ppm.
Factors taken into consideration:
1. Nature of product, whether a pure compound, an extract, raw material, or its combination
2. Route of administration
3. Method of preparation, e.g. boiling

Limit for Microbial Contaminants
Limit for Microbial Contaminations

- Microbiological Quality of Traditional Medicines
- Microbiological Quality of Health Supplements
Guidance Notes

- Control of pesticides will not be on Finished Product (FP)
  - Risk is very low due to the *small unit size and dilution effect*
  - Pesticides are *internationally regulated*; Global harmonization on regulations in process
  - Currently no other economic bloc has regulations on pesticide residues in TM and HS

Pesticide Residues
Guidance Notes

- The **onus is on suppliers of RM and manufacturers of TM and HS products.**

- Should be covered under **Good Agriculture Practice (GAP)**
Recommendations

- Pesticide Residue limits should remain under review
  - If conditions change in the future, a new assessment for the need of the limits for FP can be conducted, taking into consideration international guidelines/standards
Steps to be taken by each AMS on control

- **Promote closer cooperation and liaison** between Ministry of Health and the ministries responsible for control of pesticides and GAP in agricultural products

- To **reinforce during GMP training** on the need for manufacturers to be responsible and not to accept Raw Materials that do not comply with applicable pesticide residue limits
Recommendations

- Examples of International guidelines/standards on pesticide residues
  - WHO – following the recommendations of the Food and Agriculture Organization
  - EMEA Guideline on Specifications (CPMP/QWP/2820/00 Rev 1)
  - USP – Limits in Articles of Botanical Origin
  - BP – Limits in Herbal Drug (whole, fragmented, or cut parts of plants, algae, fungi, usually dried)

Pesticide Residues
ANNEX IV – ASEAN Guidelines for Minimising the Risk if Transmission of TSE in TM and HS
To use an ASEAN harmonized approach to minimize the risk of Transmissible Spongiform Encephalopathy (TSE) in TM and HS
Transmissible Spongiform Encephalopathies (TSE) – group of chronic degenerative diseases that is characterised by accumulation of pathologically misfolded ‘Prion’ protein (PrP) that accumulates in the Central Nervous System of infected individuals
Background

$\texttt{PrP}^{\text{TSE}}$ – pathogenic agent; highly resistant to protease and heat denaturation treatments
Forms of TSE:
- Bovine Spongiform Encephalopathy (BSE) in cattle
- Scrapie in sheep and goats
- Chronic Wasting Disease (CWD) in cervids
- Different forms of Creutzfeld-Jakob Disease (CJD) in humans
- Gerstmann-Sträussler-Scheinker Syndrome in humans
1. ASEAN Approach to minimising TSE Risk in TM and HS

- Risk management approach consistent with that recommended by WHO and EMEA

- In conjunction with the latest publications by WHO, EMEA and the Office International des Epizooites (OIE) on TSE

Guiding Principles
2. ASEAN Guidelines to manage the risk of TSE in Bovine-derived materials

- Parameters to be considered in minimising transmission risk of TSE, particularly BSE
  - Source animals and their geographical origin
  - Nature of animal material used
  - Production process(es)

Guiding Principles
2. ASEAN Guidelines to manage the risk of TSE in Bovine-derived materials

• European Directorate for the Quality of Medicines (EDQM) Certificate – source of reference for evidence of compliance
ANNEX V – ASEAN Guidelines on Stability Study and Shelf-Life of TM and HS
Aim of Stability Study:
- To determine its shelf-life as a finished product in its container closure system under the recommended storage condition
- Finished Product should meet its established physical, microbiological and/or chemical specifications
Objective

- To provide recommendations on the core stability study required for products
- Leaves sufficient flexibility to encompass the variety of practical situations that may be encountered due to specific scientific considerations and characteristics of the products being evaluated
The design of the Stability study for the product should be based on the nature of the product.

- Selection of batches
- Specifications/Testing parameters
- Testing frequency
- Storage condition
- Container Closure System
Selection of batches

- From at least two (2) batches
- Manufacturing process of batches used in stability studies should simulate that of production batches and should be of the same quality.
- Should be performed on individual strengths and/or type of container closure system
Specification/Testing Parameters

- Physical, Chemical, and Microbiological properties of a finished product
- Not intended to be exhaustive, nor is expected that every listed test is to be included for a particular Finished Product
## Specification/Testing Parameters

<table>
<thead>
<tr>
<th>TM Dosage Form</th>
<th>Organoleptic characteristics</th>
<th>Assay</th>
<th>Hardness/ friability</th>
<th>Dissolution/Disintegration</th>
<th>Water content</th>
<th>Viscosity</th>
<th>pH</th>
<th>Microbial content</th>
<th>Granules/Particle Size variation</th>
<th>Resuspendability</th>
<th>Adhesiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral powder</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hard capsule</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft capsule</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
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</tr>
<tr>
<td>Coated and</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Uncoated Tablet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
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<td></td>
</tr>
<tr>
<td>Coated and</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncoated Pill/Pellet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspension</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Design**
Testing Frequency

- Typical

<table>
<thead>
<tr>
<th>Storage Condition</th>
<th>Testing Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real Time/Long-term</td>
<td>0, 3, 6, 9, 12, 18, 24 months and annually there after through the proposed shelf-life</td>
</tr>
<tr>
<td>Accelerated</td>
<td>0, 3 and 6 months</td>
</tr>
</tbody>
</table>

- Reduced designs (matrixing and bracketing)

Design
Storage Condition

- Common Storage Conditions

<table>
<thead>
<tr>
<th>Type of Container Closure System/Study</th>
<th>Storage Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products in primary containers permeable to water vapour</td>
<td>30°C ± 2°C / 75% RH ± 5% RH</td>
</tr>
<tr>
<td>Products in primary containers impermeable to water vapour</td>
<td>30°C ± 2°C</td>
</tr>
<tr>
<td>Accelerated</td>
<td>40°C ± 2°C / 75% RH ± 5% RH</td>
</tr>
</tbody>
</table>

