MEDICINES CONTROL COUNCIL

COMPLEMENTARY MEDICINES - HEALTH SUPPLEMENTS QUALITY, SAFETY, EFFICACY

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of Health Supplements. It represents the Medicines Control Council's current thinking on the quality, safety, and efficacy of thesemedicines. It is not intended as an exclusive approach. Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The MCC is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants also adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines and the website www.mccza.com.

First publication released for comment	November 2014
Deadline for comment	26 February 2015

REGISTRAR OF MEDICINES

Table of Contents

Table of Contents

Table of Contents

1 INTRODUCTION

i) Purpose

The purpose of this Guideline is to provide clear guidance with regard to the quality, safety and efficacy (QSE) requirements for registration of Health Supplements as a subset of complementary medicines in South Africa. The intent of this document is to ensure that the levels of evidence for QSE are rigorous enough to protect public health and maintain consumer confidence, while providing a clearly defined pathway to register health supplements.

ii) Scope and Overview

This guideline provides information for the registration of health supplements in South Africa. Products which include any substance of discipline specific origin would need to follow the registration procedure indicated by the Guideline for Complementary Medicines - Quality, Safety and Efficacy (Discipline Specific).

In general Complementary Medicines (CMs) are used and sold by many people in RSA. These guidelines accompany the regulations dealing with the registration and post-marketing control of health supplements that are subject to the Medicines and Related Substances Act, 1965 (Act 101 of 1965). The guidelines give direction with regard to the required information but should not in themselves be regarded as the final reference point. Where the applicant wishes to use and submit information not found in these guidelines these would have to be justified scientifically and technically.

This mechanism of registration is restricted to schedule 0 substances identified as health supplements at specified dosages. It is acknowledged, however, that in some instances developments may dictate alternative approaches. When a deviation from a guideline is required, a detailed motivation giving the reason(s) for the deviation and justification for the alternative approach should be included in the expert report submitted with the application. Guidelines are constantly evolving as a result of scientific developments and harmonisation of the requirements of regional and international regulatory authorities. The Medicines Control Council (MCC / Council) endeavours to regularly update the guidelines to reflect current thinking and keep its technical requirements and evaluation policies in line with “best international medicines regulatory practice”.

With respect to any registration of a medicine, it is a legal requirement that data submitted for evaluation should substantiate all claims and should meet technical requirements of quality, safety and efficacy of the product for the purposes for which it is intended. The nature of registration of health supplements is such that the MCC wishes to ensure that products sold to the public which fall under this classification are of good quality and are safe. Efficacy of such products is established by the use of permitted claims associated with individual ingredients. Allowance is made for the development of multiple substance formulations and their associated claims.

Over time pharmacological classifications that relate to health supplements will be called up in a staged and systematic process. This will be in line with the published recommendations contained in this document relevant to allowable levels and claims for various substances. Multiple substance formulations will be called up for registration when all lists have been populated.

ANNEXURE_A is included to help decide what would be regarded as a Category D (Complementary Medicine) substance.

1.1 Definition

The definition of "health supplement" is provided as:

"Health supplement" means any substance, extract or mixture of substances that—

a) may—
   i) supplement the diet;
   ii) have a nutritional physiological effect, or
   iii) include pre- and probiotics when used to change the microbial balance in the human or animal intestines, and

b) are sold in pharmaceutical dosage forms not usually associated with a foodstuff and excludes injectables.

Substances that are excluded from being regarded as a health supplement include:

- injectable substances;
- substances scheduled 1 or higher (when indicated for any listed purposes in the schedule);
- substances not specified in the lists of included substances (unless duly motivated for inclusion as a health supplement as per **ANNEXURE B**), or
- isolated active ingredients not provided for in the list of health supplements.

Substances (S0) that may typically considered to be a health supplement include those substances listed under the following headings as per the attached annexures:

Probiotics	**ANNEXURE C**
Prebiotics	**ANNEXURE D**
Vitamins	**ANNEXURE E**
Minerals	**ANNEXURE F**
Amino Acids	***To Follow***
Animal Extracts, Products and Derivatives	***To Follow***
Fats, Oils and Fatty Acids	***To Follow***
Carotenoids	***To Follow***
Bioflavonoids	***To Follow***
Aminosaccharides	***To Follow***
Saccharides	***To Follow***
Enzymes	***To Follow***
Other	***To Follow***

1.2 Compliance with Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP) and Good Agricultural and Collection Practices (GACP)

All manufacturers of complementary medicines shall comply with all relevant aspects of Good Manufacturing Practice as outlined in the latest version of the MCC's "GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINES IN SOUTH AFRICA" and Good Laboratory Practice by 2016 as well asthe WHO Guidelines on Good Agricultural and Collection Practices (GACP) for Medicinal Plants if applicable.

1.3 Format of submission

Data provided in applications for registration of complementary medicines should be in the latest version of the Common Technical Document (ZA-CTD) format as published by the MCC.

Data provided in applications for registration of new complementary medicines must be in the ZA-CTD format, and must consider the information requested for registration of the various medicine types.

2 QUALITY REQUIREMENTS

Refer also to Pharmaceutical & Analytical Guideline where applicable

Information is required for a product's active ingredients and its excipients. The data are evaluated to determine the quality of the product, including the identity, impurities and stability of the ingredients. The data assessment also takes into account information about the manufacturing processes and standards of good manufacturing practice (GMP), as required.

Details of quality control measures are required to demonstrate that the product will be produced to a consistent quality. Stability data for the product are required to determine a shelf life over which the product's quality is maintained. Should the results of any testing be outside the acceptable limits then appropriate action, which may include rejection or destruction, must be taken immediately.

Any animal or plant should not be listed on the IUCN Red Data List, (http://www.iucnredlist.org/technical-documents/categories-and-criteria) or South African National Biodiversity Red List of South African Plants (http://redlist.sanbi.org/redcat.php) as Near Threatened (NT), Vulnerable (V), Endangered (EN), Critically Endangered (CE) or Extinct in the Wild (EW), unless from a licensed cultivated, legal source and must adhere to the principles of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) of which South Africa is a member. Applicants may require the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) import permit if making use of substances (e.g. Hoodia, etc.) listed under the National Environmental Management: Biodiversity Act, 2004 (Act 10 of 2004). Any complementary medicine that is of animal origin must comply with the requirements of the Animal Diseases Act, 1984 (Act 35 of 1984).

2.1 Active Ingredient(s)(Module 3.2 S)

2.1.1 Sources and Identification

Applicants may choose to follow pharmacopoeias or references of equivalent standard other than those identified that may be more appropriate for specific ingredients or products.

It is expected that if a monograph is published in one of these pharmacopoeias, the pharmacopoeial monograph specifications should be considered as minimum specifications used for testing of the medicinal ingredient and finished product. If the product specifications do not include tests and tolerance limits as per the pharmacopoeial monograph, there should be justification as to why the testing is not necessary. The current official version of the pharmacopoeia should be used in all cases. In order to comply with pharmacopoeial monographs, the monograph in its entirety should be applied, including all other pharmacopoeial requirements. It is not acceptable to apply requirements from different pharmacopoeial monographs unless the monographs are harmonized or there is a suitable rationale for the mixing of pharmacopoeial standards. The product should also meet all definitions in the pharmacopoeia and general chapter being used to determine criteria.

2.1.1 Sources and Identification - continued

The following pharmacopoeiae and international standards are currently considered acceptable in their entirety:

- United States Pharmacopeia (USP)
- British Pharmacopoeia (BP)
- European Pharmacopoeia (Ph. Eur.)
- Pharmacopée française (Ph.f.)
- Pharmacopoeia Internationalis (Ph.I.)
- Japanese Pharmacopoeia (JP)
- Food Chemicals Codex (FCC)

Any other pharmacopoeia or monograph may be used with suitable motivation of its equivalence in standing and quality to any of those listed above.

If applicants attest to meeting one of these pharmacopoeiae, then both the specific monograph and pharmacopoeia should be clearly identified. The most recent version of the relevant pharmacopoeia should also be sourced and referenced. Any additional testing that must be performed should be clarified or the scientific justification as to why the additional testing is not required must be documented.

The MCC accepts the use of alternate methods that meet pharmacopoeial requirements. When alternate methods are used for testing to meet pharmacopoeial specifications, the relevant pharmacopoeia should be consulted for information on whether or not the alternate methods are considered suitable.

The types of information and level of detail depend on the active ingredient(s).

In all cases, the information provided must include:

Description (Composition)

Any necessary information in addition to that included in the monograph/ standard description should be supplied.

Nomenclature

Provide the name of the substance.

Structure

Where possible provide the chemical structure (graphic), molecular formula, molecular weight and Chemical Abstracts Service Registry (CAS) number for the substance, unless this is provided in the relevant monograph or standard.

