ANNEX I

ASEAN GUIDING PRINCIPLES FOR INCLUSION INTO OR EXCLUSION FROM THE NEGATIVE LIST OF SUBSTANCES FOR HEALTH SUPPLEMENTS

Disclaimer:

This document is provided for information purpose only and subject to changes, pending the finalisation of the ASEAN Agreement on Regulatory Framework for Health Supplements. Official references to this document can only be made once the said Agreement has been finalised.

Purpose

The ASEAN Guiding Principles for Inclusion into or Exclusion from the Negative List of Substances for Health Supplements lists the active substances that are prohibited from being used in or being part of the composition of Health Supplements (HS). This list is prepared from the following guidelines established to govern the acceptance of active substances to the list based on scientific justification.

Guiding Principles

1. A substance must carry a scientifically demonstrated or proven safety concern that its inclusion into a HS will be harmful to human health[1].

2. A substance that qualifies for inclusion into the list should carry the following details but is not limited to:

    2.1. Identity of the substance

        2.1.1. Taxonomy classification e.g. scientific name by genus and species

[1] "Harmful to human health" is defined as any experience affecting the population resulting in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalisation or prolongation of existing hospitalisation, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered harmful when, based on appropriate medical judgment, they may jeopardise the individual and may require medical or surgical intervention to prevent one of the outcomes previously listed.

2.1.2. Common name

2.1.3. CAS No

2.2. Source of the substance (e.g. natural/synthetic/certain part or whole plant/animal)

2.3. Rationale for inclusion (e.g. toxic[2] effect of the substance e.g. acute, sub-acute, chronic, specific toxicity)

2.4. References (e.g. formulary, monograph or scientific report)

3. The negative list should only include substances that are prohibited for use in a HS.

4. This negative list should not include:

4.1. substances in the ASEAN List of Restricted Additives and Excipients for Health Supplements;

4.2. nutrients with established ASEAN maximum levels (e.g. vitamins and minerals);

4.3. naturally occurring toxic contaminants that are within established limits (e.g. lead); or

4.4. substances which are prohibited under existing wildlife protection laws of all Member States.

5. Prohibited substances in the national regulations of Member States, where applicable, are prohibited in HS. Member States are recommended to propose relevant substances from their national regulation for inclusion into the ASEAN Negative List for Health Supplements as long as their inclusion meets the criteria set in these guidelines.

6. Proposal for inclusion or exclusion of substances into the ASEAN Negative List for Health Supplements should be based on scientific rationale pertaining to human safety concerns.

7. Please refer to Appendix 1 for Negative List of Substances for Health Supplements.

[2] It is important to differentiate between potential side effects and toxic effects.

APPENDIX 1

NEGATIVE LIST OF SUBSTANCES FOR HEALTH SUPPLEMENTS[3]

Scientific Name	Common Name(s)	Harmful Animal or Plant Part(s)	Name of Harmful Compound or Compound Class	Ban Status in HS
***Abrus precatorius* L.**	Indian Licorice, Precatory bean, Jequerity, Mutual Love Bean (China), Kudri Mani (Tamil), Guru Ginja (Telegu)	Seed	Abrin, which consists of abrus agglutinin, and toxic lectins abrins	Banned
***Aconitum spp.* containing aconite alkaloids**	Monkshood, Aconite	Whole plant	Aconite alkaloids	Banned
***Adonis vernalis* L.**	Pheasant's eye	Whole plant	Cardiac glycosides, (e.g. adonitoxin)	Banned
Animals parts containing hormones	-	Parts that may contain hormones: Pituitary gland, Thyroid gland, Parathyroid glands, Adrenal glands, Pancreas, Thymus gland, Ovary, Testes, Placenta	Growth hormone, prolactin, adrenocortico-tropic hormone,Thyroid-stimulating hormone, Follicle-stimulating hormone, luteinizinghormone, oxytocin, antidiuretichormone, thyroid hormone, calcitonin, parathyroidhormone, mineralocorti-coids,glucocorti-coids, sex hormones, insulin, glucagon, thymosin, estrogens, progesterone, testosterone	Banned
***Antiaris toxicaria* Lesch.**	Upas tree (Javanese Language-arrow poison), Bark Cloth Tree	Latex, Sap	Cardiac glycoside (antiarin), Cardenolides & Alkaloids (with cardiac arresting potential)	Banned

[3] Information on the observed and predicted harmful effect and supporting references are available as a compendium of the negative list.

Scientific Name	Common Name(s)	Harmful Animal or Plant Part(s)	Name of Harmful Compound or Compound Class	Ban Status in HS
***Aristolochia* spp.**	Birthwort, Pelican flower, Sangree root, Sangrel, Serpentaria, Snakeroot, Snakeweed	Whole plant	Aristolochic acid	Banned
***Artemisia* spp. containing artemisinin**	Wormwood	Leaf	Artemisinin	Banned
***Aspidosperma quebracho-blanco* Schltdl.**	Quebracho	Bark	Aspidospermine	Banned
***Atropa belladonna* L.**	Deadly Nightshade	Whole plant	Scopolamine, Hyoscyamine, Atropine	Banned
***Azadirachta indica* A.Juss.**	Nimba, Neem	Seeds	Azadirachtin and derivatives	Banned
***Barnardia japonica* (Thunb.) Schult. & Schult.f.** **Syn. *Scilla sinensis* (Lour.) Merr.**	-	Bulb	Cardiac glycosides	Banned
***Berberis* spp. containing berberine e.g. *Berberis vulgaris* L.**	Mahonia Aquifolium: Oregon Grape, Mountain Grape, Barberry. Mahonia Repens: Creeping Barberry, Creeping Mahonia, Creeping Oregon- Grape Mahonia Nervosa: Dwarf Oregon-grape, Cascade Oregon- grape, Dull Oregon-grape	Root, bark, rhizome	Berberine	Banned
***Brucea javanica* (L.) Merr.**	Sumatrana amarissimus, Java brucea	Dried fruits & seed	Bruceine, Bruceantinol and Bruceoside	Banned

Scientific Name	Common Name(s)	Harmful Animal or Plant Part(s)	Name of Harmful Compound or Compound Class	Ban Status in HS
***Bufo gargarizans* Cantor** ***Bufo melanostictus* Schneider** ***Bufo vulgaris* Lour.**	Toad, Samsu, Kodok kerok	Venom, dried secretion, whole body, egg	Cinobufagin, Resibufagenin, Bufagins, Catecholamines: Asbufothionine	Banned
***Calotropis gigantea* (L.) Dryand.** ***Calotropis procera* (Aiton) Dryand.**	Giant milkweed Small crown flower	Whole plant	Cardiac glycosides: e.g. Calotropin	Banned
***Cannabis* spp.**	Marijuana, Cannabis	Whole plant	Cannabinoids	Banned[4]
***Catharanthus roseus* (L.) G.Don** **Syn. *Vinca rosea* L.**	Rosy Periwinkle, Madagascar Periwinkle, Old Maid	Whole plant	Vinca alkaloids	Banned
***Cerbera manghas* L.**	Dog bane, Pink eyed cerbera	Seed	Digitoxinglyco-side, Cerberine, Cerberoside, Thevetin	Banned
***Cerbera odollam* Gaertn.**	Indian Suicide Tree, Sea Mango	Seed	Cerberin, Cerebroside, Odollin, Odolotoxin, Thevetin and Cerapain	Banned
***Chelidonium majus* L.**	Celandine, Greater Celandine, Nipplewort	Whole plant	Benzophenanthridine alkaloids: e.g. Berberine, Chelidonine, Sanguinarine, Coptisine, Chelerythrine	Banned
***Chondrodendron tomentosum* Ruiz & Pav.**	Curare, Pareira, Pareira brava	Stems	Tubocurarine	Banned

[4] Except for manufacture in the Kingdom of Thailand for domestic trade and consumption in accordance with its laws and regulations.

Scientific Name	Common Name(s)	Harmful Animal or Plant Part(s)	Name of Harmful Compound or Compound Class	Ban Status in HS
***Cinchona* spp.**	Quine bark	Bark	Quinoline alkaloids: e.g. quinine and derivatives	Banned
***Citrullus colocynthis* (L.) Schrad.**	Bitter apple	Seed, fruit	Cucurbitacin	Banned
***Claviceps purpurea* (Fr.) Tul.**	Ergot	Sclerotium	Ergot alkaloids (including Ergotamine and Ergometrine)	Banned
***Colchicum autumnale* L.**	Meadow saffron	Seed	Cochicine	Banned
***Conium maculatum* L.**	Hemlock	Whole plant	Coniine	Banned
***Croton tiglium* L.**	Purging croton	Whole plant	Phorbol-esters, isoquinoline alkaloids (aporphine, morphinane, proaporphine type alkaloids) and crotin	Banned
***Datura* spp. containing hyoscyamine, atropine, scopolamine and apoatropine**	Jimson weed, Devil's apple, Green Dragon, Zombie's Cucumber, Moon Weed, Trumpet Lily, Stinkweed	Whole plant	Hyoscyamine, Atropine, Scopolamine, Apoatropine	Banned
***Delphinium staphisagria* L.**	Stavesacre	Seeds	Delphinine, Staphisine	Banned
***Digitalis* spp. containing cardenolides**	-	Whole plant	Cardenolides e.g. digoxin	Banned

Scientific Name	Common Name(s)	Harmful Animal or Plant Part(s)	Name of Harmful Compound or Compound Class	Ban Status in HS
Drimia maritima **(L.) Stearn** **Syn. *Urginea maritima* (L.) Baker**	Sea squill, red squill, sea onion, squill	Bulb	Cardiac glycosides	Banned
Dryobalanops sumatrensis **(J.F.Gmel.) Kosterm.** **Syn. *Dryobalanops aromatica* C.F.Gaertn.** ***Dryobalanops lanceolata*** **Burck**	Borneo camphor, Kapur, Malay Camphor, Sumatra camphor	Whole plant	Borneol (Borneo camphor)	Banned (in oral preparation)
Dryopteris filix-mas **(L.) Schott**	Male Fern, aspidium, Male Shield Fern	Whole plant	Filicine, Aspidinol	Banned
Euphorbia antiquorum **L.** ***Euphorbia trigona*** **Mill.**	Triangular spurge	Whole plant	Phorbol esters e.g. tigliane, ingenane and daphnane types	Banned
Excoecaria agallocha **L.**	Blinding tree	Whole plant	Excoecaria phorbol	Banned
Fritillaria **spp.**	Fritillary bulb	Dried bulb	Steroidal and isosteroidal alkaloids: e.g. peimissine, verticine, verticinone, imperialine, isoverticine, ebeiedine	Banned
Garcinia elliptica **Wall. ex Wight** ***Garcinia hanburyi*** **Hook.f.** ***Garcinia morella*** **(Gaertn.) Desr.**	Gamboge	Whole plant	Cambogic acid, β-guttiferin, α-1-guttiferin	Banned

Scientific Name	Common Name(s)	Harmful Animal or Plant Part(s)	Name of Harmful Compound or Compound Class	Ban Status in HS
***Gelsemium sempervirens* (L.) J.St.-Hil.** ***Gelsemium elegans* (Gardner & Chapm.) Benth.**	Palaung Thay, Yellow Jessamine, Heartbreak grass	Root, leaf, rhizome	Gelsemium Indole alkaloids (e.g. gelsemine & gelseminine)	Banned
***Gluta usitata* (Wall.) Ding Hou** **Syn. *Melanorrhoea usitata* Wall.**	Vanish tree	Latex	Urushic acid, Urushiol, Cardanol, Cardol, Anacardic acid	Banned
***Hyoscyamus muticus* L.** ***Hyoscyamus niger* L.**	Henbane, Henblain, Jusquaime	Whole plant	Tropane alkaloids: e.g. atropine, hyoscyamine, hyoscine	Banned
***Jatropha multifida* L.**	Coral Bush, Coral Plant, Physic nut, Guatemala rhubarb	Fruit, seed	Phytotoxin (Toxalbumin - Curcin)	Banned
***Juniperus sabina* L.**	Savin, Savine	Whole plant	Sabinyl acetate, Sabinene, Podophyllo-toxin and others	Banned
***Lantana camara* L.**	Tembelekan (tahi ayam)	Whole plant	Lantadene and Lancamaron	Banned
***Larrea tridentata* (Sessé & Moc. ex DC.) Coville** ***Larrea mexicana* Moric.**	Chaparral	Whole plant	Lignans: Nordihydrog uaiaretic acid (NDGA)	Banned

Scientific Name	Common Name(s)	Harmful Animal or Plant Part(s)	Name of Harmful Compound or Compound Class	Ban Status in HS
***Lobelia nicotianifolia* Roth ex Schult.** ***Lobelia inflata* L.** ***Lobelia chinensis* Lour.** ***Lobelia tupa* L.**	Indian tobacco	Whole plant	Piperidine alkaloids: e.g. lobeline	Banned
***Lytta vesicatoria* Linn.**	Spanish fly	Whole body	Cantharidin	Banned
***Magnolia officinalis* Rehder & E.H.Wilson**	Houpo, Houpohua, Lamp post, Officinal magnolia	Whole plant	Honokiol, magnolol, magnocurarine, benzylisoquinoline alkaloids: e.g. magnoflorine	Banned
***Melaleuca alternifolia* (Maiden & Betche) Cheel**	Tea tree	Leaf and terminal branch (Tea Tree Oil)	Tea tree oil: terpinen-4-ol, alpha-terpinene, 1,8-cineol, p-cymene, alpha-terpineol, alpha-pinene, terpinolenes	Banned
***Mitragyna speciosa* (Korth.) Havil.**	Kratom	Whole plant	Mitragynine, 7- hydroxymitragynine	Banned[5]
***Mucuna pruriens* (L.) DC.**	Cowhage, Cowage	Seed	Dopamine, Nicotine, Physostigmine	Banned
***Mylabris phalerata* Pall.** ***Mylabris cichorii* Linnaeus**	Blister beetle, Mylabris	Dried body	Cantharidin	Banned

[5] Except for manufacture in the Kingdom of Thailand for domestic trade and consumption in accordance with its laws and regulations.

Scientific Name	Common Name(s)	Harmful Animal or Plant Part(s)	Name of Harmful Compound or Compound Class	Ban Status in HS
***Nerium oleander* L.** **Syn. *Nerium indicum* Mill.**	Indian oleander, Exile Tree	Whole plant	Cardenolide glycosides: e.g. stropeside, oleandrin	Banned
***Nicotiana tabacum* L.**	Tobacco	Leaf	Nicotine	Banned
***Papaver* spp. containing morphine & derivatives and codeine**	Opium, Poppy	Whole plant	Isoquinoline alkaloids (morphinanes): e.g. morphine, codeine, rhoeadine	Banned
***Pausinystalia johimbe* (K.Schum.) Pierre ex Beille**	Yohimbe	Bark	Yohimbine	Banned
***Physostigma venenosum* Balf.**	Calabar bean	Seed	Physostigmine	Banned
***Pilocarpus microphyllus* Stapf ex Wardleworth** ***Pilocarpus jaborandi* Holmes** ***Pilocarpus pennatifolius* Lem.**	Jaborandi	Whole plant	Imidazole alkaloids: e.g. pilocarpine, pilocarpidine, pilosine	Banned
***Piper methysticum* G.Forst.**	Kava Kava	Whole plant	Kava pyrones	Banned
***Plumbago zeylanica* L.**	White leadwort	Roots	Plumbagin	Banned
***Plumbago indica* L.**	Rose-coloured leadwort	Root, root bark	Plumbagin	Banned

Scientific Name	Common Name(s)	Harmful Animal or Plant Part(s)	Name of Harmful Compound or Compound Class	Ban Status in HS
***Podophyllum emodi* Wall. ex Hook.f. & Thomson** ***Podophyllum peltatum* L.**	American mayapple, Mandrake	Root, leaf	Resin podophyllin composed of cyclolignans, e.g. podophyllotoxin, alpha and beta peltatins and their derivatives.	Banned
***Psilocybe cubensis* (Earle) Singer**	Gold caps Shrooms, Magic Mushrooms, Sacred Mushrooms	Whole plant	Psilocybine, Psilocin	Banned
***Punica granatum* L.**	Pomegranate	Stem bark and root bark	Pomegranate alkaloids	Banned
***Rauvolfia serpentina* (L.) Benth. ex Kurz** **Syn. *Ophioxylon serpentinum* L.** ***Rauvolfia vomitoria* Afzel.**	Rauwolfia, Indian snakeroot, Snakeroot	Whole plant	Indole alkaloids: e.g. reserpine, serpentine, yohimbine, ajmalicine	Banned
***Sanguinaria canadensis* L.**	Bloodroot, Indian Paint	Rhizome and root	Sanguinarine, Chelerethrin, Sanguirulin, Berberine, Protopine	Banned
***Schoenocaulon officinale* (Schltdl. & Cham.) A.Gray**	Sabadilla	Seed	Veratrine	Banned

Scientific Name	Common Name(s)	Harmful Animal or Plant Part(s)	Name of Harmful Compound or Compound Class	Ban Status in HS
***Senecio aureus* L.** ***Senecio jacobaea* L.** ***Senecio bicolor* Sch.Bip.** ***Senecio nemorensis* L.** ***Senecio vulgaris* L.** ***Senecio longilobus* Benth.** ***Senecio scandens* Buch.-Ham. ex D.Don**	-	Whole plant	Pyrrolizidine alkaloids: e.g. senecionine, riddelliine	Banned
***Solanum dulcamara* L.** ***Solanum americanum* Mill.** **Syn. *Solanum nigrum* L.**	Bittersweet, Bittersweet Nightshade, Bitter Nightshade, Black Nightshade	Whole plant	Glycosidic steroidal alkaloids: e.g. solanidine, tomatidine	Banned
***Sophora tomentosa* L.**	Sea coast Laburnum, Silver Bush	Seed	Alkaloids - Matrine, Cytisine	Banned
***Spigelia marilandica* L.**	Worm grass, Pinkroot	Whole plant	Spigeline (a strychnine-like alkaloid)	Banned
***Stephania tetrandra* S.Moore**	Fang ji Fen fang ji Han fang ji Stephania-root	Root	Tetrandrine	Banned

Scientific Name	Common Name(s)	Harmful Animal or Plant Part(s)	Name of Harmful Compound or Compound Class	Ban Status in HS
***Strophanthus* spp. containing cardenolide glycosides**	Kombe Gardenia oleander, Climbing oleander	Whole plant	Cardenolide glycosides: e.g. oubaine and aglycones: e.g. strophanthidin	Banned
***Strychnos nux-vomica* L.** ***Strychnos ignatii* P.J. Bergius** ***Strychnos lucida* R.Br.** ***Strychnos roborans* A.W.Hill**	Nux-vomica Ignatius bean, Phayaa mue lek	Seed Fruit	Indole alkaloids (e.g. strychnine) and/or bisbenzylisoquinoline alkaloids (e.g. tubocurarine)	Banned
***Symphytum officinale* L.** ***Symphytum asperum* Lepech.** ***Symphytum* × *uplandicum* Nyman** ***Symphytum peregrinum* Ledeb.**	Comfrey	Whole plant	Unsaturated pyrrolizidine alkaloids	Banned

Scientific Name	Common Name(s)	Harmful Animal or Plant Part(s)	Name of Harmful Compound or Compound Class	Ban Status in HS
***Veratrum viride* Aiton** ***Veratrum album* L.** ***Veratrum mengtzeanum* O.Loes.** ***Veratrum nigrum* L.** ***Veratrum stenophyllum* Diels** ***Veratrum maackii* Regel** ***Veratrum dahuricum* (Turcz.) O.Loes.** ***Veratrum grandiflorum* (Maxim. ex Miq.) O.Loes.** ***Veratrum taliense* O.Loes.**	American Hellebore, Indian Poke, Indian Hellebore, False Hellebore, Green False Hellebore, White Hellebore	Whole Plant	Steroid alkaloids: e.g. protoveratrines, and alkamine esters such as jervine derivatives (furanopiperidine) e.g. cyclopamine	Banned
***Vinca minor* L.**	Lesser periwinkle	Whole plant	Indole alkaloids: Vincamine, Eburnamenine	Banned

ANNEX II

ASEAN GUIDING PRINCIPLES FOR THE USE OF ADDITIVES AND EXCIPIENTS IN HEALTH SUPPLEMENTS

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Purpose

1. These guidelines apply to restricted and prohibited additives and excipients intended for use in Health Supplements (HS) in order to assist Member States in the application of agreed requirements, protection of consumers, and facilitation of fair trade.

2. These guidelines do not include flavouring agents[1].

Guiding Principles

The following criteria are guiding principles used for determination of the use of additives and excipients in HS.

1. Justification for the Use of Additives and Excipients

The use of additives and excipients is justified only when such use has an advantage, does not present an appreciable health risk to consumers, does not mislead the consumer, and serves one or more of the technological functions set out by Codex and/or international references and the needs set out from (a) through (c) below, and only where these objectives cannot be achieved by other means that are economically and technologically practicable:

(a) to preserve the quality of the product;

[1] There is no restriction or prohibition on the use of any substance as flavouring agents for as long as their use can be supported by international references.

(b) to enhance the keeping quality or stability of a product or to improve its organoleptic properties, provided that this does not change the nature, substance, or quality of the product so as to deceive the consumer; and

(c) to provide aids in the manufacture, processing, preparation, treatment, packing, transport, or storage of product, provided that the additive is not used to disguise the effects of the use of faulty raw materials or of undesirable (including unhygienic) practices or techniques during the course of any of these activities.

2. Additives and Excipients Safety

All additives and excipients must not pose hazards or unacceptable risks to consumers' health. The quantity of an additive or excipient added is at or below the maximum use level and is the lowest level necessary to achieve the intended technical effect.

3. Specifications for the Identity and Purity of Additives and Excipients

Additives and excipients should be of appropriate food or pharmaceutical grade quality and should at all times conform with the applicable Specifications of Identity and Purity recommended by the Codex Alimentarius Commission or the official pharmacopoeias or, in the absence of such specifications, with appropriate specifications developed by responsible national or international bodies. In terms of safety, food or pharmaceutical grade quality is achieved by conformance of additives and excipients to their specifications as a whole.

4. Good Manufacturing Practice (GMP)[2]

All additives and excipients used under conditions of GMP should include the following:

(a) the quantity of the additive or excipient added to HS shall be limited to the lowest possible level necessary to

[2] The term GMP should not be interpreted as GMP standards for pharmaceutical products. It should be interpreted as GMP for the use of additives or excipients. For additional information, see the Codex Alimentarius Commission Procedural Manual. Relations between Commodity Committees and General Committees - Food Additives and Contaminants.

accomplish its desired effect;

(b) the quantity of the additive or excipient that becomes a component of a HS as a result of its use in the manufacturing, processing, or packaging of such a product and which is not intended to accomplish any physical, or other technical effect in the product itself, is reduced to the extent reasonably possible; and

(c) the additive or excipient is of appropriate food or pharmaceutical grade quality and is prepared and handled in the same way as a food or pharmaceutical ingredient.

5. Lists of Restricted Additives and Excipients

The list of restricted additives and excipients used in HS goes together with their maximum use levels. The maximum use level of zero means that additive or excipient is prohibited for use. The adopted List of Restricted Additives and Excipients appears in Appendix 1.

The latest edition of the following international references can be used to substantiate the inclusion of an additive or excipient into the list of restricted additives and excipients.

1. Codex General Standard for Food Additives (GSFA) Online Database (http://www.codexalimentarius.net/gsfaonline/index.html?lang=en)

2. Handbook of Pharmaceutical Excipients

3. All Official Pharmacopoeias

   3.1 National Pharmacopoeia of each country

   3.2 British Pharmacopoeia (BP)

   3.3 The United States Pharmacopoeia – National Formulary (USP-NF)

   3.4 European Pharmacopoeia (Ph.Eur)

   3.5 The Pharmacopoeia of China

   3.6 Japanese Pharmacopoeia (JP)

3.7 The Pharmacopoeia of India

The list as well as the maximum use levels may be subjected to change upon periodic review of updated international references. Scientific data submitted from Member States can be provided for consideration in order to amend the list.

6. Procedures for Determination of the Use of Additives and Excipients in HS

Step 1 - Verify whether an additive or excipient used in HS is in the list of restricted additives and excipients.

If yes, quantity or amount of additive or excipient used is below or at the maximum level of the additive or excipient as determined in the list.

If no, go to step 2.

Step 2 - Verify whether the additive or excipient is used according to the references

If yes, the quantity of the additive or excipient added shall be limited to the lowest possible level by technological justification necessary to accomplish its desired effect.

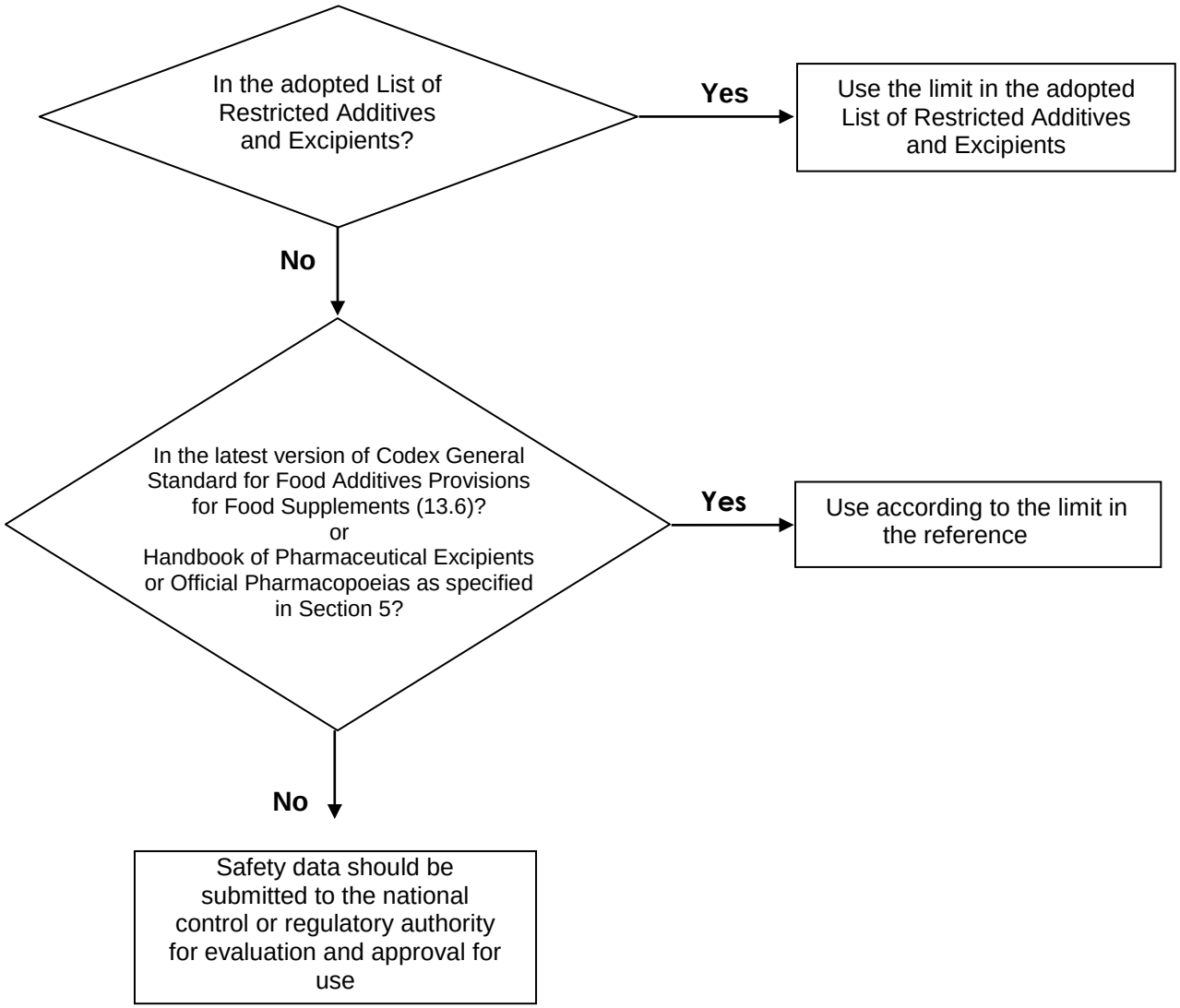
If no, go to step 3.

