GUIDELINE FOR REGULATION OF HEALTH SUPPLEMENTS

REGISTRATION DIVISION
DRUG REGULATORY AUTHORITY

2016

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REVISION HITORY

This guideline is originally released in 2016. This guideline will be revised from time to time as deemed necessary by the Authority and Registration Committee members.

ABBREVIATIONS AND ACCRONYMS

ADR: Adverse Drug Reactions

cGMP: current Good Manufacturing Practice certificate

DRA: Drug Regulatory Authority

NOC: No Objection Certificate

MAH: Market Authorization Holder

PPM: Parts per Million

QC: Quality Control

QA:Quality Assurance

RDA: Recommended Daily Allowance

DEFINITION OF THE TERMINOLOGIES USED IN THIS GUIDELINE

a. **Adverse Drug Reaction (ADR):** means any noxious, undesired, or unintended response to a drug which occurs at therapeutic dose.
b. **Authority:** refers to Drug Regulatory Authority.
c. **Evaluation:** refers to the assessment of the dossier and product sample submitted by the applicant using prescribed set of criteria.
d. **Good Manufacturing Practice (GMP):** refers to a system for ensuring that products are consistently produced and controlled according to quality standards.
e. **Health Supplements:** Health supplement refers to a product that is used to supplement a diet, with benefits beyond those of normal food, and or to support or maintain the healthy functions of the human and animal body
f. **Market Authorization Holder:** refers to a firm in whose name the product is registered/ licensed.
g. **Product dossier:** refers to the detailed product profile or technical documents generated from the product manufacturer for the purpose of product registration.
h. **Registration Committee for Product Registration:** refers to the committee as approved by the Bhutan Medicines Board for evaluation of medicinal products.
i. **Recommended Daily Allowance (RDA) value:** refers to the amount of an essential nutrient, as a vitamin or mineral, adequate to meet the average daily nutritional needs of most healthy persons according to age group and sex.
j. **Special Diet Products:** refers to food products that differ from corresponding ordinary food in composition or manufacturer.

Introduction

There are numerous health and nutritional supplements sold in the market with claims of health and nutritional benefits. These products are currently not regulated by any agencies owing to the lack of a regulatory framework and lack of clarity in the definition of health supplements. If the sale and consumption of such products are not regulated there is risk to the human and animal health.

Recognizing the importance of health supplements regulation, the Bhutan Medicines Board under the powers granted by the Act under section 5.14 and 5.15 directed the DRA to regulate the health supplements during the 15th Board meeting.

Accordingly, this guideline was drafted and presented to the 28th DTAC. This guideline provides detail information to regulate Health Supplements in Bhutan. The guideline also segregates nutritional supplements from food and medicinal products thereby enabling the regulation of these products.

As per this guideline the products available in the market will be classified under health supplements, food supplements and medicinal products and will accordingly be regulated by the relevant agencies

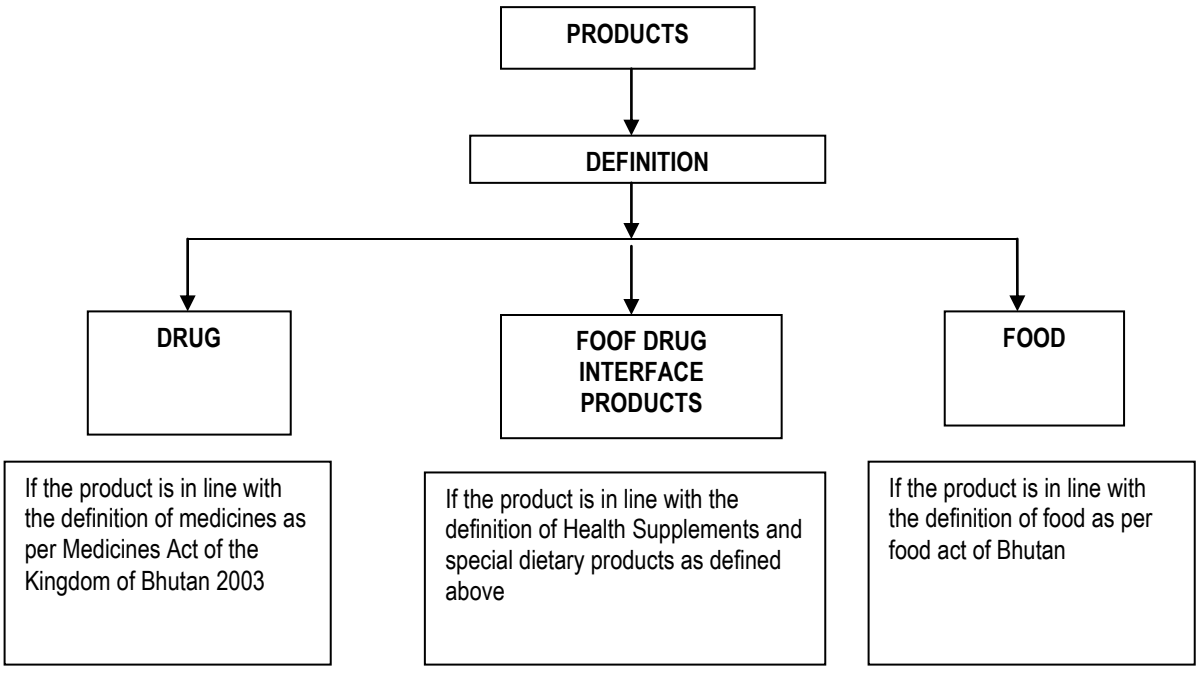
Criteria for Classification

The following criteria shall be used for the classification of interface products (Health Supplements and Special Dietary Products). The classification flow diagram should be used to assist in which category the products will fall under. If the product can be classified by using 1st Classification tree, it will not be subjected to 2nd Classification. Similarly, if the product can be classified by 1st and 2nd Classification tree, it will not be subjected to 3rd Classification.