General properties

Provide any physico-chemical information relevant to the characterisation of the substance(s) or that may be required for the manufacture, performance or stability of its intended final dosage form that is not covered by the relevant monograph or standard (e.g. solubility or particle size).

And must be sufficient to:

- adequately characterise the active ingredient;
- determine the time during which the product meets appropriate standards when stored under defined conditions, and
- demonstrate that the active ingredient(s) will be of appropriate and consistent quality.

2.1.2 Manufacture of the Active Ingredient(s) (Module 3.2.S.2)

The manufacture of the active ingredient must be described. Applicants must provide the manufacturer's name and address, and addresses of all sites involved in the manufacture/ testing of the substance.

2.1.3 Compositional Information

This is, in essence, a physicochemical definition of the substance(s).
The purpose of the compositional information is to provide detailed characterisation of the substance. For single substance formulations, this is usually straightforward and may be a simple extension of the specifications. For multiple substance formulations, the compositional information is generally more detailed and contains a significant amount of additional qualitative and quantitative data.

Where possible, a major component (constituent) or marker compound of a substance should be determined. In addition, any major or minor constituents that have significant bearing on the action of the substance/product should be determined only if the presence, absence or concentration of these compounds have any effect on the quality, safety or efficacy of the substance or product (e.g. the pulegone content of an essential oil or relative EPA/DHA concentration of a fish oil).

Many complementary medicine substances have yet to be defined or characterised in a monograph that is acceptable to the MCC. Therefore specifications and control procedures that sufficiently characterise these substances should be proposed by the applicant. In general, these should:

- sufficiently define the nature or character of a substance;
- allow the substance to be distinguished from adulterants, substitutes or counterfeit versions;
- be specific for components of safety and / or therapeutic significance;
- take into account the biological, chemical and physical variations that may reasonably occur between batches of the substance; and
- be capable of objective validation.

Data on the nature or chemistry of the active component should be provided. This may include citation of monographs, authoritative references, or in-house data that can be independently validated.

In addition, information on solubility (in water and other relevant solvents, such as dissolution media), particle size and polymorphic form (which are specific to complementary medicines) should be provided, where relevant.

2.1.4 Control of Active Ingredient / Substance – Specifications (Module 3.2.S.4)

Starting material specifications should be provided or a reference cited for each starting material. Where a pharmacopoeial reference does not apply to an ingredient, the specification should give details of the test methods and test specifications. These would need to cover identity and, where appropriate, adulteration and contamination, both chemical and microbiological.

The active ingredient specifications are a set of tests and limits that are applied to the complementary medicine substance in order to ensure that every batch is of satisfactory and consistent quality. The specifications should monitor all parameters (generally by physico-chemical testing) where variation would be likely to affect the quality or safety of the product.

The manufacturer of the active ingredient should apply specifications and control procedures for the substance at the time of its manufacture. The finished product manufacturer is also expected to ensure that the active ingredient complies with specifications before using the substance in the finished product at the time of manufacture. The two sets of specifications are not necessarily identical.

For most complementary medicines, the manufacturer of the active ingredient will not be controlled to the same extent as the finished product manufacturer, and therefore the focus will be on the specifications applied by the finished product manufacturer before the ingredient is used in the finished product.

2.1.4 Control of Active Ingredient / Substance – Specifications - continued

The specifications for the active ingredient that are applied by the manufacturer of the finished product to ensure its quality before use should be submitted. If there are any differences between the active ingredient specifications used by the active ingredient manufacturer and the finished product manufacturer, these should be identified, explained, discussed and justified.

Where non-pharmacopoeial specifications are applied, a tabulated summary of the tests, test methods and limits should be provided. The specifications applied should be justified for their ability to assure the quality and consistency of the ingredients used.

Similarly, where a pharmacopoeial monograph is used as the specification, any modification to the pharmacopoeial requirements should be justified.

For example:

- Permitted isolates and synthetic duplicates of materials of natural origin (e.g. flavonoids such as rutin and vitamins) should be identified at the raw material stage by physical description (e.g. colour, crystalline form, melting point or boiling point, optical rotation, etc.) and appropriate chemical identification tests such as infrared spectroscopy should also be performed. For example, fish oils can be characterized by the fatty acid composition of the oil, acid value, anisidine value, peroxide value, total oxidation value, specific peak retention times from chromatography compared to a reference standard and/or any other appropriate identification tests.
- If the medicinal ingredient is an enzyme, characterization includes details of the source organism. Additional details such as gel electrophoresis, substrate specificity, isoelectric point, specific activity should also be documented. Testing can be done according to pharmacopoeial methods or methods approved by the International Enzyme Commission.
- For probiotics where strain identification is necessary, applicants should refer to Guidelines for QSE for Probiotics.

2.1.4.1 Limits and Tests

If there is a recognised pharmacopoeial monograph for the active substance, it must be used unless otherwise justified. Note that the most recent edition of any pharmacopoeial standard or monograph should be used, or a well-motivated justification for not doing so provided. The requirements of the recognised pharmacopoeiae or applicable general monographs in these pharmacopoeiae must also be met except where a justification for not doing so is sufficiently motivated by the applicant.

In some cases, the pharmacopoeial requirements may not in themselves be sufficient to adequately control the quality and consistency of an ingredient, and applicants may apply additional tests. However, it is generally not acceptable to:

- adopt only some of the tests from a pharmacopoeial monograph without sufficient expert motivation;
- selectively combine some tests and/or limits from one specific pharmacopoeial monograph with some from another pharmacopoeial monograph (without having ensured full compliance with either);
- adopt an earlier edition of the pharmacopoeial monograph or standard when there is a more recent edition that has been adopted by the MCC.

Where non-pharmacopoeial specifications are applied, a tabulated summary of the tests, test methods and limits should be provided *(e.g. assay (non-aqueous titrimetry): 99,0–101,0 %).* The specifications applied should be justified in respect of their ability to assure the quality and consistency of the ingredients used.

2.1.4.1 Limits and Tests - continued

Similarly, where a pharmacopoeial monograph is used as the specification, any modification to the pharmacopoeial requirements should be justified.

The specifications for the active ingredient should be guided by the compositional information.

2.1.4.2 Impurities and Incidental Constituents (Module 3.2.S.3.2)

All starting substances and intermediates must be free of contaminants.
The absence of orthodox pharmaceutical substances or chemicals must be confirmed.
The absence of adulterants must be confirmed.

Information concerning impurities that are not dealt with in the monograph or standard should be provided. Applicants should be aware that the manufacturing process for the substance may differ from the process for the substance upon which the monograph is based and, consequently, different impurities may be present.

One of the key purposes of raw material specifications for complementary medicines is to determine whether the active raw material is free of contaminants that may have safety implications. Therefore, incidental constituents and impurities need to be considered and tests and limits included in the active ingredient specifications.

Impurities and incidental constituents are those constituents that may be present in a substance as a by-product of the production, processing or storage of a substance, and are immaterial to the nature of the substance.

The production, processing and storage of substances may result in the presence of impurities and incidental constituents; for example, micro-organisms, microbial toxins, radionuclides, metals and non-metals, pesticide residues, degradation products, general contaminants, solvent residues and manufacturing by-products. These constituents may be potentially hazardous to human health and their presence therefore needs to be minimised. Applicants should describe in detail the procedures adopted to achieve this.

Applicants should consider each type of likely impurity and incidental constituent, and determine whether it is relevant to the substance in question. They should include consideration of the following:

- microbiological limits (moulds and bacterial endotoxins)
- microbial toxins / mycotoxins e.g. aflatoxins, and ochratoxins;
- radionuclides;
- radiolytic residues;
- metals and non-metals, e.g. lead, arsenic, selenium;
- agricultural and veterinary chemicals, e.g. pesticides, fungicides;
- general contaminants, e.g. dioxins, polychlorinated biphenyls;
- solvent residues; and
- manufacturing by-products, e.g. reagents, catalysts, co-extractives, degradation products.

2.1.5 Batch Certificates of Analysis (Module 3.2.S.4.4)

Certificates of analysis should be provided, updated and maintained for at least two recent commercial-scale production batches to demonstrate routine compliance with the specification or monograph.

2.1.5 Batch Certificates of Analysis - continued

If data on commercial-scale batches are not available, certificates of analysis should be provided for pilot-scale batches manufactured using the same process as intended for commercial-scale batches.

Certificates of analysis should also be provided for any batches of material used in toxicity tests and clinical trials reported in support of the application. This will assist the MCC in determining whether the substance intended for supply is the same as that on which safety data have been provided. It is important that batch analysis data for the active ingredient are included for batches that were used in clinical trials reported in support of the application.

2.1.6 Justification of Specification (Module 3.2.S.4.5)

If an applicant proposes to use an alternative monograph or standard when a BP, Ph. Eur. or USP standard exists, well-motivated justification for doing so is required. The justification should explain why the standard(s) cannot be met and detail what alternative(s) are proposed and why.