Step 3 - The new additive or excipient is not allowed to be used in HS unless the safety assessment of that additive or excipient has been evaluated and approved for use by the national control or regulatory authority.

During the safety assessment of new additives and excipients, reference can be made to international publications such as Handbook of Pharmaceutical Excipients 5th edition (Appendix 2), Environmental Health Criteria (EHC70[3]) – Principles for the Safety Assessment of Food Additives and Contaminants in Food (Appendix 3), or other suitable literature or guidelines.

[3] EHC 70 is the publication concerned with reviewing the basis for decision-making by the Joint Expert Committee on Food Additives (JECFA) of the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO).

Diagram 1. Procedures for Determination of the Use of Additives and Excipients in HS



Glossary

For the purposes of this Annex:

(a) **additives and excipients** means any substances not normally consumed by themselves and not normally used as typical ingredients or active substances, the intentional addition of which to HS for a technological purpose in the manufacture, processing, preparation, treatment, packing, packaging, transport, or holding of such products results, or may be reasonably expected to result (directly or indirectly), in them or their by-products becoming the components of or otherwise affecting the characteristics of the products. Such substances may include colouring agents, preservatives, adjuvants, stabilizers, thickeners, emulsifiers, pH adjusters, etc.;

(b) **Codex** means the Codex Alimentarius Commission created in 1963 by FAO and WHO to develop food standards, guidelines, and related texts such as codes of practice under the Joint FAO/WHO Food Standards Programme. The main purposes of this Programme are protecting health of the consumers and ensuring fair trade practices in the food trade, and promoting coordination of all food standards work undertaken by international governmental and non-governmental organisations; and

(c) **maximum use level** means the highest concentration of an additive or excipient determined to be functionally effective and agreed to be safe by the Codex Alimentarius Commission or the official pharmacopoeias.

References Used

1. Codex Alimentarius International Food Standards. *Codex General Standard for Food Additives (GSFA) Online Database*. http://www.codexalimentarius.org/standards/gsfa/en/ (Accessed 2 Jan 2012).

2. Codex Alimentarius International Food Standards. *Codex General Standard for Food Additives*. http://www.codexalimentarius.org/standards/list-of-standards/en/ (Accessed 2 Jan 2010).

3. International Programme on Chemical Safety. *Principles for the Safety Assessment of Food Additives and Contaminants in Food.* http://www.inchem.org/documents/ehc/ehc/ehc70.htm (Accessed 2 Jan 2009).

4. Raymond C R, Paul J S, Cook, Walter G C, Marian E F. *Handbook of Pharmaceutical Excipients*, *7th edition*. London: Pharmaceutical Press, 2012.

5. Raymond C R, Paul J S, Marian E Q. *Handbook of Pharmaceutical Excipients, 6th edition*. London: The Pharmaceutical Press and the American Pharmacists Association, 2009.

6. Raymond C R, Paul J S, Sian C O. *Handbook of Pharmaceutical Excipients*, *5th edition*. London: The Pharmaceutical Press and the American Pharmacists Association, 2006.

APPENDIX 1

THE LIST OF RESTRICTED ADDITIVES AND EXCIPIENTS FOR HEALTH SUPPLEMENTS

Item	Common Name	INS No./ CAS No.	Synonym(s)	Limit (mg/kg product)	Reference (Scientific Rational and/or Technical Reference)	Note
Coloring agent						
1	Allura Red AC	129	- CI (1975) No.16035 - CI Food Red 17 - FD&C Red No.40	300	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
2	Brilliant Blue FCF	133	- CI (1975) No. 42900 - CI Food Blue 2 - FD&C Blue No.1	300	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
3	Caramel III – Ammonia process	150c	- Ammonia caramel	20,000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
4	Caramel IV – Sulphite Ammonia Process	150d	- Sulfite ammonia caramel	20,000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
5	Carmines	120	- Carmine - CI (1975) No. 75470 - CI Natural Red 4 - Cochineal carmine	300	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	

Item	Common Name	INS No./ CAS No.	Synonym(s)	Limit (mg/kg product)	Reference (Scientific Rational and/or Technical Reference)	Note
6	Carotenes, beta (vegetable)	160a(ii)	- Carotenes-natural - CI Food Orange 5 - Mixed carotenes - Natural beta-carotene	600	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
7	Carotenal, beta-apo- 8'	160e	- CI. Food Orange 6	300	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
	beta-Carotenes (B. trispora)	160a(iii)	- CI. Food Orange 5	300	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
	beta-Carotenes (synthetic)	160a(i)	- CI. Food Orange 5	300	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
	Carotenoic acid, ethyl ester, beta-apo-8'-	160f	- CI. Food Orange 7 (Ethyl Ester)	300	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
8	Chlorophylls, Copper Complexes	141(i)	- C.I. (1975) No. 75810 - CI Natural Green 3 - Copper chlorophyll - Copper phaeophytin	500	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	Surface treatment
	Chlorophyllin copper complexes, potassium and sodium salts	141(ii)	- C.I. (1975) No. 75810 - Potassium copper chlorophyllin - Sodium copper chlorophyllin	500	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	Surface treatment

Item	Common Name	INS No./ CAS No.	Synonym(s)	Limit (mg/kg product)	Reference (Scientific Rational and/or Technical Reference)	Note
9	Fast Green FCF	143	- C.I. Food Green 3 - CI (1975) No. 42053 - FD&C Green No. 3	600	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
10	Grape Skin Extract	163(ii)	- ENO - Enociania	500	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	Expressed as anthocyanin
11	Indigotine (Indigo carmine)	132	- C.I. Food Blue 1 - CI (1975) No. 73015 - FD&C Blue No. 2 - Indigo Carmine	300	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
12	Iron oxide, black	172(i)	- C.I. Pigment Black 11 - CI (1975) No. 77499	7,500	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	Surface treatment
	Iron oxide, red	172(ii)	- C.I. Pigment Red 101 - C.I. Pigment Red 102 - CI (1975) No. 77491	7,500	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	Surface treatment
	Iron oxide, yellow	172(iii)	- C.I. Pigment Yellow 42 - C.I. Pigment Yellow 43 - CI (1975) No. 77492	7,500	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	Surface treatment
13	Ponceau 4R (Cochineal Red A)	124	- CI Food Red 7 - Cochineal Red A - New Coccine	300	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	

Item	Common Name	INS No./ CAS No.	Synonym(s)	Limit (mg/kg product)	Reference (Scientific Rational and/or Technical Reference)	Note
14	Riboflavin from *Bacillus subtilis*	101(iii)	-	300	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
	Riboflavin 5' – phosphate sodium	101(ii)	- Vitamin B2 Ester Monosodium Salt	300	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
	Riboflavin, synthetic	101(i)	- Riboflavin 5'-phosphate ester monosodium salt - Vitamin B2 phosphate ester monosodium salt	300	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
15	Sunset Yellow FCF	110	- CI (1975) No. 15985 - CI Food Yellow 3 - Crelborange S - FD&C Yellow No. 6	300	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
Sweetener						
1	Acesulfame Potassium	950	- Acesulfame K	2000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	Not to exceed the maximum use level for acesulfame potassium (INS 950) singly or in combination with aspartame-acesulfame salt (INS 962)
2	Aspartame	951	- APM - Aspartyl phenylalanine methyl ester	5500	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	Not to exceed the maximum use level for aspartame (INS 951) singly or in combination with aspartame-acesulfame salt (INS 962)

Item	Common Name	INS No./ CAS No.	Synonym(s)	Limit (mg/kg product)	Reference (Scientific Rational and/or Technical Reference)	Note
3	Cyclamic acid	952(i)	- Cyclohexylsulfamic acid	1250	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	As Cyclamic acid
	Calcium cyclamate	952(ii)	-	1250	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	As Cyclamic acid
	Sodium cyclamate	952(iv)	-	1250	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	As Cyclamic acid
4	Neotame	961	-	90	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
5	Saccharin	954(i)	-	1200	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
	Calcium saccharin	954(ii)	-	1200	Codex GSFA Provisions for Food Category 13.6 updated up to 34thCAC (2012)	
	Potassium saccharin	954(iii)	-	1200	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	

Item	Common Name	INS No./ CAS No.	Synonym(s)	Limit (mg/kg product)	Reference (Scientific Rational and/or Technical Reference)	Note
	Sodium saccharin	954(iv)	-	1200	Codex GSFA Provisions for Food Category 13.6 updated up to 33rd CAC (2012)	
6	Sucralose (Trichloro-galactosucrose)	955	- 4,1',6'-trichlorogalacto sucrose	2400	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
7	Steviol glycosides	960	-	2500	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	- As steviol equivalents. - For use in chewable supplements only.
Preservatives						
1	Methyl paraben	218 / 99-76-3	- E218 - 4-hydroxybenzoic acid methyl ester - methyl p-hydroxy-benzoate - *Nipagin M* - *Uniphen P-23*	150 - 2000 (Oral solutions and suspensions) 200 - 3000 (Topical prep.)	Handbook of Pharmaceutical Excipients 5th Editions, 2006 p 466-470	
2	Benzoic acid	210	-	2000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	As benzoic acid.
	Sodium benzoate	211	-	2000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	As benzoic acid.

Item	Common Name	INS No./ CAS No.	Synonym(s)	Limit (mg/kg product)	Reference (Scientific Rational and/or Technical Reference)	Note
	Potassium benzoate	212	-	2000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	As benzoic acid.
	Calcium benzoate	213	-	2000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	As benzoic acid.
3	Bronopol	52-51-7	- 2-Bromo-2-nitro-1,3-propanediol - β-bromo- β-nitrotrimethyleneglycol - *Myacide*	100 – 1000 (w/v)	Handbook of Pharmaceutical Excipients 6th Editions, 2009 p 70-72	Topical use
4	Benzyl alcohol	100-51-6	- Alcohol benzylicus - Benzenemethanol - Phenylcarbinol - Phenylmethanol - alpha-Hydroxytoluene - alpha-toluenol	20000 (v/v)	Handbook of Pharmaceutical Excipients 6th Editions, 2009 p 64-66	
5	Cetrimide	8044-71-1	- *Bromat* - *Cetab* - *Cetavlon* - *Cetraol* - *Lissolamine V* - *Micol* - *Morpan CHSA* - *Morphans* - *Quammonium* - *Sucitide* - Centrimidum	50 (w/v)	Handbook of Pharmaceutical Excipients 6th Editions, 2009 p 152-154	Topical Use

Item	Common Name	INS No./ CAS No.	Synonym(s)	Limit (mg/kg product)	Reference (Scientific Rational and/or Technical Reference)	Note
6	Propionic acid	79-09-4	- E280 - Carboxyethane - Ethanecarboxylic acid - ethylformic acid - Metacetonic acid - methylacetic acid - Propanoic acid - Pseudoacetic acid	3000 - 10000	Handbook of Pharmaceutical Excipients 6th Editions, 2009 p 586-587	
7	Sorbic acid	200	-	2000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	As sorbic acid.
	Sodium sorbate	201	-	2000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	As sorbic acid.
	Potassium sorbate	202	-	2000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	As sorbic acid.
	Calcium sorbate	203	-	2000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	As sorbic acid.
Antioxidants						

Item	Common Name	INS No./ CAS No.	Synonym(s)	Limit (mg/kg product)	Reference (Scientific Rational and/or Technical Reference)	Note
1	Alpha-Tocopherol	10191-41-0	- *Copherol F1300* - (±)-3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-*2H*-1-benzopyran-6-ol - E307 - synthetic alpha tocopherol - all-*rac*-*α*-atocopherol - *dl*-*α* -tocopherol - 5,7,8-trimethyltocol - RRR- *α* -Tocopherolum	10 - 500 (used in oil or fat-based formulations) (v/v)	Handbook of Pharmaceutical Excipients 6th Editions, 2009 p 31-33	
2	Ascorbic acid	50-81-7	- C-97 - cevitamic acid - 2,3-didehydro-L-*threo*-hexono-1,4-lactone; - E300 - 3-oxo-L-gulofuranolactone, enol form - Vitamin C - Acidum ascorbicum	100 - 1000 (used in aqueous formulations) (w/v)	Handbook of Pharmaceutical Excipients 6th Editions, 2009 p 43-46	
3	Ascorbyl palmitate	304	- Vitamin C palmitate	500	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	As ascorbyl stearate.
	Ascorbyl stearate	305	- Vitamin C stearate	500	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	As ascorbyl stearate.

Item	Common Name	INS No./ CAS No.	Synonym(s)	Limit (mg/kg product)	Reference (Scientific Rational and/or Technical Reference)	Note
4	Butylated hydoxyanisole	320	- BHA	400	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	- Fat or oil basis. - Singly or in combination: butylated hydroxyanisole (BHA, INS 320), butylated hydroxytoluene (BHT, INS 321) and propyl gallate (INS 310).
5	Butylated hydoxytoluene	321	- BHT	400	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	- Fat or oil basis. - Singly or in combination: butylated hydroxyanisole (BHA, INS 320), butylated hydroxytoluene (BHT, INS 321) and propyl gallate (INS 310).
6	Propyl gallate	310	- Propyl Gallate	400	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	- Fat or oil basis. - Singly or in combination: butylated hydroxyanisole (BHA, INS 320), butylated hydroxytoluene (BHT, INS 321) and propyl gallate (INS 310).
7	Calcium disodium ethylenediaminetetra acetate	385	- Calcium disodium edetate - Calcium disodium EDTA	150	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	- As anhydrous calcium disodium ethylenediaminetetra acetate.

Item	Common Name	INS No./ CAS No.	Synonym(s)	Limit (mg/kg product)	Reference (Scientific Rational and/or Technical Reference)	Note
	Disodium ethylenediaminetetra acetate	386	- Calcium Disodium (Ethylene-Dinitrilo)-Tetraacetate - Calcium Disodium Edetate - Calcium Disodium EDTA - Calcium Disodium Ethylenediaminetetraacetate - Disodium Dihydrogen (Ethylene-Dinitrilo) - Tetraacetate - Disodium Edetate - Disodium EDTA - Disodium Ethylenediaminetetraacetate	150	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	- As anhydrous calcium disodium ethylenediaminetetra acetate.
Excipients (Anticaking, Emulsifier, Glazing agent, Stabilizer, Solvent, etc.)						
1	Castor oil	1503	Ricinus oil	1000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
2	Carnauba wax	903	-	5000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	Surface treatment.

Item	Common Name	INS No./ CAS No.	Synonym(s)	Limit (mg/kg product)	Reference (Scientific Rational and/or Technical Reference)	Note
3	Cetyl alcohol	36653-82-4	- *Avol* - *Cachalot* - *Crodacol C70* - *Crodacol C90* - *Crodacol C95* - Ethal - Ethol - 1-hexadecanol - *n*-hexadecyl alcohol - *Hyfatol 16-95* - *Hyfatol 16-98* - *Kessco CA* - *Lanette 16* - *Lipocol C* - palmityl - Alcohol - *Rita CA* - *Tego Alkanol 16.* - Alcohol cetylicus - HallStar CO-1695 - Nacol 16-95 - Speziol C16 Pharma - Vegarol 1695	20,000-100,000	Handbook of Pharmaceutical Excipients 6th Editions, 2009 p 155-156	Coating agent Emulsifier
4	Diacetyltartaric and fatty acid esters of glycerol	472e	- DATEM - Diacetyltartaric acid esters of mono- and diglycerides - Mixed acetic and tartaric acid esters of mono and diglycerides of fatty acids; INS	5000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	

Item	Common Name	INS No./ CAS No.	Synonym(s)	Limit (mg/kg product)	Reference (Scientific Rational and/or Technical Reference)	Note
			No. 472f - Mixed Glycerol Esters of Diacetyltartaric Acid and Fatty Acids from Food Fats - Tartaric, acetic and fatty acid esters of glycerol, mixed			
5	Magnesium Stearate	557-04-0	- Magnesium octadecanoate - octadecanoic acid - magnesium salt - stearic acid - magnesium salt - Dibasic magnesium stearate - Magnesium distearate - Magnesii stearas - Synpro 90	2500 - 50000	Handbook of Pharmaceutical Excipients 6th Editions, 2009 p 404-407	Lubricant
6	Phosphates	338; 339(i)-(iii); 340(i)-(iii); 341(i)-(iii); 342(i),(ii); 343(i)-(iii); 450(i)-(iii), (v)-(vii); 451(i), (ii); 452(i)-(v); 542	-	2200	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	As phosphorus.
7	Polydimethylsiloxane	900a	- Dimethylpolysiloxane - Dimethylsilicone fluid - Dimethylsilicone oil - Poly(dimethylsiloxane)	50	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	

Item	Common Name	INS No./ CAS No.	Synonym(s)	Limit (mg/kg product)	Reference (Scientific Rational and/or Technical Reference)	Note
8	Polyethylene glycol	1521	- Macrogol - PEG	70,000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
9	Polyoxyethylene (20) sorbitan monolaurate	432	- Polysorbate 20	25,000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
	Polyoxyethylene (20) sorbitan monooleate	433	- Polysorbate 80	25,000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
	Polyoxyethylene (20) sorbitan monopalmitate	434	- Polysorbate 40	25,000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
	Polyoxyethylene (20) sorbitan monostearate	435	- Polysorbate 60	25,000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
	Polyoxyethylene (20) sorbitan tristearate	436	- Polysorbate 65	25,000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	
10	Polyvinyl alcohol	1203	- PVOH - Vinyl alcohol polymer	45,000	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	Coating agent, Stabilizer

Item	Common Name	INS No./ CAS No.	Synonym(s)	Limit (mg/kg product)	Reference (Scientific Rational and/or Technical Reference)	Note
11	Potassium citrate	6100-05-6 / 866-84-2	- Citrate of potash - Citric acid potassium salt - E332 - Tripotassium citrate monohydrate - Kalii citras	3,000-20,000	Handbook of Pharmaceutical Excipients 6th Editions, 2009 p 574-576	Alkalizing agent Buffering agent Sequestering agent.
12	Sucroglycerides	474	-	2500	Codex GSFA Provisions for Food Category 13.6 updated up to 34th CAC (2012)	

APPENDIX 2

SAFETY ASSESSMENT OF ADDITIVES AND EXCIPIENTS BASED ON HANDBOOK OF PHARMACEUTICAL EXCIPIENTS 5TH EDITION

Specifications of Pharmaceutical Excipients

1. Nonproprietary Names
Excipient names used in the current British Pharmacopoeia, European Pharmacopoeia, Japanese Pharmacopoeia, and the United States Pharmacopoeia – National Formulary (USP-NF).

2. Synonyms

3. Chemical Name and CAS Registry Number
The unique Chemical Abstract Services number for an excipient along with the chemical name.

4. Empirical Formula and Molecular Weight

5. Structural Formula

6. Functional Category
The lists of functions that an excipient is generally thought to perform.

7. Applications in Pharmaceutical Formulation of Technology
The various applications of excipient.

8. Description
The details of physical appearance of the excipient.

9. Pharmocopoeial Specifications
The compendial standards for the excipient is obtained from the British Pharmacopoeia (BP), European Pharmacopoeia (Ph.Eur), Japanese Pharmacopoeia (JP), and the United States Pharmacopoeia – National Formulary (USP-NF).

10. Typical Properties

11. Stability and Storage Conditions
The conditions under which the bulk material as received from the supplier should be stored and storage and stability of the dosage forms that contain the excipient.

12. Incompatibilities

Incompatibilities for the excipients either with other excipients or with active ingredients, if an incompatibility is not listed it does not mean it does not occur but simply that it has not been reported or is not well known. Every formulation should be tested for incompatibilities prior to use in a commercial product.

13. Method of Manufacture

The common methods of manufacture and additional processes are used to give the excipient its physical characteristics. In some cases, the possibility of impurities will be indicated in the method of manufacture.

14. Safety

The types of formulations in which the excipient has been used and presents relevant data concerning possible hazards, adverse reactions that have been reported, and relevant animal toxicity data are also shown.

15. Handling Precautions

The possible hazards associated with handling the excipient and makes recommendations for suitable containment and protection methods. A familiarity with current Good Laboratory Practice and current GMP and standard chemical handling procedures is assumed.

16. Regulatory Status

The accepted uses in foods and licensed pharmaceuticals where known. However, the status of excipients varies from one nation to another and appropriate regulatory bodies should be consulted for guidance.

17. Related Substances

18. Comments

Include additional information and observations relevant to the excipient. Where appropriate, the different grades of the excipient available are discussed. Comments are the option of the listed author(s) unless referenced or indicated otherwise.

19. Specific References

A list of references cited within the monograph.

20. General References (if any)

The references which have general information about this type of excipients or the types of dosage forms made with these

excipients.

21. Authors

The current authors of the monograph.

22. Date of Revision

The date on which changes were last made to the text of the monograph.

APPENDIX 3

SAFETY ASSESSMENT OF ADDITIVES AND EXCIPIENTS BASED ON ENVIRONMENTAL HEALTH CRITERIA 70 (EHC 70)

Principles for the Safety Assessment of Food Additives and Contaminants in Food

1. Chemical Composition and the Development of Specifications

- 1.1. Identity and purity
- 1.2. Reactions and fate of food additives and contaminants in food
- 1.3. Specifications

2. Test Procedures and Evaluation

- 2.1. End-points in experimental toxicity studies
  - 2.1.1. Effects with functional manifestations
  - 2.1.2. Non-neoplastic lesions with morphological manifestations
  - 2.1.3. Neoplasms
  - 2.1.4. Reproduction or developmental toxicity
  - 2.1.5. In vitro studies
- 2.2. The use of metabolic and pharmacokinetic studies in safety assessment
  - 2.2.1. Identifying relevant animal species
  - 2.2.2. Determining the mechanisms of toxicity
  - 2.2.3. Metabolism into normal body constituents
  - 2.2.4. Influence of the gut microflora in safety assessment
    - 2.2.4.1. Effects of the gut microflora on the

chemical

2.2.4.2. Effects of the chemical on the gut microflora

2.3. Influence of age, nutritional status, and health status on the design and interpretation of studies

2.3.1. Age

2.3.1.1. History

2.3.1.2. Usefulness of studies involving in utero exposure

2.3.1.3. Complications of aging

2.3.2. Nutritional status

2.3.3. Health status

2.3.4. Study design

2.4. Use of human studies in safety evaluation

2.4.1. Epidemiological studies

2.4.2. Food intolerance

2.5. Setting the Acceptable Daily Intake (ADI)

2.5.1. Determination of the no-observed-effect level (NOEL)

2.5.2. Use of the safety factor

2.5.3. Toxicological versus physiological responses

2.5.4. Group ADIs

2.5.5. Special situations

2.5.6. Comparing the ADI with potential exposure

ANNEX III

ASEAN GUIDELINES ON LIMITS OF CONTAMINANTS FOR HEALTH SUPPLEMENTS

Disclaimer:

This document is provided for information purpose only and subject to changes, pending the finalisation of the ASEAN Agreement on Regulatory Framework for Health Supplements. Official references to this document can only be made once the said Agreement has been finalised.

Introduction

The ASEAN Guidelines on Limits of Contaminants for Health Supplements is developed by taking into consideration the safety and quality requirements of Health Supplements (HS).

Other limits of contaminants may be reviewed and included into the guideline as deemed necessary.

In determining the limits of microbial contamination, the following was taken into consideration:

- the nature of the product whether it is a pure compound, an extract, raw material or its combination;
- the route of administration; and
- the method of preparation, e.g. boiling.

Objective

The objective of these guidelines is to provide specifications on the limits of heavy metals and microbial contaminants of the various dosage forms to ensure their quality and safety. These guidelines also provide guidance notes on the control of pesticides in HS.

ASEAN Limits of Contaminants for HS

1. Limit on Heavy Metals:

Maximum limit for heavy metals:

1.1. Lead: not more than (NMT) 10.0 mg/kg or 10.0 mg/L (10.0ppm)

1.2. Arsenic: NMT 5.0 mg/kg or 5.0 mg/L (5.0ppm)[1]

1.3. Mercury: NMT 0.5 mg/kg or 0.5 mg/L (0.5ppm)

1.4. Cadmium: NMT 0.3 mg/kg or 0.3 mg/L (0.3ppm)

2. Limit for Microbial Contaminations

The limit used is based on British Pharmacopoeia (BP) (2013). Hence, the specifications may change as required according to the compendium requirements from time to time.

The list is not necessarily exhaustive and for a given preparation, it may be necessary to test for other microorganisms depending on the nature of the starting materials and in the manufacturing process.

Test for Microbial Contamination

Table I. Microbiological Quality of HS (not applicable to products containing viable microorganisms as active ingredients)

Route of Administration	Acceptable Criteria for Microbiological Quality		
	Total Aerobic Microbial Count (TAMC) (CFU[2]/g or CFU/ mL)	Total Combined Yeasts/Moulds Count (TYMC) (CFU/g or CFU/ mL)	Specified Microorganisms
For Oral Use			

[1] Due to special circumstances such as national regulatory requirement, the limit of arsenic in the Philippines is 0.3 mg/kg or 0.3 mg/L (0.3 ppm).

[2] CFU means Colony Forming Unit.