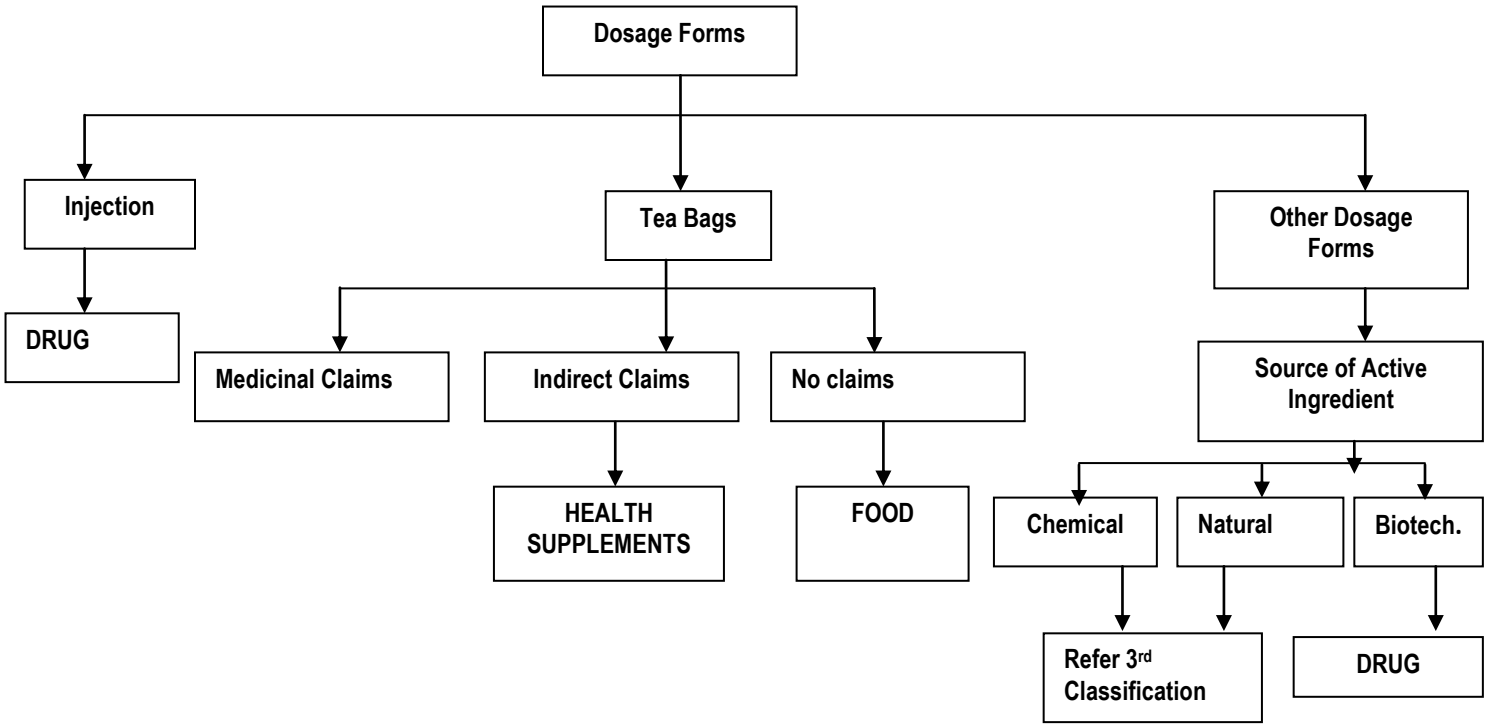
The following criteria are based on:

