APPENDIX 4: GUIDELINE ON REGISTRATION OF HEALTH SUPPLEMENTS

IMPORTANT NOTES:

This guideline will serve as an additional reference guide for the registration of health supplement products which consist of pharmaceutical active ingredients for human use as well as ingredients derived from natural sources.

Applicants are advised to refer to Drug Registration Guidance Document for the common requirements for the preparation of a well-structured dossier application to be submitted for product registration.

Outline:

4.1 DEFINITION

4.1.1 HEALTH SUPPLEMENT (HS)

A Health Supplement (HS) means any product that is used to supplement a diet and to maintain, enhance and improve the health function of human body. It is presented in small unit dosage forms (to be administered) such as capsules, tablets, powder, liquids and shall not include any sterile preparations (i.e. injectable, eyedrops). It may contain one or more, or the following combination:

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, metabolite;
iii) Synthetic sources of ingredients mentioned in (i) and (ii) may only be used where the safety of these has been proven.

4.1.2 INDICATION

i) Used as a Health Supplement;
ii) Vitamin and mineral supplements for pregnant and lactating women.

4.1.3 ROUTE OF ADMINISTRATION

Oral

4.1.4 EXCLUSION AS HEALTH SUPPLEMENTS:

Health Supplements shall NOT include:

i) Any product as a sole item of a meal;
ii) Any injectable and sterile preparation;
iii) Any cells, tissues, organs or any substance derived from the human body;
iv) Any substance listed in the Schedule of the Poison Act;
v) Any other route of administration other than the oral route.

4.1.5 EXEMPTION

Extemporaneous preparations that have been prepared and given directly to the patient by a healthcare practitioner during the course of treatment.

4.2 ACTIVE INGREDIENTS

Listed active ingredients can be checked trough http://npra.moh.gov.my/ of product search.

4.3 MAXIMUM DAILY LEVELS OF VITAMINS AND MINERALS FOR ADULTS ALLOWED IN HEALTH SUPPLEMENTS

NO.	VITAMINS & MINERALS	UPPER DAILY LIMIT
1.	Vitamin A	5000 IU
2.	Vitamin D	1000 IU
3.	Vitamin E	800 IU
4.	Vitamin K (K1 and K2) [1]	0.12mg
5.	Vitamin B1 (Thiamine)	100 mg
6.	Vitamin B2 (Riboflavine)	40 mg
7.	Vitamin B5 (Panthothenic Acid)	200 mg
8.	Vitamin B6 (Pyridoxine)	100 mg
9.	Vitamin B12 (Cyanocobalamin)	0.6 mg
10.	Vitamin C (Ascorbic Acid)	1000 mg
11.	Folic Acid	0.9 mg
12.	Nicotinic Acid	15 mg
13.	Niacinamide (Nicotinamide)	450 mg
14.	Biotin	0.9 mg
15.	Boron	6.4 mg
16.	Calcium	1200 mg
17.	Chromium	0.5 mg
18.	Copper	2 mg
19.	Iodine	0.3 mg
20.	Iron [2]	20 mg
21.	Magnesium	350 mg

NO.	VITAMINS & MINERALS	UPPER DAILY LIMIT
22.	Manganese	3.5 mg
23.	Molybdenum	0.36 mg
24.	Phosphorus	800 mg
25.	Selenium	0.2 mg
26.	Zinc	15 mg

Note:

1. *Vitamin K (K1 and K2) is restricted only for combination with other vitamins and minerals in oral preparations. Vitamin K (K1 and K2) as a single ingredient in an oral preparation is not allowed.*
2. *For pre and antenatal use, as part of a multivitamin and mineral preparation, levels higher than the 20mg limit established for adults may be permitted at the discretion of the Authority.*
3. *Any form of fluoride as an ingredient is not permitted in formulation of health supplement products.*

4.4 HEALTH SUPPLEMENT CLAIM

4.4.1 CONDITIONS

All claims made for HS shall:

i) be consistent with the definition of HS;
ii) enable consumers to make an informed choice regarding products;
iii) not be misleading or false;
iv) support the safe, beneficial and appropriate use of the product;
v) maintain the level of scientific evidence which is proportional to the type of claims;
vi) be for health maintenance and promotion purpose only;
vii) not be medicinal or therapeutic in nature, such as implied for treatment, cure or prevention of disease.

4.4.2 TYPES AND EVIDENCE OF CLAIMS

i) A health supplement claim refers to the beneficial effects of consuming HS to promote good health and well-being (physical and mental) by providing nutrition, enhancing body structure/ function, relieving physiological discomfort and/or reducing the risk of health related conditions or diseases.

ii) Types of HS claims are:
   - General or Nutritional Claims;
   - Functional Claims (medium);
   - Disease Risk Reduction Claims (high).

iii) For a HS product making a General or Functional Claim on vitamin(s) and/or mineral(s), it must contain minimum of 15% of the Codex Nutrient Reference Value (NRV) per daily dose of the vitamin(s) and/or mineral(s). Other ingredients must be substantiated by the evidences to which it has been supported.

   For example, if vitamin is less than 15% NRV, then the specific claim for this vitamin is not allowed unless there is evidence to support effect below this value.

iv) For a HS product making Disease Risk Reduction Claim, it must be substantiated by the evidences to which it has been supported.

(i) Table 1: General or Nutritional Claims

Level of claim	Definition	Examples/ Wording of claim	Criteria	Evidence to substantiate HS claims
General or Nutritional Claims	▪General Health Maintenance ▪Benefits derived from supplementation beyond normal dietary intake	▪Supports healthy growth and development ▪Nourishes the body ▪Relieves general tiredness, weakness ▪Helps to maintain good health ▪For energy and vitality ▪For strengthening the body	▪ Is in line with established nutrition knowledge in reference texts ▪ Is related to general well-being in line with scientific knowledge ▪ Claim does not refer to the structure and/or function of the human body ▪ In accordance to HS principles and practice in Malaysia	**1 or more of the following evidences:** i) Standard reference e.g. reference textbooks, pharmacopoeia, monographs ii) Recommendations on usage from reference regulatory authorities or reference organisations

Please refer to Illustrative Substantiation Evidence List for the list of acceptable references, organisations and authorities.

(ii) Table 2: Functional Claims (medium)

Claims must be adequately substantiated through ingredient-based evidence and when necessary through product-based evidence.

Types of HS claim	Definition	Examples/ Wording of claims	Criteria	Evidence to substantiate HS Claims
Functional Claims (medium)	▪ Maintains or enhances the structure or function of the human body, excluding disease-related claims	Acceptable claims based on the single ingredient e.g. ▪ Vitamin A helps to maintain growth, vision and tissue development ▪ Vitamin D helps in normal development and maintenance of bones and teeth. ▪ Chondroitin helps to promote healthy joints	For claims on established nutrients and ingredients such as vitamins & minerals with daily recommended values ▪ Meet the conditions for nutrient function claims as set by the Authority ▪ Claims have consistent scientific support according to scientific review and evaluation ▪ In accordance to HS principles and practice in Malaysia	**1 or more of the following evidence:** i) Standard reference e.g. reference textbooks, pharmacopoeia, monographs ii) Recommendations on usage from reference regulatory authorities or reference organisations iii) Good quality scientific evidence from human observational studies (refer to ASEAN Guidelines on efficacy data requirement) **(only in the event that human experimental study is not ethical, animal studies will be accepted together with epidemiological studies or other scientific literature and documented traditional use)** iv) Peer-reviewed scientific data or meta-analysis

Please refer to Illustrative Substantiation Evidence List for the list of acceptable references, organisations and authorities.

(iii) Table 3: Disease risk reduction (high)

Types of HS claim	Definition	Examples/ Wording of claims	Criteria	Evidence to substantiate HS Claims
Disease risk reduction	▪ Significantly altering or reducing a risk factor of a disease or health related condition.	▪ Helps to reduce risk of osteoporosis by strengthening bone ▪ Helps to reduce the risk of dyslipidaemia	▪ The relationship between the HS ingredient or product and disease risk reduction is supported by consistent scientific evidence ▪ Documented in authoritative reference texts ▪ Recognised by the Authority reference or international organisations or regulatory authorities ▪ Adheres to the key principles of HS claims	**Compulsory evidence:** i) Scientific evidence from human intervention study on ingredient and/or product ii) Toxicological study (chronic) iii) Pharmacological study **At least 1 additional evidence:** i) Standard reference e.g. reference textbooks, pharmacopoeia, monographs etc. ii) Recommendations on usage from reference regulatory authorities or reference organisations iii) Evidence from published scientific reviews or meta-analysis iv) Report prepared by expert committees/ expert opinion (subject to the Authority approval)

Please refer to Illustrative Substantiation Evidence List for the list of acceptable references, organisations and authorities.