Design
### Storage Condition

- For products intended in a refrigerator

<table>
<thead>
<tr>
<th>Study</th>
<th>Storage Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real Time/Long-Term</td>
<td>5°C ± 3°C</td>
</tr>
<tr>
<td>Accelerated</td>
<td>25°C ± 2°C / 60% RH ± 5% RH</td>
</tr>
</tbody>
</table>
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.
Evaluation

- Systematic approach in the presentation and evaluation of stability information
- Results from physical, chemical microbiological tests
- Not only Assay, but also other appropriate test attributes
Labeling

- Storage conditions, including temperature, light and humidity
- General precautionary statements may be included but should not be used to conceal stability problems.
  - “Protect from light.”
  - “Store in a dry place.”
- “Ambient conditions” or “Room temperature” should be avoided

Design
ANNEX VI – ASEAN Guiding Principles on Safety Substantiation of TM and HS
- Natural resources (plants, animals or natural minerals) or their synthetic equivalents are widely used in the formulation of TM/HS

- Most ingredients might be considered as safe, considering experience or history of use

- Under certain conditions, additional data will be required to prove the safety of the product (New ingredient or new combination)

**Introduction**
To provide guiding principles for safety substantiation of TM and HS
Guiding Principles

Those requiring data to substantiate safety:

a. Products with new ingredient(s)
b. Products with ingredient(s) derived from new method(s) of purification, extraction or manufacturing
c. Existing products with new combination, dosage, delivery system or use
d. Existing products with safety concern
Guiding Principles

Safety substantiation may not be necessary for:

a. Products, unless required by NRA
b. Products that do not fall under items a-d. previously mentioned
c. Products containing ingredients with lower dosage than existing ones
d. TM with a documented history of safe use
e. HS containing ingredients which have been consumed as food or food constituent
Guiding Principles

- Shall be based on Finished Product or ingredient(s), with justification
- Data should be relevant, and commensurate with the nature or character of the ingredient or product in line with the intended use
Guiding Principles

Safety information should include:

1. History of use
   - Authoritative reference texts, Documented history of use

2. Scientific evidence on safety
   - Safety data, including toxicity data derived from animal and/or human studies (WHO or OECD guidelines); teratogenicity, carcinogenicity, mutagenicity data
ANNEX VII – ASEAN Guidelines on Claims and Claims Substantiation for TM and HS
Consideration of similar guidelines that exist internationally (WHO, Codex, EU, US, Canada, Australia) and the regulatory situation and stakeholders’ interests in the ASEAN region

- TM and HS Claims – any message that states, suggests, or implies that a TM or HS ingredient/product has positive contribution and benefit to human health.

- Guidance of allowable claims and their corresponding levels of literature and scientific substantiation.

Introduction
To provide guidance on making unbiased and truthful claims, supported by adequate evidence in order to protect the consumers from misleading claims.

- Consumers to make informed choices
- Facilitate product placement of TM/HS products
- Set up requirements for efficacy data submission
Key Principles

All claims should:
- Be consistent with the ASEAN Definition of TM and HS
- Support the safe, beneficial and appropriate use of the products
- Maintain the level of traditional usage and/or scientific evidence which is proportionate to the type of claim
Key Principles

All claims should:
- Meet the dosing recommendations stated in the evidence or references for the claimed intended effects, unless otherwise justified
- Not be misleading or false
- Enable consumers to make an informed choice regarding products
Key Principles

All claims should:
- Be for health maintenance or treatment of disease in accordance with TM principles and practice (for TM products)
- Be for health maintenance and promotion purposes
Key Principles

All claims should:

- **Not be medicinal or therapeutic** in nature, such as implied for treatment, cure or prevention of diseases (for HS products)

- Be **substantiated by good quality evidence** that is relevant to the claim
GUIDANCE FOR TM CLAIMS SUBSTANTIATION
## Traditional Health Use

<table>
<thead>
<tr>
<th>Scope</th>
<th>Examples to illustrate the scope (as determined by the regulatory authority of each Member State)</th>
</tr>
</thead>
</table>
| Traditionally used for general health maintenance or enhancement | • Traditionally used to maintain health for people above 40 yrs old  
• Tonic traditionally used to restore energy and health in women after childbirth/puerperium  
• Tonic traditionally used to strengthen body by nourishing blood and invigorating vital energy |
| Scope                                                                 | Examples to illustrate the scope  
(as determined by the regulatory authority of each Member State) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditionally used to relieve or alleviate a symptom, or treat a</td>
<td>• A Traditional medicine for dizziness/vomiting during travel in car, boat and airplane</td>
</tr>
<tr>
<td>disease or medical condition according to the principles of</td>
<td>• Traditionally used to prevent cold or flu</td>
</tr>
<tr>
<td>traditional medicine, with the exception of the prohibited diseases</td>
<td>• Traditionally used to relieve cold and sore throat</td>
</tr>
<tr>
<td>according to each Member State</td>
<td>• Traditionally used to treat stomachache</td>
</tr>
<tr>
<td></td>
<td>• Traditionally used to treat constipation</td>
</tr>
<tr>
<td></td>
<td>• A traditional medicine to relieve itchiness</td>
</tr>
</tbody>
</table>

To prevent/stop/slow down the progress of a mild or self-limiting disease or medical condition, based on principles of traditional medicine.
Scientifically Established Treatment

<table>
<thead>
<tr>
<th>Scope</th>
<th>Examples to illustrate the scope (as determined by the regulatory authority of each Member State)</th>
</tr>
</thead>
</table>
| To relieve a symptom or treat a disease, disorder or medical condition substantiated by scientific evidence, which corroborates TM principles* | • For treatment of hypertension  
• To treat or relieve arthritis  
• Used to lower blood pressure  
• Used to reduce blood sugar |

*as determined by the regulatory authority of each Member State
Principles of TM Claims Substantiation

• TM claims must be in line with the respective TM principles (such as Jamu, Traditional Chinese Medicine, Ayurvedic Medicine) and supported by adequate evidence from TM based document.