1.Definition
2.Dosage forms
3.Source

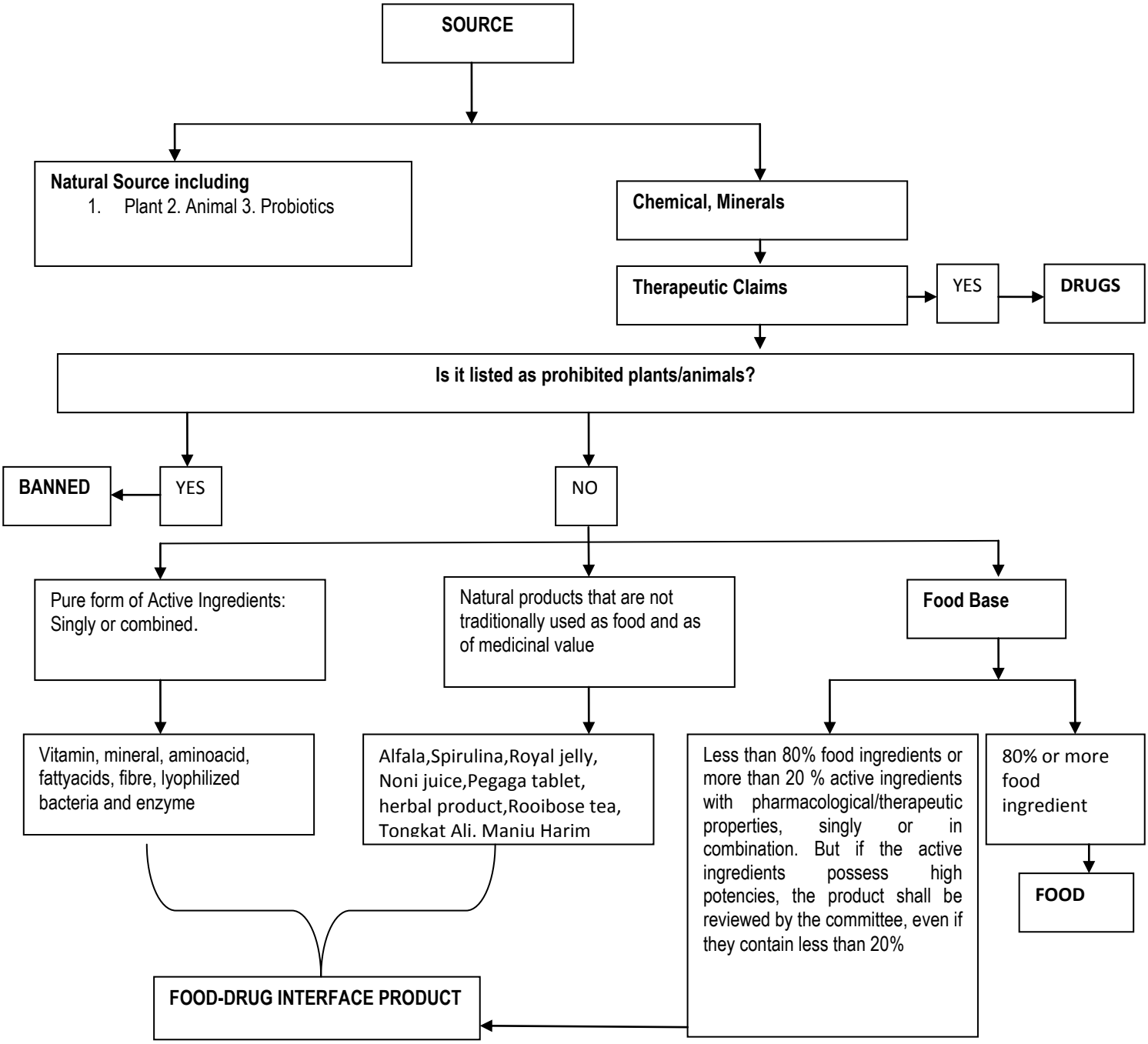
1st Criteria for Classification



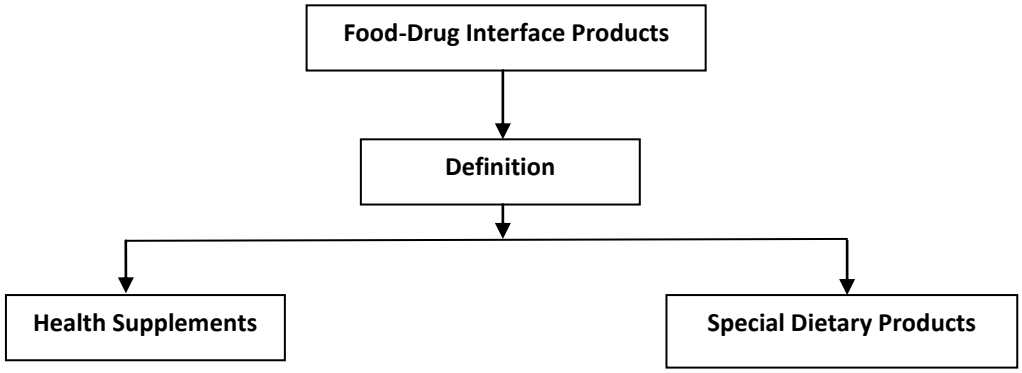
2nd Criteria for Classification



3rd Criteria for classification



Differentiation between Health Supplements and Special Dietary Products



Scope

This guideline shall apply to all Health Supplements and special diets containing vitamins and/or minerals as well as other ingredients manufactured, imported, sold and distributed in the Kingdom of Bhutan.

Definition for Health Supplements

Health supplement refers to a product that is used to supplement a diet, with benefits beyond those of normal food, and or to support or maintain the healthy functions of the human and animal body.

Following categories of products fall under the category of Health Supplements:

- **a)** Products containing vitamins, aminoacids and minerals (natural & synthetic)within the prescribed limits under Table III
- **b)** Substances derived from natural sources, including animal and plant materials in the form of extracts, concentrates, isolates;
- **c)** Foods with medicinal claims for general well being,
- **d)** The health supplements may be presented in any dosage forms such as Capsules, powders etc

Health Supplements **shall not** include any of the following:

- **a)** Any product used as an essential ingredient of a meal or diet
- **b)** Any products containing prohibited/restricted ingredients under Table IV;
- **c)** Any **injectable or sterile** preparation; and
- **d)** Any material in its crude form.Vitamin or mineral supplements intended for children below 12 years of age.

Safety and Quality Requirements

Health supplements shall:

- **a)** **not** contain any other substances except those stated on the label.
- **b)** **not** contain any substance above the limit specified in table No. I, IIIa & III b.
- **c)** **not** exceed the limits for microbial contamination and toxic heavy metals as specified in the table No. II.
- **d)** **not** contain any substance specified in the list of Prohibited Substances shown in table No. IV.
- **e)** **not** make any claim directly or indirectly related to list of conditions, disease or disorders shown in table no. V
- **f)** be of acceptable standards of quality in terms of the product stability under local climatic conditions, have adequate shelf-life period, proper packaging and labeling and are manufactured and/or assembled following current Good Manufacturing Practices (cGMP);
- **g)** be manufactured from manufacturers who take responsibility in ensuring that products are safe and that the label information is truthful and not misleading
- **h)** require permit from various agencies such as Convention on International Trade in Endangered Species of Wild Fauna and Flora import permit from the country of origination.
- **i)** Not contain any active substance that may adversely affect the health of the person taking the product
- **j)** Not contain any active substance which is a chemically defined isolated constituent of plants, animals or minerals, or a combination of any one of these.

Health Supplement Claims

- **a)** In general, claims on Health Supplements shall be consistent with the definition of Health Supplement
- **b)** Health Supplements must not be advertised or promoted for any specific medicinal purpose, i.e. treatment or prevention, implied or otherwise, of any disease or disorder. The health supplements claims must not:

i. be false, ambiguous or misleading and contradicting to public health message
ii. give rise to doubt about the safety and/or the nutritional adequacy of other foods
iii. encourage or condone excess consumption of a food
iv. state, suggest or imply that a balanced and varied diet cannot provide appropriate quantities of nutrients in general;
v. refer to changes in bodily functions which could give rise to or exploit fear in the consumer, either textually or through pictorial, graphic or symbolic representations
vi. make reference to recommendations of individual doctors or health professionals

Types and Evidence of Claims for Health Supplements

A health supplement can make three types of claim:

Health Claims

a. Health claim means any claims that states, suggest or implies that a relationship exists between a food category, a food or one of its ingredients and health

b. Health claims are permissible for products provided they contain well documented ingredients, where the function of each ingredient is supported and documented in standard reference texts

c. Examples include:

i. Relieve general tiredness, weakness.
ii. Enhance good health and growth.
iii. Supplementing nutrition
iv. Nourish the body
v. Strengthen the body (without reference to specific organs)

d. The dealers must furnish this evidence to support the claims and provide to the authority when required to do so.