4.4.3 CLAIMS SUBSTANTIATION

Claims must be in line with the respective HS principles and supported by adequate evidence. To reflect the total available usage evidence (including relevant scientific evidence), the evidence shall be summarized as part of the substantiation document for the claim as in the **Table 4** below.

Indication/ claim	Product/ Ingredient studied	Dosage and administration route	Duration of treatment	Type of evidence (scientific evidence)	Study design	Study population	Summary of findings	Limitations of the study	Source of evidence i) Author ii) Title iii) Publication details iv) Year v) Type (text, …)

Note: *Evidence not summarised as in the above format will not be further evaluated.*

4.4.4 ILLUSTRATIVE SUSBSTANTIATION EVIDENCE

i) Reference texts

a. Martindale, latest edition. The Complete Drug. Pharmaceutical Press, 2009.
b. The ABC Clinical Guide to Herbs. American Botanical Council
c. WHO Monographs on Selected Medicinal Plants
d. British Pharmacopoeia
e. United States Pharmacopoeia
f. Indian Pharmacopoeia
g. Chinese Pharmacopoeia
h. Natural Standards (www.naturalstandard.com)
i. Office of Dietary Supplements, National Institutes of Health - Dietary Supplement Fact Sheets (http://ods.od.nih.gov/Health_Information/Information_About_Individual_Dietary_Supplements.aspx)

ii) Organisations

a. American Botanical Council (www.herbalgram.org).
b. American Nutraceutical Association (www.ana-jana.org)
c. CODEX Alimentarius
d. Global Information Hub for Integrated Medicine (http://www.globinmed.com)
e. National Centre for Complementary and Alternative Medicine (http://nccam.nih.gov/)
f. Office of Dietary Supplements, National Institutes of Health (USA) (http://ods.od.nih.gov)

iii) Reference regulatory authorities

a. Australia TGA
b. Chinese Health Authority on Chinese medicinal herbs
c. European Commission
d. Health Canada
e. United States FDA

Notes:

1. *This list is not meant to be exhaustive and will be reviewed from time to time.*
2. *The Authority will nonetheless conduct a detailed evaluation of the evidence included in the report to ensure that the health claim is substantiated.*
3. *The Authority will be willing to consider review other than the listed above, if the standards of evidence are consistent with those of the Authority.*
4. *All references must be current.*

4.5 SPECIFIC DOSSIER REQUIREMENT FOR REGISTRATION OF HEALTH SUPPLEMENTS

PRODUCT VALIDATION

1. PRODUCT NAME

- May include product name, dosage form and strength (e.g. XYZ Capsule 500mg)
- Dosage form and strength of product would need to be entered as part of product name to allow for multiple dosage forms (e.g. tablet, capsule) and strengths (e.g. 200mg and 400mg) for any particular named (proprietary or generic) product.
- In any event if found that registered product name is similar to another registered product, NPRA reserve the rights to request for the change in the product name.
- Product with more than 1 active ingredient could not include strength of active ingredients in the product name.
- Product name may be included together with the brand name or trademark name, if applicable.
- Any product name which is the same or similar either in writing/ pronunciation, with the product name of an adulterated product is prohibited.

Table 5: List of Non-Permissible Product Name for Health Supplement Products

No.	Issue	Example
1.	**Prohibited use of disease names as stated in the Medicines (Advertisement and Sale) Act 1956 (revised 1983)**	Diabetes, Asthma, Cancer
2.	**Prohibited use of a single active ingredient as a product name in products containing more than one active ingredient unless product name contains words such as 'Plus, Compound, Complex, Herbanika**	If the product contain Vitamin C, Vitamin E and Fish Oil Product name: "Vitamin C" is not allowed but product name: "Vitamin C Plus" is allowed.

No.	Issue	Example
3.	**Prohibited use of superlative** Names which indicates superiority inefficacy	Power, Superior, Pure, Mustajab, Safe, Healthy, Penawar, VIP, Good, World Number 1
4.	**Prohibited use of spelling of words which may cause confusion** i)Words which involve names of/part thereof: 20 disease names prohibited in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983) ii) Other diseases without scientific proof iii) Prohibited indication	Go Out = GOUT (label) Utix
5.	**Prohibited use of names which may cause ambiguity** Ambiguous product name	B For Energy?
6.	**Prohibited use of names which may be offensive or indecent**	SENXBIG=SEnXBIG(label) Sexy, Enjoy, Paradise, Heavenly, Blue boy, Casanova, Desire
7.	**Product name which is not congruent with the active ingredient.**	The active ingredient is Evening Primrose oil (EPO) and the product name: “Marine tablet” is not allowed.
8.	**Prohibited use of product names which has elements of ludicrous belief** Statements referring to ancient believe/negative spirits/supernatural power	Words such as miracle, magic, magical, miraculous, saintly, heavenly

No.	Issue	Example
9.	**Prohibited use of product names similar to the existing approved product names** Product name similar to the spelling and pronunciation of words of an existing product names	Elegen vs L-gen vs L-jen Forte vs Fort
10.	**Prohibited use of product names which may cause ambiguity in the nature of product (drug/ food/ beverage)** Product name similar to a food/ beverage name	Juice, Health drink, Beverage, Kooky
11.	**Prohibited use of product names which represents professional advice or opinion**	Dr Sunny, Professor
12.	**Product name that symbolize a claim**	Vigour, Youthful, High, Hi
13.	**Product name that uses strength but formulation contains more than one active ingredient.**	If the product contains multivitamins and minerals. Product name: "XXX multivitamins and minerals 500mg" is not allowed.
14.	**Other prohibited product names**	Minda, IQ, Smart, Unique, Ultra Mega, Detox, Defence, Immunity
15.	**Names of organs and brain**	Heart, kidney, skin, liver

Note:

1. *This list is not meant to be exhaustive and will be reviewed from time to time.*
2. *The Authority reserves the right to disallow any other words, phrases or graphics for product label which in its opinion is misleading, improper or not factual.*

2. DOSAGE FORM

- Dosage forms allowed:
    a) Tablets
        - Caplet, Lozenge, Chewable tablet, Dispersible tablet, Effervescence tablet, uncoated tablet, enteric coated tablet, Sugar coated tablet, Film coated tablet, extended release tablet;
    b) Capsules
        - Soft capsule, Hard capsule, Enteric coated capsule, Chewable soft capsule, Extended released capsule;
    c) Powder/ Granules;
    d) Liquid
        - Emulsion, syrup, spray, suspension.
- Products in the shape of animal dosage forms are not allowed.
- Supporting data from established reference (e.g. Standard Pharmacopeia) shall be required for new dosage form.
- The form that correctly describes it in terms of its product quality control specifications and performance shall be selected.
- A separate application for registration is required for each dosage form.
- The following documents will have to be provided during submission of product dossier for **Sustained-release/ Extended-release/ Timed-release dosage form**
    i) Protocol of analysis;
    ii) In-Process Quality Control (IPQC);
    iii) Finished Product Specification (FPQC);
    iv) Certificate of Analysis (COA).

3. ACTIVE INGREDIENT

Name of Active Ingredient:

- Please select active ingredient from the search database. If substance is not listed, please select the 'Not Listed Ingredient' button. Automatic e-mail will be send to NPRA for notification.
- Approved names, pharmacopoeia names of ingredients shall be used whenever possible.

Strength of active ingredient :

- To enter the content of active ingredients (numerical) and then select the weights and measures from the given list.
- Content of ingredients shall be expressed as appropriate in the following manner:
  a. quantity per dose unit (e.g. for unit dose formulations - tablet, capsule, lozenge, etc.)
  b. percentage composition - %w/w, %w/v, %v/v, etc.
  c. weight per ml. (e.g. for solutions,suspension etc.)
  d. quantity (percentage or amount) per measured dose (e.g. oral liquids, drops, etc.)
- Metric weights and measures shall be used.