If there is no relevant monograph or standard for the active ingredient, a detailed justification for the proposed specifications should be provided. The justification should address the central function of the active ingredient specifications, which is to ensure the use of a consistently high-quality substance in the finished product. Specifically, identification, assay, control of impurities and other critical factors in the quality of the active ingredient must be addressed.

2.1.7 Stability (Module 3.2.S.&)

Refer also to the Stability guideline
Stability data must be provided for complementary medicine active ingredients to assist in identifying any particular degradants that may be formed and that must be monitored as part of the overall stability program.

2.2 Finished product (Module 3.2.P)

Generally it is only possible to test for a specific medicinal ingredient in the finished product if the ingredient is a single chemical entity, and the ease of testing is determined by the complexity of the matrix.

Additionally, the description of the final dosage form should be documented as part of the identification of the finished product. Tests for identification of the finished product might include tests such as organoleptic evaluation (sensory characteristics e.g. taste, odour, feel, appearance such as colour and shape of the capsule or tablet, etc.). Where the medicinal ingredient is a defined chemical entity, or where a marker is present, chemical identification tests (e.g. comparison of a retention time of a High Performance Liquid Chromatography (HPLC) peak with a standard) should be used.

A physical description of the finished product should always be included on the finished product specifications (e.g. clear colourless liquid, size 0 capsule red cap, blue body).

2.2.1 Description and Composition of the Product (Module 3.2.P.1)

A description of the finished product that includes the following information should be provided:

- table of the ingredients in the product and their purpose in the formulation (e.g. active, disintegrant, antimicrobial preservative);
- full/complete description of the dosage form, including any special character (e.g. modified release, film coated, uncoated);
- type of container and closure for the product, including the materials.

2.2.1 Description and Composition of the Product - continued

The table of ingredients should provide greater detail than simply the product formulation. It should include overages (additional quantities of ingredients, over the amounts nominated in the product's formulation, added during manufacture) if any.
Components of a formulation are divided into active ingredients and inactive ingredients.

2.2.1.1 Active Ingredients

Active ingredients in health supplements are those substances that have a therapeutic role in the formulation. The "therapeutic role", in the case of health supplements, means maintaining, complementing, or assisting the innate healing power or physical or mental state.

No added substances should be included in the formulation as active ingredients that do not make a direct and proven contribution to the proposed indication(s) for the medicine.

2.2.1.2 Inactive Ingredients

Inactive ingredients are substances used to aid in the manufacture of therapeutically active substances into dosage forms suitable for administration to consumers. Each inactive ingredient included in a formulation must have a justifiable excipient role and should be appropriately controlled by specifications.

Applicants should ensure that the intended use of an inactive ingredient is appropriate and that it is used in appropriate amounts to achieve its technical purpose. Applicants should also ensure that the excipient is approved for use as such.

2.2.1.3 Additives

Refer to the Pharmaceutical & Analytical Guideline.

Health supplements may not contain:

- any additive, colourant, flavourant, sweetener or preservative that is not permitted in foodstuffs *(refer to the Foodstuffs, Cosmetics, and Disinfectants Act, 1972 (Act 54 of 1972)or with directives of the EU or the register of the FDA);*
- any added fluoride in any form, or
- any additive which may contain aluminium.

In addition, the following sweeteners are not suitable for use in health supplements.
All artificial (non-nutritive) sweeteners, namely:

- Acesulfame K
- Aspartame
- Calcium cyclamate
- Calcium saccharin
- Saccharin
- Sodium cyclamate
- Sodium saccharin
- Sucralose, or
- Thaumatin

Permitted sweeteners would include:

- Stevia
- Sugar alcohols, and
- Mono-and Di-saccharides

2.2.1.4 Modified Release Products

Refer to Dissolution and Biostudies Guidelines.

Controlled release claims of modified release formulation must be demonstrated by both physico-chemical data (dissolution data) and clinical data (bioavailability data).

2.2.1.5 Batch-to-batch variations in the amount of ingredients

(i) Routine variations in inactive ingredients

It is recognised that it may be necessary to vary the quantities of certain inactive ingredients from batch to batch in order to achieve acceptable results during manufacturing.

Table 1 lists the changes to the nominal amounts of certain inactive ingredients that may be made in the manufacture of immediate release complementary medicines.

Table 1. Changes to the nominal amounts of certain excipients may be made as set out below.

Inactive ingredient type	**Acceptable range around the nominal formulation**
Quantity of ingredients whose function is to contribute to viscosity	+/– 10 %
Granulating fluid (fixed composition)	+/– 10 %
Disintegrant (even if the excipient serves more than one role in the formulation)	up to +25 %
Talc and water-soluble lubricants and glidants	–25 % to +100 %
Water-insoluble lubricants and glidants, except talc (e.g. magnesium stearate, stearic acid)	+/– 25 %
Filler (bulking agent) in hard gelatin capsules	+/– 10 %
Carriers and potency-adjusting ingredients for materials of biological and herbal origin	+ /– 10 %
Filler (bulking agent) in tablets and soft gelatin capsules to account for the changes in the item above	+ /– 10 %

(ii) Variations in content of some active ingredients

For some active ingredients the mass of the active raw material used in a batch of the formulated product may vary according to its composition.

Where the composition varies, fluctuations in the quantity of active raw material may affect the proportions of excipients present in the finished product relative to the nominal formula.

In some situations, the manufacturer may choose to compensate for the fluctuations in the mass of active raw material added by adjusting the amount of a nominated excipient in order to maintain a target mass for the batch.

This should be clearly identified in the application. Batch-to-batch approval is not normally required. The formulation given in the application should have an annotation indicating that the actual mass of active raw material will vary according to its estimated amount, and a formula should be provided showing how the amount of adjustment will be calculated. There should be an indication of which other inactive ingredients, if any, will be varied correspondingly, and the limits of the variation.

The reasons for proposed ranges in the quantities of any ingredients should be fully described in the product development summary. Validation data should be provided for the proposed ranges. Where the product is a tablet or capsule, the validation data should include dissolution or disintegration data, using the test method in the proposed finished product specifications as defined in 2.2.5

2.2.1.6 Overages

If an overage (an additional amount of an ingredient added during manufacture and greater than the amount nominated in the product's formulation) is used during manufacture, details of the overage used should be included with reference to the maximum allowed overage limit.

The application's product development summary should include a justification for the proposed overage. The use of an overage to compensate for poor analytical methodology or poor stability performance is not sufficient justification.

2.2.2 Product Development (Module 3.2.P.2)

Information on the development of and rationale for the finished product should be provided, including reference to and a discussion of the studies that led to the proposed dosage form, formulation, method of manufacture and container.

Where a medicine has modified release characteristics or an unusual method of manufacture, the product development summary should include a detailed discussion and justification of the development of those characteristics or method and any relationship with the finished product specifications. For example, for an enteric-coated tablet, dissolution and formulation studies performed during development should be described and related to the dissolution test in the finished product specifications.

If any overages are proposed, the developmental work that led to the proposed overage should also be discussed.

2.2.3 Manufacture of the Finished Product (Module 3.2.P.3)

2.2.3.1 Licensing and Control

The manufacturer's licence carries details of the types of manufacture permitted under the licence. Where a product is imported, each nominated overseas manufacturer is expected to demonstrate an acceptable standard of GMP. *Refer to SA Guide to GMP.*

2.2.3.2 Batch Formulation

A batch formulation should be provided in table format. It should include all of the components that will be used in the manufacture of the finished product and their quantities on a per batch basis (including any overages), correlated to the unit formula.

2.2.3.3 Description of Manufacturing Process and In-Process Controls

Details of the manufacturing process for the finished product should be provided for each manufacturing site. These steps should include the manufacture of the dosage form, packaging and labelling, chemical and physical testing, microbiological testing and release for sale.
The manufacturing details should include information about:

- solvents that are used, even if they are evaporated from the product during manufacture;
- polishing agents that do not appear in the formulation.

2.2.4 Control of Inactive Ingredients – Specifications (Module 3.2.P.4)

All ingredients in complementary medicines, including inactive ingredients, should have suitable specifications.
If there is no relevant monograph or standard for an inactive ingredient, full details of the specifications for each excipient are required.

2.2.5 Control of the Finished Product – Specifications (Module 3.2.P.5)

The finished product specifications are a set of tests and limits that are applied to the finished medicinal product in order to ensure that every batch is of satisfactory and consistent quality at release and throughout its shelf life. The specifications should monitor all parameters (generally by physico-chemical testing) where variation would be likely to affect the safety or efficacy of the product.

The specifications against which a finished product is tested before release for sale are referred to as the "batch release" specifications in this document; those against which the product is tested to ensure satisfactory quality throughout its shelf life are referred to as the stability specifications.

The finished product specifications should be provided, defining the physical, chemical and microbiological characteristics of the product and detailing quality-control test methods and test specifications.

2.2.5.1 Data Requirements

Release and stability specifications must be tabulated separately.