• As the usage of traditional medicine is based on accumulated experience and historical knowledge, the TM claims and rationale of ingredient or formulation should be based on the specific TM disciplines.
The substantiation of TM claims shall follow and be based on finished product, or ingredient(s) with justification as required by the regulatory authority. It is the responsibility of the company to provide the required evidence in order to comply with the criteria to make TM Claims.
Efficacy data to support Scientifically Established Treatment Claims shall be generated from studies on the finished product, or ingredient(s), with justification as required by the regulatory authority. Efficacy data should be obtained from human studies; this may be supplemented by data from non-clinical studies. In addition, summary of empirical or historical and raw data should be submitted if required by the regulatory authority.

Substantiation of TM Claims
• Human studies

Scientific data could be derived from observational or intervention human studies, that are well designed in accordance with recognized scientific principles, with statistically and clinically significant outcomes addressing the specific TM claim. The acceptable principles for human studies can be referred to internationally accepted guidelines, for example, ICH-GCP Guidelines.

Substantiation of TM Claims
• **Non-clinical (animal and in vitro) studies**

In vitro studies as well as animal studies are intended to generate the non-clinical data. Data from animal study should be derived from animal model which can represent human condition related to claim. The methodology should be an acceptable and valid procedure to measure the parameter. Data from animal studies are important to give the preliminary efficacy data prior to the conduct of human study. When data from animal and in vitro studies are submitted as substantiation of claims, an explanation on its relevance to humans should be included.

**Substantiation of TM Claims**
• For Scientifically Established Treatment Claims, a company wishing to use the same approved claim for a similar product should provide adequate scientific evidence/data to ensure adequate substantiation.

Substantiation of TM Claims
A proposed TM claim

- Traditional Health Use Claim
- Traditional Treatment Claim
- Scientifically Established Treatment Claim

Refer to Table 2 and Sections 4.2 and 4.3

Evidence of documented traditional use or history of use that may be found in the following:
- Classical TM Text
- Pharmacopoeias and Monographs
- Reference Textbooks/Journals

Evidence of documented history of traditional treatment that may be found in the following:
- Classical TM Text
- Pharmacopoeias and Monographs
- Reference Textbooks/Journals

Compulsory evidence:
Substantiation of TM claims based on scientific data, as required by the regulatory authority to be conducted on finished product or ingredient(s). Justification will have to be provided to the regulatory authority if evidence provided is based on ingredient.

At least 1 additional evidence:
Evidence of documented history of traditional treatment that may be found in the following:
- Classical TM Texts
- Pharmacopoeias and Monographs
- Reference Textbooks/Journals
Evidence of documented traditional use or history of use that may be found in the following:
- Classical TM Text
- Pharmacopoeias and Monographs
- Reference Textbooks/Journals

Evidence of documented history of traditional treatment that may be found in the following:
- Classical TM Text
- Pharmacopoeias and Monographs
- Reference Textbooks/Journals

Compulsory evidence: Substantiation of TM claims based on scientific data, as required by the regulatory authority to be conducted on finished product or ingredient(s). Justification will have to be provided to the regulatory authority if evidence provided is based on ingredient.

At least 1 additional evidence: Evidence of documented history of traditional treatment that may be found in the following:
- Classical TM Texts
- Pharmacopoeias and Monographs
- Reference Textbooks/Journals

Does it meet the criteria of well-documented TM claim based on substantiation of evidence?

**YES**
- Traditional Health Use Claim

**NO**
- Not a well-documented Traditional Health Use Claim

Does it meet the criteria of well-documented TM claim based on substantiation of evidence?

**YES**
- Traditional Treatment Claim

**NO**
- Not a well-documented Traditional Treatment Claim

Does it meet the criteria of well-documented TM claim based on substantiation of evidence?

**YES**
- Scientifically Established Treatment Claim

**NO**
- Not a well-documented Scientifically Established Treatment Claim
GUIDANCE FOR HS CLAIMS SUBSTANTIATION
### General or Nutritional

<table>
<thead>
<tr>
<th>Scope</th>
<th>Examples to illustrate the scope - as determined by the regulatory authority of each Member State</th>
</tr>
</thead>
</table>
| For Nutritional Support and General Health Maintenance. | • Supplements nutrition  
• Supports healthy growth and development  
• Nourishes the body  
• Relieves general tiredness, weakness  
• Helps to maintain good health |

Benefits derived from supplementation beyond a person’s daily dietary intake.
### Functional

<table>
<thead>
<tr>
<th>Scope</th>
<th>Examples to illustrate the scope - as determined by the regulatory authority of each Member State</th>
</tr>
</thead>
</table>
| Relate to a positive contribution to health or to the improvement of a function or to modifying or preserving health in the context of the total diet on normal functions or biological activities of the body. | - Maintains/Supports healthy joints  
- Maintains/Supports immunity  
- Maintains healthy liver function  
- Maintains/Supports alertness  
- Maintains/Supports mental performance  
- Promotes healthy skin  
- Helps to relieve post-menopausal discomforts  
- Aids in digestion to relieve indigestion  
- Bifidobacteria in product A helps to improve slow transit system in 14 days  
- Supports health in ageing  
- Supports health in menopause  
- Supports health in pregnancy |
| Maintains or enhances structure or function of the body, excluding disease related claims. | |
| Supports health and to relieve/reduce/lessen/ease minor body discomforts in some physiological processes (e.g. ageing, menopause, pregnancy)*. | |

*as determined by the regulatory authority of each Member State
### Scope

Significantly altering or reducing a risk factor of a disease or health related condition*.