Source of Active ingredient:

- To specify the source such as animal, plant, synthetic or others (to specify)

USE OF PROTECTED/ ENDANGERED INGREDIENTS

a) PROTECTED/ ENDANGERED WILDLIFE SPECIES

It is the responsibility of the applicant to ensure that the ingredient(s) derived from wildlife species its parts and derivtives used in the formulation **COMPLIES** with the Wildlife Conservation Act 2010 (Act 716) and International Trade in Endangered Species Act 2008 (Act 686). Both guidelines can be downloaded through this link http://www.wildlife.gov.my.

The applicant shall contact the following department to obtain the necessary permit/ license. A copy of the permit/ license shall be attached together with the application form for product registration.

Department of Wildlife and National Parks, Peninsular Malaysia
Km. 10, Jalan Cheras,
56100 Kuala Lumpur,
Tel: +603-90866800, Fax: +603-90753873

b) ENDANGERED BOTANICAL SPECIES

It is the responsibility of the applicant to declare the source of the botanical ingredient if it is listed under the International Trade in Endangered Species Act

2008 (Act 686). If the ingredient is from a local source, a special permit/ license shall be obtained from the:
Division of Protection and Quarantine of Plants,
Department of Agriculture,
Tingkat 1-3, Wisma Tani,
Jalan Sultan Salahuddin,
50632 Kuala Lumpur.
Tel: +603 - 20301400, Fax: +603 - 26913550.

Remarks on active ingredient (if any):

- To specify the equivalent/providing amount of active component from the raw material (e.g: Sodium ascorbate 520 mg providing.... Vitamin C)
- Declaration of species name from natural source (plant, animal or others)

Table 6: Additional data to support a new health supplement active ingredients:

No.	Types of documents	Checklist
1.	Standard/ established references	• Martindale, Pharmacopeias, Monograph etc.
2.	Information from the competent authorities of reference countries	• Information shall be provided from the competent authorities of reference countries (Refer to 9.6.5) • Example of supporting documents: ➢ Registration status and maximum registered dosage as health supplement ➢ established monograph ➢ GRAS status
3.	Clinical studies or scientific evidences	• Full published articles • Unpublished data may be considered • Mandatory for high claim
4.	Non-clinical studies to support long term-use	

No.	Types of documents	Checklist
5.	Toxicology studies with the determination of NOAEL (No observed adverse effect level)	
6.	Pharmacological study	
7.	Justification for the use of new active ingredient as health supplement	
8.	Registration status worldwide	• Registered and Marketed Date

Note: *The documentation must support the safety use and dose of new active ingredients as a health supplement.*

4. ANY ANIMAL ORIGIN

Any source from animal origin must be declared and to specify the type of animal.

5. MANUFACTURER

The requirements for Good Manufacturing Practice (GMP) of the premises are in **Table 7** as followed:

Level of claims	Requirements for GMP
General/ Functional	a) Malaysia *Guidelines on Good Manufacturing Practice for Traditional Medicine and Health Supplement latest edition*. Or b) The accepted standards for GMP will be determined by the category the product is classified in the country of origin. For example, if the product is classified as food in the country of origin, GMP certificate of food standard issued by relevant country authority will be accepted on condition that the standards are similar to those practices in Malaysia. Or c) If the product is not regulated in the country of origin and does not require GMP certification, the manufacturer will have to produce a GMP certificate issued by an independent body recognised by the Authority. Information including the standard/ regulations/ legislation to which the inspection was based upon must be mentioned.
Disease Risk Reduction	a) Malaysia *Guidelines on Good Manufacturing Practice for Traditional Medicine and Health Supplement latest edition* Or b) The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Standards. Or c) GMP certificates issued by relevant country authority will be accepted on condition that the standards are similar to PIC/S Standards

6. CONTRACT MANUFACTURER

Contract manufacturer is applicable when product owner is not the product manufacturer

7. SECOND SOURCE INFORMATION

An application for a second source may be considered where deemed necessary. This second source product shall be the same as the first product in all respects except for the site of manufacture.

8. PRODUCT CONTAINING PREMIX

Premixed active ingredient(s) is a combination of two or more active ingredients that are previously manufactured by a different manufacturer.

Certificate of GMP for manufacturer/ supplier is required for the premixed ingredient(s) in formulation. The requirements for GMP are same as in Field 5 as above.

9. REPLACEMENT PRODUCT

A product registration holder is not allowed to register/ hold two or more products with similar formulation (same active ingredient of raw material, strength and dosage form) at any one time unless product variant.

Letter of justification for replacement by product holder is required.

10. OTHER MANUFACTURER

Any manufacturer involved in Assembly, Fill & Finish, Active Ingredients, Packing, Labeling etc.

11. IMPORTED PRODUCTS

Imported product needs to be declared.

SECTION A: PRODUCT PARTICULARS

Product Description:

State, briefly, **visual and physical characteristics** of the product, including as in the following **Table 8** (where applicable):

No.	Dosage Form	Description
1.	Tablet	Shape, size, colour, odour, taste, marking, emboss, type of tablet (e.g. coated, uncoated, film, sugar etc.)
2.	Capsule	Shape, size, colour, odour, taste, marking, emboss, coating, content of capsule, type of capsule (e.g.: soft, hard, chewable etc.)
3.	Liquid	Clarity, type (e.g. solution/ suspension/ emulsion etc.), taste, odour, colour.
4.	Powder	Colour, odour, taste etc.
5.	Pill	Colour, odour, taste, size etc.
6.	Granules	Colour, odour, taste, size etc.

- **Indication/ Usage**

  State briefly recommended use(s) of product. The following indications are allowed:

  - Used as a Health Supplement; or
  - Vitamins and mineral supplements for pregnant and lactating women.

- **Recommended Dose (Dose/ Use Instruction) & Route of administration**

  State the dose (normal dose, dose range) and dosage schedule (frequency, duration if applicable). Dosage for adults and children (where appropriate) shall be stated.

- **Contraindication**

  State conditions for which or under which the product shall not be used.

  Note 1: Indicate clearly which conditions are:

  - absolutely contraindicated,
  - contraindicated but may be used under special circumstances and what precautions to be taken in such cases.
  - If there is no information available for this section, please state as 'Unknown'.

- **Warnings and Precautions**

  State briefly precautions and warnings necessary to ensure safe use of the product e.g. caution against giving to children and elderly; use in pregnancy and lactation; in infants; etc.

  Note : If there is no information available for this section, please state as 'Unknown'.

- **Drug Interactions**

  State only interactions which are observed and/or for which there is potential clinical significance. Interactions may occur with

  - other medicinal products used;
  - other herbs/ substance;
  - meals, or specific types of food.

  Note : If there is no information available for this section, please state as 'Unknown'.

- **Side Effects/ Adverse Reactions**

  State in order of severity and frequency, the side effects, adverse reactions, toxic effects, etc. (i.e. reactions, toxic effects, other than those desired therapeutically) including reactions such as allergy, hypersensitivity, dependence, addiction, carcinogenicity, tolerance, liver/ kidney toxicity etc.

  Indicate also symptoms and sites of effects/reactions.

  Note 1 : Reactions, whether minor or serious, shall be stated.

  Note 2 : Severity, reversible, frequency of occurrence shall be indicated wherever possible.

Note 3 :Clinical tests for detection of 'sensitive' patients, measure for management of adverse reactions developed shall be described wherever possible.

Note : If there is no information available for this section, please state as 'Unknown'.

- **Pregnancy and Lactation**

  Please state any effect on pregnancy and lactation if applicable.

- **Signs and Symptoms of Overdose and Treatment**

  State briefly symptoms of overdose/ poisoning, and where possible, recommended treatment and antidotes for overdose/ poisoning.

  Note : If there is no information available for this section, please state as 'Unknown'.

- **Storage Conditions**

  State the recommended storage conditions (specific temperature eg: 30^{o}C, humidity, light etc.).

  Information shall also include storage condition before first opening, after reconstitution and/or after opening and for all the listed pack types where applicable. Stability data to support such storage condition shall be available.

- **Shelf Life**

  The shelf life for all the listed pack types shall be supported by stability data.

  Information shall also include shelf life before first opening, after reconstitution and/or after opening where applicable. Stability data to support such shelf life shall be available.

  Evidence is required to demonstrate that the product is stable (meets the finished product shelf life specifications throughout its proposed shelf-life).

- **Therapeutic Code (If any)**

  Please select "Health Supplement"

SECTION B: PRODUCT FORMULA

Change of formulation whether for active ingredient or excipient is not allowed during product evaluation.

