HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

JULY 2023

GUIDELINES FOR ESTABLISHING THE SAFETY OF INGREDIENTS OF HEALTH SUPPLEMENTS AND TRADITIONAL MEDICINES

Guidelines Version 3

The information in these Guidelines may be updated from time-to-time. For the latest version of the Guidelines, please refer to our website at www.hsa.gov.sg.

HSA
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1. Introduction

1.1 Dealers of health supplements (HS), traditional medicines (TM), medicated oils, balms (MOB) and medicated plasters are required to ensure that their products are safe through careful selection and safety substantiation of ingredients used.

1.2 The objective of these guidelines is to provide guidance on safety substantiation for active ingredients in these products to ensure that the safety of these health products is supported by the appropriate level of evidence.

2. Scope of active ingredients

2.1 An active ingredient refers to the ingredient that contributes to the intended health benefit or function of the product.

2.2 HS should contain one or more, or a combination of the following active ingredients:

(a) Vitamins, minerals, amino acids, fatty acids, enzymes, probiotics and other bioactive substances
(b) Substances derived from natural sources, including animal, mineral and botanical materials in the forms of extracts, isolates, concentrates, metabolites
(c) Synthetic sources of ingredients mentioned in (a) and (b).

2.3 TM should contain one or more, or a combination of the following active ingredients:

- Substances derived from natural sources, including animal and botanical materials with uses documented in the relevant traditional references.

2.4 MOB and medicated plasters may contain one or more of the following substances as active ingredients:

(a) Any essential oil
(b) Any fixed oil derived from a plant
(c) Methyl salicylate
(d) Menthol
(e) Camphor
(f) Peppermint.

3. Information required to support the safety of active ingredients

3.1 Dealers (importers, manufacturers, wholesale dealers) and sellers are required to ensure that their products are safe, and that they conform with the applicable safety and quality standards. HS, TM, MOB and medicated plasters should also not contain:

- Ingredients listed in:
  i. Poisons Act (Chapter 234) & Poison Rules
  ii. Misuse of Drugs Act (Chapter 185) & its Regulations
  iii. ASEAN Guiding Principles for Inclusion into or Exclusion from the Negative List of Substances for Health Supplements
  iv. ASEAN Guiding Principles for Inclusion into or Exclusion from the Negative List of Substances for Traditional Medicines
- Ingredients derived from humans.

3.2 In ensuring the safety of these products, it is important for dealers to first establish the identity of the active ingredient used. The identification is important to ensure that the evidence used to support the safety is relevant to the ingredient. After establishing the identity, dealers can first conduct a literature search to look for evidence showing a history of safe use of the ingredient. If such evidence is not available, scientific evidence should be used to establish ingredient safety.

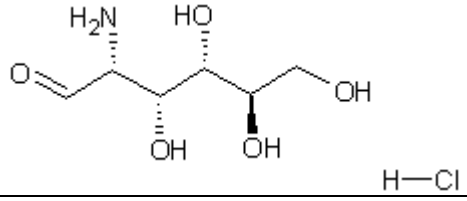
Identity of the Ingredient

3.3 The information listed in Table 1 could be used as a template in consolidating relevant information for describing the identity of an ingredient. Ingredient information is also included as examples for illustration purposes.

Table 1: Identity of the ingredient

Plant or Animal Ingredient	
Ingredient information	
Scientific (Latin) name: full systematic species name including family, genus, species, variety, subspecies, author's name, and chemotype if applicable	*Panax ginseng C. A. Mey.*
Synonyms	*Panax quinquefolius var. ginseng (C.A.Mey.)*

Plant or Animal Ingredient	
Common names	Asian ginseng, Chinese ginseng, Korean ginseng
General description of the ingredient, such as the part used and standardisation to a constituent	Plant part used: Root
Proposed health use of the ingredient to help establish the relationship between proposed use and documented use	Increase energy and enhance physical performance

Chemical Ingredient	
Ingredient information	
Chemical Abstracts Service (CAS) Number	66-84-2
International Union of Pure and Applied Chemistry (IUPAC) name	(3R,4R,5S,6R)-3-amino-6-(hydroxymethyl)oxane-2,4,5-triol;hydrochloride
Chemical structure	
Other names (e.g. synonym and common name)	Glucosamine HCl, Glucosamine hydrochloride
Proposed health use of the ingredient to help establish the relationship between proposed use and documented use	To maintain joint health

Literature evidence of safe use

3.4 An adequate safety profile may be established for a HS, TM, MOB, or medicated plaster ingredient for which a substantial documentation of human use exists, for example, substances with a long history of safe use in conventional food or TM, well-established vitamins, minerals, herbal ingredients, and food components. Positive safety assessments by regulatory authorities, or scientific bodies or institutions published on the safety of an ingredient may also suffice as literature evidence.

