Guidance for Industry

Frequently Asked Questions about

ASEAN Guiding Principles on Safety Substantiation of Traditional Medicines and

ASEAN Guiding Principles on Safety Substantiation of Health Supplements; Version 1.0

Introduction

This document is a collation of Questions and Answers (Q&A) which provide clarification and references that may be referred by the industry in order to have a better understanding of the ASEAN guidelines. It is developed by HSA based on discussions between HSA and the industry experts.

The industry may refer to this Q&A for products intended for the Singapore market. For products to be marketed in other ASEAN Member States, industry is advised to refer to regulatory guidelines provided by the regulatory authorities of the respective ASEAN Member State where your product will be exported to.

This document may be revised from time to time, to include new Q&As or to update the information due to changes made to the ASEAN guidelines.

Questions & Answers

1. Under what circumstances will safety substantiation NOT be required for a new product or new ingredient?

Safety substantiation may not be required if:

(a) Product falls under the following categories:

- Product has no new ingredient(s),
- Product has no ingredient(s) derived from new method(s) of purification, extraction or manufacturing,
- Existing product with no changes to its formulation, dosage, delivery system or target users (e.g. pregnant, lactating women, children),
- Existing product with no new safety concern identified.

(b) Product contains ingredient(s) with lower recommended dosage than existing products.

(c) Product is a Traditional Medicine (TM) with a documented history of safe use or well-established safety profile.

(d) Product is a Health Supplement (HS) containing ingredients which are known to be consumed at a higher amount as food or as a food constituent.

The safety substantiation evidence has to be made available to HSA when requested.

2. If a TM or HS ingredient is marketed in other countries but not in Singapore, will it be considered as a new ingredient?

Yes, according to the ASEAN Guiding Principles on Safety Substantiation of Traditional Medicines and the ASEAN Guiding Principles on Safety Substantiation of Health Supplements, an ingredient that has never been used in the intended market of an ASEAN country will be considered as a new ingredient for that market. A product containing a new ingredient would require safety substantiation.

3. What are considered as new methods of purification, extraction or manufacturing?

Any purification, extraction or manufacturing methods which are not documented in established references, e.g. WHO monographs, pharmacopoeias, will be considered as new methods.

4. For products containing a new combination of ingredients which were already found in existing products in the market, will they be considered as a new combination product?

Yes, ASEAN deems such products as new products if the combination of ingredients has not been approved for marketing in the intended market of an ASEAN country.

5. If a TM or HS is regarded as a new product or a new combination product, can the safety of this product be substantiated based on the safety data of its active ingredient(s)?

If the product contains only one active ingredient, the safety of the product may be substantiated by the safety data of the ingredient.

If the product contains more than one active ingredient, the safety of the product may not be adequately substantiated by the safety data of the individual ingredients. The company has to ensure that the ingredients, when combined, will not affect the product safety (such as by potentiating the side effect). Additionally, the company has to ensure that the ingredients, when combined, will not nullify the desired effects of the product.

6. What kind of data will be required in order to substantiate the safety of a new product?

Safety substantiation should be based on finished product. If it is based on the ingredient(s) in the product, justification should be provided to HSA when requested.

The data used to substantiate safety should also be relevant to the ingredient or product under review. Some of the considerations are the identity of the ingredient, the dosage consumed, frequency and duration of use, and population who have consumed the ingredient.

Safety information may include history of use, scientific evidence from animal and/or human studies using internationally accepted methodologies. Additional data such as post-marketing study and epidemiological data etc., may also be provided. For more information, please refer to the ASEAN Guiding Principles for Safety Substantiation for Traditional Medicines and the ASEAN Guiding Principles for Safety Substantiation for Health Supplements, as applicable.

You may also refer to the US FDA's Guidance for Industry on New Dietary Ingredient (NDI) Notification.

7. The guidelines state that safety substantiation may not be necessary for traditional medicines that have a documented history of safe use or with well-established safety profile. What does history of use in the ASEAN guidelines mean?

History of use refers to human exposure to the ingredient(s) when used as traditional medicine or as food. However, considerations should be given with respect to the identity of the substance, the amount, frequency and duration of use and population who have consumed the ingredient, when assessing if the data on history of use could provide adequate substantiation for safety.

8. The guidelines state that safety substantiation may not be necessary for health supplements containing ingredients which have been consumed as food or food constituent within the highest observed safe intake. What does "highest observed safe intake" mean?

For health supplements, "highest observed intake" refers to the highest amount that is known to be consumed as food or as a food constituent. For example, if the new ingredient is a specific protein purified from milk, the highest observed consumption level of cow's milk could be used to support the safety of this specific protein.

9. Can adverse event (AE) data be used for safety substantiation?

AE data can be included as part of information for safety substantiation. However, AE reporting data will be useful only if there is a robust monitoring system in place. Companies who are referencing AE statistics to substantiate safety should bear in mind that AE cases for TM and HS are usually under-reported and the causality determination is generally difficult. Hence the lack of AE reports may not be used as a basis to conclude that the product is safe.

10. What are the toxicity studies required for safety substantiation?

Toxicity data could be derived from animal studies using internationally accepted methodologies such as WHO or OECD, ICH guidelines and FDA Red Book. Acute, sub-chronic and/or chronic toxicity data may be required. The recommended duration of product usage may determine whether repeated dose sub-chronic or chronic toxicity studies are needed.

Other toxicity data such as teratogenicity, carcinogenicity, and/or mutagenicity data may also be required if necessary, such as in the case when the ingredient is intended for use during pregnancy or a cause for concern has been noted in toxicity studies.

The recommendations for safety testing are provided in the FDA's Guidance for Industry the New Dietary Ingredient (NDI) Notification and WHO's[1] Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines.

11. Will acute toxicity study data be sufficient if toxicity study is required?

Acute toxicity study data is used to facilitate diagnosis of possible overdose. Hence, longer term toxicity study data will be required for safety substantiation.

12. Can Margin of Safety (MoS) derived from No Observed Adverse Effect Level (NOAEL) be considered as an indicator for safety?

MoS is a measure of how close the estimated daily intake is to the level that has been shown to have no adverse effect in animal or human studies (the NOAEL). It is calculated as the ratio of the NOAEL to the highest total daily intake level of the ingredient, as determined from the recommended conditions of use.

[1] WHO: World Health Organization

MoS value may be used to determine if a new ingredient will be reasonably expected to be safe. You may refer to the US FDA's Guidance for Industry on New Dietary Ingredient (NDI) Notification on the use of margin of safety.

13. Which laboratories in Singapore conduct toxicity studies?

There are accredited laboratories listed in the database of Singapore Accreditation Council (SAC). For more information, you can visit the SAC website at www.sac-accreditation.gov.sg.

14. Does HSA require the toxicity studies to be conducted under GLP conditions?

Toxicity studies conducted by GLP facilities accredited by the SAC are acceptable. Toxicity studies conducted by other labs in Singapore and other countries are also acceptable if the testing methodologies applied are documented in the WHO, OECD[2], ICH[3] guidelines or FDA Red Book.

15. Are safety substantiation dossiers required to be submitted to HSA before the products are placed on the market?

Safety substantiation evidence are to be kept readily available for inspection or submitted to HSA upon request. For products that require pre-market approval, safety documents may be required at the point of product application submission.

[2] OECD: Organisation for Economic Co-operation and Development

[3] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use