A. HS products containing material of plant origin, with or without excipients, intended for the preparation of infusions and decoctions using boiling water (for example, herbal teas, with or without added flavourings)	NMT 5×10^7	NMT 5×10^5	- NMT 10^3 CFU of *Escherichia coli* in 1g or 1mL - Absence of *Salmonella* in 25g or 25mL
B. HS products containing materials of plant origin, with or without excipients, where the method of processing (for example, extraction) or pre-treatment, reduces the levels of organisms to below those stated for this category	NMT 5×10^4	NMT 5×10^2	- NMT 10^2 CFU of bile-tolerant gram-negative bacteria in 1g or 1mL - Absence of *Escherichia coli* in 1g or 1mL - Absence of *Salmonella* in 25g or 25mL
C. HS products containing materials of plant origin, with or without excipients, where it can be demonstrated that the method of processing (for example, extraction with low strength ethanol or water that is not boiling or low temperature concentration) or, of pre-treatment, would not reduce the level of organisms sufficiently to reach the criteria required under B	NMT 5×10^5	NMT 5×10^4	- NMT 10^4 CFU of bile-tolerant gram-negative bacteria in 1g or 1mL - Absence of *Escherichia coli* in 1g or 1mL - Absence of *Salmonella* in 25g or 25mL
D. HS products containing materials of natural (animal, plant, or mineral) origin for which antimicrobial pre-treatment is not feasible and for which the regulatory authority accepts TAMC of the raw material exceeding 10^3 CFU/gram or CFU/mL	NMT 2×10^4	NMT 2×10^2	- NMT 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 aureus* in 1g or 1mL
E. Aqueous preparations which does not fall under category A, B, C, or D	NMT 2×10^2	NMT 2×10	- Absence of *Escherichia coli* in 1g or 1mL
F. Non-aqueous preparations which does not fall under category A, B, C, or D	NMT 2×10^3	NMT 2×10^2	- Absence of *Escherichia coli* in 1g or 1mL

The limits for microbial contamination for HS with routes of administration not specified above shall be determined by the regulatory authority of each Member State.

3. Pesticide Residues

The safety and quality of plant materials and finished products containing materials of plant origin have become a major concern for health authorities, pharmaceutical industries, and the public. Undesirable and/or undeclared substances have been present or have been purported to be present in plant materials or products containing materials of plant origin in many parts of the world. These substances have included pesticides, radioactive particles, microbes including pathogens, mycotoxins, and heavy metals.

The control on pesticides will not be applied on finished products as:

- the risk is very low due to the small unit size and also the dilution effect from other non-pesticide containing ingredients and excipients;

- pesticides are internationally regulated and there are global harmonisations on regulations currently in process; or

- currently no other economic bloc has regulations on pesticide residues in HS.

The onus is on the suppliers of raw materials and manufacturers of HS products to ensure that the raw materials supplied and used comply with the law.

The control of pesticide residues in raw materials should be covered under Good Agriculture Practice.

Emphasis is on the raw material supply and reliance is thus placed on horizontal legislation rather than vertical legislation.

Recommendations

Pesticide Residue limits should remain under review and if conditions

change in the future, for example, from post marketing surveillance data, a new assessment for the need of the limits for the finished product can be conducted, taking into consideration international guidelines or standards.[3]

Steps to be taken by each Member State on pesticide control:

1. to promote closer cooperation and liaison between the regulatory authority responsible for HS and other agencies or ministries responsible for the control of pesticides; and

2. to reinforce, during Good Manufacturing Practice training on the need for manufacturers to be responsible and not to accept raw materials that do not comply with applicable pesticide residue limits.

[3] Below are examples of international guidelines or standards on pesticide residues for reference:

(a) World Health Organization (WHO) has suggested that the limits for pesticide residues to be established following the recommendations of the Food and Agriculture Organization of United Nations and WHO for food and animal feed. Analytical methodology for the assessment of specific pesticides residues for medicinal plant materials are described in the WHO guidelines on quality control methods for medicinal plants.

(b) European Medicines Agency guideline on specifications; test procedures and acceptance criteria for herbal substances, herbal preparations, and herbal medicinal products or traditional herbal medicinal products (CPMP/QWP/2820/00 Rev 1). The guideline states that where possible, the limit of pesticide residues should be controlled at the herbal substance and/or herbal preparations (e.g. extraction) level.

(c) BP has established limits for pesticide residues in herbal drug (i.e. whole, fragmented, or cut plants, parts of plants, algae, fungi or lichen, in an unprocessed state, usually in dried form but sometimes fresh). The United States Pharmacopoeia also has established analytical methods and limits for pesticide residues in articles of botanical origin.

ANNEX IV

ASEAN GUIDELINES FOR MINIMISING THE RISK OF TRANSMISSION OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES IN HEALTH SUPPLEMENTS

Disclaimer:

This document is provided for information purpose only and subject to changes, pending the finalisation of the ASEAN Agreement on Regulatory Framework for Health Supplements. Official references to this document can only be made once the said Agreement has been finalised.

Purpose

To use an ASEAN harmonised approach to minimise the risk of Transmissible Spongiform Encephalopathy (TSE) in Health Supplements (HS).

Background

TSEs are a group of chronic degenerative diseases that is characterised by the accumulation of pathologically misfolded 'Prion' protein (PrP) that accumulates in the central nervous systems of infected individuals.

PrP^{TSE}, which has been identified as the pathogenic agent responsible for TSEs, is highly resistant to protease and heat denaturation treatments. The occurrence of TSE spans across different species and some forms of TSE include:

- Bovine Spongiform Encephalopathy (BSE) in cattle;
- scrapie in sheep and goats;
- Chronic Wasting Disease (CWD) in cervids (deers and elks);
- different forms of Creutzfeld-Jakob Disease (CJD) in humans; and
- Gerstmann-Sträussler-Scheinker Syndrome in humans.

The World Health Organization (WHO) had concluded a causal link

between Variant CJD (vCJD)[1] and BSE through epidemiological, biochemical, and transmission studies. Studies have shown that human exposure to BSE is mainly via BSE-contaminated food.

Although WHO epidemiological analysis does not indicate medicinal products, blood and blood derived products to have been sources of vCJD infection, it is prudent to introduce measures to minimise risk of TSE transmission to humans via the use of ruminant materials in HS products.

Guiding Principles

1. ASEAN Approach to Minimising TSE Risk in HS

ASEAN has adopted a risk management approach to minimise the transmission risk of TSE in HS that is consistent with the approach recommended by the WHO and the European Medicines Agency (EMA).

These guidelines should be read in conjunction with the latest publications by the WHO, EMA, and the World Organisation for Animal Health (Office International des Epizooties (OIE)) on TSE.

Some of the existing websites are provided below:

- WHO: <http://www.who.int/zoonoses/diseases/bse/en/>
- EMA: <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_ guideline/2009/09/WC500003700.pdf>
- OIE: <http://www.oie.int/eng/normes/mcode/en_sommaire.htm>

Although the recommendations of EMA are primarily for medicinal products, the approach is applicable to health products meant for human consumption, which would include HS.

These guidelines are intended to provide guidance to dealers (including importers and manufacturers) based on the principles mentioned in preceding sections**,** with the aim to reduce the transmission risk of TSE in the HS that are made available in

[1] Details on the terms TSE, PrP^{TSE}, and vCJD can be found in references no. 1, 4, and 5 listed in the References of this set of guidelines.

ASEAN. This document will be subject to regular update and review as the development in the scientific knowledge of the diseases and the effectiveness of the recommended measures evolve with time.

2. *ASEAN Guidelines to Manage the Risk of TSE in Bovine-Derived Materials*

2.1. Scope of Guidelines

2.1.1. This set of guidelines covers all substances of ruminant origin that are used in HS.

2.1.2. The use of ruminant as raw materials, in particular bovine and ovine materials, is common in HS. This would present a risk of TSE transmission to humans via the use of such products.

2.1.3. There is no known cure for TSE in humans but the risk of infection could be minimised through the use of certain precautionary measures on the use of ruminant derived materials in HS.

2.1.4. The range of materials covered in this set of guidelines would include the raw materials and all the substances in the product as well as those that it may be exposed to during the stages of processing. This would include the active substances, excipients and adjuvants, raw and starting materials, as well as reagents used in production.

2.2. Guidelines in Managing Raw Materials

2.2.1. Minimising transmission risk of TSE, particularly BSE, is based upon considerations of three closely related parameters.

2.2.1.1. Source animals and their geographical origin (section 2.2.2)

- Materials from countries of high BSE risk[2] would not be acceptable unless justified[3];

[2] Countries of high BSE risk would include those as identified by WHO to be high risk.

[3] A product from high or undetermined BSE risk countries would be allowed only if a

and

- Source from countries where the risk of BSE in cattle is absent or low would be considered most satisfactory.

2.2.1.2. Nature of animal material used (section 2.2.3)

- Animal-derived materials of high infectivity risk would not be allowed unless justified; and

- Animal-derived materials of lowest risk should be used.

2.2.1.3. Production process(es) (section 2.2.4)

- Use of a quality assurance system at manufacturing facilities to monitor the production process so as to ensure consistency and traceability;

- Considerations to minimise the risk of cross-contamination should be taken in manufacturing process, especially for raw materials; and

- Validation should be done when production processes are claimed to contribute significantly to the safety of a product.

2.2.2. Source animals and their geographical origin

2.2.2.1. Controlled sourcing is the most important criterion to enhance the safety of a product and to minimise the risk of TSE transmission.

2.2.2.2. The most satisfactory source of ruminant raw materials is from countries where BSE risk in cattle is absent or low.

2.2.2.3. Materials sourced from countries where BSE risk is high or undetermined would not be acceptable

valid European Directorate for the Quality of Medicines (EDQM) Certificate for that product is available.

unless justified.

2.2.2.4. Currently, the BSE risk status ascribed to countries[4] is based on the classification systems of the OIE (Appendix 1). Some factors that were considered in the risk assessment include:

- reports of BSE cases in the country;
- length of time of which a country has remained BSE free from the last occurrence of BSE in that country; and
- procedures or methods taken to reduce BSE transmission within the country etc.

2.2.3. Nature of animal material used

2.2.3.1. The tables in Appendix 2 depict the levels of infectivity in different organs and secretions of BSE-infected animals or in infected humans[5].

2.2.3.2. The WHO and EMA categorise tissues and body parts into 3 categories of infectivity based on research done.

- High Infectivity (Category IA)
- Lower Infectivity (Category IB)
- Tissues with No Detectable Infectivity or PrP^{TSE} (Category IC)

2.2.3.3. Some specific Ruminant Derived Material (RDM) may be considered to be of negligible infectivity when processed appropriately. Such RDM includes:

2.2.3.3.1. Gelatin or Collagen

[4] A reference list of countries classified based on the OIE system can be found at <http://www.oie.int/animal-health-in-the-world/official-disease-status/bse/list-of-bse-risk-status/>.

[5] Source from the guidance note published by WHO: “WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies” (updated 2010) <http://www.who.int/bloodproducts/tse/en/>.

- From skin – Acid or alkaline treatment is acceptable

- From bones – Bones should be taken from BSE-free countries or countries with low BSE-prevalence. In general, alkaline treatment is preferred over acid treatment alone.

- Skull and vertebral columns should not be used.

2.2.3.3.2. Tallow and tallow derivatives

- WHO and EMA consider such substances unlikely to be infectious because production processes are rigorous.

- May be allowed without restrictions when prepared by extraction and purification processes at high temperatures and GMP is controlled[6].

2.2.3.3.3. Milk and milk derivatives

- WHO and EMA considered such substances safe, provided:

  - milk is sourced from healthy ruminants fit for human consumption; and

  - potentially infectious ruminant-derived materials are not used in manufacturing process.

2.2.3.3.4. Measures to prevent and/or reduce cross contamination of materials in Categories IA, IB, and IC should be taken into consideration when raw materials are obtained.

2.2.4. Production Process(es)

[6] Refer to European Pharmacopoeia for manufacturing conditions.

2.2.4.1. Production processes should be designed to take into considerations all available information on processes that could reduce or inactivate infectivity or remove infectivity from starting materials, as this would augment safety provided by sourcing.

2.2.4.2. WHO and EMA recommend for quality assurance systems be in place to monitor the production process in the processing of RDM e.g. in form of GMP.

2.2.4.3. If claims to increase safety of product through manufacturing process are made, relevant information should be submitted to the regulatory authority for validation when required.

2.2.5. EDQM Certificate

2.2.5.1. The EDQM Certificate is useful as a source of reference for evidence of compliance, and therefore should be obtained if possible. However, national regulators can request for more information if required.

2.3. Regulatory Requirements

2.3.1. National regulators may require a declaration by the person placing the product in the market or the manufacturer, on compliance with the recommendations in this set of guidelines. Such documents to prove compliance should be held by the person who shall make these readily available to the regulatory agencies when required to do so.

2.3.2. A sample copy of the Declaration and a suggested checklist for self-assessment are shown in Appendices 3 and 4. (The checklist may form part of the requirements for submission to the regulatory agencies during pre-marketing approvals.)

References Used

1. *WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products*. World Health Organization. Geneva: World Health Organization. 2003.

2. *WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies.* World Health Organization. Geneva: World Health Organization. 2006.

3. *WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies.* World Health Organization. Geneva: World Health Organization. 2010.

4. *Report of a WHO Consultation on medicinal and other products in relation to human and animal Transmissible Spongiform Encephalopathies, with participation with the Office international des Epizooties (OIE)*. World Health Organization. Geneva: World Health Organization. 24-26 March 1997.

5. *Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev.2-Oct 03) adopted by the Committee for Proprietary Medicinal Products (CPMP) and by the Committee for Veterinary Medicinal products (CVMP)*. Official Journal of the European Union. 2004; C 24, 28.1.2004: 6.

6. *Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products ((EMA/410/01 rev.3) adopted by the Committee for Proprietary Medicinal Products (CPMP) and by the Committee for Veterinary Medicinal products (CVMP)*. Official Journal of the European Union. 5.3.2011; C 73/1.

7. *Guidance for Industry: The sourcing and processing of gelatin to reduce the potential risk posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated products for human use*. U.S. Department of Health and Human Services: Food and Drug Administration. 1997.

8. *TGA approach to minimising the risk of exposure Transmissible Spongiform Encephalopathies (TSE)*. Australian Government Department of Health: Therapeutic Goods Administration. April 2014.

9. *Minimising the risk of transmitting TSE via medicinal products*.

European Pharmacopoeia 5.0; Sec 5.2.8.

APPENDIX 1

BSE-RISK CLASSIFICATION SYSTEMS

OIE Classification System

Categories of BSE-risk of country:

1. Undetermined BSE risk

2. Controlled BSE risk

3. Negligible BSE risk

Reference website:

Terrestrial Animal Health Chapter 11.4. Code Bovine spongiform encephalopathy
<http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_bse.htm>

Status of BSE risk
<http://www.oie.int/animal-health-in-the-world/official-disease-status/bse/list-of-bse-risk-status/>

APPENDIX 2

LEVELS OF TISSUE INFECTIVITY[7]

The information in the tables is based exclusively upon observations of naturally occurring disease or primary experimental infection by the oral route (in ruminants) and does not include data on models using strains of TSE that have been adapted to experimental animals because passaged strain phenotypes can differ significantly and unpredictably from those of naturally occurring disease.

Because the detection of misfolded prion protein (PrP^{TSE}) broadly parallels infectivity titers in various tissues, PrP^{TSE} testing results are presented in parallel with bioassay data. Although a given tissue may be positive or negative in different varieties of TSE, the expert group considered a tissue to be potentially infectious even if a positive result occurred in only a single disease. The categorical assignment of tissues will almost certainly undergo further revision as new data accumulate from increasingly sensitive tests.

Category IA – High Infectivity Tissues: CNS tissues that attain a high titre of infectivity in the later stages of all TSEs and certain tissues that are anatomically associated with the CNS.

Category IB – Lower Infectivity Tissues: peripheral tissues that have tested positive for infectivity and/or PrP^{TSE} in at least one form of TSE.

Category IC – Tissues with No Detectable Infectivity or PrP^{TSE}: tissues that have been examined for infectivity and/or PrP^{TSE} with negative results.

Data entries are shown as follows:

+	Presence of infectivity or PrP^{TSE}
-	Absence of detectable infectivity or PrP^{TSE}
NT	Not tested
NA	Not applicable

[7] This Appendix was referenced from the "WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies" (updated 2010) <http://www.who.int/bloodproducts/tse/en/>

? Controversial or uncertain results

() Data limited to one or two tested specimens (human tissues)

[ ] Infectivity or PrP^{TSE} data based exclusively on bioassays in transgenic (Tg) mice overexpressing the PrP-encoding gene or PrP^{TSE} amplification methods

A word of caution is offered about tissues in the table of Category IB for which positive results are so far limited to either detection of PrP^{TSE} using amplification techniques (PMCA), or infectivity bioassays in Tg mice that overexpress PrP. The amounts of pathological protein or infectious agent detected by these exquisitely sensitive assays may well fall below the threshold of transmissibility for normal animals and humans.

A good example is illustrated in the studies of urine and feces from deer infected with CWD: bioassays using normal deer as recipient subjects were negative; subsequent bioassays performed in Tg mice were positive. A similar discordance was observed for BSE muscle inoculated into cattle and Tg mice. Until more evidence is compiled showing that positive results in experimental PMCA and Tg mouse assays equate to a risk of transmitting disease under natural conditions, it cannot be assumed that such results imply the existence of a substantial risk to the health of animals or humans.

Considering the succession of updated tables of infectivity of the past few years, and the fact that inflammation has been shown to result in PrP^{TSE} deposition in tissues that are not normally involved in TSE pathogenesis, it is evident that as testing continues, more tissues will find their way from the table of Category IC into the table of Category IB (but probably not from either the table of Category IC or IB into the table of Category IA). It is also evident that the data generated to date are far from complete, and that a great deal more work needs to be done if conclusions about the tissue distribution and significance of infectivity in a given TSE are to be based on direct measurements rather than by analogy to other forms of the disease.

Category IA – High Infectivity Tissues

Tissues	Humans				Cattle		Sheep & goats		Elk & deer	
	vCJD		Other TSEs		BSE		Scrapie		CWD	
	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}
Brain	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	NT	+
Retina	NT	+	+	+	+	NT	NT	+	NT	+
Optic nerve[2]	NT	+	NT	+	+	NT	NT	+	NT	+
Spinal ganglia	+	+	NT	+	+	+	+	+	NT	+
Trigeminal ganglia	+	+	NT	+	+	+	NT	+	NT	-
Pituitary gland[3]	NT	+	+	+	-	NT	+	+	NT	+
Dura mater[3]	NT	(+)	+	-	NT	NT	NT	NT	NT	NT

Category IB – Lower Infectivity Tissues

Tissues	Humans				Cattle		Sheep & goats		Elk & deer	
	vCJD		Other TSEs		BSE		Scrapie		CWD	
	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}
Peripheral Nervous system										
Peripheral nerves	+	+	(-)	+	[+]	+	+	+	NT	+
Autonomic ganglia[4]	NT	+	NT	(-)	NT	+	NT	+	NT	+
Lymphoreticular tissues										
Spleen	+	+	+	+	-	-	+	+	NT	+
Lymph nodes	+	+	+	-	-	-	+	+	NT	+
Tonsil	+	+	NT	-	+	-	+	+	NT	+
Nictitating membrane	NA	NA	NA	NA	+	-	[+]	+	NT	+
Thymus	NT	+	NT	-	-	NT	+	+	NT	-
Alimentary tract[5]										
Esophagus	NT	-	NT	-	-	NT	[+]	+	NT	+
Fore-stomach[6] (ruminants only)	NA	NA	NA	NA	-	NT	[+]	+	NT	+
Stomach/ abomasum	NT	-	NT	-	-	NT	[+]	+	NT	+
Duodenum	NT	-	NT	-	-	-	[+]	+	NT	+
Jejunum[7]	NT	+	NT	-	-	+	[+]	+	NT	NT
Ileum[7]	NT	+	NT	-	+	+	+	+	NT	+
Appendix	(-)	+	NT	-	NA	NA	NA	NA	NA	NA
Colon/caecum[7]	NT	+	NT	-	-	-	+	+	NT	+
Rectum	[+]	+	NT	NT	NT	NT	NT	+	NT	+
Reproductive tissues										
Placenta[8]	NT	-	(+)	-	-	NT	+	+	NT	-
Ovary[3]	NT	- (+)	NT	-	-	NT	-	-	NT	-
Uterus[3]	NT	- (+)	NT	-	-	NT	-	-	NT	-
Other tissues										
Mammary gland/udder[9]	NT	-	NT	-	-	NT	-	+	NT	NT
Skin[3],[10]	NT	- (+)	NT	-	-	NT	-	+	[+]	[+]
Adipose tissue	NT	-	(-)	-	-	NT	NT	NT	[+]	NT
Heart/pericardium	NT	-	-	-	-	NT	-	NT	NT	+
Lung	NT	-	+	-	-	NT	-	-	NT	+
Liver[3]	NT	- (+)	+	-	-	NT	+	-	NT	-
Kidney[3,11]	NT	- (+)	+	-	-	-	[+]	+	NT	+
Adrenal	NT	+	-	-	[+]	+	+	-	NT	+
Pancreas[3]	NT	- (+)	NT	-	-	NT	+	NT	NT	+
Bone marrow[12]	-	-	(-)	-	(+)	NT	+	NT	NT	-
Skeletal muscle[13]	NT	+	(-)	+	[+]	NT	[+]	+	[+]	-
Tongue[14]	NT	-	NT	-	-	NT	[+]	+	NT	-
Blood vessels	NT	+	NT	+	-	NT	NT	+	NT	-
Nasal mucosa[15]	NT	NT	NT	+	-	NT	+	+	NT	+
Salivary gland	NT	-	NT	-	-	NT	+	NT	-	-
Cornea[16]	NT	-	+	-	NT	NT	NT	NT	NT	NT
Body fluids, secretions and excretions										
CSF	-	-	+	-	-	NT	+	-	NT	NT
Blood[17]	+	?	-	?	-	?	+	?	+	?
Saliva	NT	-	-	NT	NT	NT	-	NT	+	[-]
Milk[18]	NT	NT	(-)	NT	-	-	+	[+]	NT	NT
Urine[19]	NT	-	-	-	-	NT	-	-	- [+]	[+]
Feces[19]	NT	NT	-	NT	-	NT	-	NT	- [+]	NT

Category IC – Tissues with No Detected Infectivity or PrP^{TSE}

Tissues	Humans				Cattle		Sheep & goats		Elk & deer	
	vCJD		Other TSEs		BSE		Scrapie		CWD	
	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}
Reproductive tissues										
Testis	NT	-	(-)	-	-	NT	-	-	NT	-
Prostate/Epididymis/ Seminal vesicle	NT	-	(-)	-	-	NT	-	-	NT	-
Semen	NT	-	(-)	-	-	NT	-	-	NT	NT
Placenta fluids	NT	NT	(-)	(-)	-	NT	NT	NT	NT	NT
Fetus[20]	NT	NT	NT	NT	-	NT	-	-	NT	(-)
Embryos[20]	NT	NT	NT	NT	-	NT	?	NT	NT	NT
Musculo-skeletal tissues										
Bone	NT	-	NT	-	-	NT	NT	NT	NT	NT
Tendon	NT	-	NT	-	-	NT	NT	NT	NT	NT
Other tissues										
Gingival tissue	NT	-	-	-	NT	NT	NT	NT	NT	NT
Dental pulp	NT	-	NT	-	NT	NT	NT	NT	NT	NT
Trachea	NT	-	NT	-	-	NT	NT	NT	NT	-
Thyroid gland	NT	-	(-)	-	NT	NT	-	NT	NT	-
Body fluids, secretions and excretions										
Colostrum[21]	NT	NT	(-)	NT	(-)	-	(?)	NT	NT	NT
Cord blood[21]	NT	NT	(-)	NT	-	NT	NT	NT	NT	NT
Sweat	NT	NT	-	NT	NT	NT	NT	NT	NT	NT
Tears	NT	NT	-	NT	NT	NT	NT	NT	NT	NT
Nasal mucus	NT	-	-	NT	NT	NT	NT	NT	NT	NT
Bile	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT

1. Infectivity bioassays of human tissues have been conducted in either primates or mice (or both); bioassays of cattle tissues have been conducted in either cattle or mice (or both); and most bioassays of sheep and/or goat tissues have been conducted only in mice. In regard to sheep and goats, not all results are consistent for both species; for example, two goats (but no sheep) have contracted BSE naturally [Eurosurveillance, 2005, Jeffrey et al., 2006]. Similarly, most of the results described for CWD were derived from studies in deer, and findings may not be identical in elk or other cervids.

2. In experimental models of TSE, the optic nerve has been shown to be a route of neuroinvasion and contains high titers of infectivity.

3. No experimental data about infectivity in pituitary gland or dura mater in humans with all forms of human TSE have been reported, but cadaveric dura mater patches, and growth hormone derived from cadaveric pituitaries have transmitted disease to hundreds of people and therefore must be included in the category of high-risk tissues. PrP^{TSE} was detected by immunoblot in the dura mater of a vCJD patient who died in the US after an unusually long incubation period (see also table IB for other positive tissues: skin, kidney, liver, pancreas, ovary, and uterus)

[Notari et al., 2010]. It must be mentioned that earlier studies of numerous cases examined in the UK reported all of these tissues to be negative [Ironside et al., 2002; Head et al., 2004].

4. In cattle, PrP^{TSE} is reported to be inconsistently present in the enteric plexus in the distal ileum, but immunohistochemical examination of tissues from a single 'fallen stock' case of BSE in Japan suggested (albeit equivocally) involvement of myenteric plexuses throughout the small and large intestine [Kimura and Haritani, 2008].

5. In vCJD, PrP^{TSE} is limited to gut-associated lymphoid and nervous tissue (mucosa, muscle, and serosa are negative).

6. Ruminant forestomachs (reticulum, rumen, and omasum) are widely consumed, as is the true stomach (abomasum). The abomasum of cattle (and sometimes sheep) is also a source of rennet.

7. When a large BSE oral dose was used to infect cattle experimentally, infectivity was detected in the jejunum and the ileo-caecum junction in Tg mice overexpressing PrP [courtesy of Dr. M Groschup]. PrP^{TSE} was detected at low incidence in lymphoid tissue of ileum [Terry et al., 2003] and has been detected at an even lower frequency in jejunal lymphoid tissue of cattle similarly infected by the oral route [EFSA, 2009].

8. A single report of transmission of sporadic CJD infectivity from human placenta has never been confirmed and is considered improbable.

9. PrP^{TSE} has been detected in scrapie-infected sheep with chronic mastitis, but not from infected sheep without mastitis [Ligios et al., 2005].

10. Studies in hamsters orally infected with scrapie revealed that PrP^{TSE} deposition in skin was primarily located within small nerve fibers. Also, apical skin 'velvet' from the antlers of CWD-infected deer are reported to contain PrP^{TSE} and infectivity [Angers et al., 2009].

11. PrP^{TSE} detected by immunocytochemistry in the renal pelvis of scrapie-infected sheep [Siso et al., 2006] and in lymphoid follicles within connective tissue adjacent to the renal pelvis in CWD-infected mule deer [Fox et al., 2006].

12. A single positive marrow in multiple transmission attempts from cattle orally dosed with BSE-infected brain [Wells et al., 1999; Wells et al., 2005; Sohn et al., 2009].