*as determined by the regulatory authority of each Member State

<table>
<thead>
<tr>
<th>Examples to illustrate the scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>- as determined by the regulatory authority of each Member State</td>
</tr>
<tr>
<td>• Helps to reduce risk of osteoporosis by strengthening bone</td>
</tr>
<tr>
<td>• Helps to reduce the risk of dyslipidaemia</td>
</tr>
</tbody>
</table>
**Principles of HS Claims Substantiation**

- **Proportional degree of supporting evidence corresponding to the type of HS claims**
- The Principle of proportional degree of supporting evidence, when applying the substantiation requirement, the evidence for Functional Claim is stronger than General or Nutritional Claim. In turn the Disease Risk Reduction Claims will require proportionally stronger scientific support than Functional Claims.
• Totality of scientific evidence that demonstrates the beneficial effect
• The totality (balance and range) of the evidence to the HS claims are important. Due consideration should be given to all relevant scientific evidence relating to the claimed benefit of the product or ingredient and should not focus only on evidence that supports the effect. In proportion to the type of claims, scientific substantiation should demonstrate a consistent beneficial effect of the ingredient (or product) on specific health aspects or generally recognised biomarkers based on totality of scientific evidence encompassing human studies (observation and intervention), authoritative references, recommendations from international or authoritative bodies, scientific reviews, animal and in-vitro studies.

Principles of HS Claims Substantiation
• HS claim substantiation shall be based on finished product, or ingredient(s) with justification as required by the regulatory authority (e.g. rationale of the combination)

Principles of HS Claims Substantiation
Substantiation of HS Claims

• The substantiation of HS claims shall follow to reflect the proportional degree of supporting evidence. It is the responsibility of the company to provide the required evidence in order to comply with the criteria to make HS Claims.
• For Functional and Disease Risk Reduction Claims, a summary of the scientific evidence including published and unpublished studies should be submitted. In addition, summary of empirical or historical data shall be submitted. Raw data should be submitted when required by the regulatory authority.

Substantiation of HS Claims
Substantiation of HS Claims

• Efficacy data to support Disease Risk Reduction Claim shall be generated from studies on the finished product, or ingredient(s), with justification as required by the regulatory authority. Efficacy data should be obtained from human studies; this may be supplemented by data from non-clinical studies.
Substantiation of HS Claims

- **Human studies**

  Scientific data could be derived from observational or intervention human studies, that are well designed in accordance with recognized scientific principles, with statistically and clinically significant outcomes, if applicable, addressing the specific HS claim. The acceptable principles for human studies can be referred to internationally accepted guidelines, for example, ICH-GCP Guidelines.
• Non-clinical (animal and in vitro) studies

In vitro studies as well as animal studies are intended to generate the non-clinical data. Data from animal study should be derived from animal model which can represent human condition related to claim. The methodology should be an acceptable and valid procedure to measure the parameter. Data from animal studies are important to give the preliminary efficacy data prior to the conduct of human study. When animal and in vitro studies are submitted as substantiation of claims, mechanisms of actions to explain how the ingredient/product confers beneficial effect on health and explanation on the relevance of its findings to human should be included.

Substantiation of HS Claims
For Functional and Disease Risk Reduction Claims, a company who wishes to use the same approved claim for a similar product should provide adequate scientific evidence/data to ensure adequate substantiation.
A proposed HS claim

General or Nutritional Claim (Table 3): for nutritional support and general health maintenance and the benefits derived from supplementation beyond a person's daily dietary intake

Functional Claim (Table 3): relates to a positive contribution to health or to the improvement of a function or to modifying or preserving health in the context of the total diet on normal functions or biological activities of the body, maintains or enhances structure or function of the body, support health and to relieve minor body discomfort in some physiological processes

Disease Risk Reduction Claim (Table 3): significantly altering or reducing a risk factor of a disease or health related condition

Refer to Table 4 and Sections 5.2 and 5.3

Substantiation evidence
At least 1 of the following evidence (as determined by the regulatory authority of each Member State):
• Authoritative reference text
• Scientific opinion from scientific organizations
• Scientific opinion from regulatory authorities
• Documented history of use

Substantiation evidence
At least 1 compulsory evidence (as determined by the regulatory authority of each Member State):
• Good quality human study
• Authoritative reference texts
• Scientific opinion from scientific organizations
• Scientific opinion from regulatory authorities
At least 1 additional evidence:
• Animal study data
• Documented history of use
• Published scientific review

Compulsory evidence:
• Human intervention study data on ingredient or product

At least 1 additional evidence:
• Authoritative reference texts
• Scientific opinion from scientific organizations
• Scientific opinion from regulatory authorities
• Published scientific review

Does it meet the criteria of well documented claim based on substantiation of
NO
Not a well-documented General or Nutritional Claim

Does it meet the criteria of well documented claim based on
NO
Not a well-documented Functional Claim

Does it meet the criteria of well documented claim based on
NO
Not a well-documented Disease Risk Reduction Claim
Languages and Wordings Used for HS Claims

• Appropriate language and wordings must be used to convey the HS claims with a meaning that is proportional to the level of scientific substantiation. Language and words used in HS claims should provide a truthful and non-misleading message on the beneficial effect of the ingredient/product.
• HS claims are not allowed to imply treatment, cure or prevention of all diseases or medical conditions. For disease risk reduction claims, diseases prohibited from associating with such claims shall be determined by the regulatory authority of each Member State.
ANNEX VIII – ASEAN Guidelines on Good Manufacturing Practice for TM and HS
The purpose of these guidelines is to outline steps which shall be taken, as necessary and appropriate, by manufacturers of traditional medicines and health supplements with the objective of ensuring that their products are of the intended quality and nature.
GMP