3.5 The literature sources and authoritative references that can be used as evidence of documentation are:

- recognised reference books such as pharmacopoeias and materia medicas; or

- ingredient monographs or assessments from regulatory authorities or scientific bodies.

Examples of such references and sources are found in Appendix 1.

3.6 The ingredient should be used in accordance with documented use with respect to the source material, plant or animal part used and method of preparation.

3.7 The intended route of administration should be the same as that in the reference, and the proposed dose, duration of use and frequency of use should be within that of what has been documented.

Scientific Evidence on Ingredient Safety

3.8 For ingredients that do not have an extensive history of human use, and there is a lack of published information on the ingredient's safety, additional scientific evidence as listed in Table 2 is necessary to enable adequate assessment of safety.

3.9 All studies should be conducted in accordance with the applicable Organization for Economic Cooperation and Development (OECD) technical guidelines or The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. Please refer to the respective organisations' websites for the current edition of the guidelines.

Table 2: Types of scientific evidence

Types of evidence	Relevant OECD and ICH guidelines
Pharmacology (i.e. pharmacokinetics and pharmacodynamics) • This is necessary for defined chemical entity	
Interactions with drug, food, other TM or HS ingredients • Justification or scientific evidence considering plausible interactions should be reviewed	
Acute toxicity • This is necessary to facilitate diagnosis of possible overdose	OECD 420 OECD 423 OECD 425
Repeat-dose toxicity • At least two sub-chronic or chronic studies, as appropriate, are recommended to ensure reproducibility in data. If only one sub-chronic study is used to derive the Acceptable Daily Intake (ADI) for long term consumption, an	ICH M3 OECD 407 OECD 408

Types of evidence	Relevant OECD and ICH guidelines
additional uncertainty factor should be considered	
Genotoxicity • Minimally, tests for gene mutation in bacteria, and in vitro cytogenetic test for chromosomal damage, or in vitro mouse lymphoma Tk gene mutation assay are recommended	ICH S2 OECD 471 OECD 473 OECD 487 OECD 488
Carcinogenicity • Necessary if there is a cause for concern or recommended to be used daily for more than 6 months	ICH S1A OECD 451 OECD 453
Reproductive toxicity • Necessary if the product is intended for use during pregnancy and lactation or in children < 12 years, or where there is cause for concern	ICH S5 OECD 443 OECD 416
Human data • If human safety studies are not available, human efficacy studies that include adverse event reporting and analysis of key haematological parameters can be used to support the safety of an ingredient in human	ICH E6 Consolidated Standards of Reporting Trials (Consort) Guidelines

Adverse event reports

3.10 Where available, adverse events data from safety alerts, post marketing and/or epidemiological studies should be considered and assessed with reference to the World Health Organisation (WHO) Uppsala Monitoring Centre (UMC) causality assessment system.

4. References

4.1 ASEAN Guiding Principles for Inclusion into or Exclusion from the Negative List of Substances for Health Supplements

4.2 ASEAN Guiding Principles for Inclusion into or Exclusion from the Negative List of Substances for Traditional Medicines

4.3 ASEAN Guiding Principles on Safety Substantiation of Health Supplements

4.4 ASEAN Guiding Principles on Safety Substantiation of Traditional Medicines

Appendix 1 - Literature Sources and Authoritative References that can be used as Evidence of Documentation

Generally, sources of evidence used to support the safe use of an ingredient should clearly indicate the following information:

- Source material
- Plant part used (where applicable)
- Method of preparation
- Route of administration
- Dose, duration, frequency of use
- Health related purpose

The reference should also be recognised by the regulatory authority as supporting information in the product or ingredient safety assessment process:

- Current edition of recognised reference books such as pharmacopoeias and materia medicas:
    - British Pharmacopeia
    - British Herbal Pharmacopoeia
    - Pharmacopoeia of the People's Republic of China
    - European Pharmacopoeia
    - United States Pharmacopoeia
- Ingredient monograph or assessment from regulatory authorities or scientific bodies:
    - Australia Therapeutic Goods Administration – Therapeutic Goods (Permissible Ingredients) Determination
    - European Medicines Agency – European Union Herbal Monograph
    - European Scientific Cooperative on Phytotherapy (Monographs for Herbal Medicinal Plant)
    - German Commission E Monographs
    - Handbook of Ayurvedic Medicinal Plants
    - Health Canada – Natural Health Products Ingredient Monographs
    - World Health Organisation Monographs on Selected Medicinal Plants
    - Joint FAO/WHO Expert Committee on Food Additive (JECFA) monographs

Revision History

Version	Date of publication	Summary of changes*
1	March 2022	New document
2	July 2022	Updated references
3	July 2023	Included medicated oils, balms and medicated plasters

*Editorial changes are not reflected

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