13. Muscle homogenates have not transmitted disease to primates from humans with sporadic CJD, or to cattle from cattle with BSE. However, intracerebral inoculation of a semitendinosus muscle homogenate (including nervous and lymphatic elements) from a single cow with clinical BSE has transmitted disease to transgenic mice that overexpress PrP at a rate indicative of trace levels of infectivity [Buschmann and Groschup, 2005]. Also, recent published and unpublished studies have reported the presence of PrP^{TSE} in skeletal muscle in experimental rodent models of scrapie and vCJD [Beekes et al., 2005] in experimental and natural scrapie infections of sheep and goats [Andreoletti et al., 2004], in sheep orally dosed with BSE [Andreoletti, unpublished data], and in humans with sporadic, iatrogenic, and variant forms of CJD [Glatzel et al., 2003; Kovacs et al., 2004; Peden et al., 2006]. Bioassays of muscle in transgenic mice expressing cervid PrP have documented infectivity in CWD-infected mule deer [Angers et al, 2006], and experiments are underway to determine whether detectable PrP^{TSE} in other forms of TSE is also associated with infectivity.

14. In cattle, bioassay of infectivity in the tongue was negative, but the presence of infectivity in palatine tonsil has raised concern about possible infectivity in lingual tonsillar tissue at the base of the tongue that may not be removed at slaughter [Wells et al., 2005; EFSA, 2008]. In sheep naturally infected with scrapie, 7 of 10 animals had detectable PrP^{TSE} in the tongue [Casalone et al., 2005; Corona et al., 2006].

15. Limited chiefly to regions involved in olfactory sensory reception.

16. Because only one case of iatrogenic CJD has been certainly attributed to a corneal transplant among hundreds of thousands of recipients (one additional case is considered probable and another case only possible), cornea has been categorised as a lower-risk tissue; other anterior chamber tissues (lens, aqueous humor, iris, conjunctiva) have been tested with a negative result both in vCJD and other human TSEs, and there is no epidemiological evidence that they have been associated with iatrogenic disease transmission.

17. A wealth of data from studies of blood infectivity in experimental rodent models of TSE have been extended by recent studies

documenting infectivity in the blood of sheep with naturally occurring scrapie and in sheep transfused with blood from BSE-infected cattle [Houston et al., 2008]; of deer with naturally occurring CWD [Mathiason et al., 2006]; and (from epidemiological observations) in the red cell fraction (which includes significant amounts of both plasma and leukocytes) of four blood donors in the pre-clinical phase of vCJD infections [reviewed in Brown, 2006; Hewitt et al., 2006]. Plasma Factor VIII administration has also been potentially implicated in a subclinical case of vCJD in a hemophilia patient [Peden et al., 2010]. Blood has not been shown to transmit disease from humans with any form of 'classical' TSE [Dorsey et al., 2009], or from cattle with BSE (including fetal calf blood). A number of laboratories using new, highly sensitive methods to detect PrP^{TSE} are reporting success in a variety of animal and human TSEs. However, several have experienced difficulty obtaining reproducible results in plasma, and it is not yet clear that positive results imply a potential for disease transmissibility, either because of false positives, or of 'true' positives that are due to sub-transmissible concentrations of PrP^{TSE}. Because of these considerations (and the fact that no data are yet available on blinded testing of specimens from naturally infected humans or animals), the expert group felt that it was still too early to evaluate the validity of these tests with sufficient confidence to permit either a negative or positive conclusion.

18. Evidence that infectivity is not present in milk from BSE-infected bovines includes temporo-spatial epidemiologic observations failing to detect maternal transmission to calves suckled for long periods; clinical observations of over a hundred calves suckled by infected cows that have not developed BSE; and experimental observations that milk from infected cows reared to an age exceeding the minimum incubation period has not transmitted disease when administered intracerebrally or orally to mice [Middleton and Barlow, 1993; Taylor et al., 1995]. Also, PrP^{TSE} has not been detected in milk from cattle incubating BSE following experimental oral challenge [SEAC, 2005]. However, low levels (µg to ng/L) of normal PrP have been detected in milk from both animals and humans [Franscini et al., 2006]. PrP^{TSE} has been detected in the mammary glands of scrapie-infected sheep with chronic mastitis [Ligios et al., 2005], and very recently it has been reported that milk (which in some cases also contained colostrum) from scrapie-infected sheep transmitted disease to healthy animals [Konold et al., 2008; Lacroux et. al., 2008].

19. A mixed inoculum of urine and feces from naturally infected CWD

deer did not transmit disease during an 18-month observation period after inoculation of healthy deer with a heterozygous (96 G/S) *PRNP* genotype [Mathiason et al., 2006]. However, recent bioassays in Tg mice have transmitted disease from both urine [Haley et al., 2009] and feces [Tamgüney et al., 2009]. In addition, mice with lymphocytic nephritis that were experimentally infected with scrapie shed both PrP^{TSE} and infectivity in urine, when bioassayed in Tg mice [Seeger et al., 2005]. Very low levels of infectivity have also been detected in the urine (and histologically normal kidneys) of hamsters experimentally infected with scrapie [Gregori and Rohwer, 2007; Gonzalez-Romero et al., 2008]. Finally, in an experimental scrapie-hamster model, oral dosing resulted in infectious feces when bioassayed in Tg mice overexpressing PrP [Safar et al., 2008].

20. Embryos from BSE-affected cattle have not transmitted disease to mice, but no infectivity measurements have been made on fetal calf tissues other than blood (negative mouse bioassay) [Fraser and Foster, 1994]. Calves born of dams that received embryos from BSE-affected cattle have survived for observations periods of up to seven years, and examination of the brains of both the unaffected dams and their offspring revealed no spongiform encephalopathy or PrP^{TSE} [Wrathall et al., 2002].

21. Early reports of transmission of sporadic CJD infectivity from human cord blood and colostrum have never been confirmed and are considered improbable. A bioassay from a cow with BSE in transgenic mice overexpressing bovine PrP gave a negative result [Buschmann and Groschup, 2005], and PrP^{TSE} has not been detected in colostrum from cattle incubating BSE following experimental oral challenge [SEAC, 2005].

APPENDIX 3

SAMPLE OF TSE DECLARATION FORM

TSE Submission Form
Brand & Product Name:
Kit Name:

Ingredient		Quantity	Animal Species	Tissue Used	Infectivity Category	Country of Origin	Reasons for Using

I hereby undertake that the abovementioned product imported / manufactured (delete where appropriate) by my company complies with the ASEAN Guidelines for Minimising the Risk of Transmission of Transmissible Spongiform Encephalopathies in Health Supplements, and I hold evidence to demonstrate that the product is prepared:

- from ruminant-derived materials without any risk of exposure to TSE, and the relevant authority in the country of origin has endorsed that the materials are sourced from TSE-free herds;

- by manufacturing process with adequate measures taken to prevent cross-contamination between different tissues from different categories of infectivity; and

- by a manufacturing process that has shown experimentally to minimise the TSE transmissible agent, if the above product contains tallow and/or gelatin derived from ruminant-derived materials (including those for making capsule shells).

I shall retain all the necessary evidence at all times and would supply the evidence to the regulatory authority if required to do so. I shall report any changes in the TSE status of the ruminant-derived materials of the above product to the regulatory authority as soon as possible.

I hereby declare that the information on this form is current and correct.

I undertake the responsibility to check and ensure compliance to the latest ASEAN Guidelines for Minimising the Risk of Transmission of Transmissible Spongiform Encephalopathies in Health Supplements.

Name: …… Designation: ……

Company Name: ……

Tel: ……..…… Fax: ……..……....

Manufacturer Name: ……..…….....Date: ……..……..……..

Company Stamp: …… Signature: ……..……

APPENDIX 4

SAMPLE OF CHECKLIST FOR SELF-ASSESSMENT

Check if Available	Document	Enclosure Number
	1. Source of Animal	
□	Updated notification of BSE cases in country where each animal material is sourced, where applicable	
□	Justification for using animal materials from BSE-positive countries (if applicable)	
□	Documentary proof issued by health authorities in source country to show that the raw materials used are sourced from TSE-free herds	
	2. Nature of Animal Tissue Used in Manufacturing	
□	Detailed information on the nature and quantity of each animal-derived material: • Used in the manufacturing process (whether or not this is present in the final products) • Present in the final product formulation	
□	Letter of confirmation or assurance from the raw materials supplier and/or manufacturer that: • Considerations to reduce cross contamination between different tissues have been taken when obtaining the raw materials	
	3. Manufacturing Process(es)	
□	Letter of confirmation or assurance from the manufacturer that: • Considerations to TSE inactivation or reduction methods have been taken when developing manufacturing methods • If claims have been made to inactivate TSE agents during manufacturing process, then the necessary documentary proof are held in possession and will be made available to the regulatory authority if needed • Quality assurance system is taken into consideration in developing and implementing the manufacturing processes	
	4. Other Documentation	
□	Company's assessment report for risk of TSE	
□	Certificate of Suitability issued by the European Directorate for the Quality of Medicines	

ANNEX V

ASEAN GUIDELINES ON STABILITY STUDY AND SHELF-LIFE OF HEALTH SUPPLEMENTS

Disclaimer:

This document is provided for information purpose only and subject to changes, pending the finalisation of the ASEAN Agreement on Regulatory Framework for Health Supplements. Official references to this document can only be made once the said Agreement has been finalised.

Introduction

Stability is an essential factor of quality in Health Supplements (HS). It is determined by a series of tests conducted, namely to ensure maintenance of the specifications of the finished product when packed in its specified packaging material and stored in the established storage condition within the determined shelf-life.

The aim of conducting a stability study on HS is to determine its shelf-life as a finished product in its container closure system under the recommended storage condition, within which the finished product still meets its established physical, microbiological, and/or chemical specifications.

Objective

These guidelines are intended to provide recommendations on the core stability study required for products. Nevertheless, it leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the products being evaluated.

Design

1. General

The design of a stability study for the product should be based on the nature of the product. It should take into account the following:

- selection of batches;
- specifications or testing parameters;
- testing frequency;
- storage condition; and
- container closure system.

2. Selection of Batches

Stability data should be provided for batches of the same formulation and dosage form in the container closure system intended for marketing.

- Stability data from at least two batches would be required, derived either from pilot scale, primary scale, production scale or their combination.
- The manufacturing process of batches used in stability studies should simulate that of production batches and should be of the same quality as well as meet the same specification as those batches intended for marketing.
- Stability studies should be performed on individual strengths of the product and/or type of container closure system in which the finished product is packed unless bracketing or matrixing is applied as in Appendix 1.

3. Specification or Testing Parameters

A stability study should cover the testing of the physical, chemical, and microbiological properties of a finished product that are susceptible to change during storage and are likely to influence quality when changed.

The list of testing parameters is presented as a guide for the types of tests to be included in a stability study as in Appendix 2.

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.

For a product containing ingredients without known marker(s),

physical parameters may be used as surrogate indicators during storage, when the use of such parameters can be justified. The physical parameters of the finished product can be checked by at least one of the following test methods:

(a) gross organoleptic analysis (examination by general impression); or

(b) other scientifically valid criteria.

For a combination product containing multiple active ingredients, although it may not be necessary to assay all the active ingredients, it may be appropriate to assay one, and in some cases, more than one active ingredient, or a surrogate marker that is known to be susceptible to change during storage and is likely to influence the quality of the combination product. A valid justification shall be submitted.

4. Testing Frequency

For accelerated and real time stability studies, frequency of testing should be sufficient to establish the stability profile of the finished product. At the accelerated storage condition, a minimum of three time points, including the initial and final time points, for example, 0, 3, and 6 months for a 6-month study, is recommended.

The frequency of testing at real time storage conditions should normally be every three months over the first year, every six months over the second year and annually thereafter through the proposed shelf-life. A typical testing frequency is as shown in Table 1.

Table 1. A Typical Testing Frequency

Storage Condition	Testing Frequency
Real Time	0, 3, 6, 9, 12, 18, 24 months and annually thereafter through the proposed shelf-life
Accelerated	0, 3, and 6 months

Reduced designs, i.e., matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied, if justified, as in Appendix 1.

Where an expectation (based on development experience) exists that outcomes from accelerated studies are likely to approach significant change criteria, i.e. parameters tested are out of the specifications set, it is advised an increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

If the “significant change” occurs within the first three months of testing at the accelerated storage condition, a justification should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipping or handling. This justification can be supported, if appropriate, by further testing on a single batch of the product for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through the remaining months when a “significant change” has occurred within the first three months, and as such the shelf-life shall be based on real time data.

If “significant change” occurs between three and six months of testing at the accelerated storage condition, shelf-life shall be based on real time data.

5. Storage Condition

In general, HS as a finished product should be evaluated under its storage conditions (with appropriate tolerances) that test its thermal stability under recommended storage conditions and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use, for example, after reconstitution or dilution as recommended in the labelling.

Specific recommended temperature and relative humidity conditions for storage applied to stability studies and types of container closure system are based on the nature of the products and the type of primary container used, in accordance with recommended storage condition on product label. Common storage conditions are shown in Table 2.

Table 2. Common Storage Conditions

Type of Container Closure System or Study	Storage Condition
Products in primary containers permeable to water vapour	30°C ± 2°C/75% RH ± 5% RH
Products in primary containers impermeable to water vapour	30°C ± 2°C
Accelerated studies	40°C ± 2°C/75% RH ± 5% RH

If submitted data is based on conditions that are less stressful (e.g. 30°C/65% RH) than those required, the data should be accompanied by appropriate complementary data which will permit to conduct a proper scientific evaluation. Factors to be taken into consideration will include:

- whether any instability is seen;
- whether data have also been provided under accelerated conditions; and
- the type of container closure system.

Other storage conditions are allowable, if justified. Examples would include:

- Heat sensitive products which should be stored under lower temperature condition which will eventually become the designated long term storage temperature.
    - Products containing less stable active ingredients and formulations not suitable for storage at elevated temperature will need real time stability studies.
    - Where a lower temperature condition is used, the six month accelerated testing should be carried out at a temperature at least 15°C above the expected actual storage temperature (together with appropriate relative humidity conditions for that temperature). For example, for a product to be stored long term under refrigerated conditions, accelerated testing should be conducted at 25ºC ±

2ºC, 60% RH ± 5% RH. The designated real time testing conditions will be reflected in the labelling and shelf-life (expiration date). Typical storage conditions recommended for stability studies on products intended for storage in a refrigerator as shown in Table 3.

Table 3. Typical Storage Conditions Recommended for Products Intended in a Refrigerator

Study	Storage Condition
Real Time	5°C ± 3°C
Accelerated	25°C ± 2°C/60% RH ± 5% RH

- Products which change physically or even chemically at lower storage temperature conditions e.g., suspensions or emulsions.

Data from the accelerated stability studies can be used to evaluate the effect of short-term excursions outside the label storage conditions such as during shipping. The data from accelerated study and ongoing real time stability study can be used to justify an interim extrapolated shelf-life. However, the actual shelf-life should be based ultimately on the real time stability data at the recommended storage conditions.

6. Container Closure System

Stability testing should be conducted on the product packaged in the primary container closure system proposed for marketing including, as appropriate, any secondary packaging.

Finished products packed in moisture-impermeable primary containers are not required to be tested under high humidity conditions. Generally considered moisture-impermeable containers include aluminum or aluminum blisters, High Density Polyethylene (HDPE) or glass bottles fitted with metal or HDPE closures.

When using moisture-permeable containers for packaging, due consideration should be given to the stability of the contents under high humidity conditions. Moisture may have an undesirable effect on chemical and physical stability of a finished product.

The issue of the different permeability of various packaging materials should be addressed e.g. the effect of high humidity on solid dosage forms packaged in containers permeable to moisture should be supported by data and an indication, like “keep in a dry place or protect from moisture” should be added to the label. Examples of moisture permeable containers include polyvinyl chloride blisters, low density polyethylene (LDPE) bottles, glass or HDPE bottles when fitted with polypropylene closures.

7. Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, and microbiological tests. Any evaluation should consider not only the assay, but also other appropriate test attributes. A recommended presentation of the summary table of stability results appears as in Appendix 3.

8. Labelling

The storage conditions that include temperature, light, and humidity indicated on the label should be based on the stability evaluation of the product. General precautionary statements, such as “Protect from light” and/or “Store in a dry place”, may be included, but should not be used to conceal stability problems of the finished product. Specific instruction on storage condition should be provided. Terms such as “ambient conditions” or “room temperature” should be avoided.

Glossary

For the purposes of this Annex:

(a) **assay** means a test procedure for measuring or determining the quantity of active ingredient or marker in a finished product;

(b) **batch** means a quantity of the finished product produced during a given cycle of manufacture and from a specific formulation order, that is uniform in character and quality (the essence of a manufacturing batch is its homogeneity);

(c) **container closure system** means the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if latter are intended to provide additional protection to the finished product. A packaging system is equivalent to a container closure system;

(d) **disintegration** means the rate that tablets or capsules disintegrate within the prescribed time when placed in a liquid medium and under the experimental conditions as prescribed in references such as official pharmacopoeia;

(e) **dissolution** means the quantity of active substance dissolved in a specified time, expressed as a percentage of the content stated on the product label;

(f) **expiry date** means the date placed on the container label of a finished product designating the time prior to which a batch of the product is expected to remain within the approved shelf-life specification if stored under defined conditions;

(g) **hardness or friability** means the resistance to crushing of tablets, measured by the force needed to disrupt it by crushing;

(h) **impermeable containers** means containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes, sealed glass ampoules for solutions;

(i) **microbial content** means the amount of microorganisms including bacteria, yeast, and mold present in the product;

(j) **pH value of an aqueous solution** means a number describing its acidity or alkalinity. A pH is the negative logarithm (base 10) of the concentration of hydrogen ions (equivalent per liter). The pH value

of a neutral solution is 7. An acidic solution has a pH less than 7, while a basic solution has a pH greater than 7, up to 14;

(k) **pilot scale batch** means a batch of substances or product manufactured by procedure fully representative of and simulating that to be applied to a full production scale batch. A pilot scale is generally, at minimum, one tenth that of a full production scale;

(l) **primary scale batch** means a batch of product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. A primary scale may comprise ten to one hundred percent of a full production scale;

(m) **production scale batch** means a batch of product manufactured at production scale by using production equipment in a production facility as specified in the application;

(n) **shelf-life** (also referred to as expiration date period) means the time period during which a product is expected to remain within the approved specification provided it is stored under the condition defined on the container label;

(o) **specification** means a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described (it establishes the set of criteria to which a substance, product, or material at other stages of its manufacture should conform to be considered acceptable for its intended use). "Conformance to specification" means that the substance and product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval;

(p) **stability studies** means real time and accelerated studies or testing undertaken on primary batches according to a prescribed stability protocol to establish or confirm the re-test period of a substance or shelf-life of a finished product.

- Accelerated Stability Studies

  Studies designed to increase the rate of chemical degradation or physical change of a finished product by using exaggerated storage conditions as part of the formal stability studies. (Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects

at non-accelerated condition and to evaluate the effect of short term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes; see also Stability and related terms).

- Real Time Stability Studies

  Stability studies under the recommended storage condition for the re-test period or shelf-life proposed (or approved) for labelling.

(q) **stability study protocol** means a document describing rationale, goals, methodology, and statistical methods of the stability study which specifies the terms and conditions under which the stability study must be conducted and managed;

(r) **storage condition** means condition for intended storage of a finished product defined on the container label based on the stability study;

(s) **viscosity** means the tendency of a fluid to resist flowing because of molecular attraction (cohesion). It is a property of liquid that is closely related to its resistance to flow; and

(t) **water content** means a measure of free water content of product when surrounded by air at a specified relative humidity and temperature.

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APPENDIX 1

REDUCED DESIGN (BRACKETING AND MATRIXING)

A full study design is one in which samples for every combination of all design factors are tested at all time points whereas a reduced design is one in which samples for every factor combination are not all tested at all time points. A reduced design can be a suitable alternative to a full design when multiple design factors are involved.

Any reduced design should have the ability to adequately predict the shelf-life. Before a reduced design is considered, certain assumptions should be assessed and justified. The potential risk when establishing a shorter shelf-life using a reduced design should be considered due to the reduced amount of data collected compared to data derived from a full design.

During the course of a reduced design study, a change to full testing or to a less reduced design can be considered if justification is provided and the principles of full designs and reduced design studies are followed. However, proper adjustments should be made to the statistical analysis, where applicable, to account for the increase in sample size as a result of the change. Once the design is changed, full testing or less reduced testing should be carried out through the remaining time points of the stability study.

Bracketing

Bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors, for example, strength, container size and/or fill, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

Design Example

An example of a bracketing design is given in Table 1. This example is based on a product available in three strengths and three container sizes. In this example, it demonstrated that the 15 ml and 500 ml high-density polyethylene container sizes truly represent the extremes. The batches for each selected combination should be tested at each time point as in a full design.

Table 1. Example of a Bracketing Design

Strength		50 mg			75 mg			100 mg		
Batch		1	2	3	1	2	3	1	2	3
Container Size	15 ml	T	T	T				T	T	T
	100 ml									
	500 ml	T	T	T				T	T	T

Key: T = Sample tested

Matrixing

Matrixing is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations would be tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same finished product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and possibly, in some cases, different container closure systems.

When a secondary packaging system contributes to the stability of the finished product, matrixing can be performed across the packaging systems. Each storage condition should be treated separately under its own matrixing design. Matrixing should not be performed across test attributes. However, alternative matrixing designs for different test attributes can be applied if justified.

Design Examples

Examples of matrixing designs on time points for a product in two strengths (Sl and S2) are shown in Table 2. The terms "one-half reduction" and "one-third reduction" refer to the reduction strategy initially applied to the full study design. For example, a "one-half reduction" initially eliminates one in every two time points from the full study design and a "one-third reduction" initially removes one in every three. In the examples shown in Table 2, the reductions are less than one-third due to the inclusion of full testing of all factor combinations at some time points. These examples include full testing at the initial, final, and 12-month time points as shown in Table 2.

Table 2. Example of Matrixing Design on Time Points for a Product with Strengths "One-Half Reduction"

Time point (months)			0	3	6	9	12	18	24	36
Strength	S1Sl	Batch1	T	T		T	T		T	T
		Batch2	T		T		T	T		T
	S2S2	Batch1	T		T		T		T	T
		Batch2	T	T		T	T	T		T
				At least 6 out of 12 time points				At least 4 out of 8 time points		

Examples of Matrixing Designs on Time Points for a Product with Strengths "One-Third Reduction"

Time point (months)			0	3	6	9	12	18	24	36
Strength	S1Sl	Batch1	T	T		T	T	T	T	T
		Batch2	T	T	T		T	T		T
	S2S2	Batch1	T		T	T	T	T	T	T
		Batch2	T	T		T	T		T	T
				At least 8 out of 12 time points				At least 6 out of 8 time points		

Time point (months)			0	3	6	9	12	18	24	36
Strength	S1SI	Batch1	T	T		T	T	T	T	T
		Batch2	T	T	T		T	T		T
	S2S2	Batch1	T		T	T	T	T		T
		Batch2	T	T		T	T		T	T
	S3S3	Batch1	T		T	T	T	T	T	T
		Batch2	T	T		T	T		T	T

At least 12 out of 18 time points

At least 8 out of 12 time points

Key: T = Sample tested

APPENDIX 2

TABULATED LIST OF STABILITY INDICATING PARAMETERS FOR HEALTH SUPPLEMENT

The tabulated list of parameters for each dosage form is presented as a guide for the following types of tests to be included in a stability study.

HS Dosage Form

Testing Parameters / HS Dosage Form	Organoleptic Characteristics	Assay	Hardness or Friability	Dissolution or Disintegration	Water Content	Viscosity	pH	Microbial Content	Granules or Particle Size	Resuspendability
Oral powder	√	√			√			√		
Hard capsule	√	√		√	√			√		
Soft capsule	√	√		√				√		
Coated and Uncoated Tablet	√	√	√	√	√			√		
Coated and Uncoated Pill or Pellet	√	√		√	√			√		
Suspension	√	√				√	√	√	√	√
Solution	√	√				√	√	√		
Emulsion	√	√				√	√	√		
Granules	√	√			√			√	√	

APPENDIX 3

RECOMMENDED PRESENTATION OF THE SUMMARY TABLE OF STABILITY RESULTS

Product Name	:.....	Storage Conditions	: .....
Dosage Form	:.....	Batch No.	: .....
Strength	:.....	Manufacturing Date	: .....
Container	:.....	Date of Report	: .....
Pack Size	:.....	Period of the Study	: .....

Testing Parameters (as applicable)	Permissible Level or Acceptance Criteria	Testing Frequency (Months)							
		0	3	6	9	12	18	24	
Organoleptic Characteristics									
Assay									
Hardness or Friability									
Dissolution or Disintegration									
Water Content									
Viscosity									
pH									
Microbial Content									
Granules or Particle Size Variation									
Resuspendability									

Conclusion:

Prepared by Checked by Approved by

ANNEX VI

ASEAN GUIDING PRINCIPLES ON SAFETY SUBSTANTIATION OF HEALTH SUPPLEMENTS

Disclaimer:

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Introduction

Natural resources (plants, animals, or natural minerals) or their synthetic equivalents are widely used in the formulation of Health Supplements (HS).

Most ingredients might be considered as safe, considering the experience or history of use of HS products. When an ingredient is well known for a specific use, the assessment may be limited to published data. However, under certain conditions, additional data will be required to prove the safety of the product, e.g. for a new ingredient or a new combination.

Objectives

This document aims to provide guiding principles for safety substantiation of HS.

Guiding Principles

Data to substantiate the safety of the following products shall be required:

(a) Products with new ingredient(s).

(b) Products with ingredient(s) derived from new method(s) of purification, extraction, or manufacturing.

(c) Existing products with new combination, new dosage, new delivery system or use in special, or new target population

(e.g. pregnant, lactating women, children).

(d) Existing products with safety concern. Safety concern may be newly emerging or established, and in some cases may need additional information to support safe usage in HS.

However, safety substantiation may not be necessary, for the following products, unless required by the regulatory authority:

- products that do not fall under items (a), (b), (c), or (d) mentioned above;
- products containing ingredient(s) with lower dosage than the existing ones; and
- HS containing ingredients which have been consumed as food or food constituent within the highest observed safe intake.

Safety substantiation shall be based on finished product or ingredient(s), with justification as required by the regulatory authority (e.g. rationale of combination).

The safety data that will be required to substantiate the safety of a product should be relevant, and commensurate with the nature or character of the ingredient or product in line with the intended use.

The safety information should include the following:

History of use

Ingredients with a known history of human consumption evidences (e.g. documented history of use, authoritative reference texts) may be considered for safety substantiation. In the case when the anticipated intake of this ingredient is significantly higher than the estimated historical intake, or for which the historical intake cannot be assessed, additional safety data may be required; and/or

Scientific evidence on safety

Safety data, including toxicity data, could be derived from animal and/or human studies using internationally accepted methodologies such as World Health Organization or Organisation for Economic Co-operation and Development guidelines. Acute, sub-chronic, and/or chronic toxicity data may be required, however expected duration of product usage may

determine the types of toxicity study. Other toxicity data such as teratogenicity, carcinogenicity, and/or mutagenicity data may be required, when necessary.