Manufacture

– the making or assembling of the finished product,

– the enclosing or packing of the finished product in any container in a form suitable for administration or application, and the labelling of the container

– the carrying out of any process in the course of any of the foregoing activities.
GMP
(Element)

1. Quality Management
2. Personnel
3. Premises & Equipment
4. Sanitation & Hygiene
5. Documentation
6. Production
7. Quality Control
8. Contract Manufacture & Analysis
9. Complaints & Recalls
10. Self-Inspection
Annexes

1. List of Internationally accepted References for Test Methods
2. Verification
Quality Management

Attainment of a quality objective which is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company’s suppliers and by the distributors.
Quality Management (Quality Assurance)

- It is the sum total of the organized arrangements made with the object of ensuring the products are of the quality required for their intended use.
  - traditional medicines and health supplements are not sold or supplied before a head of Quality Control / Quality Assurance has certified that each production batch has been produced and controlled in accordance with the requirements of the NRA.
Quality Management
(Quality Assurance)

– satisfactory arrangements exist to ensure, that the traditional medicines and health supplements are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;

– there is a procedure for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Quality Assurance system.
Quality Management (GMP)

• Good Manufacturing Practice is that part of Quality Assurance which ensures that products are consistently manufactured and controlled to the quality standards appropriate to their intended use and as required by the NRA or product specification.
Quality Management (GMP)

– all manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing traditional medicines and health supplements of the required quality and complying with their specifications

– critical steps of manufacturing processes and significant changes to the process are verified;
Quality Management (GMP)

- a system is available to recall any batch of product, from sale or supply
- complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent recurrences.
Quality Management (QC)

• Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures.

  – adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing for RM, PM, FG & intermediate bulk
Quality Management (QC)

– the finished products contain active materials complying with the qualitative and quantitative requirements of the NRA

– records are made of the results of inspection and that testing of material, intermediate, bulk, and finished products is formally assessed against specification

– sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary
Quality Management
(Product Quality Review)

• Regular periodic or rolling quality reviews of all traditional medicines and health supplements, including export only products, shall be conducted with the objective of verifying the consistency of the existing process.
Quality Management
(Product Quality Review)

– review of starting materials and packaging materials used for the product, especially those from new sources.

– review of critical in-process controls and finished product results

– review of all batches that failed to meet established specification(s) and their investigation
Quality Management
(Product Quality Review)

– review of all changes carried out to the processes or analytical methods
– review of product authorization variations submitted/ granted/ refused, including those for third country (export only) dossiers
– review of the results of the stability monitoring programme and any adverse trends
– review of all quality-related returns, complaints and recalls and the investigations performed at the time
Quality Management
(Product Quality Review)

– qualification status of relevant equipment and utilities, e.g. Heating, Ventilation and Air Conditioning (HVAC), water, compressed gases, etc

– review of Contractual Agreements to ensure that they are up to date

– review of post-marketing commitment for new product/variation
Personnel

• There shall be an adequate number of personnel at all levels having knowledge, skill and capabilities relevant to their assigned function, and capable of handling their duties properly. They shall have the attitudes for achieving the goals of Good Manufacturing Practice (GMP)
Premises & Equipment

• Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out.

• Layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products
Premises & Equipment

• Defined areas for the following operations are required:
  – Receiving and quarantine of incoming materials
  – Sampling
  – Storage of starting and packaging materials
  – Weighing /Dispensing
  – Processing
Premises & Equipment

– Storage of bulk/intermediate products
– Packaging
– Equipment washing
– Storage of quarantine finished products
– Storage of approved finished products
– Designated area for quality control
• Buildings shall be effectively ventilated with air control facilities (including temperature, humidity and filtration), appropriate both to the operations undertaken within and to the external environment.

• Separate areas shall be used for the production of finished products intended for external use or application and finished products intended for internal consumption solely.
Premises
(Production)

• Premises for the packaging of traditional medicines and health supplements shall be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

• Adequacy of working space, which shall allow orderly and logical placement of equipment and materials and to suit the operation, efficient flow of work, communication & supervision.
Premises
(Production)

• Changing rooms shall be directly connected to but separated from processing areas.
  – shall have adequate hand washing and / or sanitizing facilities
  – Facilities for changing clothes, and for washing and toilet purposes shall be easily accessible and appropriate for the number of users.

• Crude (i.e. unprocessed) natural materials shall be stored in separate areas.
Equipment

• Manufacturing equipment shall be designed so that it can be easily and thoroughly cleaned. It shall be cleaned according to detailed and written procedures and stored only in a clean and dry condition.

• Dedicated equipment used to manufacture products intended for internal consumption solely shall be separated from equipment used for the manufacturing of products intended for external use or application.
Equipment

- Pipes, hoses, pumps and valves used for treated water, starting materials and the products shall be cleaned and sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.
Sanitation & Hygiene

• A high level of sanitation and hygiene shall be practiced in every aspect of the manufacturing of traditional medicines and health supplements.
Sanitation & Hygiene (Personnel)

• All personnel, prior to employment shall undergo health examinations. During the course of their employment they shall also routinely undergo health examinations which shall include relevant examinations.

• Direct contact shall be avoided between the operator's hands and raw materials, intermediate or bulk product.
Sanitation & Hygiene (Personnel)

• Proper washing of hands and wearing of gloves shall be used if contact with hands is unavoidable.