Nutrient Content Claims

a. A statement on a food or dietary supplement product label that describes the amount of a nutrient or dietary substance in a product

b. Such claims are permitted only when the relevant vitamin and mineral used in the product amounts to >30% of the RDA* (Recommended Daily allowance) value. If the amount of nutrient is less than 30% of the RDA, the amount may be declared on the labeling but the said nutrient must not be emphasized on the labeling.

c. Examples of nutrient claims for dietary supplement products include fortified, high, rich in, excellent source of, good source of etc.

d. Comparative Nutrient content claims which uses words like “more than”, “better than”, “richer than”, “equivalent to” etc. are NOT permitted

Structure/Function Claims

a. A statement on health supplement label that describes how a product may affect the organs or systems of the body a specific disease cannot be mentioned.

b. The dealer must provide with the text of the claim to the authority when required to do so. This product is not intended to diagnose, treat, cure, or prevent any disease.

c. The claims should not imply that the product is necessary to play a role in diseased states

d. Functional claims permitted include:

i. General enhancement/ maintenance of healthy functions.

ii. Supports healthy function of the human body such as maintaining healthy joints, support natural physiological processes e.g. immune system, circulation, etc.

Labeling Requirements

a) Labeling must be prominently and conspicuously displayed on the point of sale. Where the size, shape or nature of the final product or package does not permit the full listing of the labeling information, the use of inserts, leaflets, hang tags, in appropriate format, will be allowed. However, the name of the health supplement product, the recommended dosage, the batch reference and relevant precautionary statements must be displayed on the final product or package, as the case may be.

b) The information should be in English and/or Dzongkha and should be printed in a clear and legible manner.

c) The names of the ingredients on the label should be i n scientific names, where appropriate.

d) The types of information to be provided on the label are as shown below:

i. Name of the product
ii. Names and quantities of all the active ingredients and their recommended daily allowances (RDA) wherever applicable
iii. Names of inactive ingredients including sweeteners, preservatives, colorants, and other additives, if present.
iv. Recommended daily dosage
v. Instructions on proper usage
vi. Pack size
vii. Expiry date
viii. Batch number, name and address of the manufacturer & packer
ix. Name and address of dealers (importer, wholesale dealer where appropriate).
x. Mandatory precautionary label/ statement, where necessary
xi. Label should display the statements like “Food/Dietary supplement only” indicating that the product is not a medicine.
xii. Information regarding the minimum age to use the product wherever necessary
xiii. Storage instructions

Advertisement Control of Health supplements

Health supplements are subject to medicinal advertisement control, and shall comply with Bhutan Medicines Rules and Regulation 2012.

Reporting of Suspected Adverse reactions

Any adverse reaction or side effects related to the use of the health supplements should be reported using the prescribed ADR Form to the relevant Pharmacovigilance Centers or to the National Pharmacovigilance Center by the following persons:

a. Health professionals / competent person, and traders who supervise import, distribute or sale the Health Supplements;
b. Patients/ consumers, who uses the products;
c. Manufacturers of the Health Supplements; and
d. Any individual who have seen the adverse effect of the product

Special Diet Products

a. Special diet products mean food products that differ from corresponding ordinary food in composition or manufacturing. Because of differences in composition or manufacturing, special diet products are suitable for persons with absorption and metabolic disorders or persons who because of their special physiological status benefit from a controlled intake of substances in certain foods.

b. Special diet products include baby foods, non-gluten food and low-lactose/lactose-free dairy products. Also some products intended for weight control, losing weight or for athletes are special diet products.

c. The essential feature is that the energy content of Health supplements is minor, while special diet products are used to substitute for meals, parts of meals or even the normal daily diet.

d. The special diet products must comply with the standards for safety, claims and labeling in this guideline.

e. However any products intended for infant and young child should not contain any information that may discourage breastfeeding; neither should the product imply that the designated products are substitute for mothers' milk and natural health infant foods.

f. Manufactures, importers, distributers and promoters of special diet products shall neither produce nor distribute any education or information materials related to infants and young child feeding through any means of communication without prior approval from the competent authority.

Appendix

Safety and Quality Specifications

The safety and quality levels/limits are specified in the following tables. These limits shall be subjected to revisions from time to time, as and when new information is available and when necessary.

Table No. (I) : Upper Limits of Heavy Metals

Classification	Quantity (PPM)
Class 1A (Platinum (Pt), Palladium (Pd))	10
Class 1 B (Iridium (Ir), Rhodium (Rh), Ruthenium (Ru) Osmium (Os))	10
Class 1 C Molybdenum (Mo) , Nickel (Ni), Chromium (Cr), Vanadium (V) Metals with significant safety concerns	30
Class 2 Copper (Cu), Manganese (Mn) Metals with low safety concerns	250
Class 3 Iron (Fe), Zinc (Zn) Metals with minimal safety concerns	1300

Ref: European Medicines Agency. Guidelines on the specification limits for residues of metal catalysts. Jan 2007.

Substance	Quantity (PPM)
Arsenic	5
Lead	20
Mercury	0.5

Ref: HSA. Health Supplement Guidelines, Sept. 2012.

Table No. (II): Microbial Contamination Limits

Total aerobic microbial count:	Not more than 10^5 per gram or ml
Yeast and mould *:	Not more than $5x10^2$ per gram or ml
Escherichia coli, *Salmonellae* and *Staphylococcus Aureus* :	Nil in 1 gm or ml of the product

Ref: HSA. Health Supplement guidelines, Sept. 2012.