Tighter limits are usually applied at batch release to critical parameters to allow for possible changes to the product during storage (e.g. decomposition of the active ingredient).

The batch release limits must be chosen in order to guarantee that all batches will comply with the expiry specifications throughout the product's shelf life.

As a minimum, the stability specifications should include all of the tests in the batch release specifications.

Identification

- The final product must be identified by accepted pharmacopoeial methods or, when not available, by validated in-house methods. Product identification must be supported by a carefully documented paper trail.

Assay

- Suitable pharmaceutical or therapeutic markers may be used in conjunction with accepted and validated test procedures to determine the concentration or strength of starting substances and/or final products.
- Concentrations or quantities of scheduled substances must be specified and controlled within the limits stated for a specific Schedule.

2.2.5.2 Impurity Requirements for Non-pharmacopoeial Products

The specifications for finished products for which there is neither a BP, Ph. Eur. nor USP monograph for a closely related finished product, should include tests and limits for impurities related to the active ingredient.

For impurity limits, the results of stability studies should be taken into account and reference should be made to information on toxicity. Specifically, the amount and types of impurities that were detected in the stability studies should be consistent with the stability specifications and the proposed shelf life.

Consideration also needs to be given to the materials examined in the toxicity studies so that the product is consistent with the submitted safety data.

Unless otherwise stipulated by the MCC for a particular product, limits on impurities in finished products apply to impurities from all sources except water.

2.2.5.3 Residual Solvents

In addition to controlling residual solvents in the active ingredient, it is necessary to consider the total quantity of residual solvents that may be present in the finished product. This includes solvent residues that are present in the active ingredient and all inactive ingredients and solvent residues resulting from the manufacture of the finished product.

Depending on the quantities and types of solvent residues from each of these sources, it may be appropriate to include a test and limits for residual solvents in the finished product specifications.

2.2.5.4 Microbiological Requirements

Sterile Products

Generally, products that are required to be sterile (e.g. for ophthalmic use) will require extremely stringent microbiological specifications together with detailed information on manufacturing steps that ensure sterility.

Non-Sterile Products

All non-sterile dosage forms should include limits for microbial content in the finished product batch release and stability specifications.

Products with significant water content (e.g. creams, gels and oral liquids) are likely to support microbial growth. Such products should include tests and limits for microbial content in both the batch release and expiry specifications.

For products containing an antimicrobial preservative, both the batch release and stability specifications should include physico-chemical tests and limits for content of preservatives. As the effectiveness of many preservatives is pH dependent, the specifications for such products should usually include requirements for pH that will ensure preservative efficacy. The stability limits for the preservative should be supported by preservative efficacy testing that is performed during stability testing.

If animal-derived proteins are used as raw materials or in the manufacturing process, there must be evidence of no risk of transmitting infectious viral agents (such as BSE) or effective viral inactivation or removal in the manufacturing process.

Antimicrobial Ingredients

Antimicrobial preservatives are ingredients added to dosage forms to protect them from microbiological growth and associated degradation. Where antimicrobial preservatives are added to a product other than as an active ingredient, tests must be utilised that demonstrate the effectiveness of antimicrobial protection are performed on the product. Test methods used and tolerance limits should be as specified in an acceptable Pharmacopoeia (e.g. current USP <51>; Ph. Eur. 5.1.3), and should be performed on the final dosage form with suitable limits included.

The concentration of the preservatives shown to be effective in the final dosage form should be below a level that may be toxic to human beings, and should be at the lowest concentration necessary to preserve the product.

2.2.5.5 Tablets and Capsules

Dissolution may be an indicator for bioavailability and is then considered an important part of quality control for solid oral dosage forms. *Refer to Dissolution Guideline.*
Modified release products must include dissolution testing in the finished product specification.

2.2.5.6 Analytical Procedures & Validation

Details should be provided of all analytical methods used in the specifications, together with validation data that demonstrate (among other things) accuracy, precision, specificity (e.g. freedom from interference by degradation products and other likely impurities), and linearity.

2.2.5.7 Justification of Finished Product Specifications

The suitability and acceptability of the tests, limits and test methods proposed for the finished product should be justified with reference to the results of the method validation studies and the ability of the specifications to guarantee the quality and consistency of the finished product.

A detailed commentary or justification for any unusual features in the finished product specifications must be included.

The limits applied at batch release should be justified in terms of their ability to ensure that the product will remain within the expiry specification throughout its shelf life. For example, if the batch release and stability limits for assay are identical, the implication is that there will be no loss of the active ingredient throughout the shelf life. Any changes or unusual variability in the results obtained in the stability studies require adequate explanation.

The reasons for proposed ranges in the quantities of any ingredients should be appropriately outlined and justified in the application.

2.2.6 Batch Certificates of Analysis and Quantification

At least three certificates of analysis for the final product to demonstrate compliance with batch release specifications must be provided and made available on request. These certificates should relate to one or more production batches of the medicine or to trial batches if production batches have not been manufactured.

In such a case, the applicant should identify any differences between the trial process and the manufacturing process. The batch certificate for the trial batch, as well as the first production batch (if available) must be submitted. The applicant should identify any differences between the trial process and the manufacturing process.

For imported products, each batch must be accompanied by a Certificate of Analysis and an identification and assay test must be performed locally before such a batch is released for sale in order to demonstrate that product integrity has not been prejudiced during transit, unless exemption from this requirement has specifically been granted by the Council.

Refer to the Post-Importation Testing Guideline.

If the transport method is appropriately monitored and the transport complies with the storage conditions, then only a description and an identification test by the importer are required. Exemption from these requirements may be considered per product.

Quantification in analysis may take place by assay or input.

2.2.6.1 Quantification by Assay

Quantification by assay is a method for determining the presence or quantity of a component or ingredient. In the case of medicinal ingredients that are single chemical entities, those that contain a constituent that is used to standardize a product, or for those who have a known biological activity, quantitative assay tests can be done at the finished product stage according to appropriate analytical methods described in the pharmacopoeiae (e.g. USP, Ph. Eur.).

Botanical ingredients including extracts

Specific marker compounds may be assayed in whole herbs and extracts of botanical ingredients. If no pharmacopoeial standard is available for assaying the marker, then it is the product's applicant (proposed/holder of certificate of registration) responsibility to determine appropriate limits for the marker based on data on safety and efficacy of the product and natural variability of the marker.

Quantitative tests for a particular component in an extract can be done at either the finished product stage or at the extract ingredient stage using appropriate analytical methods. If the evidence supporting a claim is based on the quantity of a particular active component, then quantification of that component should be performed at the finished product stage. The quantification of a component of any extract can be recorded in the product registration application under the column entitled 'potency'. When a marker compound is declared in the application and the label tolerance limits for quantification should be set such that there is an upper and a lower limit.

When the component that is analysed is found in several ingredients in the product, e.g. caffeine in green tea and guarana, then the total amount of the component should be reflected on the label and specifications should be set to reflect the total amount from all sources.

Tolerance limits above 120 % may be used if scientifically justified. Safety of higher limits and degradation products should always be considered.

Vitamins and minerals

For vitamins, quantitative tests should be done on the finished product according to appropriate analytical methods described in an acceptable pharmacopoeia or other internationally accepted methods. Tolerance limits for the quantity of vitamins and minerals should be as per USP limits for the individual vitamins and minerals. In the absence of a pharmacopoeial standard, licence holders should have a scientific rationale for quantities that are outside the general tolerance limits of 80 - 120 %. It is recommended that the lower limit for the assay be set at 90 % of the label claim to ensure an appropriate amount of the medicinal ingredient at the expiry date. Potency of vitamins and minerals can be declared where appropriate.

Overage is used to compensate for the loss of vitamins and minerals during manufacture of the product or loss/degradation of vitamins and minerals during shelf-life of the finished product.

Isolates and synthetic duplicates

When ingredients are isolates or synthetic duplicates and no pharmacopoeial standard is available, tolerance limits of 80 to 120 % of the label claim are generally appropriate. The safety of degradation products should be taken into account when considering the expansion of tolerance limits.

Enzymes

The quantity per dosage unit must include the activity of the enzyme. Tolerance limits for the activity of enzymes should be 80 % to 150 % of the label amount. The activity is measured according to the reaction catalyzed by individual enzymes (substrate specificity). Methods and units (e.g. FCC Lipase Units, FCC Lactase Units) specified in the Food Chemicals Codex (FCC) should be used. Quantitative tests for a particular component in an extract can be done at either the finished product stage or at the extract ingredient stage using appropriate analytical methods. If the quantity of an enzyme is declared by mass, the activity should be declared as a potency. It is the responsibility of the applicant to ensure that all products meet a minimum of 80 % of the label claim for potency/activity at the end of the shelf-life.