• Appropriate protective garments shall be worn. Soiled uniforms shall be stored in closed containers until properly laundered.
Visitors or untrained personnel shall, preferably, not be taken into the production and quality control areas. If this is unavoidable, they shall be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They shall be closely supervised.
Sanitation & Hygiene
(Premises)

- The preparation, storage and consumption of food and beverages shall be restricted to specific areas, such as meal rooms and canteen.
- Meal rooms and canteen rooms shall not have direct access to controlled areas (e.g. production area and areas used to store materials used for production and finished products).
Sanitation & Hygiene
(Premises)

• Waste material shall not be allowed to accumulate. It shall be collected in suitable receptacles for removal to collection points outside the buildings and disposed off safely and in a sanitary manner at regular and frequent intervals.

• Pets are not allowed within the vicinity of the manufacturing plant.
Sanitation & Hygiene (Equipment)

• Cleaned equipment shall be kept or stored in a clean condition and identified with the status of cleaning, and checked for cleanliness prior to each use.

• Cleaning agents, washing and cleaning equipment shall not be a source of contamination. The choice of cleaning method and agents shall be carefully considered and justified.
Sanitation & Hygiene
(Equipment)

• Records of cleaning, including the appropriate sanitising and inspection conducted prior to use shall be maintained.
Documentation

• Clearly written documentation prevents errors from spoken communication and permits tracing of batch history of the product, from receiving of starting materials to the distribution of finished products.

• A documentation system must be prepared. The system consisting of manufacturing formulae and instructions, specifications, procedures and records must be free from errors and clearly established.
Documentation

• Quality Control Documents
  – Specifications
  – Sampling procedures
  – Testing procedures and records (including analytical worksheets and/or laboratory notebooks)
  – Analytical reports and/or certificates
  – Data from environmental monitoring, where appropriate
  – Procedures for and records of the calibration of instruments and maintenance of equipment
Documentation

• Production Documents
  – Manufacturing Formula and Processing Instructions
  – Packaging Instructions
  – Batch Processing Records
  – Batch Packaging Records

• Standard Operating Procedures (SOPs) and Records
Production

• Defined manufacturing procedures are necessary to ensure that production, quality control and other relevant personnel are instructed on the details of the processes concerned.

• Production shall be performed and supervised by competent people.
Production

• Water used as ingredients or for final rinsing of production equipment shall be treated to minimise microbial contamination.
Production

• Verification

• Prevention of Cross-Contamination in Production
  – Cross-contamination shall be avoided by appropriate technical or organisational measures.
  – Measures to prevent cross-contamination and their effectiveness shall be checked periodically according to set procedures.
Production

- Starting Materials
  - Starting materials shall only be purchased from approved suppliers named in the relevant specification where possible, directly from the producer.
  - If one material delivery is made up of different batches, each batch shall be considered as separate for sampling, testing and release.
  - Only starting materials which have been released by the Quality Control Department and which are within their shelf life shall be used.
Production

• Processing Operations: Intermediate and Bulk Products
  – Production personnel shall follow defined and authorised procedures for every stage of each manufacturing process.
  – Before any manufacturing begins, steps shall be taken to ensure that the work area and equipment are free from any materials, products, or documents, not required for the current operation.
Production

• Packaging Materials
  – The purchase, handling and control of primary and printed packaging material shall be accorded attention similar to that given to starting materials.
  – Each delivery or batch of printed or primary packaging material shall be given a specific reference number or identification mark.
  – Out dated or obsolete primary packaging material or printed packaging material shall be destroyed and this disposal recorded.
Production

• Packaging Operations
  – The name and batch number of the product being handled shall be displayed at each packaging station or line.
  – The correct performance of any printing operation to be done separately or in the course of the packaging shall be checked and recorded.
  – Attention shall be paid to printing by hand which shall be re-checked at regular intervals.
– Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced shall be investigated and satisfactorily accounted for before release.

– Upon completion of a packaging operation, any unused batch-coded packaging materials shall be destroyed and the destruction recorded. A documented procedure shall be followed if uncoded printed materials are returned to stock.
Production

• Rejected, Recovered and Returned Materials
  – Rejected materials and products shall be clearly marked as such and stored separately in restricted areas.
  – The reprocessing of rejected products shall be exceptional. It is only permitted if the quality of the final product is not affected. Record shall be kept of the reprocessing.
QC

• The Quality Control Department shall have a designated area with sufficient and well trained staff to perform any required analysis before, during and after manufacture.

• If the in-house Quality Control Department cannot perform certain specific analysis, the services of accredited/recognized external laboratory can be used to conduct the tests.
QC

• Quality Control personnel shall have particular expertise in products in order to be able to carry out identification tests and recognize adulteration, the presence of fungal growth, infestations, and non-uniformity when receiving and checking crude materials.
The stability of the finished product shall be monitored according to a continuous appropriate programme that will permit the detection of any stability issue associated with the formulation in the marketed package.
• Sampling
  – The sample taking shall be done in accordance with approved written procedures.
  – Reference samples shall be representative of the batch of materials or products from which they are taken.
  – Reference samples from each batch of finished products shall be retained till one year after the expiry date.
QC

• Testing
  – All testing operations described in the marketing authorization shall be carried out according to approved methods which shall be internationally accepted (Refer to Annex 1).
  – The results obtained shall be recorded and verified to make sure that they are consistent with each other.
QC

– Special attention shall be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media.

– Laboratory reagents intended for prolonged use shall be marked with the preparation date and the signature of the person who prepared them.
On Going Stability Programme

- The purpose of the on-going stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.

- The on-going stability programme shall be described in a written protocol and results formalized as a report.
QC

– Out of specification or significant atypical trends shall be investigated.
– A summary of all the data generated, including any interim conclusions on the programme, shall be written and maintained. This summary shall be subjected to periodic review.
Contract Manufacture and Analysis

• There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties and responsibilities of each party.