**The above limits are not applicable to probiotics or products derived from fermentation processes.*
**For Health Supplements derived from herbs without extraction and heat processing, compliance with microbial count is required.*

Table No. (III): Limits for Vitamins and Minerals.

If the product exceeds the limits it shall come under the purview of medicinal product and shall comply with the procedure for registration and licensing.

A. Limits for Vitamins

Vitamins	**Maximum Limits**
Vitamin A (acetatate or palmitate of ß-carotene)	**10,000IU**/unit dose
Vitamin B1 (hydrochloride or mononitrate of thiamine)	**50 mg** of Vitamin B1/unit dose and also contains vitamin B6 and/or B12 together.
Vitamin B6 (pyridoxine hydrochloride)	**50 mg** of Vitamin B6 /unit dose and also contains vitamin B1 and/or B12 together.
Vitamin B12 (cyanocobalamine, cobalamine)	**100 mcg** of Vitamin B12/unit dose and also contains vitamin B1 and/or B6 together
Niacin (nicotinic acid)	Only if the product is for specific therapeutic treatment
Vitamin E (α- tocopherol)	**800 IU** of Vitamin E activity/unit dose
Vitamin D (Cholecalciferol (Vit D3) Ergo-calciferol (Vit D2)	**1000 IU** of Vitamin D activity/unit dose

Vitamin K1 **Phylloquinone, phytomenadione, phytonadione** **Vitamin K2** **Menaquinone, menatetrenone**	Restricted to oral dosage forms of multi-vitamin/ mineral preparations for adults with maximum limits of 120mcg per day for general health.

B. Limits for Minerals

Minerals	**Limit (should not exceed)**
Iron	**30 mg** of elemental iron/unit dose
Iodine	**300 mcg** of elemental iodine/unit dose
Potassium	**200 mg** of elemental potassium/unit dose
Copper	**3 mg** of elemental copper/unit dose

Ref: HSA. Health Supplement Guidelines, Sept. 2012.

Table No. (IV): List of Prohibited / Restricted Substance as ingredients of Health Supplements

Table No. (IV) List of Prohibited/Restricted Substance as ingredients of Health Supplements

Sl.NO	Ingredients	Potent Constituents	Justification
1	Aconitum napellus (aconite) and other species of Aconite	Aconine, aconitine,	
2	Acorus calamus	Bicyclic sesquiterpenes, α, β- asarone	Carcinogenic
3	Angelica archangelica	Furocoumarins such as angelicin, Xanthotoxin	Toxic, can Cause photodermatitis
4	Areca catechu	Arecaine & other alkaloids	CNS stimulant and toxic alkaloid
5	Aristolochia sp.,		

	Akebia sp., Asarum, clematis sp., Coccollus sp., Stephania ap., etc	Aristolochic acid	Toxic
6	Artemisia absinthium	Oil of Absinth	Poisonous
7	Atropa belladonna	Atropine	Poisonous (anticholinergic)
8	Catharanthus roseus	Ajmalicine, vincristine, vinblastine,carisidine	Toxic (Vincristine and Vinblastine are known for their cytotoxic activity)
9	Cedris sp., (including Cedar leaf)	Thujone	Renal damage, allergy, contact dermatitis
10	Chaparral	Nordihydroguaiatic acid (NDGA	Prohibited in Health Supplements
11	Citrullus colocynthis (colocynth)	Curcubitacin	Potent ourgative, kidney damage
12	Coenzyme Q10	Ubidecarenone	Restricted to 150 mg per day; shows interaction with warfarin
13	Colchicum autumnale	Colchicine	Cytotoxic
14	Corydalis ambigua, C. bulbosa, C. amurensis, C. Pallida, C.racemosa,etc	Corydaline, corydine, etc.	-
15	Corynanthine yohimbe	Yohimbine	-
16	Cimicifuga racemosa	-	Liver damage reported in some individuals
17	Cytisus scoparius	Sparteine, scoporaside, Tyramine	Emetic, Narcotic
18	Danthron, suprofen	Danthron, suprofen	-
19	Datura stramonium	Tropane alkaloids e.g. atropine, hyoscyamine,	-

		hyoscine, etc.	
20	Dehydroepiandrostero Ne (DHEA)	DHEA	Androgenic hormone
21	Dimethyl sulfoxide (DMSO)	DMSO	Poisonous
22	Dimethylaminoethano L	Deanol	Poisonous
23	Dipteryx odorata, D. oppositifolia (Tonka bean)	Coumari n, dihydrocoumarin	Poisonous (anticoagulant)
24	Doping substances	Anabolic Steroids Performance Enhancing Drugs	-
25	Ephedra sinica (ma huang)	Ephedrine	1% and above is not allowed in HS
26	Euonymus europeaus, Europeaus atropurpereaus	Euonymol, euonysterol, atropurol,etc	Diarrhoea, vomiting, seizures, etc
27	Eupatorium Perfoliatum	Kaempferol, astragalin, Eupatorin	Hepaatotoxic, allergic reactions
28	Gamma hydroxybutyric acid (GHB), gamma butyrolactone	1,4-butanediol	Toxic
29	(GBL)	-	-
30	Heliotropium Europeaum	Cynoglossin and related Alkaloids	Toxic
31	Humic acid & fulvic Acid	-	Accociated with blackfoot and Kashin-Beck disease
32	Hydrastis Canadensis, Berberis vulgaris, Berberis	Berberine	-
33	aquifolium, Coptis chinensis, Coptis teeta, Chelidonium majus, Mahonia aquifolium	-	-
34	M. repens, M. nervosa,	-	-