- **Batch Manufacturing Formula**

State the batch size and actual batch manufacturing master formula. Data from validation step will be captured in terms of substance name, type (active ingredient or excipient), function and quantity per unit dose. Other information will need to be entered.

An **attachment** of the Batch Manufacturing Formula documentation must be provided. The documents must be verified by authorized personel.

Example of BMF documentation:

ABC Sdn. BHD.
Batch Manufacturing Formula
Product Name:
Batch Quantity: 1,000,000 capsules

Name	Function	Quantity per capsule	Batch quantity	Overage
Pyridoxine HCl	Active	_ mg	_ kg	_ %
Cholecalciferol	Active	_ mg	_ kg	_ %
Glycerin	Excipient	_ mg	_ kg	None
Gelatin	Excipient	_ mg	_ kg	None
Purified water	Excipient	0 mg *	_ kg	None
		Total: _ mg	Total: _ kg	

* evaporated, does not exist in final formulation

(Signature)
Post of authorized person
Name of authorized person
Date:

- **Manufacturing process**

  State a brief description of the manufacturing process. Essential points of each stage of manufacturing process and a description of the assembling of the product into final containers shall be covered. If the product is repacked/assembled by another manufacturer, details of repacking/assembly and quality control must be supplied.

  An **attachment** of the manufacturing process, in the form of a flow chart can be made.

- **In Process Quality Control (IPQC)**

  To provide a summary of the tests performed, stages at which they are done, and the frequency of sampling and number of samples taken each time. Specifications for quality assurance of the product shall be supplied.

Example of In Process Quality Control:

Company Name/ Address:

Applicant/ Client Name/ Address:

Date:

In-Process Quality Control: Test performed during manufacturing process

No.	Test Done (example)	Stage Done (example)	Frequency of testing (example)	Quantity sample taken (example)	Specifications (example)	Method (example)
1.	Appearance	Before weight, after encapsulation	2	10 gram	Blue like orange	Organoleptic test
2.	Disintegration	After compression	2	10 tablet	NMT 30 minutes	Equipment etc
3.	Uniformity of weight	After tableting, Packaging	4	20 Tablets	1 gram/tab	

* Declaration (if any)
Signature (authorized personnel)
Name:
Designation:

*** The above parameters are only as an example; other test may be required for specific product.**

- **Finished Product Quality Specification**
- **Provide details of quality control specifications including a list of tests for both release and shelf life specifications (if they are different) and state the limits of acceptance.**

Example of Finished Product Quality Specification

Finished Product Quality Control (FPQC) - Finished product Specification/ Specification Sheet

Company name/Address:
Product Name:
Batch no.
Dosage form:
Packaging:
Date of manufacture:
Date of expiry:

No.	Test	Method	Specification	Reference
1.	Appearance/ Organoleptic: Odour Colour	Ex: Macroscopic/ Microscopic	To describe the characteristic	In-house/ pharmacopoeia (e.g. BP/USP etc)
2.	Assay: (All active ingredients/ compounds claim on label)	HPLC/ GC/ MS/ UV	To specify	To specify
3.	Disintegration/Dissolution	To specify	DRGD	DRGD
4.	Uniformity of weight	To specify		
5.	Water content	To specify		
6.	Microbial contamination TAMC, TYMC, specified microorganism	To specify	DRGD	DRGD
7.	Heavy Metal Contamination: Lead, Arsenic, Cadmium, Mercury	To specify	DRGD	DRGD
8.	Etc:			

Signature:
Name:
Designation: (At least by Quality Assurance Manager or equivalent)
Date of signature:

*** The above parameters are only as an example; other test may be required for specific product.**

- **Certificate of Analysis of Finished Product**

  Starting from 1st January 2018, **2 batches of Certificate of Analysis (COA) for Finished Product** must be submitted upon submission of new product registration for Natural Product / Health Supplement with the general claim.

  (Reference: Directive No.3 Year 2017, BPFK/PPP/07/25(8)Jld 1 : Direktif Untuk Menguatkuasakan Keperluan Sijil Analisa Produk Siap (Certificate of Analysis (COA) For Finished Product) Semasa Permohonan Pendaftaran Baru Produk Semulajadi dan Produk Suplemen Kesihatan Dengan General Claim)

Example of Certificate of Analysis for Finished Product (Health Supplement)

Certificate of Analysis

Company name/ Address :

Product Name :

Batch no. :

Dosage form :

Packaging :

Date of manufacture :

Date of expiry :

Test Parameter	Specifications	Results	Method
Appearance/ Organoleptic: Odour Colour	To describe the characteristic		
Disintegration	DRGD		
Uniformity of weight			
Assay: (All active ingredients/ compounds claim on label)	To specify		
Microbial Contamination Test TAMC, TYMC, specified microorganism	DRGD		
Heavy Metal Contamination			
Lead (Pb)	NMT 10 ppm		
Cadmium (Cd)	NMT 0.3 ppm		
Mercury (Hg)	NMT 0.5 ppm		
Arsenic (As)	NMT 5 ppm		

NMT = Not More Than

Signature :
Name :
Designation : (At least by Quality Control Manager or equivalent)
Date of signature :

Note: The above parameter are only as an example, other tests may be required for specific product.

- **Stability Data**

Table 9:

No.	Stability Study	Shelf Life
1.	i) 2 batches of complete real-time stability study at 30 ± 2 ºC / RH 75± 5% for the claimed shelf-life. OR ii) 2 batches of on-going real time stability study (at least 6 months) at 30 ± 2 ºC / RH 75 ± 5% + Letter of commitment (LOC) to submit complete real time stability data when study is complete/ when requested. AND 2 batches of 6 months accelerated stability study at 40ºC.	- Shelf life will be based on data stability at 30ºC of not more than 5 years. - 3 years
2.	i) 2 batches of complete real time stability study at a temperature and relative humidity (RH) different from the Zone IVB for at least 2 years + LOC to conduct real time stability study at Zone IVB and submit when the study is complete/ when requested OR ii) 2 batches of on-going real time and accelerated stability study (at least 6 months) at a temperature/ relative humidity (RH) different from Zone IVB + LOC to conduct real time stability study at Zone IVB and submit when the study is complete/ when requested.	- Shelf life will be based on data stability at specified temperature. - 2 years at specified temperature in the stability study.

3.	2 batches of complete real-time stability study at temperature and RH other than zone IVB for very unstable active ingredient(s)/ product (must be substantiated).	- Shelf life will be based on data stability at specified temperature.

Storage Conditions with Type of Container Closure System/ Stability Study

Table 10:

No.	Type of Container Closure System/ Study	Storage Condition
1.	Products in primary containers permeable to water vapour	30°C ± 2°C/75% RH ± 5%RH
2.	Products in primary containers impermeable to water vapour	30°C ± 2°C
3.	Accelerated studies	40°C ± 2°C/75% RH ± 5%RH

Reports of stability studies shall provide details of:

- the batches placed under study (a minimum of 2 batches are required).
- containers/ packaging type.
- conditions of storage during study (temperature, humidity, etc).
- duration of study and frequency (interval) of the tests/ observations.
- the tests performed and acceptance limits.

Example of Stability Data

STABLITY DATA

PRODUCT NAME: TABLET ABC 500MG **BATCH NO.:**

MANUFACTURING DATE: dd/mm/yy **TEMPERATURE:** 30 °C ± 2 °C

EXPIRY DATE: dd/mm/yy **RELATIVE HUMIDITY**: 75 % ± 5%

Tests	Specification	Frequency of Testing							
		0	3	6	9	12	18	24	36
Product description	Film-coated tablet, brownish in colour								
Disintegration test	NMT 30 minutes								
Assays	eg: 90% -120% (ref….)								
Microbial Contamination test: Total Aerobic Microbial Count Total Yeasts & Moulds Count Test for Specified Microorganisms	 NMT 2 x 10^4 NMT 2 x 10^2 ➢ NMT 2 x 10^2 CFU of bile-tolerant gram- negative bacteria in 1g or 1ml ➢ Absence of Salmonella in 10g or 10ml ➢ Absence of Escherichia coli in 1g or 1ml ➢ Absence of Staphylococcus								
Heavy metal test: Lead Arsenic Mercury Cadmium	 ≤10.0 mg/kg (≤ 10ppm) ≤5.0 mg/kg (≤ 5ppm) ≤0.5 mg/kg (≤ 0.5ppm) ≤0.3 mg/kg (≤ 0.3ppm)		NA						

Conclusion ----------

Analyst name: (signature) Verified by: (signature)