• The contract must clearly state the way in which the authorized person releasing each batch of product for sale exercises his full responsibility.
Contract Manufacture and Analysis

• The Contract Giver
  – The Contract Giver shall provide the Contract Acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the NRA requirements.
  – The Contract Giver shall ensure that all products and materials delivered by the Contract Acceptor comply with their specifications.
Contract Manufacture and Analysis

• The Contract Acceptor
  – The Contract Acceptor should have adequate premises, equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the Contract Giver.
  – The Contract Acceptor shall not pass to a third party any of the work entrusted to him under the contract without the Contract Giver’s prior evaluation and approval of the arrangements.
Contract Manufacture and Analysis

• The Contract
  – A contract shall be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities relating to the manufacture and the control of the product.
  – The contract shall specify the way in which the head of Quality Control Department releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of the NRAs.
Contract Manufacture and Analysis

– The contract shall describe clearly who is responsible for purchasing materials, testing and releasing materials, undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis.

– In case of contract analysis, the contract shall state whether or not the Contract Acceptor shall take samples at the premises of the manufacturer.
Contract Manufacture and Analysis

– The contract shall permit the Contract Giver to visit the facilities of the Contract Acceptor.

– In the case of contract analysis, the Contract Acceptor shall understand that he is subject to inspection by the competent Authorities.
Complaints & Product Recalls

• Product Complaints
  – All complaints shall be investigated and evaluated. Written procedures describing the handling of all written and verbal complaints regarding the product shall be established and followed.
  – A person shall be designated responsible for handling the complaints.
Complaints & Product Recalls

– There shall be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

– Any complaint concerning a product defect shall be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control shall be part of the team.
Complaints & Product Recalls

• Product Recalls
  – Any action taken to recall a product suspected or known to be defective or hazardous, shall be done immediately and in accordance with a pre-determined plan.
  – A person shall be designated as responsible for execution and co-ordination of recalls and shall be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency.
Complaints & Product Recalls

– Recalled products shall be identified, recorded and stored separately in a secure area while awaiting a decision on their fate.

– The effectiveness of the arrangements for recalls shall be evaluated regularly.
Self-Inspection

• Self-inspections shall be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice principles and to propose necessary corrective measures.
ANNEX IX – ASEAN Guidelines on Labeling Requirements for TM and HS
- Applies to TM and HS products to ensure the safe and effective use of TM and HS among consumers and facilitate registration process among the ASEAN Member States.

- Promotes proper storage and logistic condition
Guiding Principles

TM/HS product shall not be described or presented on any label or in any labeling in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its character in any aspect.
Guiding Principles

TM/HS product shall not be described or presented on any label or in any labeling by words, pictorial or other devices which refer to or are suggestive either directly or indirectly, of any other product.
Guiding Principles

The principal display panel shall be large enough to accommodate all the mandatory label information required to be placed there on with clarity and conspicuousness and without obscuring design.
Guiding Principles

The label information should be English and/or official/national language(s) subject to the regulation of each Member State and be written clearly and easy to understand. Languages other than English may be included on labels with a required declaration to confirm that the meaning in the other languages is the same as that given in the English and/or official language(s).
The following information shall appear on the label of TMHS product:

- Product name
- Dosage form
- Name and Strength of Active ingredient
- Batch or Lot number
- Manufacturing and expiry date or Expiry date only
- Directions of use
- Indication or Intended use
- Storage condition

General Labeling Requirements
The following information shall appear on the label of TMHS product:

- Registration Number
- Name and address of manufacturer
- Name and address of MAH
- Warning (if any)
- Pack size
- Special statements
Small Label

Should declare at least the following:

- Product name and brand name, if applicable
- Registration Number
- Batch or Lot number
- Manufacturing and expiry date or Expiry date only
- Other information according to general labeling requirements should be declared on package insert and / or another container or accompanied with a catch cover.
Should declare at least the following:

- Product name and brand name, if applicable
- Registration Number
- Batch or Lot number
- Manufacturing and expiry date or Expiry date only
- Other information according to general labeling requirements should be declared on package insert and / or another container or accompanied with a catch cover.

Strip/Blister Pack Label
Country specific requirements are allowed if they are deemed necessary for the reasons of identification, safety, quality, culture and religion. However, minimization of country specific requirement should be encouraged. Such country specific requirements with reasons should however be made known to the other member states and be updated into the compilation of country specific requirement for TM/HS from member states in a timely manner.
Country Specific Requirements

<table>
<thead>
<tr>
<th>TM</th>
</tr>
</thead>
</table>
| **Drug classification statement.**  
  Note: Rx, OTC or Household remedy. |
| **Statement on additive added (Preservative, colorant, flavour, sweetener).** |
| **Font size**  
  Note: For prescription product, the Rx symbol should be printed in a type size no less than 1/5 of the height of the principal display panel. |
| **Therapeutic claim/ Pharmacologic category**  
  Note: As per Administrative Order No. 172 s.2004 Guidelines on the Registration of Herbal Medicines |
| **Claimed application/ folkloric use**  
  Note: As per Administrative Order No. 184 s.2004 Guidelines on the Registration of Traditionally-Used Herbal Products |
## Country Specific Requirements