	Phellodendron Amurense		
35	Hyoscyamus niger	Atropine, hyoscine, Hyoscyamine	Prohibited
36	Piper ,methysticum	Kavapyrones, Kavalactones	-
37	Lobelia inflate, L. tupa	Lobeline	0.1% and above is not allowed in HS
38	Mucuna Pruriens	L-dopa, dopamine, nicotine, physostigmine, serotonine, etc	-
39	N-acetyl cysteine	N-acetyl cysteine	-
40	Senna	Sennasoids	Laxative
41	Petasites sp. Including but not limited to P.hybridus, P, officinales, P. vulgaris, P. frigidus, P. palmatus	Unsaturated Pyrrolizidine Alkaloids	Liver toxicity
42	Pituitary gland, somatropin Human growth hormone,	Pituitary and other galndulalar and steroidal hormones	Affects growth, development of secondary sex characters.
43	Suprarenal gland, thyroid gland, sex hormone, pregnenolone, androstenedione	Podophyllotoxin, podophyllin Resin	Podophyllum resin 1.5%and above is not allowed.
44	Podophyllum peltatum	Tetrahydropalmitine	-
45	Pomegranate (except bark) ; not present in Polygala sp.	Reserpine, rescinnamine, ajmaline, Serpentine	Toxaemia of Pregnancy, suicidal tendency, hypotensive agent
46	Rauwolfia serpentina	Lovastatin	1% and above not allowed (hypolipedemics)
47	Red yeast rice	Furanocoumarins, 5-methoxypsoralen,	-

		8-methoxypsoralen	
48	Ruta graveolens	Sanguinarine, peotopine, Berberine	Hypotensive, shock, coma
49	Sanquinaria Canadensis	Sanguinarine, peotopine, Berberine	-
50	Sassafras albidum, S. officinale, S. varifolium	Safrole	Carcinogenic, hepatotoxic
51	Senecio aureus, S. cineraria, S. jacobaea	Floridanine , florosenine, Otosenine	Liver toxicity
51	Solanum dulcamara	Solanine, Dulcamarine, Solamarine	Paralysis
52	Spigelia marilandica	Strychnine	-
53	Stevia rebaudiana	Steviosides	-
54	Symphytum peregrinum, Symphytum officinale	Pyrrolizidine	Hepatotoxic
55	Tanacetum vulgare	Thujone (toxic terpene)	Renal toxicity, allergy, contact dermatitis.
56	Thuja occidentalis		
57	Tussilago farfara	Pyrrolizidine alkaloids such as senkirine, Senecionine	Hepatotoxic
58	Viscum album, V. abietis, V. austriacum, Phoradendron falvescens.	Acetylcholine, β-Phenylethylamine , Histamine, Tyramine	Bradycardia, delirium, Hepatitis, coma, cardiac arrest
59	Vitamin B15	Pangemic acid/	-

		Dimethylglycine (DMG	
60	Vitamin B17	Amygdalin/ Nitrilosides	-
61	Vitamin K		Affects coagulation cascade of blood.
62	Vinca minor	Vincristine, Vinblastine, Vinpocetine	Cytotoxic

Note: The above list is not exhaustive and shall be updated as and when new information is available and when necessary.

Ref: HSA. Health Supplement Guidelines, Sept. 2012.

Table No. (V) List of prohibited diseases and conditions.

1.	Blindness	21.	Cancer
2.	Cataract	22.	Conception & pregnancy
3.	Serious drug addiction	23.	Deafness
4.	Diabetes	24.	Epilepsy or fits
5.	Frigidity	25.	Hypertension
6.	Infertility	26.	Insanity
7.	Impotency	27.	Kidney diseases
8.	Leprosy	28.	Menstrual disorder
9.	Paralysis	29.	Sexual function
10.	Tuberculosis	30.	Dementia
11.	Hepatitis	31.	Alzheimer's disease
12.	Liver cirrhosis	32.	Musculo skeletal disease
13.	Ulcers	33.	Urinary Tract Infections
14.	Gastritis	34	Nephritis
15.	Depression	35.	Asthma
16.	Diarrhea	36.	Tuberculosis
17.	Allergies	37.	Pigmentation disorders
18.	STDs	38.	Reproductive disease
19.	AIDS	39.	Hematological disorders
20.	Obesity		

The above list is not exhaustive and shall be updated from time to time.

REGISTRATION REQUIREMENTS AND REGULATION MODALITIES

General

1. The Health Supplement or Special Dietary Product shall be regulated in the similar manner as to the General Sale List medicines as enshrined in the chapter XV of the Bhutan Medicine Rules and Regulation 2014.

2. The sale of Health Supplement or Special Dietary Product shall not be restricted to pharmacies, but will also be permitted for sale from grocery shops.

3. The import of Health Supplement or Special Dietary Product shall be permitted to MAHs or any other person who has obtained NOC from the MAH.

Procedure for Application for Registration:

Application for Registration

1. The application for registration of Health Supplement or Special Dietary Product shall made to the Drug Regulatory Authority using the application form VI-FPR of the Bhutan Medicines Rules and Regulation 2012 as annexed in annexure 1 of this guideline.

2. The application for registration must be accompanied by the token fee of Nu. 150 (one hundred fifty only), which may be revised from time to time along with the documents.

3. A separate application is required for each Health Supplement or Special Dietary Product, i.e. Health Supplement or Special Dietary Product containing different ingredients or manufactured at different manufacturing sites or Health Supplement or Special Dietary Product and Special Dietary Product containing the same nutritional composition but differing in forms.

General Requirements of the Dossiers

The dossier should be:

i. In English or Dzongkha or both. Where original certificates are in another language, copies shall be presented together with certified English translation.
ii. Properly bonded
iii. In A4 size paper
iv. Contain price structure of the Health Supplement or Special Dietary Product and Special Dietary Product
v. Pages of the dossier shall be sequentially numbered.
vi. Be complete as per the specifications detailed in this guideline
vii. Contain certificates or testimonies obtained from other agencies or authorities in original or in case of duplicate or electronic submission, attested by the Public Notary or a Court of Justice.