Name: Name:

Designation Designation

Date: Date:

Stability study data checklists are as in **Table 11** below:

Data Required	Remarks
Company name	- From product holder/ manufacturer/ third party lab
Product name	- To be same with other documentation
Dosage form	- To be same with A3
Packaging particulars	- Material and pack size must be stated - To be same with C1
Storage condition	- Temperature and humidity must be stated - Shall comply with ASEAN Zone IV requirement (30±2°C/75±5%RH) - If different storage condition (e.g. 25°C, 2-8°C), must provide justification/ supporting data.
Frequency of testing	For example: - 0, 3, 6, 9, 12, 18, 24 months and annually for the proposed shelf life
List of relevant tests	- All tests required for each dosage form shall be conducted, for example: o Physical appearance changes o Disintegration test (if applicable) o Chemical Assays for active ingredients (if applicable) o Microbial tests
Specifications	- Acceptance limit for each test must be stated - To be supported by established references (e.g. USP, BP) if available
Results for each test	- Must meet the specifications
Approval by authorized person	- Must have the name, post and signature of authorized person

Testing Parameters of Stability Study for each type of dosage forms are shown in **Table 12** below:

Testing Parameters / Dosage Form	Appearance/ organoleptic (odor, color, taste)	Assay*	Hardness/ friability	Disintegration or dissolution rate	Moisture content	Viscosity	pH	Microbial content	Granules/ Particle Size variation	Re-suspendability
Oral powder	√	√			√			√		
Hard capsule	√	√		√	√			√		
Soft capsule	√	√		√				√		
Coated and Uncoated Tablet	√	√	√ (uncoated)	√	√			√		
Coated and Uncoated Pill/ Pellet	√	√		√	√			√		
Suspension	√	√				√	√	√	√	√
Solution	√	√				√	√	√		
Emulsion	√	√				√	√	√		
Granules	√	√			√			√	√	

Notes:

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

** Assay to determine the stability of a single active ingredient or a single marker/surrogate indicator that is susceptible to change during storage and is likely to influence quality shall be sufficient to infer the overall stability of the TM/HS product irrespective of whether the finished product contains single or multiple active ingredients.*

2. Justification must be given if one of the tests is not conducted for relevant dosage form.

SECTION C: PARTICULARS OF PACKING

- **Packaging**

➢ Maximum pack size allowed for tablets, pills, capsules is based on daily dosing for a quantity not exceeding six (6) months usage.

➢ Maximum pack size allowed with disease risk reduction claim for 1 month supply of products unless justified.

➢ Product with dosage form of softgel with tail (twist and squeeze) shall come with children proof cap.

- Packing particulars to the listing of packing as follows ;
  - C1: pack size and fill details by weight, or volume or quantity;
  - C2 : container type
  - C3 : Barcode/ serial No (optional);
  - C4 : recommended distributor's price (optional);
  - C5 : recommended retail price (optional);

SECTION D: LABELLING REQUIREMENTS

- The information shall present on the label of a product at outer carton, immediate container or blister/ strips:

  Please refer *Appendix 9: Labelling Requirements* **for:**

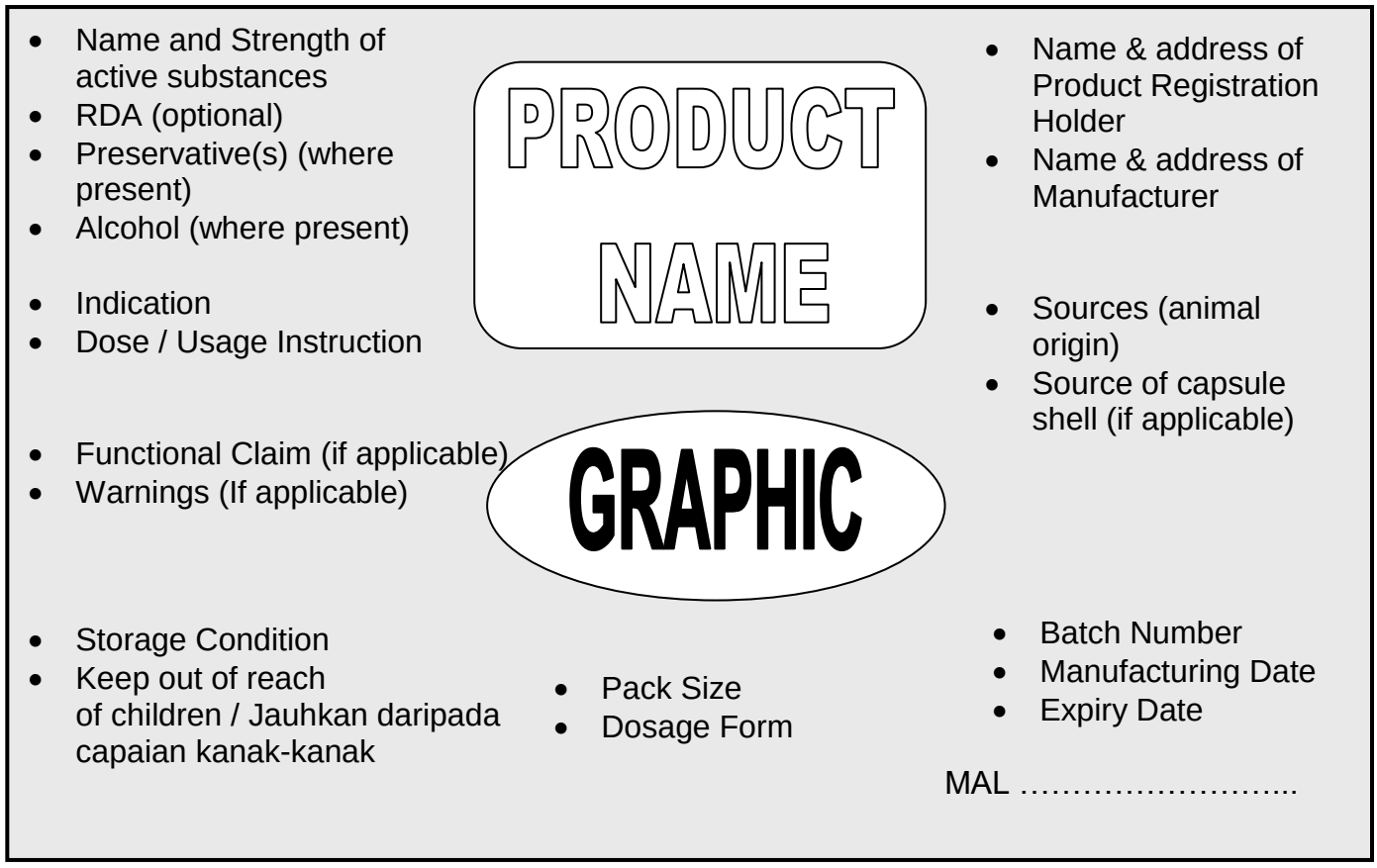
  a) **General Labelling Requirements - Label (mock-up) for immediate container and outer carton;**
  b) **Consumer Medication Information Leaflet (RiMUP);**
  (For health supplement with high claims/ disease risk reduction)
  c) **Specific Labelling Requirement**
  (For specific substances, e.g. alfalfa, arginine, bee pollen, chitosan, Boswellia serrata etc.)

- **Additional Requirements for Labelling**
  - Information on the Product Name; and Name and Strength of active ingredient(s) must be printed repeatedly (for blister/ strip).
  - Product with dosage form of soft gel with tail (twist and squeeze) shall include the statement 'Under parent supervision' in the label.
  - For products containing animal origin(s), please add this statement: *This product contains substance(s) from animal origin.*
  - For products containing porcine, please add this statement: *This product contains animal part(s) (porcine/pig).*

- Health supplement products with disease risk reduction claims (high) are encouraged to be dispensed under the supervision of pharmacists or medical practitioners. At such, the label and package insert of health supplement products with disease risk reduction claims (high) shall have the following statement**:**

  "Please consult a doctor/ pharmacist before taking this product".