<table>
<thead>
<tr>
<th><strong>TM</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>The statement ”The traditional application/use of this product has not been evaluated by the Food &amp; Drug Administration” shall be in an outlined box parallel to the base of the label located in the information panel.</td>
</tr>
<tr>
<td><strong>Note:</strong> As per Administrative Order No. 184 s.2004 Guidelines on the Registration of Traditionally-Used Herbal Products</td>
</tr>
<tr>
<td><strong>Official name of the product shall be printed inside an outlined box.</strong></td>
</tr>
<tr>
<td><strong>Note:</strong> As per Administrative Order No. 172 s.2004 Guidelines on the Registration of Herbal Medicines and Administrative Order No. 184 s.2004 Guidelines on the Registration of Traditionally-Used Herbal Products</td>
</tr>
<tr>
<td><strong>The following phrases shall be printed on all labeling materials:</strong> “If symptoms persist, consult your doctor.” “Not allowed for use in pregnant, lactating mothers, and children below 18 years.”</td>
</tr>
<tr>
<td><strong>Note:</strong> As per Administrative Order No. 184 s.2004 Guidelines on the Registration of Traditionally-Used Herbal Products</td>
</tr>
<tr>
<td>HS</td>
</tr>
<tr>
<td>----</td>
</tr>
<tr>
<td>“Food supplements” / “Dietary supplements”</td>
</tr>
<tr>
<td>Recommended daily allowance (RDA) for vitamins/minerals used as food/dietary supplements.</td>
</tr>
<tr>
<td>Note: Revised standard terms as 2002 Recommended Energy and Nutrients Intakes (RENI) per day (adopted as per Bureau Circular No.16 s.2005)</td>
</tr>
<tr>
<td>The caption “NO APPROVED THERAPEUTIC CLAIMS” shall be printed in the principal display panel of all labeling materials, font size 14, font type Arial, all capital and bold letters.</td>
</tr>
<tr>
<td>Note: As per Bureau Circular No.2 s. 1999</td>
</tr>
</tbody>
</table>
ANNEX X – ASEAN General Principles for Establishing Maximum Levels of Vitamins and Mineral in HS
- To ensure manufacturer only include safe level of vitamins and minerals in their health supplement products so that the normal use of the products under the instructions of use provided by the manufacturers will be safe for the consumers.

- The maximum levels are not intended to be used as levels of vitamins and minerals in HS that would bring beneficial effects.
## Scope

<table>
<thead>
<tr>
<th>Vitamins</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (Retinol)</td>
<td>Vitamin B$_6$</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Folic Acid</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Vitamin B$_{12}$</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Biotin</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Nicotinic Acid</td>
</tr>
<tr>
<td>Vitamin B$_1$</td>
<td>Nicotinamide</td>
</tr>
<tr>
<td>Vitamin B$_2$</td>
<td>Pantothenic Acid</td>
</tr>
</tbody>
</table>
### Minerals

<table>
<thead>
<tr>
<th>Calcium</th>
<th>Fluoride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>Iodine</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Iron</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Manganese</td>
</tr>
<tr>
<td>Boron</td>
<td>Molybdenum</td>
</tr>
<tr>
<td>Chromium</td>
<td>Selenium</td>
</tr>
<tr>
<td>Copper</td>
<td>Zinc</td>
</tr>
</tbody>
</table>
1. Principles for Establishing Upper Limit based on WHO Model

2. Principles for Establishing Maximum Level based on ERNA Model
# ASEAN Maximum Levels of Vitamins and Minerals in HS

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Maximum Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (Retinol)</td>
<td>1.5mg/day (5000IU/day)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>0.025mg/day (1000IU/day)</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>536mg/day (800IU/day)</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>0.12mg/day</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>1000mg/day</td>
</tr>
<tr>
<td>Vitamin B₁</td>
<td>100mg/day</td>
</tr>
<tr>
<td>Vitamin B₂</td>
<td>40mg/day</td>
</tr>
</tbody>
</table>
# ASEAN Maximum Levels of Vitamins and Minerals in HS

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Maximum Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B$_6$</td>
<td>100mg/day</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>0.9mg/day</td>
</tr>
<tr>
<td>Vitamin B$_{12}$</td>
<td>0.6mg/day</td>
</tr>
<tr>
<td>Biotin</td>
<td>0.9mg/day</td>
</tr>
<tr>
<td>Nicotinic Acid</td>
<td>15mg/day</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>450mg/day</td>
</tr>
<tr>
<td>Pantothenic Acid</td>
<td>200mg/day</td>
</tr>
</tbody>
</table>
## ASEAN Maximum Levels of Vitamins and Minerals in HS

<table>
<thead>
<tr>
<th>Mineral</th>
<th>Maximum Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>1200mg/day</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>800mg/day</td>
</tr>
<tr>
<td>Magnesium</td>
<td>350mg/day</td>
</tr>
<tr>
<td>Boron</td>
<td>6.4mg/day</td>
</tr>
<tr>
<td>Chromium</td>
<td>0.5mg/day</td>
</tr>
<tr>
<td>Copper</td>
<td>2mg/day</td>
</tr>
</tbody>
</table>
# ASEAN Maximum Levels of Vitamins and Minerals in HS

<table>
<thead>
<tr>
<th>Mineral</th>
<th>Maximum Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodine</td>
<td>0.15mg/day</td>
</tr>
<tr>
<td>Iron</td>
<td>15mg/day</td>
</tr>
<tr>
<td>Manganese</td>
<td>3.5mg/day</td>
</tr>
<tr>
<td>Molybdenenum</td>
<td>0.36mg/day</td>
</tr>
<tr>
<td>Selenium</td>
<td>0.2mg/day</td>
</tr>
<tr>
<td>Zinc</td>
<td>0.5mg/day</td>
</tr>
</tbody>
</table>
ASEAN Maximum Levels of Vitamins and Minerals in HS

Notes:

1. Conditions of use of Vitamin K
   - Application: For use in oral dosage form of multivitamin/mineral preparations for adults and not as a single ingredient health supplement
   - Vitamin K form: Only Vitamin $K_1$ and/or Vitamin $K_2$
   - Cautionary statement: “Consult a health care practitioner prior to use if you are on anticoagulant therapy/taking blood thinners such as warfarin.”
ASEAN Maximum Levels of Vitamins and Minerals in HS

Notes:

2. The maximum levels of Potassium and Fluoride in HS are not established. These can be used in HS subject to the approval of the NRA.

3. Certain national requirements by other ASEAN Member States
Balancing Innovation and Sound Regulation