2.2.6.2 Quantification by input

Quantification by input means that the active ingredients are not assayed at the finished product stage. The objective evidence that the quantity of a medicinal ingredient (e.g. a plant material) has been added to the finished product is calculated using the manufacturing batch record controlled by appropriate application of GMP and in-process controls. Generally, the quantity of a medicinal ingredient is expressed as the targeted mass (e.g. mg) of the processed substance in each unit of the dosage form. It is the responsibility of the applicant to ensure that quantification by input is appropriate for the ingredient.

Quantification by input may be appropriate when the active ingredient is a whole herb or a complex extract. In the case of medicinal ingredients where the formulation of the health supplement is of such complexity that a validated assay method for the quantity of an ingredient is unavailable or difficult to achieve (e.g. there is no published method of analysis for the medicinal ingredient, or the non-medicinal ingredients interfere with analysis), quantification by "input" may be considered to be acceptable.

It may also be acceptable to quantify an ingredient by input for a multi-ingredient product (e.g. multi-vitamin mineral products). In this case the product applicant uses controls other than assay for some of the ingredients present, and assays critical ingredients. Raw material specifications for the medicinal ingredient(s) to be quantified by input should be comprehensive to ensure that adequate control of the medicinal ingredient(s) occurs and should be available upon request. Standard operating procedures (SOPs) and batch records should clearly document the controls that are in place during manufacturing to ensure an adequate amount of medicinal ingredient is added to the mix during processing to achieve the labelled quantity per dosage unit. These documents should indicate the target quantity for the medicinal ingredient (i.e. 100 % of the label claim) and include controls on mass variation during tabletting or encapsulation. Generally a 5 % variation in mass for individual dosages is acceptable. A description of how batch homogeneity will be controlled should also exist and be available to the MCC on request if more than one medicinal ingredient is mixed, or if the medicinal ingredient is mixed with non-medicinal ingredients.

2.2.7 Container (Module 3.2.P.7)

Refer to Pharmaceutical & Analytical Guideline

A description of the container and closure system should be provided, including the materials used. The suitability of the container should be justified in terms of its compatibility with the product and its ability to protect the product physically and also in protecting it from moisture and light.

2.2.8 Finished Product Stability (Module 3.2.P.8)

Refer to Stability Guideline

All applications to register a complementary medicine must include stability data for the proposed finished product. The stability data must be sufficient to demonstrate, or indicate with a high probability, that the product intended for market will remain safe, of consistent quality and efficacious throughout the product's shelf-life. The stability data will form the basis for setting a shelf-life and recommended storage conditions for the product.

The following headings are recommended:

- study design;
- test methods;
- commentary on the results obtained in the studies for individual parameters (including any trends);
- conclusions and summary of claims.

2.2.8 Finished Product Stability (Module 3.2.P.8) - continued

The minimum permitted shelf-life is two years unless otherwise stated or the applicant can present data to suitably motivate for the allowance of shelf lives less than two years. The maximum permitted shelf-life is 5 years for stable salts.

2.3 Amendments

For any amendments or changes to finished products, refer to the Amendments Guideline.

3 SAFETY AND EFFICACY REQUIREMENTS

3.1 General

Underlying general principles regarding the registration and subsequent sale of Health Supplements, all products associated within this classification of Complementary Medicines shall:

- not contain any other substances except those stated on the label;
- not contain any human part or substance derived from any part of the human body;
- not contain undesirable substances
- not contain scheduled substances (above S0)(when indicated for any listed purposes in the schedule);
- not be in the form of an injectable;
- not contain any active substance which is a chemically-defined isolated constituent of plants, fungi, algae, seaweeds, lichens, animals or minerals, or a combination of any one or more of these, that is documented to exert pharmacological action for medicinal use unless otherwise explicitly provided for in the list of substances associated with each classification;
- not contain agents that can lead to animal-transmissible diseases such as Transmissible Spongiform Encephalopathy (TSE), if they contain ingredients derived from animal sources;
- not contain any colourant, flavourant, preservative or sweetener that is not permitted in foodstuffs (Foodstuffs, Cosmetics and Disinfectants Act, 1972 (Act 54 of 1972))

Unless otherwise stipulated or provided for in another manner, health supplements may contain ingredients that are classified as being Generally Regarded as Safe (GRAS) (http://www.fda.gov/food/IngredientspackagingLabeling/GRAS/). Applicants are required to make reference to the relevant GRAS listing and ensure that that the substance complies with specified requirements.

In general, health supplements should not be intended for supply to any children under the age of seven (7) months old unless where supplementation is medically warranted. Applicants are expected to include such information on their labelling (label/s, PIL, and PI).

3.1.1 Single Substance Formulations

Products containing single substances must conform to the dosage range provided in the relevant **ANNEXURE**. All products are required to display any prescribed warnings on the label, Package Insert and Patient Information Leaflet.

3.1.2 Multiple Substance Formulations

Applicants must present sufficient data demonstrating that the combination of such substances is safe in the dosages indicated. Ideally, specific data demonstrating the safe administration that is product specific should be included in any application. Literature (including references, other acceptable sources and monographs) must be submitted in substantiation of the safety profile of the product.

3.1.2 Multiple Substance Formulations - continued

Any multiple substance formulation which contains a substance of discipline specific origin and other substances defined as health supplements must be submitted as a "combination product" Discipline Specific product. Applicants will need to demonstrate explicit, cogent philosophies of use amongst all ingredients and the traditional use and/or associated clinical evidence should accord with the provided claim. *For combination products refer to Guideline for Complementary Medicines - Quality, Safety and Efficacy (Discipline Specific)*

3.2 Labelling and Allowable Claims

Health supplements should be labelled according to labelling regulations as stipulated by the Medicines and Related Substances Act, 1965 (Act 101 of 1965).

In general and unless specifically pre-approved as a disease risk reduction claim, indications that refer (explicitly or implied) to the treatment, or cure of specific diseases are not suitable for use for health supplements. Applicants are therefore required to ensure that the following disclaimer appears on their labelling where an approved disease risk reduction claim is not used: "Registered health supplements are not intended to diagnose, treat, cure or prevent any disease, unless under the supervision of a registered health professional."

3.2.1 Single Substance Formulations

With reference to single substance formulations, only those claims provided in relevant **ANNEXURES** shall be permitted. The applicant is expected to select that claim which matches the intention of the product with the intended age or sex of the intended user, where applicable.

Applicants must account for the dosage ranges provided for in the relevant **ANNEXURE** provided hereto. Any substance which falls above the maximum will not permit registration as a Health Supplement. In the case of single substance formulations that fall below the minimum dosage, no claim may be used from those stipulated for the relevant substance(s). Applicants may motivate for a claim for such products provided that efficacy for the product (backed up by appropriate clinical evidence) can be proven related to such claim.

Products of single substance formulation sold without any claims but will still be required to be registered and as such duly comply with any relevant Quality and Safety standards as provided herein.

3.2.2 Multiple Substance Formulation Claim Development

Claims for multiple substance formulations that conform to the definition of a health supplement may be formulated by the applicant should such not be provided for. Such claims will only be allowed should they conform to general principles contemplated below and with specific motivation that all ingredients would reasonably allow for the maintenance of such a claim.

Due to the nature of multiple substance formulations, standardised claims are not always provided in the relevant **ANNEXURES** below. As such, applicants may be required to propose an acceptable health supplement claim that will adequately provide for the intended action of the product.

A health supplement claim is a statement that indicates the intended beneficial effect of a product when used in accordance with its recommended conditions of use. The term "recommended use or purpose" is often used interchangeably with "health claim" or "indications for use." Claims associated with single substances may be used for the generation of claims related to multiple substance formulations, provided that the claim is sufficiently substantiated and accords with the other substances found in the formulation.

3.2.2 Multiple Substance Formulation Claim Development - continued

The choice of wording would include any of:

- General health enhancement without any reference to specific diseases[1]
- Health maintenance, including nutritional support.

The use of the words “contributes”, “assists”, “helps”, “aids”, or “maintains” are the basis for claim formulation together with a beneficial physiological effect based on generally accepted scientific evidence. The applicant is expected to formulate a claim which matches the intention of the product with the intended age or sex of the intended user, where applicable.

The use of any claim must take account of minimum and maximum dosage levels prescribed for all substances where the claim must relate to levels permitted in the relevant **ANNEXURE** and must also account for the action of all other included substances in the product. A suitable justification from various allowable sources is required to substantiate any developed claim.

Below in **Table 2** is a list of terms and claims (including wording of similar meaning) that may **not** be used in association with the development of any claim. The list is not exhaustive and will be updated from time to time.

Table 2: Undesirable Terms and Claims for Health Supplements

Magical	Anti-ageing
Miracle / Miraculously	Longevity
The only product to use	Breast enhancement, enlargement, growth
World’s best	Penis enlargement
100% safe	Height enhancement / growth
No side effects	Enhance intelligence / Increase IQ
Guaranteed	Hormone releaser/enhancer/amplifier
Other drugs / products cannot compare with it	Enhancement of sexual organs
Sensational relief	Sexual powers
The No. 1 (unless substantiated)	Arousal, Libido
Efficacious/Effective	Reference to the cure, treatment or diagnosis of
Perpetual youth	any disease unless specifically provided for.
Or any terms that would reasonably infer a similar meaning or intention in English or any other language.	