Data Requirements

The requirement is classified into mandatory and non-mandatory requirements

Mandatory Requirements:

1. Company profile

Brief information on the company including following must be submitted:

i. Brief history of company
ii. Address including phone and fax number.
iii. List of the product category manufactured
iv. Name and qualification of the key personnel (Head of Quality Assurance-Quality Control. Store and production) where possible with the signatures of the personnel against name

2. Current Good Manufacturing Practices (cGMP) certificate

cGMP Certificate or ISO certificate to indicate the company's adherence to the quality standard must be submitted. It should be valid during the time of submission.

3. Evidence of free sale

The document indicating the free sale of the Health Supplement or Special Dietary Product and Special Dietary Product in the country of origin must be submitted. It must be issued by the authorized authority from the country of origin and must include:

i. Name of the Health Supplement or Special Dietary Product and Special Dietary Product
ii. Dosage form and strength
iii. Complete name and address of manufacturer

4. Manufacturing license

5. Letter of Authorization from the manufacturer

The letter of authorization from the manufacturer should fulfill following conditions:

1. In case of the dealer being involved, letter of authorization issued by the manufacturer must be submitted. The authorization letter should include the list of Health Supplement or Special Dietary Product authorized by the manufacturer to the dealer.
2. If the letter has provision of validity, the letter must be valid.

6. Price Structure

The price structure should:

i. Indicate price applicable to the wholesaler, retailer and the maximum retail price.
ii. Include value indicated either in USD, Indian Rupee or local Bhutanese currency (Ngultrum).

7. Sample of Health Supplement or Special Dietary Product

i. Samples of finished Health Supplement or Special Dietary Product submitted for registration shall be taken at random from an actual production batch.
ii. Samples submitted must be intact and it must be in final commercial pack with original labels.
iii. Minimum of 1 multi dose container, if packed in multi dose container and if packed in sachets and other forms, minimum of 5 numbers is required.
iv. Samples of Health Supplement or Special Dietary Product submitted must have a remaining shelf-life of at least two (2) years or not less than 75% of its shelf life.

8. Specimen of Package and Label

Specimen of the original package including package and label must be furnished. However, if commercial specimens are not available, the art work or photographs must be submitted.

9. List of raw materials used in the production

Detail list of ingredients along with its scientific name must be submitted.

10. Batch Manufacturing Formula

11. Certificate of analysis for the finished Health Supplement or Special Dietary Product:

The specification and results for the finished Health Supplement or Special Dietary Product inclusive of following reports where applicable must be submitted:

i. Content of Ingredients
ii. Disintegration test
iii. Microbial limit test
iv. Test on heavy metal
v. Dioxin level certificate/ results analysis in (finished Health Supplement or Special Dietary Product/ raw active ingredient) if derived from marine source
vi. Hormone test certificate and declaration letter if the Health Supplement or Special Dietary Product is derived from placenta.

The analysis report must be countersigned by the QC head/ Manager

Processing of Applications

1. Application shall only be accepted and processed only if it is complete.

2. The Authority may during evaluation of the Health Supplement or Special Dietary Product request for clarification or additional information or samples from the applicant. The processing of the application shall be kept on hold until such information is provided.

3. The certificate will be issued within 30 working days excluding the period when the application is kept on hold pending clarification or submission of additional information. In such case, the party will be informed.

4. Applicants will be informed after the processing of their application has been completed. If the application is successful, the Health Supplement or Special Dietary Product will be registered.

Rejection of the Application

a. An application for registration will be rejected in following:

i. If the applicant fails to respond to the enquiries or submit the required additional documents within six (6) months from the last correspondence date. ***OR***
ii. The applicant fails to submit all the required documents and complete the registration formalities within one (1) year.

b. Once the application is rejected, the applicant will be informed and the dossiers will be handed over to the applicant.

c. If the applicant wishes to re-process the same, the application must be re-submitted along with complete set of documents and token fee. The dossier will then be considered new.

Regulatory Decision

1. Decisions of the Drug Regulatory Authority

A regulatory decision is made based on the outcome of the evaluation of the dossier by the Registration Committee for Registration of the Medical Product. The decision will be accordingly communicated to the applicant.

2. Issuance of the Registration Certificate

The certificate for registered Health Supplement or Special Dietary Product will be issued in the specified format after payment of Nu.1500 (one thousand five hundred only) as registration fee

Appeal against Regulatory Decisions

Any applicant aggrieved by the Regulatory Decisions may submit a written petition to the Bhutan Medicines Board within thirty (30) days from the date of issue of the decision as per chapter XVII of the Bhutan Medicines Rules and Regulation.

Validity of the Health Supplement or Special Dietary Product Registration Certificate

The registration of a Health Supplement or Special Dietary Product shall be valid for a period of three (3) years and shall be specified on the certificate, unless cancelled or deregistered.

Cancellation of Registration

The Authority may, in the interest of public safety, reject or cancel the registration of any Health Supplement or Special Dietary Product, if:

1. Any of the conditions of registration of the Health Supplement or Special Dietary Product has been contravened. This may include the mismatch between the documents submitted at the time of registration and physical GMP audit;

2. Any report on adverse drug reactions of serious nature have been received from National Pharmacovigilance Centre or any other national or international sources;

3. MAH defaults timely renewal beyond three month of grace period;

4. Manufacturer or MAH obstructs the inspection of the Manufacturing firms or premises; Or

5. For any other matters as specified by the Board at the time of cancellation.

Such Health Supplement or Special Dietary Product may not be imported, manufactured, sold, supplied or possessed for sale.

Renewal of Health Supplement or Special Dietary Product Registration

1. Application for renewal shall be submitted in form VIII-PRR of the regulation attached as annexure 2 at least 30 days before expiry date of registration along with the token fee.

2. A grace period of three months may be given if the current MAH provides a written justification with evidence of having carried out the renewal process with the manufacturers prior to the date of expiry.

3. Upon the completion of the grace period or failure to provide the evidence, the Health Supplement or Special Dietary Product shall be deemed deregistered from the actual registration expiry date. Once de-registered, the application will be considered new and full documents must be submitted.

4. The procedure for the renewal of the registration is same as the initial registration. However, one time renewal of registration shall be granted with the fulfillment of the following conditions and documents.