- **Standard Labelling for Health Supplements**



Note:

- *Product label shall follow the standard labelling for Health Supplement.*
- *Information stated in the left and right panel is interchangeable.*
- *All information on the label must be truthful and not misleading to the consumers.*
- *Batch number, manufacturing date, expiration date: can be stated on label, on top of cap or bottom of bottle.*
- *The front panel must contain the information as above. However, the information on the side panels is interchangeable. Additional cautionary labelling relating to the safety of the product may be imposed.*

- **Package inserts (Optional**)

The following information is required to be included in a package insert:

(i) Brand or Product Name
(ii) Name and Strength of Active Substance(s)
(iii) Product Description
(iv) Indication
(v) Dose/ Use Instruction
(vi) Contraindications
(vii) Warnings and Precautions
(viii) Interactions with Other Medications
(ix) Statement on usage during pregnancy and lactation
(x) Adverse Effects/ Undesirable Effects
(xi) Overdose and Treatment
(xii) Storage Conditions (may be omitted if the information is stated on the label or outer carton labels)
(xiii) Dosage Forms and packaging available
(xiv) Name and Address of manufacturer/ product registration holder
(xv) Date of Revision of Package Insert

- **Prohibited Visual/ Graphics on Label,** as shown in **Table 13** below:

No.	Issue	Example	Note
1.	Marketing strategy	**Example:** "Money back guarantee" "Buy 1 free 1" "Backed by RM5 million product Liability Insurance"	Such statements are prohibited on labels, as per Medicines (Advertisement and Sale) Act 1956 guideline requirements
2.	Usage guide which promotes use of other product(s)	**Example:** "After consumption of this product (Product A), for better results, it is recommended to take Product B"	Prohibited on product label
3.	Consumer testimonial		Prohibited on product label
4.	Clinical Trial results or any information on clinical trial done on product	Example : "Clinically Tested" "Randomized Double Blind Placebo Control Clinical Study"	Such statements are prohibited on labels (as per Medicines (Advertisement and Sale) Act 1956 guideline Requirement
5.	Reference to Hadith/ Al-Quran/ Bible/ Religious books		Prohibited on product label
6.	Opinion of prominent figure(s) on product or its active ingredient/ content	**Example:** Opinion of product/formulation inventor	Prohibited on product label

No.	Issue	Example	Note
7.	Label design (graphic and color) similar to labels from another company		Prohibited on product label
8.	Statement on active ingredient origin	**Example:** Source from the Mountains of Alps	Allowed if proven true
9.	Introduction of founder/ Manufacturer		Prohibited on product label
10.	Logo with certification	**Example:** SIRIM/ ISO / GMP/ HACCP	Prohibited on product label because certification renewal is on a yearly basis
11.	Name/ Statement/ Logo/ registered trademark which does not satisfy the specifications	**Example:** “Dr.ABC’s Formula” “Nothing like it”	Prohibited on product label
12.	Patency claim/ Patency number/ Special technique used/ superiority in ingredients (Example: capsule coat)	**Example:** Patented technique	Allowed if proven true
13.	Nutritional claims with analysis certificate attached	**Example:** Calorie, Fat, Protein and others	Prohibited on product label
14.	Graphics or picture of internal organs	**Example:** Kidney, Heart, Nerves.	Prohibited on product label

No.	Issue	Example	Note
15.	Gender symbol (male or female)	(♀ and/or ♂)	Prohibited on product label
16.	Indecent photographs/ pornography/ graphics/ images		Prohibited on product label
17.	Graphics which are incoherent with the indication	**Example:** - Noted indication is for constipation, but graphics on label shows a slim-looking lady which denotes indication for weight loss - Indication for urination but label graphics contains picture of a water hose.	Prohibited on product label
18.	Highlighting unnecessary body parts	**Example:** Indication is for general health but graphics on label highlights male and female sexual organ parts	Prohibited on product label
19.	Graphics of plants or animal which may cause confusion	**Example:** Radix Ginseng which is improvised as a male sexual part	Prohibited on product label
20.	Photograph of celebrities	**Example** - Artiste, sports person(s), politician	Prohibited on product label
21.	Statement on sugars	**Example** - This product contains no added sugar	Allowed on product label provided the product contains no fructose, glucose, sucrose, or other kind of sugars with a

No.	Issue	Example	Note
			potential to affect diabetics are not included in the formulation
22.	Negative statement	**Example** - No gluten, yeast etc	Prohibited on product label
23.	Other statements	**Example:** - This product is blended with premium quality - Certified chemical residue free	Prohibited on product label

Notes:

1. *The list is not meant to be exhaustive and will be reviewed from time to time.*
2. *The Authority reserves the right to disallow any other words, phrases or graphics for product label which in its opinion is misleading, improper or not factual.*

SECTION E: PARTICULAR OF PRODUCT OWNER, MANUFACTURER, IMPORTER AND OTHER MANUFACTURER

- Please select whether the product owner is the product holder, manufacturer or both product holder and the manufacturer.
- If the product owner is neither product holder nor the manufacturer, please select name and address of the product owner (applicable for imported product only).
- Other details such as product owner, manufacturer, repacker, other manufacturer involved in the manufacturing process, store address and importer (If any) have to filled. It is mandatory for the repacker to acquire GMP certificate.

SECTION F: SUPPLEMENTARY DOCUMENTS

- **Letter of authorization of product owner**

This is applicable for imported product in which the product owner appoints the product holder (in Malaysia) as their product holder in Malaysia

- **Letter of appointment of contract manufacturer and/ or repacker**

Applicable if the product is contract manufactured by a manufacturer who is not the product holder.

- **Letter of acceptance as contract manufacturer and/ or repacker**

Applicable if the product is contract manufactured by a manufacturer who is not the product holder.

- **Certificate Of Pharmaceutical Product (CPP), Free Sale Certificate (CFS) and Good Manufacturing Practice (GMP)**

CPP can be attached as a replacement of CFS and GMP certificate if the product is classified as pharmaceutical product in the country of origin:

GMP/ CFS Template

Authority name, address, country

Type of certificate

Company name (product owner/ manufacturer)
Product name
Product formulation if available
Dosage form

Statement of freely sold (similar meaning) if for CFS certificate
Standard of GMP and compliance status if for GMP certificate
Duration of certification

Name, signature and designation of authorized personnel
Date of signature

Note: The certificate must be in English or translated into English (certified true by issuance or embassy or notary public)

- **Attachment of Protocol Analysis**

Protocol analysis is attached here.

- **Finished Product Quality Control (FPQC)**
  - The certificate must be complete with the product specification and result. The list of tests and specifications must be same with finished product specification document.
  - Quality Control Test For Health Supplement Product are as follows:

1. Limit Test for Heavy Metals

a) Lead : NMT 10.0 mg/kg or 10.0 mg/litre (10.0ppm)
b) Arsenic : NMT 5.0 mg/kg or 5.0 mg/litre (5.0ppm)
c) Mercury : NMT 0.5 mg/kg or 0.5 mg/litre (0.5ppm)
d) Cadmium : NMT 0.3 mg/kg or 0.3 mg/litre (0.3ppm)

** Required for products with ingredients from natural sources.*
The test shall be conducted on the finished product.

2. Disintegration Test (for tablets, capsules and pills)

Disintegration time:

a)	Uncoated tablets	: NMT 30 minutes
b)	Film-coated tablets	: NMT 30 minutes
c)	Sugar-coated tablets	: NMT 60 minutes
d)	Enteric-coated tablets	: Does not disintegrate for 120 minutes in acid solution but to disintegrate within 60 minutes in buffer solution
e)	Capsules	: NMT 30 minutes
f)	Pills	: NMT 120 minutes

3. Test for Uniformity of Weight (tablets and capsules only)

i) Tablet

- For tablet with average weight of 130mg or less: Not more than 2 tablets differ from the average weight by more than 10% AND no tablets differ from the average weight by more than 20%
- For tablet with average weight between 130-324mg: Not more than 2 tablets differ from the average weight by more than 7.5% AND no tablet differs from the average weights by more than 15%
- For tablets with average weight more than 324mg: Not more than 2 tablets differ from the average weight by more than 5% AND no tablet differs from the average weight by more than 10%

ii) Capsule

Individual weight of the capsule to be within the limit of 90-110% of the average weight.