Notwithstanding the requirements above, other form(s) of scientific explanation to substantiate the safety of a product may be submitted. Furthermore, any available information on safety data from animal or human studies; reports of adverse events, safety alerts, post marketing study and epidemiological data, should be submitted.

Glossary

For the purposes of this Annex:

(a) **new combination** means the instance when no product of the same active ingredients has been approved for marketing in the respective Member State;

(b) **new delivery system** means a change in the method of administration and/or the dosage form of an existing HS in the respective Member State;

(c) **new dosage means** the quantity of active ingredients or substances administered per dose or per day that is different from the administered per dose or per day currently used for the approved product in the respective Member State; and

(d) **new ingredient** means an HS active ingredient or substance that has never been used in the respective Member State.

References Used

1. World Health Organization, *General Guidelines for Methodologies on Research and Evaluation of Traditional Medicines*, 2000.

2. World Health Organization, *Guidelines for regulation of herbal medicines in the South East Asia*, 2003.

3. World Health Organization, R*esearch Guideline for Evaluating the Safety and Efficacy of Herbal Medicine*, 2003.

4. The Organisation for Economic Co-operation and Development. *OECD Guidelines for the Testing of Chemicals, Section 4*, 2014 [cited 26 August 2014]. http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788
DOI: 10.1787/20745788

ANNEX VII

ASEAN GUIDELINES ON CLAIMS AND CLAIMS SUBSTANTIATION FOR HEALTH SUPPLEMENTS

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Introduction

The ASEAN Guidelines on Claims and Claims Substantiation for Health Supplements is developed by taking into consideration similar guidelines that exist internationally (World Health Organization, Codex, European Union, United States, Canada, and Australia) and the regulatory situation and stakeholders' interests in the ASEAN region.

The Health Supplements (HS) claims refer to any message that states, suggests, or implies that a HS ingredient or product has positive contribution and benefit to human health. A balanced approach between consumer protection and encouraging science and innovation is important in implementing the harmonised ASEAN Guidelines on Claims and Claims Substantiation for Health Supplements.

It should also be underlined that this document deals with the guidance of allowable claims and their corresponding levels of literature and scientific substantiation. Certain HS claims need to be substantiated by efficacy data, and these data requirements are defined in the guidelines.

Objective

This document aims to provide guidance on making unbiased and truthful claims, supported by adequate evidence in order to protect the consumers from misleading claims. This will enable consumers to make informed choices in taking care of their health. Furthermore, this document will facilitate the product placement of HS products and set up requirements for efficacy data submission for certain HS claims.

Key Principles of ASEAN HS Claims and Claims Substantiation

All claims made for HS should:

- be consistent with the ASEAN definition of HS;
- support the safe, beneficial, and appropriate use of the products;
- maintain the level documented usage and/or scientific evidence which is proportionate to the type of claim;
- meet the dosing recommendations stated in the evidence or references for the claimed intended effects, unless otherwise justified;
- not be misleading or false;
- enable consumers to make an informed choice regarding products;
- be for health maintenance and promotion purpose;
- not be medicinal or therapeutic in nature, such as implied for treatment, cure, or prevention of diseases; and
- be substantiated by good quality evidence that is relevant to the claim.

The claimed benefit or efficacy of a product and/or its ingredient(s) shall be based on the totality of the substantiation evidence provided including human, non-clinical, and empirical or historical data, as well as other documented evidence, where applicable. Please refer to Table 2.

Guidance for HS Claims Substantiation

HS claims refer to the beneficial effects of consuming HS to promote good health by providing nutrition, enhancing body structure or function, improving a function, enhancing or preserving health, and/or reducing the risk of health related conditions or diseases.

1. Types of HS claims

The three types of HS claims are stated in Table 1:

- General or Nutritional Claims

- Functional Claims
- Disease Risk Reduction Claims

Functional Claims and Disease Risk Reduction Claims shall be substantiated by the proportional degree of data from efficacy studies and relevant documentation.

Table 1. Scope and Examples of the Three Types of HS Claims

Type of HS Claim	**Scope**	**Examples to Illustrate the Scope** *(as determined by the regulatory authority of each Member State)*
General or Nutritional	For Nutritional Support and General Health Maintenance. Benefits derived from supplementation beyond a person's daily dietary intake.	• Supplements nutrition • Supports healthy growth and development • Nourishes the body • Relieves general tiredness, weakness • Helps to maintain good health
Functional	Relate to a positive contribution to health or to the improvement of a function or to modifying or preserving health in the context of the total diet on normal functions or biological activities of the body. Maintains or enhances structure or function of the body, excluding disease related claims. Supports health and to relieve, reduce, lessen, or ease minor body discomforts in some physiological processes (e.g. ageing, menopause, pregnancy)*. **as determined by the regulatory authority of each Member State*	• Maintains or supports healthy joints • Maintains or supports immunity • Maintains healthy liver function • Maintains or supports alertness • Maintains or supports mental performance • Promotes healthy skin • Helps to relieve post-menopausal discomforts • Aids in digestion to relieve indigestion • Bifidobacteria in product A helps to improve slow transit system in 14 days • Supports health in ageing • Supports health in menopause • Supports health in pregnancy
Disease Risk Reduction	Significantly altering or reducing a risk factor of a disease or health related condition*. **as determined by the regulatory authority of each Member State*	• Helps to reduce risk of osteoporosis by strengthening bone • Helps to reduce the risk of dyslipidaemia

2. Principles of HS Claims Substantiation

The type of claim must be substantiated by an adequate level of

evidence. The major principles of HS claim substantiation are:

(a) Proportional degree of supporting evidence corresponding to the type of HS claims

The Principle of proportional degree of supporting evidence is illustrated in Table 2. When applying the substantiation requirement stated in Table 2, the evidence for Functional Claim is stronger than General or Nutritional Claim. In turn the Disease Risk Reduction Claims require proportionally stronger scientific support than Functional Claims.

(b) Totality of scientific evidence that demonstrates the beneficial effect

The totality (balance and range) of the evidence to the HS claims are important. Due consideration should be given to all relevant scientific evidence relating to the claimed benefit of the product or ingredient and should not focus only on evidence that supports the effect. In proportion to the type of claims, scientific substantiation should demonstrate a consistent beneficial effect of the ingredient (or product) on specific health aspects or generally recognised biomarkers based on totality of scientific evidence encompassing human studies (observation and intervention), authoritative references, recommendations from international or authoritative bodies, scientific reviews, animal and in-vitro studies.

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

3. Substantiation of HS Claims

The substantiation of HS claims shall follow Table 2 to reflect the proportional degree of supporting evidence. It is the responsibility of the company to provide the required evidence in order to comply with the criteria to make HS Claims.

For Functional and Disease Risk Reduction Claims, a summary of the scientific evidence including published and unpublished studies should be submitted. In addition, summary of empirical or historical data shall be submitted. Raw data should be

submitted when required by the regulatory authority.

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

(a) Human studies

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

(b) Non-clinical (animal and in vitro) studies

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

Summary of Total Available Scientific Data

The total available published and/or unpublished scientific data should be summarised as part of the substantiation documentation. It should contain the following information:

(a) Product or Ingredient Studied

(b) Intended Use

(c) Type of Claim

(d) Dosage and Administration

(e) Type of Study (example, Human or Animal)

(f) Study Design (example, Observation or Experimental)
(g) Study population

(h) Duration of the Study

(i) Study End points

(j) Limitation of the Study

(k) Study Results

(l) Source of Evidence

  (i) Author

  (ii) Title

  (iii) Publication Details (year)

  (iv) Type

(m) Other information, if any

  (i) Ethics Committee approval

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

Table 2. Degree of Evidence Required to Support Different Types of HS Claims [1]

Type of HS Claim	Level of Evidence	Criteria for Well-documented HS Claims	Evidence to Substantiate HS Claims
General or Nutritional	General	• The claim is related to human health in line with scientific or traditional knowledge • Documented in authoritative reference texts • Recognised by reputable or international organisations or regulatory authorities • Claim is not referring to structure and function of body • Adheres to the key principles of ASEAN HS claims • For a HS product making nutritional claim based on vitamin and/or mineral, it is recommended to contain a minimum of 15% Codex NRV (Nutrient Reference Value) per daily dose of the vitamin and/or mineral to qualify it being the source of that vitamin or mineral or as determined by regulatory authorities	**At least 1 of the following evidence** (as determined by the regulatory authority of each Member State): • Authoritative reference texts e.g. reference textbooks, pharmacopoeia, monographs, and scientific journals • Scientific opinion from scientific organisations • Scientific opinion from regulatory authorities • Documented history of use e.g. classical texts, published document from scholar or expert that reports the traditional use of the ingredient concerned
Functional	Medium	• Functional claim is in line with established knowledge on nutrition and physiology • Documented in authoritative reference texts • Recognised by reputable or international organisations or regulatory authorities • Adheres to the key principles of ASEAN HS claims • For a HS product making functional claim based on vitamin and/or mineral, it is recommended to contain a minimum of 15% Codex NRV (Nutrient Reference Value) per daily dose of the vitamin and/or mineral to qualify it being the source of that vitamin or mineral or as determined by regulatory authorities	**At least 1 compulsory evidence** (as determined by the regulatory authority of each Member State)**:** • Good quality scientific evidence from human studies (only in the event that human experimental study is not ethical, animal studies shall only be acceptable together with epidemiological studies or other scientific literature and documented traditional use). In case the end point of a human study is not feasible, a surrogate end point can be used. • Authoritative reference texts e.g. reference textbooks, pharmacopoeias, monographs • Scientific opinion from scientific organisations • Scientific opinion from regulatory authorities

[1] References that are used to substantiate a HS claim include Member States' official pharmacopoeias and monographs.

Type of HS Claim	Level of Evidence	Criteria for Well-documented HS Claims	Evidence to Substantiate HS Claims
			At least 1 additional evidence: • Scientific evidence from animal studies • Documented history of use (e.g. classical texts, published document from scholar or expert that reports the traditional use of the ingredient concerned) • Evidence from published scientific review Relevant company owned scientific data (published and unpublished) can be submitted, if available
Disease Risk Reduction	High	• 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 reputable or international organisations or regulatory authorities • Adheres to the key principles of ASEAN HS claims • For a HS product making disease risk reduction claim based on ingredient, it must contain the amount of the active ingredient that has been shown to be effective in the substantiation data	**Compulsory evidence:** • Scientific evidence from human intervention study on ingredient or product **At least 1 additional evidence:** • Authoritative reference texts e.g., pharmacopoeia, monographs • Scientific opinion from scientific organisations • Scientific opinion from regulatory authorities • Evidence from published scientific reviews or meta-analysis Relevant company owned scientific data (published and unpublished) can be submitted, if available

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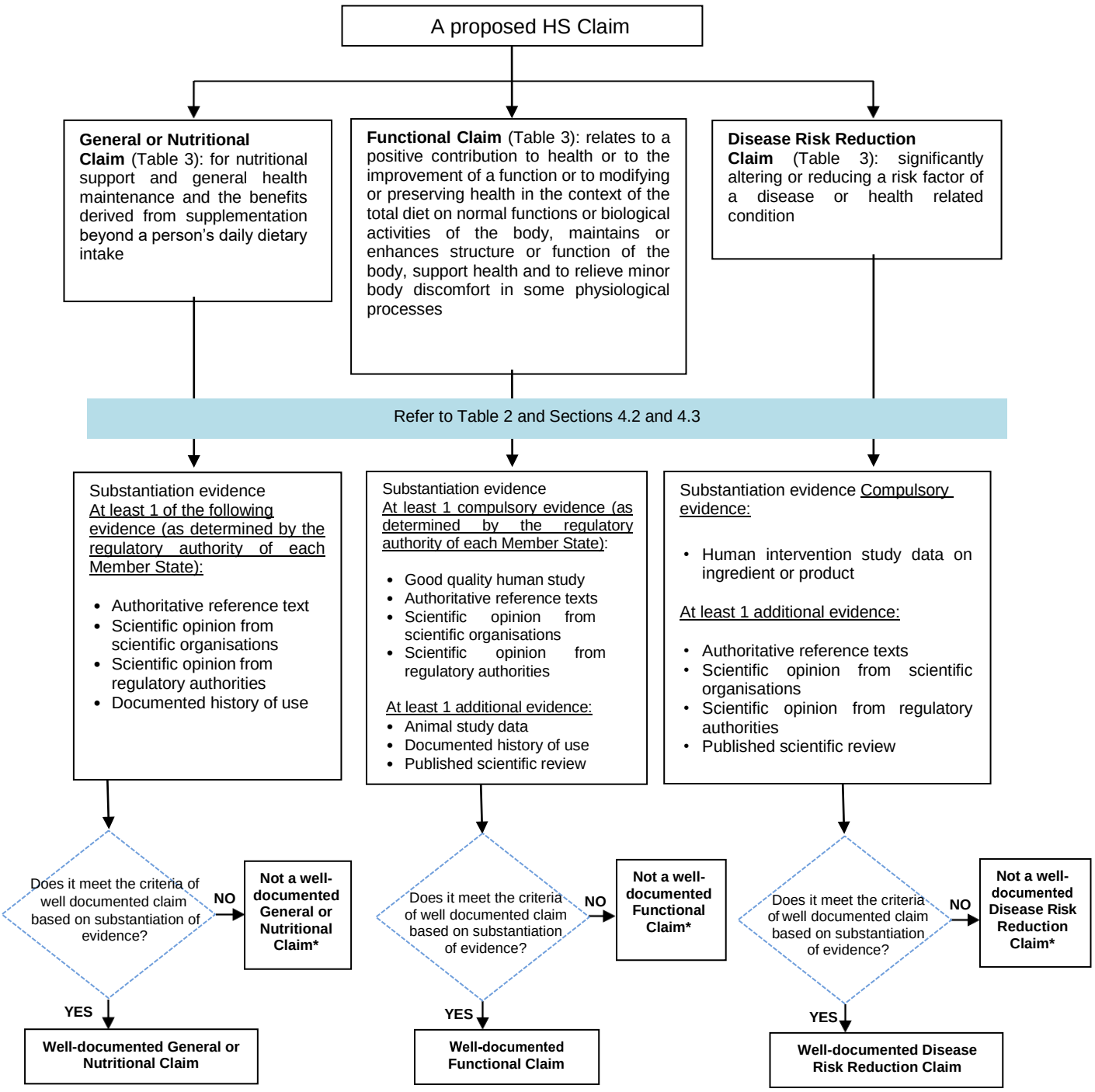
Decision tree on the evidence required to support HS claims appears as Figure 1. Please note that Figure 1 should be read in conjunction with the details in Table 2 for full information.

Figure 1. Decision Tree on the Evidence Required to Support the Different Types of HS Claims



4. Languages and Wordings Used for HS Claims

Appropriate language and wordings must be used to convey the HS claims with a meaning that is proportional to the level of scientific substantiation. Language and words used in HS claims should provide a truthful and non-misleading message on the beneficial effect of the ingredient or product.

5. Prohibited HS Claims

HS claims are not allowed to imply treatment, cure, or prevention of any disease or medical condition. For disease risk reduction claims, diseases prohibited from associating with such claims shall be determined by the regulatory authority of each Member State.

ANNEX VIII

ASEAN GUIDELINES ON GOOD MANUFACTURING PRACTICE FOR HEALTH SUPPLEMENTS

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Introduction

Good Manufacturing Practice (GMP) is an essential component in the manufacture of Health supplements (HS). The primary objective of GMP is to ensure that the quality requirements of all products are met and consistently maintained to safeguard public health.

Manufacture is defined as:

(a) the making or assembling of the finished product;

(b) the enclosing or packing of the finished product in any container in a form suitable for administration or application, and the labelling of the container; and

(c) the carrying out of any process in the course of any of the foregoing activities.

GMP shall be implemented in the manufacture of HS, such that there is overall control to ensure the consumer receives good quality of product for its intended use. Haphazard operations shall not be permitted in the manufacturing processes of finished products.

Recognising that there are similar GMP guidelines that are in existence and used internationally and by the regulatory authority with international obligation, this document aims to provide guidance for GMP. Whilst these guidelines are not intended to place any restraint for the development of new concepts or new technologies, where needed, justifications shall be provided to demonstrate that innovative measures proposed or to be implemented are able to provide equivalent or better controls over the quality system and manufacturing process. Importantly, the safety and quality of HS must be assured while using

measures other than those described in these guidelines.

The starting materials used in the production of HS are often natural in origin. These materials, such as plants and animal parts, are prone to contamination, deterioration, and variation in quality. Therefore, the control of the starting materials, storage, and processing of HS is important. The control is also required because of the often complex and variable nature, the number and the small quantity of defined active materials in many HS.

Materials such as animal parts may spread undesirable disease (e.g. Transmissible Spongiform Encephalopathy, therefore the source of animals, the nature and quantity of animal tissue used in manufacturing, whether there are measures employed in the manufacturing process to inactivate the infectious agents and whether there are adequate measures to prevent cross-contamination shall be submitted to the regulatory authority during the product evaluation and registration stage for assessment, when required by the regulatory authority. Only materials that have gone through scientific product assessment and subsequently authorised, as deemed necessary by the respective Member State, are allowed to be used for manufacturing of HS.

The manufacture of HS depends on the starting materials, manufacturing processes, building, equipment, and personnel involved. It is important to recognise that Quality Control (QC) cannot be tested into products; i.e., quality shall be built in by design. All HS shall be manufactured under strictly controlled and monitored conditions, and shall not rely solely in finished product testing.

The purpose of these guidelines is to outline steps which shall be taken, as necessary and appropriate, by manufacturers of HS with the objective of ensuring that their products are of the intended quality and nature.

CHAPTER 1

QUALITY MANAGEMENT

Principle

HS shall be manufactured so as to ensure that they are fit for their intended use, comply with the requirements of the regulatory authority and do not place the health of the consumers at risk due to inadequate safety and quality. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers, and by the distributors. To achieve the quality objective reliably there shall be a comprehensively designed and correctly implemented system of Quality Assurance (QA) incorporating GMP and thus QC. It shall be fully documented and its effectiveness monitored. All parts of QA system shall be adequately resourced with competent personnel, suitable and sufficient premises, equipment, and facilities.

1.1. The basic concept of QA, GMP, and QC are interrelated. They are described here in order to emphasise their relationships and their fundamental importance to the production and control of HS.

QA

1.2. QA is a wide-ranging concept which covers all matters which individually or collectively influence the quality of a product. It is the sum total of the organised arrangements made with the object of ensuring the products are of the quality required for their intended use. QA therefore incorporates GMP plus other factors outside the scope of these guidelines.

The system of QA appropriate for the manufacture of HS shall ensure that:

1.2.1. HS are designed and developed in a way that takes account of the requirements of GMP;

1.2.2. production and control operations are clearly specified and GMP adopted;

1.2.3. managerial responsibilities are clearly specified;

1.2.4. arrangements are made for the manufacture, supply, and use of the correct starting and packaging materials;

1.2.5. all necessary controls on intermediate products, and any other in-process controls are carried out;

1.2.6. the finished product is correctly processed and checked, according to the defined procedures;

1.2.7. HS are not sold or supplied before a head of QC or QA has certified that each production batch has been produced and controlled in accordance with the requirements of the regulatory authority and any other procedures relevant to the production, control, and release of HS;

1.2.8. satisfactory arrangements exist to ensure, that the HS are stored, distributed, and subsequently handled so that quality is maintained throughout their shelf-life; and

1.2.9. there is a procedure for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the QA system.

1.3. GMP is that part of QA which ensures that products are consistently manufactured and controlled to the quality standards appropriate to their intended use and as required by the regulatory authority or product specification.

GMP is concerned with both production and QC. The basic requirements of GMP are that:

1.3.1. all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing HS of the required quality and complying with their specifications;

1.3.2. critical steps of manufacturing processes and significant changes to the process are verified;

1.3.3. all necessary facilities for GMP are provided including:

1.3.3.1. appropriate qualified and trained personnel;

1.3.3.2. adequate premises and space;

1.3.3.3. suitable equipment and services;

1.3.3.4. correct materials, containers, and labels;

1.3.3.5. approved procedures and instructions; and

1.3.3.6. suitable storage and transportation.

1.3.4. instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;

1.3.5. operators are trained to carry out procedures correctly;

1.3.6. records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken, and that the quantity and quality of the products were as expected. Any significant deviations are fully recorded and investigated;

1.3.7. records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

1.3.8. the distribution of the products minimises any risk to their quality;

1.3.9. a system is available to recall any batch of product, from sale or supply; and

1.3.10. complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken with respect to the defective products and to prevent recurrences.

QC

1.4. QC is that part of GMP which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

The basic requirements of QC are that:

1.4.1. adequate facilities, trained personnel, and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;

1.4.2. samples of starting materials, packaging materials, intermediate products, bulk products, and finished products are taken by personnel and by methods approved by QC;

1.4.3. test methods are either internationally accepted or other validated methods (refer to Appendix 1);

1.4.4. records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;

1.4.5. the finished products contain active materials complying with the qualitative and quantitative requirements of the regulatory authority, are of the quality required, and are enclosed within their proper containers and correctly labelled;

1.4.6. records are made of the results of inspection and that testing of material, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;

1.4.7. no batch of product is released for sale or supply prior to

certification by a head of QC or QA that it is in accordance with the requirements of the regulatory authority; and

1.4.8. sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

Product Quality Review

1.5. Regular periodic or rolling quality reviews of all HS, including export only products, shall be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements. Such reviews shall normally be conducted and documented annually, taking into account previous reviews, and shall include at least:

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

1.5.2. a review of critical in-process controls and finished product results;

1.5.3. a review of all batches that failed to meet established specification(s) and their investigation;

1.5.4. a review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken;

1.5.5. a review of all changes carried out to the processes or analytical methods;

1.5.6. a review of product authorisation variations submitted, granted, or refused, including those for third country (export only) dossiers;

1.5.7. a review of the results of the stability monitoring programme and any adverse trends;

1.5.8. a review of all quality-related returns, complaints, and recalls and the investigations performed at the time;

1.5.9. a review of adequacy of any other previous product process or equipment corrective actions;

1.5.10. the qualification status of relevant equipment and utilities, e.g. Heating, Ventilation and Air Conditioning, water, compressed gases, etc.;

1.5.11. a review of contractual agreements to ensure that they are up to date; and

1.5.12. a review of post-marketing commitment for new product or variation.

1.6. The manufacturer and manufacturing authorisation holder shall evaluate the results of this review and an assessment shall be made whether corrective and preventive action shall be undertaken. Reasons for such corrective actions shall be documented. Agreed corrective and preventive actions shall be completed in a timely and effective manner. There shall be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, etc. where scientifically justified.

1.7. Where the product owner is not the manufacturer, there shall be a technical agreement or contract in place between the various parties that defines their respective responsibilities in producing the quality review. The authorised person responsible for final batch certification together with the product owner shall ensure that the quality review is performed in a timely manner and is accurate.

CHAPTER 2

PERSONNEL

Principle

There shall be an adequate number of personnel at all levels having knowledge, skill, and capabilities relevant to their assigned function and capable of handling their duties properly. They shall have the attitudes for achieving the goals of GMP.

Organisation, Qualification, and Responsibilities

2.1. The manufacturer shall have an organisation chart. People in responsible positions shall have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There shall be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of GMP. The organisational structure of the company shall be such that the Production and the QC Departments shall be independent of each other. Key posts shall be occupied by full-time personnel (direct supervision during operation) and shall be given full authority necessary to execute his or her duties effectively. An adequate number of trained personnel shall be available to carry out the production and the QC operations in accordance with established procedures and specifications.

2.2. The head of Production Department shall be adequately trained and possess good practical experience and adequate knowledge in manufacturing HS, which can enable to perform his functions effectively.

The head of Production Department shall have full authority and responsibilities to manage production of products covering operations, equipment, production personnel, production area, and records.

The head of Production Department generally has the following responsibilities:

2.2.1. to ensure those products are manufactured and stored according to the appropriate documentation in order to

obtain the required quality;

2.2.2. to approve the instructions relating to production operations, including the in-process controls and to ensure their strict implementation;

2.2.3. to ensure that the production records are evaluated and signed by a designated person before they are made available to the QC Department;

2.2.4. to check the maintenance of the department, premises, and equipment;

2.2.5. to ensure that the critical processes are appropriately verified; and

2.2.6. to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

2.3. The head of QC Department shall have adequate training and practical experience, which can enable the person to perform the functions effectively. He or she shall be given full authority and responsibility in all QC duties such as establishment, verification, and implementation of all QC procedures. He or she shall have the sole authority to approve starting materials, intermediates, bulk, and finished products that meet the specification or to reject those which do not conform to the relevant specification or which were not manufactured in accordance with approved procedures and under the defined conditions.

The head of QC shall have the following responsibilities:

2.3.1. to approve or reject starting materials, packaging materials and intermediate, bulk, and finished products;

2.3.2. to evaluate batch records;

2.3.3. to ensure that all necessary testing is carried out;

2.3.4. to ensure that the critical processes are appropriately verified;

2.3.5. to approve sampling instructions, specification, test methods, and other QC procedures;

2.3.6. to approve and monitor tests carried out under contract;

2.3.7. to check the maintenance of the department, premises, and equipment;

2.3.8. to establish expiration date and shelf-life specifications on the basis of stability test or available stability data related to storage conditions;

2.3.9. to approve those suppliers of raw materials and packaging materials who are capable of reliably supplying products meeting the company's established quality standards;

2.3.10. to evaluate all complaints received or deficiencies noted about any batch, if necessary in conjunction with other departments, and to take appropriate action accordingly;

2.3.11. to maintain adequate analytical records concerning the examinations of all samples taken;

2.3.12. to recommend contract-manufacturing operations which shall meet the company's specified quality standards; and

2.3.13. to ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

2.4. The heads of Production Department and QC Department shall share a joint responsibility:

2.4.1. to ensure that written procedures are established and to authorise written procedures and relevant document including amendments;

2.4.2. to monitor and control the manufacturing environment, sanitation and hygiene;

2.4.3. to verify critical processes;

2.4.4. to train personnel;

2.4.5. to approve and monitor the suppliers of materials and contract manufacturers;

2.4.6. to establish and monitor the storage conditions for materials and products;

2.4.7. to retain records;

2.4.8. to monitor compliance with the requirements of GMP; and

2.4.9. to inspect, investigate and take samples, in order to monitor factors which may affect product quality.

Training

2.5. All personnel shall be trained in the particular operations and in the principles of GMP.

2.6. Training in GMP shall be on a continuing basis and with adequate frequency to assure that employees remain familiar with GMP requirements relevant to their functions. Training in GMP shall be in accordance with written programmes approved by the head of Production Department and the head of QC Department.

2.7. Personnel training records including GMP shall be maintained and the effectiveness of training programmes shall be assessed periodically.

2.8. The concept of QA and all the measures capable of improving its understanding and implementation shall be fully discussed during the training sessions.

CHAPTER 3

PREMISES AND EQUIPMENT

Principle

Premises and equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products.

Premises

General

3.1. Premises for manufacturing shall be of suitable size, design, construction, and location to facilitate proper operation, cleaning, and maintenance.