For multiple substance formulations where any constituents fall below the allowable minimums, no claim may be used from those stipulated for the relevant substance(s). Applicants may motivate for a claim for such products provided that efficacy for the product (backed up by appropriate clinical evidence) can be proven related to such claim.

[1] *Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.*

4 GLOSSARY OF TERMS

This glossary is not exhaustive and does not include many terms that are 'technically' specific to some areas of MCC; in particular, it does not interpret terms, which are used exclusively for, or in connection with the manufacture of prescription medicines or therapeutic devices.

Refer also to The Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended, for definitions.

This document includes terms used only in relation to medicines. It does not include terms related to medical devices. See also Regulations for Medical Devices.

This glossary provides clarity on not only the use of terms in this document but also to the terminology that may be relevant to the registration process or CMs in general.

Act

The *Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended*

Active ingredient

The therapeutically active component in a medicine's final formulation that is responsible for its physiological or pharmacological action which may include a whole substance such as a single herb.

Active pharmaceutical ingredient (API)

Therapeutically active component in the final formulation of the medicine, or

A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active ingredient.

Active raw material

The unformulated active chemical substance, usually a powder or a liquid, in the form in which it is used to manufacture a dosage form, usually in combination with excipients.

Analysis

Includes deconstruction and interpretation of data, examination and testing.

Animal

An invertebrate or vertebrate member of the animal kingdom.

Applicant

Holder / Proposed holder of certificate of registration

Application

An application for registration made to MCC in terms of the provisions of Act 101 of 1965.

Batch

A quantity of a product that is:

a) uniform in composition, method of manufacture and probability of chemical or microbial contamination; and
b) made in one cycle of manufacture and, in the case of a product that is sterilised or freeze dried, sterilised or freeze dried in one cycle.

Bioburden

The quantity and characteristics of micro-organisms present in the medicines or substances or to which the medicines or substances may be exposed in a manufacturing environment.

Biological products

Products in which the active ingredient is a biological substance including antisera, antivenins, monoclonal antibodies and products of recombinant technology.

Biological substance

Substances of biological origin, which are frequently chemically complex and have a molecular mass greater than 1 000, such as hormones, enzymes and related substances, but not including herbal substances and antibiotics. Biological substances are not uniquely defined by a chemical name because their purity, strength and composition cannot readily be determined by chemical analysis. Substances which can be isolated as a low molecular mass pure substance, such as purified steroids, digoxin and ergotamine, are considered to be chemical substances.

Clinical trial

A planned study in humans designed to investigate or report upon the effectiveness and / or safety of a medicine which may also include qualitative evidence from appropriately designed studies.

Combination product

means a single product that contains:

a) a mixture of substances of various discipline-specific origin or philosophy, or
b) a mixture of at least one substance of discipline-specific origin and one or more health supplements.

Complementary medicine *(as proposed in R716 GG 37995 of 15 Sep 2014)*

means any substance or mixture of substances that—

(a) originates from plants, fungi, algae, seaweeds, lichens, minerals, animals or other substance as determined by Council, and

(b) is used or purporting to be suitable for use or manufactured or sold for use—
  (i) in maintaining, complementing, or assisting the innate healing power or physical or mental state, or
  (ii) to diagnose, treat, mitigate, modify, alleviate or prevent disease or illness or the symptoms or signs thereof or abnormal physical or mental state ,
  of a human being or animal, and

(c) is used—
  (i) as a health supplement, or
  (ii) in accordance with those disciplines as determined by Council, or

(d) is declared by the Minister, on recommendation by the Council, by notice in the Gazette to be a complementary medicine;

Contract manufacture

Where all or part of the manufacturing process of the medicine is carried out on a contract basis by a GMP licensed person other than the applicant. Can include principal manufacturers and other (sub) manufacturers.

Counterfeit medicine

A medicine in respect of which a false representation has been made with regard to its contents, identity or source by any means including its labelling and packaging;

Dosage form

The pharmaceutical form in which a product is presented for therapeutic administration, e.g. tablet, cream.

Drug

See **Medicine**. Note that legislative definitions apply in both singular and plural forms.

Excipient

Any component of a finished dosage form other than an active ingredient (in some cases the distinction between an active ingredient and an excipient may not be clear cut, e.g. use of sodium chloride to adjust tonicity of an injection is an excipient). An inactive ingredient.

Expiry date

The date (expressed as the month and year) after which the medicines should not be used.

Finished product

The finished or final dosage form of the complementary medicines when all stages of manufacture, other than release for sale, have been completed.

Formulation

A list of the ingredients used in the manufacture of a dosage form and a statement of the quantity of each ingredient in a defined weight, volume, unit or batch.

Good manufacturing practice (GMP)

The acronym GMP is used internationally to describe a set of principles and procedures which, when followed by manufacturers of medicines, helps ensure that the products manufactured will have the required quality. A basic tenet of GMP is that quality cannot only be tested into a batch of product but must be built into each batch of product during all stages of the manufacturing process.

Health supplement

means any substance, extract or mixture of substances that—

a) may—
   i) supplement the diet;
   ii) have a nutritional physiological effect, or
   iii) include pre- and probiotics when used to change the microbial balance in the human or animal intestines, and
b) are sold in pharmaceutical dosage forms not usually associated with a foodstuff and excludes injectables.

Indications

The specific therapeutic uses of medicines.

Individual patient data

In relation to complementary medicines, individual patient data means information, derived from clinical trials or observational data recorded during clinical practice, relating to individuals before, during and after the administration of the medicines to those individuals, including but not limited to, demographic, biochemical and haematological information.

Label

A display of printed information:

a) on or attached to the complementary medicine **OR**
b) on or attached to a container or primary pack in which the medicines are supplied **OR**
c) supplied with such a container or pack **AND**

in accordance with Regulation 8 of the Regulations to the Medicines Act.

Licence

A licence under Section 22C of the Act

Licence number

The number of the licence issued by the MCC to a manufacturer of complementary medicines for use in humans.

Manufacture

The production of medicines or any part of the process of producing medicines or bringing the medicines to their final state, including engaging in the processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for supply of the medicines or of any component or ingredient of the medicines as part of that process.

Manufacturer

Corporation or person carrying out one or more of the steps specified in the definition of manufacture.

Manufacturing licence

A licence granted under Section 22 of the Act, relating to manufacturing of complementary medicines.

Medicine

'medicine' means any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in-

a) the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man; or

b) restoring, correcting or modifying any somatic or psychic or organic function in man, and includes any veterinary medicine.

Medicinal product

An alternative term to medicine for the finished, packaged product.

Nutritional physiological effect

A beneficial physiological effect brought about by substances originating from or associated with foodstuffs.

Oral

Taken through the mouth into the gastrointestinal system.

Pack size

The size of the product in terms of the quantity contained in the container (e.g. volume in a multi-use container) and / or the number of items in the primary / unit pack (e.g. number of tablets in a bottle).

Presentation

The way in which the complementary medicines are presented for supply, and includes matters relating to the name of the medicines, the labelling and packaging of the medicines, and any advertising or other informational material associated with the medicines.

Primary pack

The complete pack in which the complementary medicine, or the medicines and their container, are to be supplied to consumers.

Principal manufacturer

The manufacturer who manufactures the medicines or who performs one or more steps in the manufacture of the medicines and also contracts with, or controls the use of other manufacturers for the performance of the remaining steps in manufacture of the medicines.

Product

The commercial presentation or marketed entity of complementary medicine, *excluding pack size*.

Proprietary name

The registered trademark of the complementary medicine or the unique name assigned to the medicine by the applicant and appearing on the label.

Quality

Includes the composition, strength, potency, stability, sterility, purity, bioburden, design, construction and performance characteristics of the medicine.

Regulations

Regulations to the Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended.

Route of administration

Route by which a complementary medicine is applied on or introduced into the body.

Scheduling

In relation to a substance, means the schedule or schedules in which the name or a description of the substance is already or is to be included in the list of scheduled substances made in terms of Section 22A(2) of the Medicines Act.

Step in manufacture

Any part of the process of bringing medicines to their final state and which may be completed separately from other parts of the process.

Strength

The quantity or quantities of an ingredient or ingredients in a medicine or a formulation expressed, for discrete units, as the nominal weight of the ingredient in the unit for other dosage forms, as the nominal weight or volume per unit weight or volume.

Supply

Includes supply by way of sale, exchange, gift, lease, loan, hire or hire purchase. It also includes whether free of charge or otherwise, samples or advertisements, supply for testing the safety or efficacy, and for treatment of person or animal.