Condition for renewal

a. Following mandatory conditions must be fulfilled by the Health Supplement or Special Dietary Product in question for renewal with minimal documents

i. There should not be change in the manufacturing site/premise of the particular Health Supplement or Special Dietary Product;

ii. There should not be change in the ingredients used for the formulation of the particular Health Supplement or Special Dietary Product;

iii. There should not be change in the formulation including colour, size, dosage forms and dosage;

iv. There should not be change in label claims

v. There should not be change in the type of packaging or packaging material

Documents required for renewal

If all the above conditions for the renewal are fulfilled; one time renewal will be done on submission of the following information:

i. Renewed Authorization letter

ii. Sample for Health Supplement or Special Dietary Product

iii. Price structure

Health Supplement or Special Dietary Product Registration Transfer

The market authorization of the registered Health Supplement or Special Dietary Product may be transferred to another individual or firm authorized by the Authority. However, following conditions and data requirements for Health Supplement or Special Dietary Product registration transfer must be fulfilled.

1. Conditions:

a. An application to transfer the marketing authorization of a Health Supplement or Special Dietary Product shall be submitted by the proposed new MAH.

b. The manufacturer agrees to withdraw the authorization granted previously to the existing MAH and issue new letter of authorization to the proposed new MAH.

c. The existing Health Supplement or Special Dietary Product registration shall have a remaining validity period of at least one (1) month. If the period is less than one month, the Health Supplement or Special Dietary Product must be renewed by the existing MAH before the transfer application is submitted.

2. Data Requirements:

a. The original letter of authorization from the principle manufacturer including the name of the Health Supplement or Special Dietary Product(s) to the proposed MAH.

b. No objection certificate/letter from the current MAH of the Health Supplement or Special Dietary Product.

3. If without any justifiable reason, the existing MAH denies to give No Objection certificate/letter, the Authority may consider the letter of authorization as sole documentation requirement for change of MAH.

4. Once the Health Supplement or Special Dietary Product Registration has been transferred, the new MAH will be responsible for all matters relating to the Health Supplement or Special Dietary Product registration and its performance.

5. No fee will be charged for the application and the outcome of the transfer application will be notified to both the old and new Authorization Holder.

Change in the Particulars of the Registered Health Supplement or Special Dietary Product- Post Registration Changes

1. No change in Health Supplement or Special Dietary Product name, specifications, packing, contents of label or Health Supplement or Special Dietary Product literature, or any relevant particulars of the registered Health Supplement or Special Dietary Product shall be made without the prior approval of the Authority.

2. The MAH may apply for any post registration changes during the valid period of registration under the following procedure and conditions:

a. Apply to the Authority in form VIIa-PRC of the regulation as attached as annexure 3 to this guideline with proposed changes.

b. Import the Health Supplement or Special Dietary Product only upon the confirmed incorporation of the post registration changes by the Authority.

3. Only following post registration change is accepted. The change must be submitted with supporting document as indicated against each proposed change:

Type of post registration change: Change in Health Supplement or Special Dietary Product name	
Conditions to be fulfilled	There is no change to the Health Supplement or Special Dietary Product (formulation, release and shelf-life specifications, manufacturing source and process etc) except for the Health Supplement or Special Dietary Product name change.
Documents to be submitted	1. Official letter from principle manufacturer requesting for the change of Health Supplement or Special Dietary Product name 2. Revised draft package insert and label incorporating the proposed variation. 3. Health Supplement or Special Dietary Product Sample with proposed name

Type of post registration change: Change in the specimen of Package Insert, unit carton label and/or inner label. Includes: Change of the layout/artwork Addition/deletion/replacement of pictures, diagrams, bar code, logos and/or texts on the package and label Change in information in the insert	
Conditions to be fulfilled	There is no change to the Health Supplement or Special Dietary Product (formulation, release and shelf-life specifications, manufacturing source and process etc) except for the above specified change.

Documents to be submitted	1. Official letter from principle manufacturer requesting for the change of Health Supplement or Special Dietary Product name 2. Current approved Health Supplement or Special Dietary Product labeling. 3. Proposed Health Supplement or Special Dietary Product labeling, a clean and annotated version highlighting the changes made. 4. Health Supplement or Special Dietary Product Sample with proposed change

Type of post registration change: Change of pack size/fill volume and/or change of shape or dimension of container	
Conditions to be fulfilled	1. The new size is consistent with the dosage regimen and duration of use 2. The change only concerns the same packaging type and material.
Documents to be submitted	1. Justification for the proposed pack size. 2. Revised drafts of the package insert and labeling incorporating the proposed changes (where applicable). 3. Price structure for the new pack 4. Information and data on package and label 5. Health Supplement or Special Dietary Product Sample with proposed change

Type of post registration change: Change of outer carton pack sizes for a finished Health Supplement or Special Dietary Product	
Conditions to be fulfilled	1. Primary packaging materials remain unchanged. 2. No other changes except for the change of outer carton pack sizes for a finished Health Supplement or Special Dietary Product.
Documents to be submitted	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Letter of declaration from the manufacturer stating that no other changes except for the change of outer carton pack sizes for a finished Health Supplement or Special Dietary Product.

Type of post registration change: Change of the name or address (for example: postal code, street name) of the manufacturer of finished Health Supplement or Special Dietary Product	
Conditions to be fulfilled	**1.** The manufacturing site remains the same. **2.** Not applicable to the case in which it involves change in ownership of the manufacturer. **3.** No other changes except for the change of the name and/or address of a manufacturer of the finished Health Supplement or Special Dietary Product.
Documents to be submitted	**1.** Official letter from the manufacturer requesting for the change in name/address of the plant. **2.** A valid GMP certificate with new name **3.** Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). **4.** Health Supplement or Special Dietary Product sample **5.** Price Structure, if applicable

Type of post registration change: price structure	
Conditions to be fulfilled	There is no change to the Health Supplement or Special Dietary Product except for the intended change
Documents to be submitted	Price structure of the Health Supplement or Special Dietary Product