3.2. Premises shall be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They shall be cleaned and, where applicable, disinfected according to detailed written procedures.

3.3. Steps shall be taken in order to prevent the entry of unauthorised people. Production, storage, and QC areas shall not be used as a right of way by personnel who do not work in them.

3.4. Lighting, temperature, humidity, and ventilation shall be appropriate and such that they do not adversely affect, directly or indirectly, either the products during their manufacture and storage, or the accurate functioning of equipment.

3.5. Premises shall be located at a suitable site approved by the relevant authorities.

3.6. Premises shall be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

3.7 In order to minimise the risk of a serious hazard due to cross-

contamination, dedicated and self-contained facilities must be available for the production of particular products such as highly sensitising materials (e.g. penicillins) or biological medicinal products (e.g. vaccines) i.e. these products shall not be produced in the same facilities used to produce HS). When Traditional Medicines and HS are sharing the same manufacturing facilities, cross-contamination shall be adequately addressed (examples include: by performing cleaning verification or the use of separate equipment, etc.).

3.8. Premises shall be designed, constructed, and maintained to protect against access and harboring of vermin, rodents, birds, insects, or other animals.

3.9. Design shall consider prevention of mix-up between different products or their components and the possibility of cross-contamination by other substances.

3.10. Special attention must be given for processing operations that generate dust. Measures shall be taken to prevent the generation and dissemination of dust.

3.11. Defined areas for the following operations are required:

3.11.1. receiving and quarantine of incoming materials;

3.11.2. sampling;

3.11.3. storage of starting and packaging materials;

3.11.4. weighing or dispensing;

3.11.5. processing;

3.11.6. storage of bulk or intermediate products;

3.11.7. packaging;

3.11.8. equipment washing;

3.11.9. storage of quarantine finished products;

3.11.10. storage of approved finished products; and

3.11.11. designated area for QC.

Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine shall give equivalent security.

Production Areas

3.12. Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors, and ceilings) shall be smooth, free from cracks and open joints, and shall not shed particulate matter and shall permit easy and effective cleaning and, if necessary, disinfection. The coving of junctions between walls and floors in the production areas is encouraged to facilitate cleaning.

3.13. Any open channels shall be avoided, but if required they shall be shallow enough to facilitate cleaning and disinfecting. All drainage shall have trapped gullies.

3.14. Buildings shall be effectively ventilated with air control facilities (including temperature, humidity, and filtration), appropriate both to the operations undertaken within and to the external environment.

3.15. Production areas shall be well lit, particularly where visual on-line controls are carried out.

3.16. Pipework, light fittings, ventilation points, and other services shall be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they shall be accessible from outside the manufacturing areas.

3.17. Separate areas shall be used for the production of finished products intended for external use or application and finished products intended for internal consumption solely.

3.18. In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions shall be taken to avoid cross-contamination and facilitate cleaning.

3.19. Premises for the packaging of HS shall be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

3.20. Premises shall preferably be laid out in such a way as to allow the

production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

3.21. Adequacy of working space, which shall allow orderly and logical placement of equipment and materials and to suit the operation, efficient flow of work, effective communication and supervision as well as to avoid crowding and disorders.

3.22. Changing rooms shall be directly connected to but separated from processing areas.

3.23. Changing rooms into the production areas shall have adequate hand washing and/or sanitising facilities.

Storage Areas

3.24. Storage areas shall be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials; intermediate, bulk and finished products; products in quarantine, released, rejected, or recalled.

3.25. Storage areas shall be designed or adapted to ensure good storage conditions. In particular, they shall be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these shall be provided, checked, and monitored.

3.26. Segregated and secure areas shall be provided for the storage of rejected, recalled, or returned materials or products.

3.27. Highly active materials or products (e.g. flammable, explosive, or toxic substances) shall be stored in separate, safe, and secure areas.

3.28. Receiving and dispatch bays shall protect materials and products from the weather. Reception areas shall be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

3.29. There shall normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it shall be conducted in such a way as to prevent contamination or cross-contamination.

3.30. Printed packaging materials are considered critical to the conformity of the products, and special attention shall be paid to the safe and secure storage of these materials.

3.31. Crude (i.e. unprocessed) natural materials shall be stored in separate areas. The store area shall be well ventilated and equipped in such a way as to give protection against insects or other animals, especially rodents. Effective measures shall be taken to prevent the spread of any such animals and microorganisms brought in with the crude natural materials to prevent fermentation, mould growth, and cross-contamination. Containers shall be located in such a way as to allow free air circulation.

3.32. Special attention shall be paid to the cleanliness and good maintenance of the storage areas particularly when dust is generated.

3.33. Storage of plant materials, animal materials including parts, microorganisms, extracts, tinctures, and other preparations that require special conditions of temperature, humidity, or light protection; these conditions shall be provided and monitored.

QC Areas

3.34. If testing is done within the premises, QC laboratories should be separated from production areas. This is particularly important for laboratories for the handling of microorganisms.

3.35. Control laboratories shall be designed to suit the operations to be carried out in them. Sufficient space shall be given to avoid mix-ups and cross-contamination. There shall be adequate suitable storage space for samples and records.

3.36. Separate rooms may be necessary to protect sensitive instruments from vibrations, electrical interference, humidity, etc.

3.37. Special requirements are needed in laboratories handling particular substances such as microorganisms.

Ancillary Areas

3.38. Rest and refreshment rooms and toilets shall be separated from other areas and shall not have direct access to controlled areas

(e.g. production and storage areas).

3.39. Facilities for changing clothes, and for washing and toilet purposes shall be easily accessible and appropriate for the number of users.

3.40. Maintenance workshops shall be separated from production areas. Whenever parts and tools are stored in the production area, they shall be kept in rooms or lockers reserved for that use.

3.41. Animal houses shall be well isolated from other areas with separate entrance (animal access) and air handling facilities.

Equipment

3.42. Manufacturing equipment shall be designed, placed, and maintained to suit its intended use.

3.43. Manufacturing equipment shall be installed so as to prevent contamination or minimise the risk of error and, where necessary, tested to ensure the equipment operate appropriately.

3.44. Manufacturing equipment shall be located at a distance from other equipment sufficient to avoid congestion and cross-contamination.

3.45. Fixed pipework shall be clearly labelled to indicate the contents and direction of flow.

3.46. Balances and measuring equipment of an appropriate range and precision shall be available for production and control operation.

3.47. Measuring, weighing, recording and control equipment shall be calibrated and checked at defined intervals by appropriate methods. Adequate records of such activities shall be maintained.

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

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

3.50. Defective equipment shall, if possible, be removed from production and QC areas or at least be clearly labelled as defective.

3.51. Repair and maintenance operations shall not present hazard to the quality of the products. Any missing components such as nuts, springs, clips, etc. shall be reported and investigated immediately.

3.52. Production equipment (including transfer pipes and hoses) shall not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

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

CHAPTER 4

SANITATION AND HYGIENE

Principle

A high level of sanitation and hygiene shall be practised in every aspect of the manufacturing of HS.

The scope of sanitation and hygiene covers personnel, premises, equipment, and utensils; in fact, anything that could become a source of contamination to the product.

All employees shall be instructed and encouraged to report to their immediate supervisor any conditions (plant, equipment, or personnel) that they consider may adversely affect the quality of products.

Personnel

4.1. All personnel, prior to employment shall undergo health examinations. During the course of their employment they shall also routinely undergo health examinations which shall include relevant examinations appropriate to the tasks that they are required to perform.

4.2. All personnel shall practise good personal hygiene. They shall be trained in the practices of personal hygiene. High level of personal hygiene shall be observed by all those concerned with manufacturing processes.

4.3. Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products shall not be allowed to handle raw materials, packaging materials, in-process materials, and finished products until the condition is improved.

4.4. Direct contact shall be avoided between the operator's hands and raw materials, intermediate or bulk product. Proper washing of hands and wearing of gloves shall be used if contact with hands is unavoidable.

4.5. To assure protection of the product from contamination as well as the safety of the personnel, appropriate protective garments shall be worn. Soiled uniforms shall be stored in closed containers until

properly laundered.

4.6. Only authorised personnel shall be allowed to enter production areas. Visitors or untrained personnel shall, preferably, not be taken into the production and QC areas. If this is unavoidable, they shall be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They shall be closely supervised.

4.7. Smoking, eating, drinking and chewing, or keeping of plants, food, drink, smoking materials, and personal medicines shall be restricted to specific areas and not permitted in production, laboratory, storage, or other areas where they might adversely influence product quality.

4.8. The wearing of makeup, wrist watches and jewellery shall be prohibited in the production area however for jewellery or objects that cannot be removed; it must be covered by material that is maintained in an intact, clean, and sanitary condition.

Premises

4.9. Premises used for the manufacturing of products shall be of suitable design and construction so as to facilitate good sanitation.

4.10. Adequate employee's washing and well ventilated toilet facilities and changing rooms shall be provided at suitable locations.

4.11. Suitable locker facilities shall be provided at appropriate locations for the storage of employees' clothing and personal property.

4.12. The preparation, storage, and consumption of food and beverages shall be restricted to specific areas, such as meal rooms and canteen. Facilities in such rooms must meet sanitary standards. Meal rooms and canteen rooms shall not have direct access to controlled areas (e.g. production area and areas use to store materials used for production and finished products).

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

4.14. Rodenticide, insecticides, fumigating agents, and sanitising

materials used must not contaminate equipment, raw materials, packaging materials, in-process materials, or finished products. There shall be a pest control programme, documents such as layout, trending and expectations. Contract agreements shall be established, where applicable.

4.15. There shall be written procedures assigning responsibility for sanitation and describing cleaning schedules, methods, equipment, materials to be used and facilities to be cleaned in sufficient detail. Such written procedures shall be followed.

4.16. Pets are not allowed within the vicinity of the manufacturing plant.

Equipment and Utensils

4.17. Equipment and utensils shall be cleaned both inside and outside after use according to established procedures. Cleaned equipment shall be kept or stored in a clean condition and identified with the status of cleaning, and checked for cleanliness prior to each use.

4.18. Vacuum or wet cleaning methods are to be preferred. Compressed air and brushes shall be used with care or avoided if possible, as they increase the risk of product contamination.

4.19. Cleaning agents, washing and cleaning equipment shall not be a source of contamination. The choice of cleaning method and agents shall be carefully considered and justified.

4.20. Adequate space, preferably separated from processing areas, shall be provided for cleaning and storing mobile equipment and utensils including the storage of cleaning materials.

4.21. Written procedures shall be established and followed for cleaning and sanitising of equipment, utensils, and containers used in the manufacture of HS.

4.22. These procedures shall be prepared to prevent equipment contamination by cleaning or sanitising agents and shall at least include the following:

4.22.1. responsibility for cleaning;

4.22.2. cleaning schedule;

4.22.3. cleaning methods;

4.22.4. equipment and materials used in cleaning operations;

4.22.5. methods of disassembling and reassembling equipment;

4.22.6. removal of previous batch identification; and

4.22.7. protection of clean equipment and utensils from contamination prior to use.

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

CHAPTER 5

DOCUMENTATION

Principle

Good documentation constitutes an essential part of the QA system. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history of the product, from purchasing of starting materials to the distribution of finished products. It shall be able to record executed activities for maintenance, storage, QC, distribution, and other specific matters linked to GMP.

For manufacturing activities, a documentation system must be prepared. The system consisting of manufacturing formulae and instructions, specifications, procedures, and records must be free from errors and clearly established.

General

5.1. The system of documentation shall be able to record the complete history of each batch. It shall be adequate to permit investigation and tracing of any defective products.

5.2. Documents shall contain all necessary information, to be kept up to date and any amendment shall be formally authorised. It shall include provision for periodic review and revision as necessary.

5.3. Product related records shall be retained for at least one year after the expiry date of the finished product.

5.4. Documents shall be designed, prepared, reviewed, and distributed with care. The reproduction of working documents from master documents should not allow any error to be introduced to the reproduction process. Reproduced documents shall be clear, legible, and duly authorised.

5.5. Documents shall be approved, signed, and dated by the appropriate and authorised person.

5.6. Documents shall have unambiguous contents; title, nature, and purpose shall be clearly stated. They shall be laid out in an orderly fashion and easy to be checked.

5.7. Documents shall be regularly reviewed and kept up to date. When a document has been revised, systems shall be operated to prevent inadvertent use of superseded documents.

5.8. Documents shall not be hand-written; although, where documents require the entry of data, these entries may be made in clear, legible, and indelible handwriting. Sufficient space shall be provided for such entries.

5.9. Any alteration made to the entry on a document shall be signed and dated and, where appropriate, the reason of the alteration to be recorded. The alteration shall permit the reading of the original information.

5.10. The records shall be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of the product are traceable.

5.11. Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed procedure relating to the system in use shall be available and the accuracy of the records shall be checked and verified. If documentation is handled by electronic data processing methods, only personnel who have been authorised shall be able to enter or modify data in the computer, and there shall be a record of changes and deletions; access shall be restricted by passwords or other means, and the result of entry of critical data shall be independently checked and verified. Batch records electronically stored shall be protected and back-up. It is particularly important that the data are readily available throughout the period of retention.

5.12. The manufacturer shall practice what is documented in the written procedures. Under circumstances where there is a change in the practice, the written procedures shall be promptly updated. On the other hand, if a written procedure was revised, appropriate training shall be provided to ensure that the personnel carry out the work in accordance to the revised procedure.

QC Documents

5.13. The following shall be readily available from the QC Department:

5.13.1. specifications;

5.13.2. sampling procedures;

5.13.3. testing procedures and records (including analytical worksheets and/or laboratory notebooks);

5.13.4. analytical reports and/or certificates;

5.13.5. data from environmental monitoring, where appropriate; and

5.13.6. procedures for and records of the calibration of instruments and maintenance of equipment.

5.14. Any QC documentation relating to a batch record shall be retained for at least one year after the expiry date of the finished product.

Specifications

5.15. The materials used in the product shall be handled in an appropriate manner and manufactured in an appropriate controlled condition to prevent cross-contamination. Documented traceability of the material and suppliers is fundamental to the quality of the finished products and shall be made available.

Specifications for Natural Materials

5.16. The specifications for natural material shall, where appropriate, include the following:

5.16.1. scientific name and if possible with reference to the authors;

5.16.2. details to the source of the natural material (country or region of origin, and where applicable, cultivation, time of harvesting, collection procedures, possible pesticides used, etc.);

5.16.3. whether the whole plant or animal or only a part is used;

5.16.4. when dried plant or animal is purchased, drying system shall be specified;

5.16.5. pictorial demonstration or description of natural material,

macroscopical and/or microscopical examination;

5.16.6. storage conditions and precautions, when necessary; and

5.16.7. shelf-life, where applicable.

5.17. Testing procedures shall be available if the following tests are conducted, where appropriate:

5.17.1. identification tests including, where possible, tests for known active constituents, or markers;

5.17.2. assay, where possible, of constituents of known therapeutic activity or markers;

5.17.3. limit tests such as ash value, and presence of essential oils and loss on drying;

5.17.4. tests for heavy metals and for likely contaminants, foreign materials and adulterants;

5.17.5. tests for radioactivity, mycotoxin, fungal and microbial contamination;

5.17.6. test for residual solvents in extracts or finished products, where applicable; and

5.17.7. other tests, as required.

Specifications for Starting Materials and Packaging Materials

5.18. Specifications for starting materials and packaging materials shall, if applicable, include the following:

5.18.1. a description of the materials, including:

5.18.1.1. the designated name and the internal code reference;

5.18.1.2. the reference, if any, to a pharmacopoeia monograph;

5.18.1.3. the approved suppliers and, if possible, the original producer of the products; and

5.18.1.4. a specimen of printed materials;

5.18.2. directions for sampling and testing or reference to procedures;

5.18.3. qualitative and quantitative requirements with acceptance limits;

5.18.4. storage conditions and precautions; and

5.18.5. the maximum period of storage before re-examination.

When, starting material is a natural material, please refer to paragraph 5.16.

Specifications for Intermediate and Bulk Products

5.19. Specifications for intermediate and bulk products shall be available if these are purchased or transferred, or if data obtained from intermediate products are used for the evaluation of the finished product. The specifications shall be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for Finished Products

5.20. The specifications for finished product where appropriate shall include the following tests:

5.20.1. microbial limits;

5.20.2. heavy metals limits;

5.20.3. uniformity of weight (for tablets and capsules), disintegration (for tablets, capsules, and pills), hardness and friability (for tablets), and viscosity (for internal and external liquids);

5.20.4. physical appearance such as colour, taste, texture, size, etc.; and

5.20.5. other tests, as required.

5.21. The specifications shall also include:

5.21.1. the designated name of the product and the internal code reference where applicable;

5.21.2. the formula or a reference to such formula;

5.21.3. a description of the dosage form and package details;

5.21.4. directions for sampling and testing or a reference to procedures, where applicable;

5.21.5. the qualitative and quantitative requirements, with the acceptance limits, where applicable;

5.21.6. the storage condition and any special handling precautions, where applicable; and

5.21.7. the shelf-life.

Production Documents

Manufacturing Formula and Processing Instructions

Formally authorised Manufacturing Formula and Processing Instructions shall exist for each product and batch size to be manufactured. They are often combined in one document.

5.22. The Manufacturing Formula shall include:

5.22.1. the name of the product, with a product reference code relating to its specification;

5.22.2. a description of the product dosage form, strength of the product, and batch size;

5.22.3. a list of all starting materials to be used with the amount of each, described using the designated name and a reference which is unique to that material; mention shall be made of any substance that may disappear in the course of processing; and

5.22.4. a statement of the expected final yield with the acceptable limits and of relevant intermediate yields, where applicable.

5.23. The Processing Instructions shall include:

5.23.1. a statement of the processing location and the principal equipment to be used;

5.23.2. the methods, or reference to the methods, to be used for setting up the equipment (e.g. cleaning, assembling, calibrating);

5.23.3. detailed stepwise processing instruction (e.g. checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures);

5.23.4. the instructions for any in-process controls with their limits;

5.23.5. where necessary, the requirements for bulk storage of the products; including the container, labelling and special storage conditions where applicable; and

5.23.6. any special precautions to be observed.

5.24. The processing instructions shall describe the different operations carried out upon the crude material such as sorting, cleaning, drying, crushing, and sifting, and include drying time and temperatures, and methods used to control fragment or particle size. It shall also describe the sieving process or other methods of removing foreign materials.

5.25. In particular, there shall be written instructions and records, which ensure that each container of the product is carefully examined to detect any adulteration or substitution or presence of foreign matter, such as metal or glass pieces, animal parts or excrement, stones, sand, etc., or rot and signs of decay.

5.26. For product preparation, instructions shall include details of base or solvent, time and temperatures of extraction, details of any concentration stages and methods used.

Packaging Instructions

5.27. There shall be formally authorised Packaging Instructions for each product, pack size and type. These shall normally include or have a reference to the following:

5.27.1. name of the product;

5.27.2. description of its product dosage form, and strength where applicable;

5.27.3. the pack size expressed in terms of the number, weight or volume of the product in the final container;

5.27.4. a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;

5.27.5. where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf-life of the product;

5.27.6. special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;

5.27.7. a description of the packaging operation, including any significant additional operations, and equipment to be used; and

5.27.8. details of in-process controls with instructions for sampling and acceptance limits.

Batch Processing Records

5.28. Batch Processing Record is that part of Batch Manufacturing Record and shall be kept for each batch processed. It shall be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions. The method of preparation of such records shall be designed to avoid transcription errors. The record shall carry the batch number of the product being manufactured.

5.29. Before any processing begins, there shall be recorded verification that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that equipment is clean and suitable for use.

5.30. During processing, the following information shall be recorded at the time each action is taken and, after completion, the record shall be dated and signed in agreement by the person responsible for the processing operations:

5.30.1. the name of the product;

5.30.2. dates and times of initiation, of significant intermediate stages and of completion of production;

5.30.3. name of the person responsible for each stage of production;

5.30.4. date and the signature of the operator of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g. weighing);

5.30.5. the batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed materials added);

5.30.6. any relevant processing operation or event and major equipment used;

5.30.7. a record of the in-process controls and the date and signature of the person(s) carrying them out, and the results obtained;

5.30.8. the product yield obtained at different and pertinent stages of manufacture; and

5.30.9. notes on special problems including details, with signed authorisation for any deviation from the manufacturing formula and processing instructions.

Batch Packaging Records

5.31. A Batch Packaging Record is part of Manufacturing Record and shall be kept for each batch or part of batch processed. It shall be based on the relevant parts of the Packaging Instructions and the method of preparation of such records shall be designed to avoid transcription errors. The record shall carry the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained.

5.32. Before any packaging operation begins, there shall be recorded checks that the equipment and work station are clear of previous products, documents, or materials not required for the planned packaging operations, and that equipment is clean and suitable for use.

5.33. The following information shall be entered at the time each action is taken and, after completion, the record shall be dated and signed in agreement by the person(s) responsible for the packaging operations:

5.33.1. the name of the product;

5.33.2. the date(s) and times of the packaging operations; when there is the risk of contamination, the packaging activity shall be done within the day itself;

5.33.3. the name of the responsible persons carrying out the packaging operation;

5.33.4. the date and signature of the operators of the different significant steps;

5.33.5. records of verification for identity and conformity with the packaging instructions including the results of in-process controls;

5.33.6. details of the packaging operations carried out, including references to equipment and the packaging lines used;

5.33.7. whenever possible, samples of printed packaging materials used, which include the batch or lot number, expiry date and any additional overprinting;

5.33.8. notes on any special problems or unusual events

including details, with date and signed authorisation from the manufacturing formula and processing instructions; and

5.33.9. the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation.

Standard Operating Procedures (SOPs) and Records

5.34. There shall be written procedures and records for the receipt of each delivery of each starting materials and packaging material.

The records of the receipts shall include:

5.34.1. the name of material on the delivery note and the containers;

5.34.2. the “in-house” name and/or code of material (if different from paragraph 5.34.1);

5.34.3. date of receipt, date and signature of the receiving staff;

5.34.4. supplier’s name and manufacturer’s name;

5.34.5. manufacturer’s batch or reference number;

5.34.6. total quantity and number of containers received;

5.34.7. the batch number assigned after receipt; and

5.34.8. any relevant comment (e.g. state of the containers).

5.35. There shall be written procedures for the internal labelling, quarantine and storage of starting materials, packaging materials, and other materials, as appropriate.

5.36. Standard operating procedures shall be available for the operation of each equipment and placed in close proximity to the instrument or equipment.

5.37. There shall be standard operating procedures for sampling, which specify the person(s) authorised to take samples, sampling tools,

and the sampling instructions.

5.38. There shall be a standard operating procedure describing the details of the batch or lot numbering system, with the objective of ensuring that each batch of intermediate, bulk, or finished product is identified with a specific batch number. The batch numbering procedures shall assure that the same batch numbers will not be repeatedly used; this applies also to reprocessing.

5.39. Batch number allocation shall be immediately recorded, e.g. in a logbook. The record shall include date of allocation, product identity, and size of batch.

5.40. The standard operating procedures for batch numbering that are applied to the processing stage and to the respective packaging stage shall be related to each other.

5.41. Written procedure for quarantine, release and rejection shall be available for materials and products, and in particular for the release for sale of the finished product by the authorised person.

5.42. Records shall be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.

5.43. Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached shall be available for:

5.43.1. equipment assembly;

5.43.2. operation of analytical apparatus and calibration;

5.43.3. maintenance, cleaning, and sanitisation of equipment and premises;

5.43.4. personnel matters including qualification, GMP training, clothing, and hygiene;

5.43.5. environmental monitoring;

5.43.6. pest control;

5.43.7. adverse product reactions, complaints, and product recalls;

5.43.8. returns and recovered products, rejected products or

materials;

5.43.9. disposal and destruction of the rejected products or materials; and

5.43.10. self-inspection or quality audit.

5.44. Logbooks shall be kept for major or critical equipment and shall record, as appropriate, any calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.

5.45. Logbooks shall be recorded in chronological order for the use of all equipment and the areas where the products have been processed.

5.46. Several of the abovementioned procedures, specifications, and/or records may be combined together in one specific document.

CHAPTER 6

PRODUCTION

Principle

With the premises and equipment provided, the processes used in production shall be capable of yielding finished products which conform to their specifications. Defined manufacturing procedures are necessary to ensure that production, QC, and other relevant personnel are instructed on the details of the processes concerned.

General

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

6.2. All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging, and distribution shall be done in accordance with written procedures or instructions and, where necessary, recorded.

6.3. All incoming materials shall be checked to ensure that the consignment corresponds to the order. Containers shall be cleaned where necessary and labelled with the prescribed data.

6.4. Damage to containers and any other problem, which might adversely affect the quality of a material, shall be investigated, recorded, and reported to the QC Department.

6.5. Incoming materials and finished products shall be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

6.6. Intermediate and bulk products purchased as such shall be handled on receipt as though they were starting materials.

6.7. All materials and products shall be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.

6.8. Checks on yields, and reconciliation of quantities shall be carried out as necessary to ensure that there are no discrepancies

outside acceptable limits.

6.9. Operations on different products shall not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.

6.10. At every stage of processing, products and materials shall be protected from microbial and other contamination. Any treatment used to reduce fungal or microbial contamination or other infestation shall be documented.

6.11. When working with dry materials and products, special precautions shall be taken to prevent the generation and dissemination of dust.

6.12. At all times during processing, all materials, bulk containers, major items of equipment and where appropriate, rooms used shall be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication shall also mention the stage of production.

6.13. Labels applied to containers, equipment, or premises shall be clear, unambiguous, and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example, quarantined, accepted, rejected, clean, etc.).

6.14. Checks shall be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

6.15. Access to production premises shall be restricted to authorised personnel.

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

Verification

6.17. Verification work that is needed to prove control of critical aspects of particular operations shall be identified and documented. Significant changes to the facilities, equipment, testing and the processes which may affect the quality of the product shall be verified. A risk assessment approach shall be used to determine

the scope and extent of verification.

Please refer to details in Appendix 2.

Prevention of Cross-Contamination in Production

6.18. Contamination of a starting material or of a product by another material or product shall be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays, or organisms from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated.

6.19. Cross-contamination shall be avoided by appropriate technical or organisational measures, for example:

6.19.1. production in segregated area, or by campaign (separation in time) followed by appropriate cleaning;

6.19.2. providing appropriate air-locks and air extraction;

6.19.3. minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

6.19.4. wearing protective clothing inside areas where products with special risk of cross-contamination are processed;

6.19.5. using the approved cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;

6.19.6. using "closed systems" of production;

6.19.7. testing for residues and use of cleaning status labels on equipment; and

6.19.8. specific provisions for sampling, weighing, mixing and processing operations of crude plants whenever dust is generated.

6.20. Measures to prevent cross-contamination and their effectiveness shall be checked periodically according to set procedures.

Starting Materials

6.21. The purchase of starting materials is an important operation which shall involve personnel who have a particular and thorough knowledge of the suppliers.