Therapeutic use / Therapeutic role

In the case of health supplements, means maintaining, complementing, or assisting the innate healing power or physical or mental state.

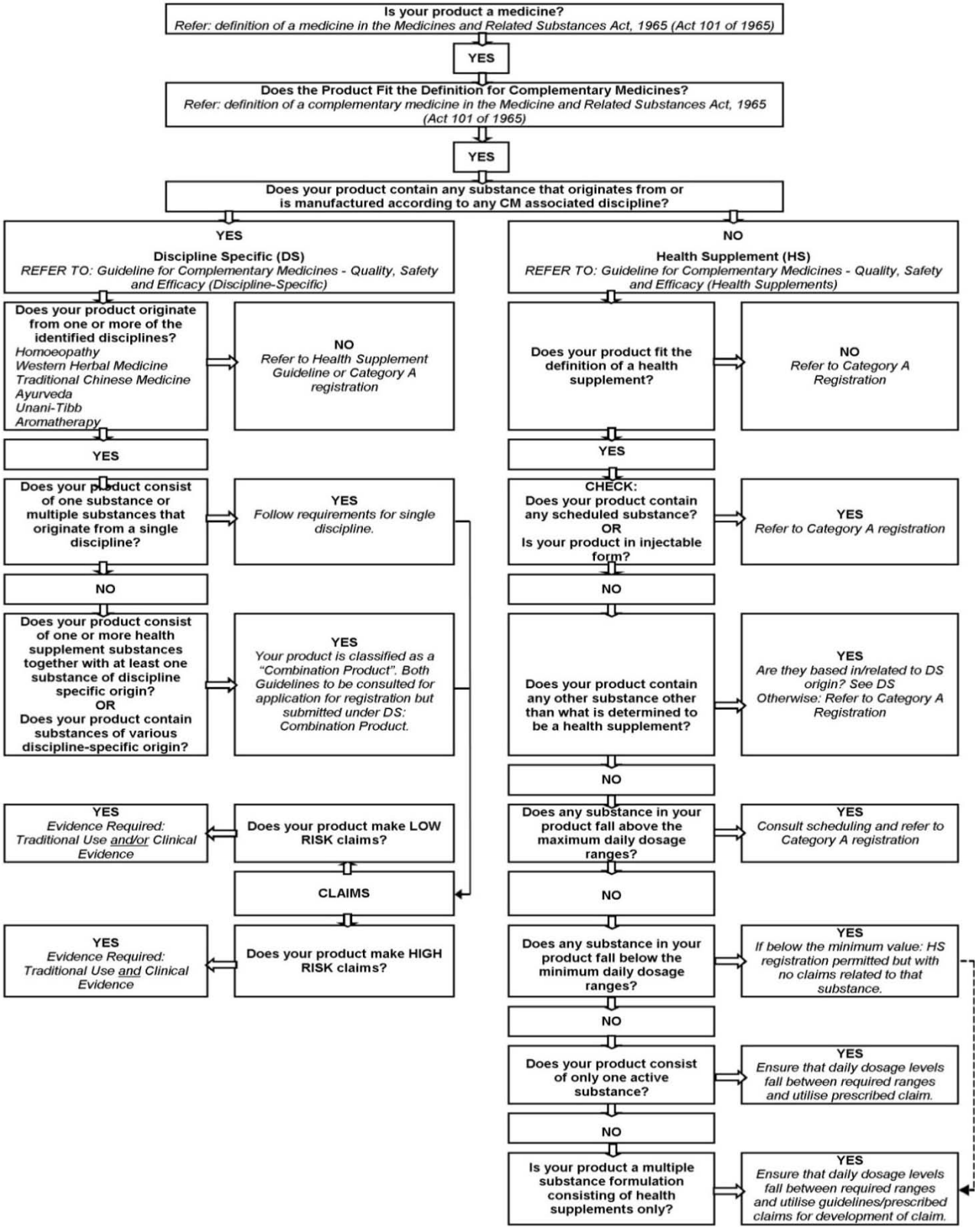
Topical

Applied to a certain area of the skin for a localised effect.

5 UPDATE HISTORY

Date	Reason for update	Version & publication
Nov 2014	First publication released for comment	v1 Nov 2014
26 Feb 2015	Deadline for comment	

ANNEXURE A
Category D Decision Tree



ANNEXURE B

Motivation for inclusion of Substance as Health Supplement

If any substance is not listed in the annexures provided as a health supplement, applicants may submit an application to the MCC for consideration of the substance as a health supplement which outlines:

- The recognition of another international regulatory body with a similar regulatory mechanism/standard as a nutritional substance, dietary supplement, nutritional form or health supplement;
- The safety profile of the product including:
  - Therapeutic profile;
  - Minimum effective doses;
  - Maximum safe values;
  - Known side effects;
  - Contraindications, and
  - All known interactions (including interactions with medicines, other complementary medicines, health supplements, disease processes or diagnostics procedures), and
- Any other literature or motivation in substantiation of such substance as a health supplement and under specific circumstances.

The origin of any complementary medicine is defined to be from plants, fungi, algae, seaweeds, lichens, minerals, animals or other substance as determined by Council. Where any medicine is not to be of plants, fungi, algae, seaweeds, lichens, minerals or animals the applicant should demonstrate that such a substance accords with its use as a health supplement with respect to substantiation of dietary supplementation or nutritional physiological support.

NOTE: scheduled substances or injectable forms of substances will not be considered as health supplements. Chemically-defined isolated constituents of plants, fungi, algae, seaweeds, lichens, animals or minerals, or a combination of any one or more of these will generally not be regarded as health supplements, unless explicit motivation including recognition by other international regulatory bodies with a similar regulatory mechanism/standard and sufficient safety data is presented.

ANNEXURE C

Allowable Levels and Claims: Probiotics

Note: Any claims provided may be used with any of the stipulated dosage ranges.
[1]Minimum: Minimum Daily Levels Required for use of Health Supplement Claim

Probiotic	Health Supplement Claim	Minimum[1]
Bifidobacteriumadolescentis ***Bifidobacteriumanimalis subsp. Animalis*** ***Bifidobacteriumanimalis subsp. Lactis*** ***Bifidobacteriumbifidum*** ***Bifidobacterium breve*** ***Bifidobacteriumlactis*** ***Bifidobacteriumlongum subsp. Infantis*** ***Bifidobacteriumlongum subsp. Longum*** ***Lactobacillus acidophilus*** ***Lactobacillus brevis*** ***Lactobacillus caucasicus*** ***Lactobacillus casei*** ***Lactobacillus fermentum*** ***Lactobacillus gasseri*** ***Lactobacillus helveticus*** ***Lactobacillus johnsonii*** ***Lactobacillus lactis*** ***Lactobacillus paracasei*** ***Lactobacillus plantarum*** ***Lactobacillus reuteri*** ***Lactobacillus rhamnosus*** ***Lactobacillus salivarius***	"When ingested on a regular basis, probiotics should improve or normalise the microbial balance in the human intestines and thereby improve the functioning of the digestive tract/gut."	≥1 x 10^9 CFU per dosage unit

ANNEXURE D

Allowable Levels and Claims: Prebiotics

Note: Any claims provided may be used with any of the stipulated dosage ranges.
[1]Minimum: Minimum Daily Levels Required for use of Health Supplement Claim
[2]Maximum: Maximum Daily Levels Permitted as Health Supplement

Prebiotic	Health Supplement Claim (Single Substance Formulations)	Health Supplement Claim (Multiple Substance Formulations)	Minimum[1]	Maximum[2]
Inulin	Source of fibre for the maintenance of good health. Prebiotics such as *[name of specific prebiotic]* beneficially affects the intestinal flora by selectively stimulating the growth of the good/ beneficial gut flora/micro-organisms / positively affects intestinal health. An average of 6 g prebiotics is needed daily for general digestive health	Prebiotics such as *[name of specific prebiotic]* beneficially affects the intestinal flora by selectively stimulating the growth of the good/ beneficial gut flora/micro-organisms / positively affects intestinal health. An average of 6 g prebiotics is needed daily for general digestive health	2 g Advisory: Average of 6 g daily	15 g
Fructooligosaccharides (FOS)				
Galactooligosaccharides (GOS)				
Oligofructose				
Polydextrose				
Trans-galactooligosaccharide				
Xylooligosaccharides (fXOS)				

ANNEXURE E

Allowable Levels and Claims: Vitamins

Note: Any claims provided may be used with any of the stipulated dosage ranges.
Minimum: Minimum Daily Levels Required for use of Health Supplement Claim
Maximum: Maximum Daily Levels Permitted as Health Supplement