4. Tests for Microbial Contamination, as shown in **Table 14** below:

Route of Administration	TAMC (CFU/g or CFU/ml)	TYMC (CFU/g or CFU/ml)	Specified micro-organisms
Non-aqueous preparations for oral use	NMT 2 x 10^3	NMT 2 x 10^2	Absence of *Escherichia coli* (1 g or 1 ml)
Aqueous preparations for oral use	NMT 2 x 10^2	NMT 2 x 10^1	Absence of *Escherichia coli* (1 g or 1 ml)
Special Ph. Eur. provision for oral dosage forms containing raw materials of natural (animal, vegetal or mineral) origin for which antimicrobial pretreatment is not feasible and for which the competent authority accepts TAMC of the raw material exceeding 10^3 CFU/g or CFU/mL.	NMT 2 x 10^4	NMT 2 x 10^2	Not more than 10^2 CFU of bile-tolerant gram-negative bacteria (1 g or 1 ml) Absence of *Salmonella* (10 g or 10 ml) Absence of *Escherichia coli* (1 g or 1 ml) Absence of *Staphylococcus aureus* (1 g or 1 ml)

Notes:

TAMC : Total Aerobic Microbial Count

TYMC : Total Yeasts & Moulds Count

NMT : Not more than

[Reference: British Pharmacopoeia 2012]

- **Specifications and Certificate of Analysis of Active Ingredient**

Certificate of analysis for each active ingredient (raw material) is required pre-registration. The certificate must consist of specifications and results of analyses.

- **Other Supporting documents**

  - For the submission of other supporting documents.

  - Additional requirement for safety and quality of active ingredient/ product (e.g.; dose for children, pregnant etc.)

  - Quality testing for specific ingredient:
    - For product containing Aphanizomenon flos-aquae, applicants would have to provide certificates of analysis showing that the microcystin-LR or total microcystins content of the raw material does not exceed 1µg/g and the finished product has been tested for microcystin-LR using an acceptable method

  - Quality testing for specific product:
    - Certificate of Analysis for the level of dioxin (PCDDs and PCDFs) and dioxin-like polychlorinated biphenyls (PCBs) is required for product containing ingredient(s) derived from seafood. *(The acceptable limit for these tests shall follow standard references such as United States Pharmacopoeia (USP) and European Regulation.)*
    - Certificate of Analysis for proof of hormone-free is required for product containing placenta

ATTACHMENT 1

CHECKLIST OF DOSSIER REQUIREMENT FOR HEALTH SUPPLEMENTS

- Depending on the level of claims, submission may follows the route as outlined:
  i) General/ Nutritional and Medium Claims - Abridge evaluation
  ii) Disease Risk Reduction Claims - Full evaluation

Table 15: Checklist for General/ Nutritional and Medium Claim

No.	Field	General or Nutritional Claims	Functional Claims
A1	Product Name	√	√
	Brand name and product name		
A2	Product Description	√	√
	- Describe visual and physical characteristics of the product including shape, size, superficial markings, colour, odour, taste, type of coating, type of capsule etc where applicable		
	- Animal shape is only allowed for 'For Export Only' (FEO) Products		
A3	Dosage Form	√	√
	- COA capsule shell is required		
	- Colouring agent used in capsule		
	- Letter to verify the source of gelatin used		
A4	Product indication/ Usage	√	√
A5	Dose/ Use Instruction	√	√
	- Quantity and frequency		
	- Dosing schedule must be stated (e.g. take before/ after/ with meal)		
A6	Contraindication, if applicable	√	√
A7	Warning/ Precautions, if applicable	√	√
A8	Drug Interaction, if applicable	√	√
A9	Side Effects/ Adverse Reactions, if applicable	√	√
A10	Signs and Symptoms of overdose and treatment, if applicable	√	√

No.	Field	General or Nutritional Claims	Functional Claims
A11	Storage Condition - According to stability data	√	√
A12	Shelf life - Must be supported by stability study - Please refer to B5	√	√
A13	Therapeutic Code - As a health supplement	√	√
B1.1	Batch Manufacturing Formula	√	√
B1.2	List of Active ingredient(s)	√	√
B1.3	List of excipient(s)	√	√
B1.4	Attachment of Batch Manufacturing Formula - Shall be on the product owner's/ manufacturer's original letterhead, product details, date and signature & designation of authorized personnel	√	√
B2.1	Manufacturing Process	√	√
B2.2	Attachment of Manufacturing Process Document or Manufacturing Flow Diagram	√	√
B3	In-Process Quality Control (IPQC)	√ *LOC to submit data during post registration	√
B4	Finished Product Specification (FPQC)	√ * LOC to submit data during post registration	√
B5	Stability Data (Please refer page 24)	√	√
D1	Label for immediate container	√	√
D2	Label for outer carton (if applicable)	√	√
D3	Proposed package insert / Product information leaflet (if applicable)	√	√

No.	Field	General or Nutritional Claims	Functional Claims
E1	Company name and address of product owner	√	√
E2	Company name and address of manufacturer(s)	√	√
E3	Company name and address of repacker (if applicable)	√	√
E4	Company name and address of other manufacturer (if applicable)	√	√
E5	Store address(s)	√	√
E6	Importer(s)	√	√
F1	Letter of authorization from product owner to product registration holder (if applicable)	√	√
F2	Letter of Appointment of Contract Manufacturer/ Repacker from Product Owner (if applicable)	√	√
F3	Letter of Acceptance from Contract Manufacturer/ Repacker (if applicable)	√	√
F4	Certificate of Pharmaceutical Product (CPP) - Applicable to imported products, must be issued by the competent authority in the country of origin. CPP issued by reference country may be considered.	√	√
F5	Certificate of Free Sale (CFS) - Applicable if CPP is not available, must be issued by the competent authority in the country of origin/ products owner country.	√	√
F6	Certificate of Good Manufacturing Practice (GMP) - Applicable if CPP is not available, must be issued by the competent authority in the manufacturing country.	√	√

No.	Field	General or Nutritional Claims	Functional Claims
F9	Attachment of protocol analysis	√ - dosage form extended release * LOC to submit during post for other types of dosage form	√ - dosage form extended release - validation of analytical method for new actives or new combination dosage
F10	Attachment of Certificate of finished product (COA of finished product)	√	√
F11	Attachment of Specifications and Certificate of Analysis (COA) of Active Ingredient	√	√
F12	Examples of supporting documents		
	Dioxin level test results (for product containing ingredients derived from seafood)	√	√
	Certificate of Good Manufacturing Practice (GMP) for premixed active ingredients		
	Hormone free test results (for placenta products)		
	Declaration letter from product manufacturer on the hormone - free status for product containing placenta		
	Manufacturing process validation report if applicable		
	Letter of commitment if applicable		
	Etc.		

No.	Field	General or Nutritional Claims	Functional Claims
* Complete stability study conducted at 30 ± 2 ºC / RH 75 ± 5%, IPQC, FPQC, protocol analysis and COA of finished product are required to be submitted 2 years after product registration with SAMPLE of the products. Failure on submission will cause the product be suspended until the complete documents are submitted, the registration of the product will be terminated if the complete documents still cannot be produced upon renewal of product registration.			

- Dossier Requirement for Disease risk reduction as in **Table 15 above** and **Table 16** below:

Table 16: Additional Quality Data Checklist for Disease Risk Reduction Claim

No.	Field	Disease Risk Reduction Claim
PART P	**P. HEALTH SUPPLEMENT PRODUCT** P1. Description and Composition P2. Pharmaceutical Development P2.1 Information on Development Studies P2.2 Components of the Health Supplement Product P2.3 Finished Product P2.4 Manufacturing Process Development P2.5 Container Closure System P2.6 Microbiological Attributes P2.7 Compatibility P3. Manufacturer P3.1 Batch Manufacturing Formula P3.2 Manufacturing Process & Process Control P3.2.1 Manufacturing Process Flowchart P3.3 Control of Critical Steps & Intermediates P3.4 Process Validation and Evaluation P4. Control of Excipients P4.1 Specifications	√

No.	Field	Disease Risk Reduction Claim
	P4.2 Analytical Procedure P4.3 Validation of Analytical Procedures P4.4 Justification of Specification P4.5 Excipient of Human or Animal Origin P4.6 Novel Excipients P5. Control of Finished Product P5.1 Specification P5.2 AnalyticalProcedures P5.3 Validation of Analytical Procedures P5.4 Batch Analyses P5.5 Characterization of impurities P5.6 Justification of Specification P6. Reference Standards or Materials P7. Container Closure System P8. Stability P9. Product Interchangeability/Equivalent evidence	
PART S	**S. HEALTH SUPPLEMENT SUBSTANCE** S1. General Information S1.1 Nomenclature S1.2 Structure S1.3 General Properties S2. Manufacture S3. Characterisation S4. Control of Health Supplement Substance S4.1 Specification S4.2 Analytical Procedures S4.3 Validation of Analytical Procedure S4.4 Batch Analysis S4.5 Justification of Specification S5. Reference Standards or Materials S6. Container Closure System S7. Stability	√