6.22. Starting materials shall only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials are discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labelling, and packaging requirements as well as complaints and rejection procedures are discussed with the manufacturer and the supplier. The supplier of the materials shall be adequately assessed and the assessment shall be recorded.

The supplier assessment programme shall include the establishment of an approved supplier list which may include alternative supplier, initial assessment before placing the supplier on the approved supplier list and periodic assessment thereafter, provision for on-site audit of the supplier premises, etc.

6.23. For each delivery, the containers shall be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.

6.24. If one material delivery is made up of different batches, each batch shall be considered as separate for sampling, testing, and release.

6.25. Starting materials in the storage areas shall be appropriately labelled. Labels shall bear at least the following information:

6.25.1. the designated name of the product and the internal code reference where applicable;

6.25.2. a batch number given at receipt; and

6.25.3. where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected).

6.26. There shall be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn shall be

identified.

6.27. Only starting materials which have been released by the QC Department and which are within their shelf-life shall be used.

6.28. Starting materials shall only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

6.29. Each dispensed material and its weight or volume shall be independently checked and the check recorded.

6.30. Materials dispensed for each batch shall be kept together and conspicuously labelled as such.

Processing Operations: Intermediate and Bulk Products

6.31. Before the introduction of a Master Formula it shall be evaluated sufficiently to determine that it is suitable for routine processing operations, and the ability of the process to be reproducible.

6.32. Production personnel shall follow defined and authorised procedures for every stage of each manufacturing process.

6.33. Any deviation from defined procedures shall be recorded and agreed upon between the head of Production Department and the head of QC Department.

6.34. Before any manufacturing begins, steps shall be taken to ensure that the work area and equipment are free from any materials, products, or documents, not required for the current operation.

6.35. Any necessary in-process controls and environmental controls shall be carried out and recorded.

6.36. Before applying labels or marks to materials and equipment, all irrelevant labels or marks previously used shall be removed.

6.37. The final yield of each production stage shall be recorded and checked against the theoretical yield range. Any significant deviation from the expected yield shall be recorded and investigated.

6.38. Storage of materials and bulk products must be under controlled

condition.

Packaging Materials

6.39. The purchase, handling, and control of primary and printed packaging material shall be accorded attention similar to that given to starting materials.

6.40. Particular attention shall be paid to printed materials. They shall be stored in adequately secure condition such as to exclude unauthorised access. Cut labels and other loose printed materials shall be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials shall be issued for use only by authorised personnel following an approved and documented procedure.

6.41. Each delivery or batch of printed or primary packaging material shall be given a specific reference number or identification mark.

6.42. Outdated or obsolete primary packaging material or printed packaging material shall be destroyed and this disposal recorded.

Packaging Operations

6.43. When setting up a programme for the packaging operations, particular attention shall be given to minimising the risk of the cross-contamination, mix-ups, or substitutions. Different products shall not be packaged in close proximity unless there is physical segregation.

6.44. Before packaging operations, steps shall be taken to ensure that the work area, packaging lines, printing machines, and other equipment are clean and free from any products, materials, or documents previously used, if these are not required for the current operation. The line-clearance shall be performed according to an appropriate checklist.

6.45. The name and batch number of the product being handled shall be displayed at each packaging station or line.

6.46. All products and packaging materials to be used shall be checked on delivery to the packaging department for quantity, identity, and conformity with the Packaging Instructions.

6.47. Containers for filling shall be clean before filling. Measures shall be taken to prevent any contaminants such as glass fragments and metal particles.

6.48. Normally, filling and sealing shall be followed as quickly as possible by labelling. If it is not the case, appropriate procedure shall be applied to ensure that no mix-ups or mislabelling could occur.

6.49. The correct performance of any printing operation (for example batch or lot numbers, expiry dates) to be done separately or in the course of the packaging shall be checked and recorded. Attention shall be paid to printing by hand which shall be re-checked at regular intervals.

6.50. Special care shall be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.

6.51. Checks shall be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly.

6.52. Printed and embossed information on packaging materials shall be distinct and resistant to fading or erasing.

6.53. On-line control of the product during packaging shall include at least checking the following:

6.53.1. general appearance of the packages;

6.53.2. whether the packages are complete;

6.53.3. whether the correct products and packaging materials are used;

6.53.4. whether any over-printing is correct; and

6.53.5. correct functioning of line monitors.

6.54. Samples taken away from the packaging line shall not be returned.

6.55. Products which have been involved in an unusual event shall only be reintroduced into the process after special inspection, investigation, and approval by authorised personnel. Detailed record shall be kept of this operation.

6.56. Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced shall be investigated and satisfactorily accounted for before release.

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

Finished Products

6.58. Finished products shall be held in quarantine until their final release under conditions established by the manufacturer.

6.59. The evaluation of finished products and documentation which is necessary before release of product for sale is described in Chapter 7 (Quality Control).

6.60. After release, finished products shall be stored as usable stock under conditions established by the manufacturer.

Rejected, Recovered, and Returned Materials

6.61. Rejected materials and products shall be clearly marked as such and stored separately in restricted areas. They shall either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken shall be approved and recorded by authorised personnel.

6.62. The reprocessing of rejected products shall be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. Record shall be kept of the reprocessing.

6.63. The recovery of all or part of earlier batches which conform to the required quality by incorporation into a batch of the same product at the defined stage of manufacture shall be authorised beforehand. This recovery shall be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life. The recovery shall be recorded.

6.64. The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, shall be considered by the QC Department.

6.65. Products returned from the market and which have left the control of the manufacturer shall be destroyed unless without doubt their quality is satisfactory; they may be considered for re-sale, re-labelling, or recovery in a subsequent batch only after they have been critically assessed by the QC Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued shall all be taken into account in this assessment. Where any doubt arises over the quality of the product, it shall not be considered suitable for reissue or reuse, although basic chemical reprocessing to recover active ingredient may be possible. Any action taken shall be appropriately recorded.

CHAPTER 7

QUALITY CONTROL

Principle

Every manufacturing establishment shall have a QC system so designed as to ensure that the product is manufactured in accordance with adequate conditions and procedures and continue to meet the established specifications.

QC is not confined to laboratory operations but must involve all decisions which may concern the quality of the product.

For this purpose, there shall be an appropriate and independent QC Department.

General

7.1. QC is concerned with sampling, specifications, testing, organisation, documentation, and release procedures which ensure that the necessary tests are in fact carried out, and that the materials are not released for use, nor products released for sale and supply until their quality has been assessed to be satisfactory.

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

7.3. If the in-house QC Department cannot perform certain specific analysis, the services of accredited or recognised external laboratory can be used to conduct the tests.

7.4. Finished products assessment shall embrace all relevant factors, including production condition, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification, and examination of final finished pack.

7.5. QC personnel shall have access to production areas for sampling and investigation as appropriate.

7.6. QC personnel shall have particular expertise in products in order

to be able to carry out identification tests and recognise adulteration, the presence of fungal growth, infestations, and non-uniformity when receiving and checking crude materials.

7.7. The identity and quality of materials and finished products shall be checked or tested. The presence of individual ingredient in pre-mixes shall be confirmed.

7.8. Besides these principal duties, the QC Department as a whole will also have other duties, such as to establish and implement all QC procedures, keep the reference samples of materials and products, ensure the correct labelling of containers of materials and products, ensure the monitoring of the stability of the products, etc. All these operations shall be carried out in accordance with written procedures and recorded.

7.9. The stability of the finished product shall be monitored according to a continuous appropriate programme that will permit the detection of any stability issue associated with the formulation in the marketed package.

Sampling

7.10. Due to the fact that crude material shall be an aggregate of individual natural materials i.e. contain an element of heterogeneity, the sampling has to be carried out with special care by competent personnel. Each batch shall be identified by its own documentation.

7.11. The sample taking shall be done in accordance with approved written procedures that describe:

7.11.1. the method of sampling;

7.11.2. the equipment to be used;

7.11.3. the amount of the sample to be taken;

7.11.4. instructions for any required subdivision of the sample;

7.11.5. the type and condition of the sample container to be used;

7.11.6. the identification of containers sampled;

7.11.7. the storage conditions; and

7.11.8. instructions for the cleaning and the storage of sampling equipment.

7.12. Reference samples shall be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process).

7.13. Sample containers shall bear a label indicating the contents, with the batch number, the date of sampling, and the containers from which samples have been drawn.

7.14. Reference samples from each batch of finished products shall be retained till one year after the expiry date. Finished products shall usually be kept in their final packaging and stored under the recommended conditions. Samples of starting materials (other than solvents, gases and water) shall be retained for at least two years after the release of the product if their stability allows. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter. Reference samples of materials and products shall be of a size sufficient to permit at least a full re-examination.

Testing

7.15. All testing operations described in the marketing authorisation shall be carried out according to approved methods which shall be internationally accepted (refer to Appendix 1) or other validated test methods.

7.16. The results obtained shall be recorded and verified to make sure that they are consistent with each other. Any calculations shall be critically examined.

7.17. The test performed shall be recorded, and the records shall include at least the following data:

7.17.1. name of the material or product and, where applicable, dosage form;

7.17.2. batch number and, where appropriate, the manufacturers and/or supplier;

7.17.3. references to the relevant specifications and testing procedures;

7.17.4. test results, including observations and calculations, and reference to any certificates of analysis;

7.17.5. dates of testing, the name of the analyst, and the name of the external laboratory, if applicable;

7.17.6. date and signature of the persons who performed the testing;

7.17.7. date and signature of the persons who verified the testing and the calculations, where appropriate; and

7.17.8. a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

7.18. All the in-process controls, including those made in the production area by production personnel, shall be performed according to methods approved by QC and the results recorded.

7.19. Special attention shall be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media. They shall be prepared in accordance with written procedures and recorded.

7.20. Laboratory reagents intended for prolonged use shall be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and culture media shall be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardisation and the last current factor shall be indicated.

7.21. For some kinds of data (e.g. analytical test results, yields, environmental controls) it is recommended that records in a manner permitting trend evaluation be kept.

7.22. In addition to the information which is part of the batch record, other original data such as laboratory notebooks and/or reports shall be retained and readily available.

On-Going Stability Programme

7.23. After marketing, the stability of the product shall be monitored according to a continuous appropriate programme that will permit the detection of any stability issue associated with the formulation in the marketed package.

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

7.25. This mainly applies to the product in the package in which it is marketed or sold, but consideration shall also be given to the inclusion in the programme of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product shall be evaluated and studied under ambient conditions. In addition, consideration shall be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored on an on-going basis. However, when relevant, the stability of reconstituted product can also be monitored.

7.26. The on-going stability programme shall be described in a written protocol and results formalised as a report. The equipment used for the on-going stability programme (stability chambers among others) shall be qualified and appropriately maintained.

7.27. The protocol for an on-going stability programme shall extend to the end of the shelf-life period and shall include the following parameters:

7.27.1. number of batch(es) per strength and different batch sizes, where applicable;

7.27.2. relevant physical, chemical, microbiological and biological test methods, stability indicating parameters, where applicable;

7.27.3. acceptance criteria;

7.27.4. reference to test methods;

7.27.5. description of the container closure system(s);

7.27.6. testing intervals (time points);

7.27.7. description of the conditions of storage; and

7.27.8. other applicable parameters specific to the finished product.

7.28. The protocol for the on-going stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorisation dossier provided that this is justified and documented in the protocol.

7.29. The number of batches and frequency of testing shall provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, shall be included in the stability programme (unless none are produced during that year). Scientific justification has to be provided in the event that the principle of bracketing and matrixing designs is applied.

7.30. In certain situations, additional batches shall be included in the on-going stability programme. For example, an on-going stability study shall be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing, or recovery operation shall also be considered for inclusion.

7.31. Results of on-going stability studies shall be made available to key personnel and, in particular, to the Authorised Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there shall be a written agreement between the parties concerned. Results of on-going stability studies shall be available at the site of manufacture for review by the regulatory authority.

7.32. Out of specification or significant atypical trends shall be investigated. Any confirmed out of specification result, or significant negative trend, shall be reported to the regulatory authority. The possible impact on batches on the market shall be considered in accordance with Chapter 9 (Complaints and Product Recalls) and in consultation with the regulatory authority.

7.33. A summary of all the data generated, including any interim conclusions on the programme, shall be written and maintained. This summary shall be subjected to periodic review.

7.34. For stability study requirements, reference shall be made to the Annex V (ASEAN Guidelines on Stability Study and Shelf-Life of Health Supplements).

CHAPTER 8

CONTRACT MANUFACTURE AND ANALYSIS

Principle

Contract manufacture and analysis must be correctly defined, agreed, and controlled in order to avoid misunderstandings which could result in a product or work of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties and responsibilities of each party. The contract must clearly state the way in which the authorised person releasing each batch of product for sale exercises his full responsibility.

Contract Manufacture

8.1. Contract manufacture shall have a written contract agreement between the Contract Giver and the Contract Acceptor, which clearly establishes the duties and responsibilities of each party. All arrangements for contract manufacture, including any proposed changes in technical or other arrangements, shall be in accordance with the regulatory authority requirements for the product concerned.

Contract Analysis

8.2. Contract analysis must have a written contract agreement between the Contract Giver and the Contract Acceptor which clearly establishes the duties and responsibilities of each party.

8.3. All arrangements for contract analysis, including any proposed changes in technical or other arrangements, shall be in accordance with the regulatory authority's requirements for the product concerned.

The Contract Giver

8.4. The Contract Giver shall be responsible for assessing the competency of the Contract Acceptor in successfully carrying out the work or test required and for ensuring by means of the contract that the principles of GMP described in these guidelines are followed.

8.5. The Contract Giver shall provide the Contract Acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the regulatory authority requirements. The Contract Giver shall ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products.

8.6. The Contract Giver shall ensure that all products and materials delivered by the Contract Acceptor comply with their specifications.

The Contract Acceptor

8.7. The Contract Acceptor has adequate premises, equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the Contract Giver. Contract manufacture shall be undertaken only by a manufacturer who is the holder of a manufacturing authorisation issued by the regulatory authority.

8.8. The Contract Acceptor shall ensure that all products or materials received are suitable for their intended purpose.

8.9. The Contract Acceptor shall not pass to a third party any of the work entrusted to him under the contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party shall ensure that the manufacturing and the analytical information is made available in the same way as between the original Contract Giver and Contract Acceptor.

8.10. The Contract Acceptor shall refrain from any activity that may adversely affect the quality of the product manufactured or tested for the Contract Giver.

The Contract

8.11. A contract shall be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities relating to the manufacture and the control of the product. Technical aspects of the contract shall be drawn up by competent persons suitably knowledgeable in HS manufacturing, analysis and GMP. All arrangement for manufacture and analysis must be

in accordance with the regulatory authority requirement and agreed by both parties.

8.12. The contract shall specify the way in which the head of QC Department releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of the regulatory authority.

8.13. The contract shall describe clearly who is responsible for purchasing materials, testing and releasing materials, undertaking production and QC, including in-process controls, and who has responsibility for sampling and analysis. In case of contract analysis, the contract shall state whether or not the Contract Acceptor shall take samples at the premises of the manufacturer.

8.14. Manufacturing, analytical, and distribution records, and reference samples shall be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect or recall procedures of the Contract Giver.

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

8.16. In the case of contract analysis, the Contract Acceptor shall understand that he is subject to inspection by the regulatory authority.

CHAPTER 9

COMPLAINTS AND PRODUCT RECALLS

Principle

All complaints and other information concerning potentially defective products must be kept and reviewed according to written procedures. In order to provide for all contingencies, a system shall be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

Product Complaints

9.1. Product complaints are usually concerned with the quality of the product such as its physical properties, or condition of its packaging. Complaints (internal or external) could be made to the manufacturer, verbally or in writing, by consumers, distributors, or the regulatory authority.

9.2. All complaints shall be investigated and evaluated. Written procedures describing the handling of all written and verbal complaints regarding the product shall be established and followed. Such procedures shall include provisions for review by the QC unit. A written record of each complaint shall be maintained in a file designated for product complaints.

9.3. A person shall be designated responsible for handling the complaints.

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

9.5. Any complaint concerning a product defect shall be recorded with all the original details and thoroughly investigated. The person responsible for QC shall be part of the team.

9.6. Special attention shall be given in establishing whether the product which is the subject of a complaint is a genuine or counterfeit product.

9.7. If a product defect is discovered or suspected in a batch, consideration shall be given to check other batches in order to

determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch shall be investigated.

9.8. All decisions and measures taken as a result of a complaint shall be recorded and referenced to the corresponding batch records.

9.9. Complaint records shall be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.

9.10. For recurring problem, a trending shall be established in order to identify the possible systemic defects.

9.11. The regulatory authority shall be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, or any other serious quality problems with a product.

9.12. The regulatory authority and the complainant shall be furnished with a summary of the action taken.

Product Recalls

9.13. Responsibility and procedures for recall of the product shall be established by the manufacturer to facilitate the recall of a batch from any link of the distribution chain when this becomes necessary.

9.14. The recall procedures shall take into account the degree and level of recall which is in line with the regulatory authority requirement.

9.15. Any action taken to recall a product suspected or known to be defective or hazardous, shall be done immediately and in accordance with a pre-determined plan. The procedures to be followed shall be specified in writing and made known to all that may be concerned.

9.16. A person shall be designated as responsible for execution and coordination of recalls and shall be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person shall normally be independent of the sales and the regulatory authority requirements.

9.17. There shall be established written procedures, regularly checked and updated when necessary, in order to organise any recall activity.

9.18. Recall operation shall be capable of being initiated immediately and at any time.

9.19. All regulatory authorities of all countries to which products may have been distributed shall be informed immediately if products are intended to be recalled because they are, or are suspected of, being defective.

9.20. The distribution records shall be readily available to the person(s) responsible for recalls, and shall contain sufficient information on distributor, importer, retailer, or wholesalers and directly supplied customers (with latest and valid addresses, contact number including mobile phone, phone and/or fax numbers inside and outside working hours, batches, and amounts delivered), including those for exported products.

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

9.22. The progress of the recall process shall be recorded and a final report issued, including reconciliation between the delivered and recovered quantities of the products.

9.23. The effectiveness of the arrangements for recalls shall be evaluated regularly.

Complaints on Adverse Product Reactions

9.24. Unexpected adverse product reactions resulting from the use of the product must be thoroughly investigated and documented. Reports of serious unexpected adverse reactions shall be immediately forwarded to the regulatory authority.

CHAPTER 10

SELF-INSPECTION

Principle

Self-inspections shall be conducted in order to monitor the implementation and compliance with GMP principles and to propose necessary corrective measures.

10.1. Personnel matters, premises, equipment, documentation, production, QC, distribution of the products, arrangements for dealing with complaints and recalls, and self-inspection, shall be examined at intervals following a pre-arranged programme in order to verify their conformity with the principles of QA.

10.2. Self-inspection shall be conducted in an independent and detailed way by designated competent person(s) from the company. The independent audits by external experts may also be useful.

10.3. All self-inspections shall be recorded. Reports shall contain all the observations made during the inspections and, where applicable, proposals for corrective actions and preventive actions, and corresponding time frames. Statements on the actions subsequently taken shall also be recorded.

Glossary

For the purposes of this Annex:

(a) **adverse product reactions** means an allergic or any other untoward reaction, toxic reaction, fatal or near fatal reaction etc., which are unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of a disease;

(b) **authorised person means** a person who is formally and properly empowered and has the authority to perform specified duties associated with the company;

(c) **batch number** means a designation (in numbers, or letters, or combination of both) that identifies the batch and that permits the complete history of the batch including all stages of production, control and distribution, to be traced and reviewed;

(d) **batch or lot** means a quantity of any HS produced during a given cycle of manufacture and from a specific formulation order, that is uniform in character and quality (the essence of a manufacturing batch is its homogeneity);

(e) **bracketing means** it is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or fill) are tested at all time points as in a full design;

(f) **bulk product** means any product that has completed all processing stages up to, but not including, final packaging;

(g) **critical steps** or **critical processes** means a step or process which can manifest as a gain or loss of specific activity and/or an increase or decrease in an impurity level, or whether the operating point is near the edge of failure and how well this can be controlled which can affect the safety, purity, or efficacy of a product;

(h) **crude means** existing in a natural state and unprocessed form;

(i) **designated name means** a name assigned to specific material or item to distinguish one from another;

(j) **documentation** means all written procedures, instructions, and records involved in the manufacture of a HS;

(k) **expiry date** means a date fixed for each individual batch before

which the batch still meets the required standard specifications for quality;

(l) **finished product** means a HS which has undergone all the stages of manufacture;

(m) **in-process control** means checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control;

(n) **intermediate product** means any material or mixture of materials which have to undergo one or more stages of processing to become a bulk product;

(o) **markers** means constituents of a natural material, which is chemically defined, and of interest for control purposes;

(p) **marketing authorisation** means an official document issued by the regulatory authority for the purpose of marketing or free distribution of a product after evaluation;

(q) **material** means any substance or component with certain physical properties that are used as components in production or manufacturing;

(r) **matrixing** means it is a design in the conduct of stability studies in such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point;

(s) **natural materials** means comminuted or powdered natural materials, extracts, tinctures, fatty or essential oils, resins, gums, balsams, expressed juices, etc. prepared from plant, animal, or mineral, and preparations whose production involves a fractionation, purification or concentration process, excluding chemically defined isolated constituents. A natural ingredient can be regarded as the active ingredient whether or not the constituents with therapeutic activities are known;

(t) **packaging means** all operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product;

(u) **packaging materials** means any material, including printed material, employed in the packaging of an HS, such as containers,

closures, bags, packing, label materials (labels, inserts, etc.), seals, binding materials, adhesives, and tapes;

(v) **product recall** means an action taken to remove a product from the market. Recalls may be initiated by the regulatory authority or a voluntary action on the part of manufacturer and distributor to carry out their responsibility to protect the public health and well-being from products that present a risk of injury or gross deception or are otherwise deceptive;

(w) **qualification** means action approving and documenting the equipment or ancillary systems are properly installed, work correctly and actually lead to expected results;

(x) **quarantine** means the status of starting materials, intermediate, bulk, and finished products set apart (physically or by system) while awaiting a decision on their suitability for processing, packaging, or distribution;

(y) **raw materials** means all materials whether active or inactive that are employed in the processing of HS;

(z) **reference** sample means a sample representing the batch of starting or packaging materials, or intermediate or finished products from which they are taken, stored for the purpose of being analysed shall the need arise during the shelf-life of the batch concerned;

(aa) **rejected** means the status of starting materials, intermediate, bulk, or finished products which are not permitted to be used for processing, packaging, or distribution and shall be discarded in a safe manner;

(bb) **released** means the status of starting materials, intermediate, bulk, or finished products which are allowed to be used for processing, packaging, or distribution;

(cc) **reprocessing** means a method of repeating the process of all or part of a batch with an unacceptable quality to undergo special or additional processing before release;

(dd) **sanitation** means hygienic control on manufacturing processes, including personnel, premises, equipment, and handling of materials (from starting materials to finished products);

(ee) **starting materials** means any substance or mixture of substances

(pre-mix) used in the production of a HS excluding packaging material; and

(ff) **verification** means confirmation, through the provision of objective evidence, that the requirements for any procedure, process, equipment, material, activity, or system have been fulfilled.

APPENDIX 1

LIST OF INTERNATIONALLY ACCEPTED REFERENCES FOR TEST METHODS[1]

1. Internationally accepted Pharmacopoeia including European Pharmacopoeia, US Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia

2. International Organization for Standardization (ISO)

   - ICS 67 – Food Technology
   - ICS 67.050 – General methods of tests and analysis for food products

3. American Herbal Pharmacopoeia (AHP)

4. Food Chemical Codex (FCC)

5. Association of Official Analytical Chemist International: Official Methods of Analysis

6. Microbiologicals: Food and Drug Administration Bacteriological Analytical Manual

7. Office of Dietary Supplement, National Institute of Health. US: Dietary Supplement Analytical Methods/Reference Materials (AMRM) Program
   http://ods.od.nih.gov/Research/AMRMProgramWebsite.aspx

8. WHO – Quality Control Methods for Herbal Materials

9. TLC Atlas of Chinese Crude Drugs in Pharmacopeia of The People's Republic of China Vol. 1

[1] The use of this list is subject to the consideration, regulations, and prerogative of each national regulatory authority. Other references may be considered by national regulatory authority, provided that the test methods are validated against guidelines or parameters defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use or ASEAN Guidelines for Validation of Analytical Procedures.

APPENDIX 2

VERIFICATION

Principle

1. This Appendix describes the principles of verification which are applicable to the manufacture of HS products.

   Accordingly, and in this Appendix, verification shall refer to the documented act or conduct of confirmation that the control or procedure required in a particular critical aspect of manufacturing operation has been complied with or satisfactorily implemented by the manufacturer based on risk assessment and risk management.

   Re-verification shall be performed if there are significant changes to the facilities, systems, processes, and equipment that may have impact on the quality of the finished products, and the changes would require regulatory approval. Where there are no significant changes, periodic review shall be performed to show that the facilities, systems, processes, and equipment continue to meet the prescribed requirements.

Documentation

2. A Verification Programme which includes written procedure(s) shall be established to specify how the verification activities will be carried out. The documentation provided will demonstrate the QA systems needed to produce quality HS. This includes the QA systems, which consist of elements that address matters such as roles and responsibilities, employee training, document management, equipment calibration and maintenance, manufacturing and laboratory control procedures, and product shelf-life evaluation.

   A report that cross-references the verification programme and procedure shall be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including the recommending changes necessary to correct the deficiencies.

Verification of Machinery and Equipment

3. Equipment and machinery shall be periodically verified to determine if they are still operating in a valid state.

During verification it is important to use calibrated reference material e.g. NIST traceable calibrated thermometer to verify the temperature of process to determine its valid state.

Machinery and equipment to be used shall have been verified prior to the verification of process and staff taking part in verification work shall have been appropriately trained.

Verification of Process

4. General

Verification of process contributes to assuring product quality and the basic principle of QA is that a product shall be produced under such condition that is fit for its intended use.

The basic principle of QA is that a product shall be consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation and product specification.

5. Verification of process may involve demonstration, testing and analysis, and in-process control, or other relevant activities to confirm that critical processes are kept under control. A process verification report shall be prepared to provide evidence that the process has been verified.

(a) <u>Demonstration</u>

Demonstration is the operation of an item to provide evidence that it can meet its predetermined specifications and quality attributes.

Demonstrations can be conducted in actual or simulated environments.

(b) <u>Testing and Analysis</u>

Testing is the application of scientific principles and procedures to determine the properties or functional

capabilities of items. Testing is similar to demonstration, but is more exacting, generally requiring specialised test equipment, configuration, data, and procedure in order to verify that the item satisfies the requirement.

Analysis is the use of established technical or mathematical models or simulations, algorithms, or other scientific principles and procedures to provide evidence that the item meets its stated requirements.

(c) In-Process Control

Critical parameters shall be determined and monitored, checks performed during production in order to monitor and if necessary to adjust the process to ensure that the products confirm to its specification. The control of the environment or equipment may also be regarded as a part of in-process control.

Change Control

6. Written procedures shall be in place to describe the actions to be taken if a change is proposed to a starting material, product component, process equipment, process environment (or site), method of production or testing, or any other change that may affect product quality or reproducibility of the process. Change control procedures shall ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specifications.

7. All changes that may affect product quality or reproducibility of the process shall be formally requested, documented, and approve by the relevant department. The likely impact of the change of facilities, systems, and equipment on the product shall be evaluated, including risk analysis. The need for, and the extent of, re-verification of machinery and equipment and re-verification of process shall be determined.

ANNEX IX

ASEAN GUIDELINES ON LABELLING REQUIREMENTS FOR HEALTH SUPPLEMENTS

Disclaimer:

This document is provided for information purpose only and subject to changes, pending the finalisation of the ASEAN Agreement on Regulatory Framework for Health Supplements. Official references to this document can only be made once the said Agreement has been finalised.

Introduction

The ASEAN Guidelines on Labelling Requirements for Health Supplements applies to Health Supplements (HS) to ensure the safe and effective use of HS among consumers and facilitate registration process among Member States. It also promotes proper storage and logistic condition.

Guiding Principles

1. HS shall not be described or presented on any label or in any labelling in a manner that is false, misleading, or deceptive or is likely to create an erroneous impression regarding its character in any aspect.

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

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

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

Languages used for labelling in each Member State are as follows:

- in Brunei Darussalam, the official language is Bahasa Melayu or Malay. Label information shall be in Malay and/or English. However, in the event there is contradiction, the interpretation provided in Malay will prevail. Nevertheless, English is still recognised in Brunei Darussalam as an authentic text;

- in Cambodia, the official language is Khmer. Label information shall be in Khmer. However, other languages, such as English and French, may be used in addition to Khmer;

- in Indonesia, the official and national language is Bahasa Indonesia, therefore the language in the label shall be written in Bahasa Indonesia. However, other languages may be used in addition to Bahasa Indonesia;

- in Lao PDR, the official language is Lao. Label information shall be in Lao. However, other languages in smaller fonts, such as English, may be used in addition to Lao;

- in Malaysia, the official language is Malay, however, the label information shall be in Malay and/or English. Other languages, such as Mandarin, Tamil, Arabic, if any, may be used in addition to these two languages;

- in Myanmar, the official language is Myanmar, therefore, the language in the label shall be in Myanmar. However, other languages, such as English, may be used in addition to Myanmar;

- in the Philippines, the official languages are Filipino and English. Label information shall be in English and/or Filipino. Other languages, if any, may be used in addition to these two languages;

- in Singapore, the official languages are Malay, Chinese, Tamil, and English. However, label Information shall be in English. Other languages, if any, may be used in addition to English;

- in Thailand, the official and national language is Thai, therefore, the language in the label shall be in Thai.

However, other languages, such as English, may be used in addition to Thai; and

- in Viet Nam, the official language is Vietnamese. Label information shall be in Vietnamese. However, other languages may be used in a font size not larger than Vietnamese.

General Labelling Requirements for HS

The following information shall appear on the label of HS.

1. Product Name

The product name and the brand name, if applicable, should not be misleading or deceptive to the consumer. The product and brand names should be deemed appropriate by the respective Member States.

2. Dosage Form

3. Name and Strength of Active ingredient

The name and quantity of plants or animals from which the active ingredient is derived should be declared in scientific name followed by plant part constituting the crude drug and type of preparation, where applicable. The use of the common or local name of the active ingredient is optional. For mineral, common or chemical name should be used.

For example:

- Each capsule contains: Curcuma longa (rhizome) 350 mg.
- Each capsule contains: Compound herbal extract 20 mg.
- Prepared from leaves of Plant A, Root of Plant B, and leaves of Plant C

4. Batch or lot number

Each container shall be printed or permanently marked. The batch or lot number shall be preceded by title such as “Batch number”, “BN”, etc.

5. *Manufacturing and expiry date, or expiry date only*

The manufacturing date and expiry date, or expiry date only should be declared as month and year and preceded by title such as “Manufacturing date”, “MFG” “Expiry date”, “EXP”, etc.

6. *Directions of use*

Directions of use must clearly state the route of administration as well as the dose for each target population for which the product is intended.

7. *Indication or Intended use*

The statement of the purpose or intention of use for HS should be declared according to the Annex VII (ASEAN Guidelines on Claims and Claims Substantiation for Health Supplements).

8. *Storage condition*

The statement declares a condition to which the HS should be stored properly until the expiry date. Refer to Annex V (ASEAN Guidelines on Stability Study and Shelf-Life of Health Supplements).

9. *Country’s registration, listing, or notification number (if applicable)*

The combination of numbers, symbols, and letters assigned to the HS which is approved by the regulatory authority shall be declared, if applicable.

10. *Name and address of manufacturer*

The complete name and address of the manufacturer of the product shall be declared.

11. *Name and address of marketing authorisation holder or importer*

The complete name and address of the marketing authorisation holder or importer of the product shall be declared.

12. *Warning (if any)*

The statement declares a warning for consumers’ awareness before using HS. The warning statement assigned by the regulatory authority should be declared. The term “Warning” can

be used interchangeably, but is not limited to terms such as “Side Effects”, “Contraindications”, and “Precautions” as appropriate.

13. Pack size

The net contents shall be declared in the metric system. The net contents shall be declared in the following manner:

- for liquid form, by volume;
- for solid form such as tablet, soft capsule, hard capsule, powder, etc. by weight or amount; and
- for semi-solid or viscous form, either by weight or volume.

14. Special statements

- alcohol content, if any
- for external use, as applicable

Small Label

The small label should declare at least the following:

1. product name and brand name, if applicable;
2. country‘s registration, listing, or notification number (country specific);
3. batch or lot number;
4. manufacturing and expiry date, or expiry date only; and
5. other information according to general labelling requirements should be declared on package insert and/or another container or accompanied with a catch cover.

Strip or Blister Pack Label

The label on strip or blister pack should declare at least the following:

1. product name and brand name, if applicable;

2. country‘s registration, listing, or notification number (country specific);

3. batch or lot number;

4. manufacturing and expiry date, or expiry date only; and

5. other information according to general labelling requirements should be declared on package insert and/or another container or accompanied with a catch cover.

Country Specific Requirements for HS

Country specific requirements are allowed if they are deemed necessary for the reasons of identification, safety, quality, culture, and religion. Such country specific requirements with reasons should however be made known to the other Member States and be updated into the compilation of country specific requirement for HS from Member States in a timely manner. However, minimisation of country specific requirement should be encouraged.

The compilation of country specific requirement for HS from Member States appears in Appendix 1.

Glossary

For the purposes of this Annex:

(a) **active ingredient** means a substance produces the intended activity of a HS;

(b) **batch or lot number** means a designation (in numbers, or letters, or combination of both) that identifies the batch and that permits the complete history of the batch including all stages of production, control, and distribution, to be traced and reviewed;

(c) **container** means an article that contains and protects the HS. This includes primary packaging components and/or secondary packaging components, if latter are intended to provide additional protection to the product. The packaging components shall be a blister pack, strip pack, bottle, sachet, tube, or other similar articles, but does not include an article intended for ingestion;

(d) **country's registration, listing, or notification number** means the combination of numbers, symbols, and letters reflecting the identification of a HS issued by the regulatory authority;

(e) **dosage form** means the form in which HS are marketed for use (e.g. tablet, capsule, solution, powder, etc.) that contains active ingredient(s) generally, but not necessarily, in association with excipients;

(f) **expiry date** means a date fixed for each individual batch before which the batch still meets the required standard specifications for quality;

(g) **indication or intended use** means a statement of the purpose or purposes for which HS is intended to be used;

(h) **labelling** means all information that appears on the container, including that on the outer packaging such as carton;

(i) **manufacturer** means a company that carries out at least one step of production as well as the final release of the finished product;

(j) **manufacturing date** means a date fixed for the individual batch, indicating the starting date of the manufacture;

(k) **marketing authorisation holder** means the company or corporate or legal entity in the field of HS in whose name the marketing

authorisation has been granted. This party is responsible for all aspects of the product, including quality and compliance with the conditions of marketing authorisation. The party must be subjected to legislation in the country that issued the marketing authorisation, which normally means being physically located in that country;

(l) **package insert** means any printed information supplied with the container or primary pack;

(m) **small label** means a label with very limited space to display minimal information requirements in the small container as described in the general labelling requirements for HS. The dimension of small label shall be determined by each Member State; and

(n) **strip or blister pack label** means a label affixed to or printed on the strip or blister pack. The strip or blister pack needs to be repacked in another container or accompanied with a catch cover whose label can display information described in general labelling requirements for HS so that consumers can obtain such information at the point of purchase.

References Used

1. *CODEX Alimentarius International Food Standards. General Standard for the Labelling of Prepackaged Foods. Labelling of Prepackage Food (CODEX STAN 1-1985) 2008:1-7.*

2. Therapeutic Goods Administration (TGA). Registration of Complementary Medicines. Australian Regulatory Guidelines for Complementary Medicines (ARGCM) 2005.

3. *Therapeutic Goods Administration (TGA). General requirements for labels for medicines Therapeutic Goods Act 1989: Therapeutic Goods Order No.69 2001.*

4. *EUROPEAN COMMISSION. Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use. Belgium: 2006.*

5. *ASEAN Guidelines on Good Manufacturing Practice for Health Supplements.*

APPENDIX 1

COUNTRY SPECIFIC REQUIREMENTS FOR LABELLING OF HEALTH SUPPLEMENTS

Country	Country Specific Requirements
Brunei Darussalam	Sources of ingredients derived from animal origin including gelatine
Cambodia	"Health supplements" / "Food supplements" / "Dietary supplements" *Note:* - *The product name should be clearly stated on the label.*
	"This product is not medicine and it is not intended to replace medicine"
	Font size *Note: The size of the letter of the health supplement's name must be bigger than the size of the other letters.*
Indonesia	"Health supplements" / "Food supplements" / "Dietary supplements" *Note:* - *The product must be labelled with the words "suplemen kesehatan"*
	Statement on additive added (preservative, colorant, flavour, sweetener) in line with Indonesian regulations
	Sources of ingredients derived from animal origin including gelatine *Note:* - *If porcine, this parameter is justified by Act & Decrees.* - *For product containing porcine, in line with Indonesian regulations, add this statement that this product contains animal part(s) (porcine or pig), but written in Indonesian language as follows:* **MENGANDUNG BABI**

Country	Country Specific Requirements
	Recommended daily allowance (RDA) for vitamins or minerals used as health supplements in line with Indonesian regulations
	Font size *Note:* - *The size of the letter of the health supplement's name must be bigger than the size of the other letters.* - *2D barcode should be applied on the label.*
Lao PDR	"Health supplements" / "Food supplements" / "Dietary supplements"
	"This product is not medicine and it is not intended to replace medicine"
Malaysia	Statement on additive added (preservative, colorant, flavour, sweetener) *Note: Name and content of preservative(s), where present.*
	Hologram
	Sources of ingredients derived from animal origin including gelatine *Note:* - *For product containing animal part(s), please add this statement: This product contains animal part(s).* - *For product containing animal origin(s), please add this statement: This product contains substance(s) from animal origin.* - *For product containing porcine, please add this statement: This product contains animal part(s) (porcine or pig).*
	The words "Keep out of reach of children" or words bearing similar meaning in both Malay & English
	Use of the HALAL logo will be considered for HS for both the local and export market, provided that such products have been certified and approved as HALAL by the local authority
Myanmar	"Health supplements" or alike
	General labelling requirements as issued by Department of Traditional Medicine and Myanmar Consumer Protection Commission
Philippines	"Food supplements" / "Dietary supplements"

Country	Country Specific Requirements
	Recommended daily allowance (RDA) for vitamins or minerals used as food or dietary supplements *Note: Revised standard terms as 2002 Recommended Energy and Nutrients Intakes (RENI) per day (adopted as per Bureau Circular No.16 s.2005).*
	The caption "NO APPROVED THERAPEUTIC CLAIMS" shall be printed in the principal display panel of all labelling materials, font size 14, font type Arial, all capital and bold letters *Note: As per Memorandum Circular No.2 s. 1999.*
	Allergen information, as applicable and Nutrition Information/Facts and Expiry or Expiration Date Format – Day Month Year *Note: As per Administrative Order 2014-0030 Revised Rules and Regulations Governing the Labeling of Prepackaged Food Products further amending certain provisions of Administrative Order No. 88-B s. 1984 or the Rules and Regulations Governing the Labeling of Pre-packaged Food Products Distributed in the Philippines", and for Other Purposes.*
	Guidelines on Generic Labelling requirements as issued by the Food and Drug Administration (Philippines) such as: Administrative Order No. 2016-0008 Revised Rules and Regulations Governing the Generic Labeling Requirements of Drug Products for Human Use
Singapore	-
Thailand	"Food supplements" *Note: Notification No.293 (2005 Re: Food Supplement).*
	Statement on food additives added (i.e. preservative, colorant, flavour, sweetener) *Note: Notification No.293 (2005 Re: Food Supplement).*
	The term "Warning" shall be used with the following statement: "Should not be consumed by children and pregnant women" "Should eat varieties of five food categories regularly in appropriate proportion" "No effect for prevention or treatment of diseases" *Note: Notification of the Ministry of Public Health (No. 411) B.E.2562 Issued by virtue of the Food Act B.E. 2522 Re: Food Supplements (no.4).*

Country	Country Specific Requirements
Viet Nam	“Health supplements” / “Food supplements” / “Dietary supplements”
	“This product is not medicine and it is not intended to replace medicine”

ANNEX X

ASEAN GENERAL PRINCIPLES FOR ESTABLISHING MAXIMUM LEVELS OF VITAMINS AND MINERALS IN HEALTH SUPPLEMENTS

Disclaimer:

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Purpose

The main purpose of establishing maximum daily intake levels (ML)[1] of vitamins and minerals in Health Supplements (HS) for ASEAN (ASEAN ML) is to ensure manufacturers only include safe levels of vitamins and minerals in their HS products so that the normal use of the products under the instructions of use provided by the manufacturers will be safe for the consumers. The ASEAN MLs are not intended to be used as the levels of vitamins and minerals in HS that would bring beneficial effects to the ASEAN population.

Scope

The following vitamins and minerals widely found in HS may be considered for the establishment of ASEAN ML:

Vitamins	**Minerals**
Vitamin A (Retinol)	Calcium
Vitamin D	Potassium
Vitamin E	Phosphorous
Vitamin K	Magnesium
Vitamin C	Boron

[1] ML means a risk management value for the highest safe intake level of Vitamins and Minerals in HS in a population.

Vitamin B1	Chromium
Vitamin B2	Copper
Vitamin B6	Fluoride
Folic acid	Iodine
Vitamin B12	Iron
Biotin	Manganese
Nicotinic acid	Molybdenum
Nicotinamide	Selenium
Pantothenic acid	Zinc

Only one set of ASEAN ML should be developed for the normal healthy adult population. As far as possible, the needs of specific population groups should be factored into the setting of ASEAN ML. If this is not possible, the needs of these subgroups could be addressed by a more targeted approach through labelling or by individual dietary advice provided by qualified health professionals. ASEAN ML for children should be developed in a more targeted approach after the development of the ASEAN ML for adults.

The establishment of ASEAN ML should consist of risk assessment and risk management. The risk assessment component involves the derivation of upper limit (UL)[2] of a nutrient based on the World Health Organization (WHO) Model. The risk management component involves managing the risk of population intake exceeding UL when deriving ASEAN ML based on the European Responsible Nutrition Alliance (ERNA) Model.

The WHO Model has limited applicability in the derivation of UL of a vitamin or mineral that has no reported adverse effects. If there is no basis for a UL because there is no evidence of adverse effects for that particular vitamin or mineral, the Highest Observed Intake (HOI), as defined in the WHO Model, should be identified.

There is no scientific basis for the use of Recommended Dietary Allowance (RDA) or Recommended Dietary Intake (RDI) in establishing ULs. The RDA or RDI is a measurement of nutritional adequacy and not a measurement of health risk due to excess intake. When the maximum

[2] UL means a risk assessment value for no adverse effects.

levels are set, due account may be taken of the reference intake values of vitamins and minerals for the population as outlined in the ERNA Model. This provision should not lead to setting of maximum levels that are solely based on RDA or RDI.

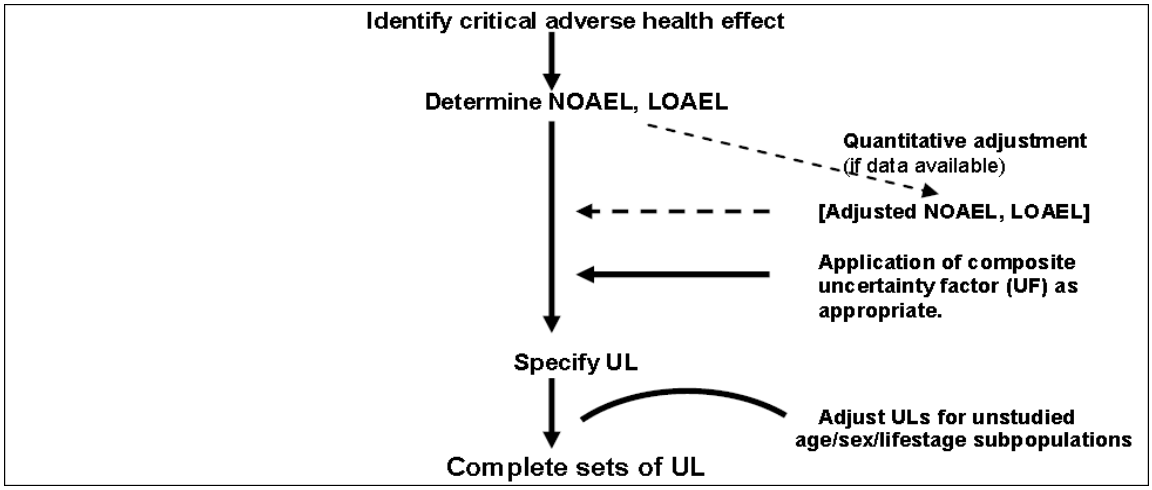
Despite the establishment of the ASEAN MLs of vitamins and minerals, Members States may consider exemption in their countries under special circumstances such as national requirements based on country exposure assessment, consumption survey, or product classification type. Such exemptions with reasons should however be made known to the other Member States.

Guiding Principles

1. Principles for Establishing Upper Limits (UL) Based on WHO Model

1.1. The model for nutrient risk assessment developed by the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Technical Workshop on Nutrient Risk Assessment 2006 (WHO Model) should be used as the guiding principle in the development of UL. In this context, consideration of existing reports by authoritative scientific bodies i.e. European Food Safety Authority (EFSA), Expert Group on Vitamins and Minerals (EVM), and Institute of Medicine, National Academies of Science (IOM) (EFSA, 2006; EVM, 2003; IOM, 1997, 1998, 2000, 2001) that had incorporated some or all of the principles of the WHO Model in their nutrient risk assessments would be informative to the development of the UL.

1.2. The UL should be derived by following the steps of quantifying UL outlined in the WHO Model i.e. identifying the critical adverse effects of the nutrient, choosing the decisive scientific data upon which Lowest Observed Adverse Effect Level (LOAEL) or No Observed Adverse Effect Level (NOAEL) is based, deciding on the value of Uncertainty Factor (UF) to assign and finally calculating UL using the formula (NOAEL ÷ UF) or (LOAEL ÷ UF). The following is a schematic representation of the steps taken from Figure 4-3 in page 40 of WHO (2006).



1.3. For the purpose of accelerating the establishment of UL, the selection of parameters to be used in the derivation of the UL, namely critical adverse effects, decisive data, LOAEL or NOAEL and UF, can be based on the data already established by EFSA, EVM, and IOM and if necessary, adjusted by newly available scientific data. The newly available scientific data should be obtained from widely recognised, authoritative, established references which have been published or peer reviewed.

1.4. UL should be derived from maximum supplement intake data wherever possible. UL can also be derived from maximum total dietary intake data if there are no relevant maximum supplement intake data. If food consumption data showed that the contributions of a specific vitamin or mineral from food were a significant fraction of the UL, the food intake data should be deducted to calculate the ASEAN ML for HS.

1.5. The rationale for the determination of each parameter used in the derivation of UL for each vitamin and mineral should be scientifically sound and properly documented. The tabulation of comparative data from EFSA, EVM, and IOM and the final set of data chosen for the derivation of UL accompanied by appropriate justification or explanation in a table format for each vitamin and mineral is deemed sufficient for this purpose.

2. Principles for Establishing Maximum Level Based on ERNA Model

2.1. The model for nutrient risk management developed by ERNA (ERNA Model) should be used as the guiding principle in the development of ASEAN ML.

2.2. Following the derivation of UL, the nutrients should be divided into three groups according to the risk of population intakes exceeding UL. Group A is for nutrients that do not have reported adverse effects and there is no risk of excessive population intakes causing human health problems. Whereas Group B and C are for nutrients with reported adverse effects. Group B is for nutrients with a low risk whereas Group C is for nutrients with a potential risk of excessive population intakes causing human health problems.

2.3. Population Safety Index (PSI), which is a measurement of the safety margin between the maximum level from supplementation and population intake from food of a particular nutrient, should be used to assign nutrients to Group B or C. Nutrients with PSI of more than 1.5 (i.e. higher safety margin) are assigned to Group B and those with PSI of equal or less than 1.5 (i.e. lower safety margin) are assigned to Group C.

Adverse Effects	**Risk Categorisation of Nutrients**	**PSI**	**Risk of Excessive Intakes Causing Human Health Problems**
None reported	Group A	-	None
Reported	Group B	> 1.5	Low
	Group C	<= 1.5	Potential

The following formula should be used for the calculation of PSI of nutrients with reported adverse effects.

PSI = (UL – Mean Highest Intakes (MHI)[3]) ÷ Reference Labelling Value (RLV)

To enable the calculation of PSI, the MHI, and the RLV of these nutrients must be established. MHI should refer to

[3] MHI means the mean of highest intakes of a nutrient from foods at 95 or 97.5 percentile.

the mean of highest intakes of a nutrient from foods (e.g. at 95 or 97.5 percentile) whereas RLV should refer to the labelling RDA of that nutrient which is being used as a surrogate of the desired population intake. Appropriate foreign MHI or RLV values should be considered in the absence of credible data from ASEAN Member States. All MHI and RLV values should be reviewed periodically.

2.4. The following formulas may be used to establish ASEAN ML:

ASEAN ML of Group A nutrients = HOI ÷ UF – MHI

ASEAN ML of Group B nutrients = UL – MHI

ASEAN ML of Group C nutrients = UL – MHI

However, appropriate risk management measures proportionate to the relative risk associated with each risk group of nutrients should be taken when using these formulas to establish the respective ASEAN ML.

For nutrients that have no established hazards at high intakes, their maximum intake levels with sufficient evidence of safety (observed safe level) may be used to establish ASEAN ML.

Special effort must be taken in the derivation of the ASEAN ML for Group C nutrients to minimise the chance of exceeding UL. In addition, appropriate risk communication can be instituted for certain Group C nutrients on a case-by-case basis if necessary.

ASEAN ML

The list of established ASEAN ML of vitamins and minerals appears as Appendix 1.

References Used

1. Joint FAO/WHO Technical Workshop on Nutrient Risk Assessment. *A model for establishing upper levels of intake for nutrients and related substances*. Geneva: World Health Organization, 2006.

2. Scientific Committee on Food and Scientific Panel on Dietetic Products, Nutrition and Allergies. *Tolerable Upper Intake Levels for Vitamins and Minerals. Parma*: European Food Safety Authority, 2006.

3. Expert Group on Vitamins and Minerals. *Safe Upper Levels for Vitamins and Minerals*. London: Food Standards Agency, 2003.

4. Institute of Medicine. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*. Washington, DC: The National Academies Press, 1997.

5. Institute of Medicine. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*. Washington, DC: The National Academies Press, 1998

6. Institute of Medicine. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington, DC: The National Academies Press, 2000.

7. Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.* Washington, DC: The National Academies Press, 2001.

8. Scientific Advisors to ERNA and EHPM. *Vitamin and mineral supplements: a risk management model*. Brussels: European Responsible Nutrition Alliance, 2004.

APPENDIX 1

ASEAN MAXIMUM LEVELS OF VITAMINS AND MINERALS IN HEALTH SUPPLEMENTS

Vitamin A (Retinol)	1.5 mg/day (5000 IU/day)
Vitamin D	0.025 mg/day (1000 IU/day)
Vitamin E	536 mg/day (800 IU/day)
Vitamin K	0.12 mg/day
Vitamin C	1000 mg/day
Vitamin B1	100 mg/day
Vitamin B2	40 mg/day
Vitamin B6	100 mg/day
Folic acid	0.9 mg/day
Vitamin B12	0.6 mg/day
Biotin	0.9 mg/day
Nicotinic acid	15 mg/day
Nicotinamide	450 mg/day
Pantothenic acid	200 mg/day
Calcium	1200 mg/day
Phosphorous	800 mg/day
Magnesium	350 mg/day
Boron	6.4 mg/day
Chromium	0.5 mg/day
Copper	2 mg/day
Iodine	0.15 mg/day
Iron	15 mg/day
Manganese	3.5 mg/day
Molybdenum	0.36 mg/day
Selenium	0.2 mg/day
Zinc	15 mg/day

Notes:

1. The conditions of use of Vitamin K are as follows:

Application:	For use in oral dosage form of multivitamin or mineral preparations for adults and not as a single ingredient HS
Vitamin K form:	Only Vitamin K1 and/or Vitamin K2
Cautionary statement:	"Consult a health care practitioner prior to use if you are on anticoagulant therapy or taking blood thinners such as warfarin"

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

3. However, due to special circumstances such as national requirements based on country exposure assessment, consumption survey, or product classification type, the established maximum levels of Vitamin A, Vitamin D, Vitamin E, Vitamin K, Vitamin B6, Folic acid, Nicotinamide, Calcium, Boron, Iodine, Iron, Molybdenum, and Selenium are not applicable to the Member States listed below. Some national maximum levels of Member States are shown in parenthesis.

Vitamin A	: Thailand (0.8 mg/day)
Vitamin D	: Thailand (0.005 mg/day)
Vitamin E	: Indonesia (400 IU (268 mg)/day) Thailand (10 mg/day)
Vitamin K	: Thailand (0.08 mg/day)
Vitamin B6	: Thailand (2 mg/day)
Folic acid	: Thailand (0.2 mg/day)
Nicotinamide	: Thailand (20 mg/day)
Calcium	: Thailand (800 mg/day)
Boron	: Thailand
Iodine	: Malaysia (0.3 mg/day) Thailand
Iron	: Indonesia (30 mg/day) Malaysia (20 mg/day[4])
Molybdenum	: Thailand (0.16 mg/day)
Selenium	: Thailand (0.07 mg/day)

[4] For pre and antenatal use, as part of a multivitamin and mineral preparation, levels higher than the 20 mg limit established for adults may be permitted at the discretion of the Drug Control Authority, Malaysia.