PART III: NON-CLINICAL DATA

- Applicable to disease risk reduction claims
  (For new active ingredient, new combination of active ingredients and new dose)

Table 17:

No.	Field	Disease Risk Reduction Claims
1.	Overview of non-clinical testing strategy	√
	- nomenclature	
	- structure	
	- general properties	
2.	Pharmacology	√
	- related information (including academic literature) of pharmacology studies on the declared efficacy	
3.	Pharmacokinetics	√
	- related information (including academic literature) of pharmacokinetics studies on the declared efficacy	
4.	Toxicology	√
	- related information (including academic literature) of toxicology studies	
5.	Integrated overview and conclusions	√
6.	Other toxicity studies if available	√
7.	References	√
	- List of references used	

- All information must be provided in the following format/ table:

Study Title	Type of Study	Product (formulation)	Study Summary - Study Design (e.g. case control, randomised placebo controlled, in vitro data, cohort study) - Dosage - Subject - Study Duration - Outcome parameters	Summary findings (Includes scientific details such as strength of evidence [e.g. p-values], conclusions, any shortcomings, etc. For traditional evidence include enough information to demonstrate relevance)

PART IV: CLINICAL DOCUMENTS

- Applicable to disease risk reduction claims (for new active ingredient, new combination of active ingredients and new dose).

Table 18:

No.	Field	Disease Risk Reduction Claims
1.	Clinical overview	√
2.	Production Development Rational	√
3.	Overview of Bio-pharmaceutics	√
	- To include associated analytical methods	
4.	Overview of Clinical Pharmacology	√
	- Summary of clinical pharmacology studies	
5.	Overview of Efficiency	√
	- Summary of clinical efficacy	
6.	Overview of Safety	√
	- Summary of clinical safety	
7.	References	√
	- List of all clinical studies	
	- List of key literature references	
	- Published clinical papers	

- All information must be provided in the following format/table:

Forms of study	Sample size	Duration	Randomisation of groups	Endpoint	Statistical analysis of data
Randomised, controlled, and preferably blinded intervention studies	Must be justified and must involve sufficiently large number of subjects to estimate incidence and nature of potential adverse reactions	Must be justified and must be of sufficient duration to ensure no safety concerns with respect to long term use	All groups shall have comparable baseline values, particularly for those factors that are known to be, or may be, confounders or risk factors	As a decrease incidence of the disease or a reduction of a factor, or a surrogate thereof, of the many that contribute to the development of a disease	Methods to calculate the sample size, setting the power and the significance level at conventional 80% and $p<0.05$ respectively shall be utilised Meta-analysis shall combine only studies with similar design, populations, interventions and outcome measure

ATTACHMENT 2

Table 19: Allowable claims for specific active ingredients in HS products

Ingredients	Claims		
	General	**Functional**	**Reduced Risk Reduction Claim**
Vitamin A	• Maintenance of good health	• Helps to maintain growth, vision and tissue development • Aids in maintaining the health of the skin and mucous membrane	
Vitamin C		• For healthy bones, **(cartilage),** teeth, gums as well as general make-up of the body	
Vitamin D	• Maintenance of good health	• Helps in normal development and maintenance of bones and teeth • Helps the body utilize calcium and phosphorus • Claim for specific population subgroups: Elderly people who are confined indoors	
Vitamin E	• Maintenance of good health		

Ingredients	Claims		
	General	**Functional**	**Reduced Risk Reduction Claim**
Beta Carotene	• Maintenance of good health	• Helps in maintenance of growth, vision and tissue differentiation	
Vitamin B1 (Thiamine)	• Helps to maintain good health	• Helps in maintenance of growth, vision and tissue differentiation	
Riboflavin (Vitamin B2)	• A factor in maintenance of good health	• Helps the body to utilize energy from food/ metabolize protein, fats and carbohydrates • Claim for specific population subgroups: -Additional amounts of Riboflavin are required during pregnancy and breast feeding when diet does not provide a sufficient daily intake	
Niacin (Vitamin B3)	• A factor in maintenance of good health	• Helps normal growth and development • Helps the body in utilization of energy from food	

Ingredients	Claims		
	General	**Functional**	**Reduced Risk Reduction Claim**
Pyridoxine (Vitamin B6)	• A factor in maintenance of good health	• Helps the body to metabolize proteins, fats and carbohydrates	
Cyanocobalamine (Vitamin B12)	• Helps in maintenance of good health	• Helps in the formation of red blood cell	
Folic Acid		• Helps in formation of red blood cell	• Helps prevent neural tube defects for women who are planning a pregnancy before conception and during 12 weeks of pregnancy at a dose of 400 mcg daily
Biotin	• Helps in maintenance of good health	• Helps to metabolize fats and carbohydrates	
Panthothenic Acid	• Helps in maintenance of good health	• Helps to metabolize fats and carbohydrates	

Ingredients	Claims		
	General	**Functional**	**Reduced Risk Reduction Claim**
Calcium	• Helps in maintenance of good health	• Helps in the formation and maintenance of bones and teeth • Claim for specific subgroup: - Additional calcium is required for pregnant and lactating women, when diet does not provide a sufficient daily intake to help in proper bone formation in developing baby	
Phosphorus	• Helps in maintenance of good health	• Helps in the formation and maintenance of bones and teeth	
Magnesium	• Helps in maintenance of good health	• Helps the body to metabolize carbohydrate	
Iron	• Helps in maintenance of good health	• Helps in the formation of red blood cell	• Helps to prevent iron anemia • Helps to prevent anemia due to iron deficiency
Iodine	• Helps in maintenance of good health	• Helps in the function of the thyroid glands	

Ingredients	Claims		
	General	**Functional**	**Reduced Risk Reduction Claim**
Zinc	• A factor in maintenance of good health	• Helps to metabolize carbohydrates, fats and protein	
Copper	• A factor in maintenance of good health	• Helps in the formation of red blood cell	
Manganese	• A factor in maintenance of good health	• Helps to metabolize carbohydrates and proteins	
Probiotics		• Helps to improve a beneficial intestinal microflora	

Notes:

1. *This list is not meant to be exhaustive and will be reviewed from time to time.*
2. *The Authority will nonetheless conduct a detailed evaluation of the evidence included in the report to ensure that the health claim is substantiated.*
3. *The Authority will be willing to consider review other than the listed above, if the standards of evidence are consistent with those of the Authority.*
4. *All references must be current.*

ACKNOWLEDGEMENTS

The National Pharmaceutical Regulatory Division acknowledges its indebtedness to the members from the industries, government agencies and universities as stated below, who provided comments and advices during the preparation of these guidelines.

Government agencies:

i) *Bahagian Keselamatan dan Kualiti Makanan (BKKM), KKM*
ii) *Bahagian Perubatan Tradisional & Komplementari, KKM*
iii) *Institut Penyelidikan dan Perubatan (IMR), KKM*
iv) *Kementerian Pertanian & Industri Asas Tani Malaysia*
v) *Unit Perancang Ekonomi, Jabatan Perdana Menteri*

Universities:

i) *Jabatan Pemakanan dan Dietetik, Fakulti Perubatan & Sains Kesihatan, Universiti Putra Malaysia*
ii) *Jabatan Pemakanan dan Dietetik, Fakulti Sains Kesihatan Bersekutu, Universiti Kebangsaan Malaysia*
iii) *Pejabat Dietetik, Pusat Perubatan Universiti Malaya*
iv) *Program Sains Makanan, Fakulti Sains dan Teknologi, Universiti Kebangsaan Malaysia*

Industries/ Associations:

i) *Biotropic Malaysia Berhad*
ii) Direct Selling Association of Malaysia (DSAM)
iii) Federation of Chinese Physician and Medicine-Dealers Association of Malaysia (FCPMDAM)
iv) Malaysian Biotechnology Corporation (BiotechCorp)
v) Malaysian Dietary Supplement Association (MADSA)
vi) Malaysian Direct Distribution Association (MDDA)
vii) *Persatuan Industri Farmaseutikal Malaysia (MOPI)*
viii) *Persatuan Pengeluar-pengeluar Ubat Tradisional Melayu Malaysia (PURBATAMA)*
ix) *Perubatan Traditional India Malaysia (PEPTIM)*
x) Pharmaceutical Association of Malaysia (PhAMA)