<table>
<tr><th rowspan="2">Vitamin</th><th rowspan="2">Health Supplement Claim (Single Substance Products)</th><th rowspan="2">Health Supplement Claim (Multiple Substance Products)</th><th colspan="2">Children</th><th colspan="2">Adults</th></tr>
<tr><th>Minimum</th><th>Maximum</th><th>Minimum</th><th>Maximum</th></tr>
<tr><td rowspan="8">Vitamin A</td><td>Contributes to the maintenance of normal vision</td><td>Contributes to the maintenance of eyesight, skin, membranes and immune function</td><td>10 months - 3 years
30 µg</td><td>600 µg</td><td rowspan="8">65 µg</td><td rowspan="8">≤ 5 000 I.U.
(1 500 µg)</td></tr>
<tr><td>Contributes to the development and maintenance of night vision</td><td>Contributes the development and maintenance of night vision</td><td>4 - 8 years
30 µg</td><td>900 µg</td></tr>
<tr><td>Has a role in the process of cell differentiation</td><td>Contributes to the development and maintenance of bones and teeth</td><td>9 - 13 years
30 µg</td><td>≤1 500 µg</td></tr>
<tr><td>Contributes to normal growth</td><td>A factor in the maintenance of good health</td><td rowspan="4">14 - 18 years
65 µg</td><td rowspan="4">≤1 500 µg</td></tr>
<tr><td>Contributes to normal iron metabolism</td><td rowspan="3">Multi-vitamin supplement/
Multi-vitamin/mineral supplement</td></tr>
<tr><td>Contributes to the maintenance of normal mucous membranes</td></tr>
<tr><td>Contributes to the maintenance of normal skin</td></tr>
</table>

Vitamin	Health Supplement Claim (Single Substance Products)	Health Supplement Claim (Multiple Substance Products)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
	Contributes to the normal function of the immune system					
	Contributes to the development and maintenance of bones and teeth					
	A factor in the maintenance of good health					
Vitamin B1 (Thiamine)	Helps to metabolise carbohydrates	Helps to metabolise carbohydrates, fats and proteins	**1- 13 years** 0,04	≤100 mg	0,07 mg	≤ 100 mg
	Helps to metabolise proteins	Contributes to normal growth	**14-18 years** 0,07 mg	≤ 100 mg		
	Helps to metabolise fats	A factor in the maintenance of good health				
	Contributes to normal energy-yielding metabolism	Multi-vitamin supplement/ Multi-vitamin/mineral supplement				
	Contributes to the normal functioning of the nervous system					
	Contributes to normal psychological function					
	Contributes to the normal function of the heart					
	Contributes to normal growth					
	A factor in the maintenance of good health					

Vitamin	Health Supplement Claim (Single Substance Products)	Health Supplement Claim (Multiple Substance Products)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Vitamin B2 (riboflavin)	Helps to metabolise carbohydrates	Helps to metabolise carbohydrates, fats and proteins	**1- 13 years** 0,04 mg	≤100 mg	0,08 mg	≤ 100 mg
	Helps to metabolise fats and proteins	Contributes to tissue formation	**14-18 years** 0,08 mg	≤1 00 mg		
	Contributes to normal energy-yielding metabolism	A factor in the maintenance of good health				
	Contributes to the normal functioning of the nervous system	Multi-vitamin supplement/ Multi-vitamin/mineral supplement				
	Contributes to the maintenance of normal mucous membranes					
	Contributes to the maintenance of normal skin					
	Contributes to the maintenance of normal vision					
	Contributes to the normal metabolism of iron					
	Contributes to the protection of cells from oxidative stress					
	Contributes to the reduction of tiredness and fatigue					
	Contributes to tissue formation					
	A factor in the maintenance of good health					

Vitamin	Health Supplement Claim (Single Substance Products)	Health Supplement Claim (Multiple Substance Products)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Vitamin B3, Nicotinic Acid, Niacin and derivatives)	Helps to metabolise carbohydrates, fats and proteins	Helps to metabolise carbohydrates, fats and proteins	**1 - 3 years** 0,6 mg	10 mg	1 mg	≤ 35 mg
	Contributes to the maintenance of normal mucous membranes	Contributes to normal growth and development	**4 - 8 years** 0,6 mg	15 mg		
	Contributes to the maintenance of normal skin	A factor in the maintenance of good health	**9 - 13 years** 0,6 mg	20 mg		
	Contributes to normal psychological function	Multi-vitamin supplement/ Multi-vitamin/mineral supplement	**14 - 18 years** 1 mg	30 mg		
	Contributes to the reduction of tiredness and fatigue					
	Contributes to normal growth and development					
	A factor in the maintenance of good health					
Vitamin B3 - Nicotinamide (niacinamide)	Helps to metabolise carbohydrates, fats and proteins	Helps to metabolise carbohydrates, fats and proteins	**1 - 3 years** 0,6 mg	10 mg	2,4 mg	≤ 500 mg
	Contributes to normal growth and development	Contributes to normal growth and development	**4 - 8 years** 0,6 mg	15 mg		
	A factor in the maintenance of good health	A factor in the maintenance of good health	**9 - 13 years** 0,6 mg	20 mg		
		Multi- Vitamin supplement/ Multi-vitamin/mineral supplement	**14 - 18 years** 1 mg	30 mg		

Vitamin	Health Supplement Claim (Single Substance Products)	Health Supplement Claim (Multiple Substance Products)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Vitamin B5 (Pantothenic Acid)	Helps to metabolise carbohydrates, fats and proteins	Helps to metabolise carbohydrates, fats and proteins	**1 – 13 years** 0,2 mg	≤ 200 mg	0,4 mg	≤ 200 mg
	Contributes to normal energy-yielding metabolism	Contributes to tissue formation	**14 – 18 years** 0,4 mg	≤ 200 mg		
	Contributes to normal synthesis and metabolism of steroid hormones, vitamin D and some neurotransmitters	A factor in the maintenance of good health				
	Contributes to the reduction of tiredness and fatigue	Multi-vitamin supplement/ Multi-vitamin/mineral supplement				
	Contributes to normal mental performance					
	Contributes to tissue formation					
	A factor in the maintenance of good health					
Vitamin B6 (pyridoxine)	Helps to metabolise carbohydrates, fats and proteins	Helps to metabolise carbohydrates, fats and proteins	**1 - 3 years** 0,05 mg	30 mg	0,1 mg	≤ 100 mg
	Contributes to normal cysteine synthesis	Contributes to tissue formation	**4 - 8 years** 0,05 mg	40 mg		
	Contributes to normal energy-yielding metabolism	A factor in the maintenance of good health	**9 - 13 years** 0,05 mg	60 mg		

Vitamin	Health Supplement Claim (Single Substance Products)	Health Supplement Claim (Multiple Substance Products)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Vitamin B6 (pyridoxine) ***cont.***	Contributes to normal functioning of the nervous system	Multi-vitamin supplement/ Multi-vitamin/mineral supplement	**14 - 18 years** 0,1 mg	80 mg		
	Contributes to normal homocysteine metabolism					
	Contributes to normal protein and glycogen metabolism					
	Contributes to normal psychological function					
	Contributes to normal red blood cell formation					
	Contributes to the normal function of the immune function					
	Contributes to the reduction of tiredness and fatigue					
	Contributes to the regulation of hormonal activity					
	Contributes to tissue formation					
	A factor in the maintenance of good health					

Vitamin	Health Supplement Claim (Single Substance Products)	Health Supplement Claim (Multiple Substance Products)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Vitamin B12 (cyanoco balamin)	Helps to metabolise carbohydrates, fats and proteins	Helps to metabolise carbohydrates, fats and proteins	**1 – 13 years** 0,09 µg	≤ 100 µg	0,14 µg	≤ 100 µg
	Plays a role in the process of cell division	Contributes to normal red blood cell formation	**14 – 18 years** 0,14 µg	≤ 100 µg		
	Contributes to normal red blood cell formation	A factor in the maintenance of good health				
	Contributes to normal energy-yielding metabolism	Multi-vitamin supplement/ Multi-vitamin/mineral supplement				
	Contributes to normal functioning of the nervous system					
	Contributes to normal homocysteine metabolism					
	Contributes to normal psychological function					
	Contributes to the normal function of the immune system					
	Contributes to the reduction of tiredness and fatigue					
	A factor in the maintenance of good health					

Vitamin	Health Supplement Claim (Single Substance Products)	Health Supplement Claim (Multiple Substance Products)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Vitamin C (Ascorbic Acid)	Contributes to iron absorption from food	Helps to metabolise fats and proteins	**1 - 3 years** 2,2 mg	400 mg	6 mg	≤ 1 000 mg
	Helps to metabolise fats and proteins	Helps in the development and maintenance of bones, cartilage, teeth and gums	**4 - 8 years** 2,2 mg	650 mg		
	Contributes to cell protection from free radical damage	Helps in connective tissue formation	**9 - 13 years** 2,2 mg	≤ 1 000 mg		
	Contributes to maintain the normal function of the immune system during and after intense physical stress **(the claim may be used for a daily intake of 200 mg in addition to recommended daily intake)**	Helps in wound healing	**14 - 18 years** 6 mg	≤ 1 000 mg		
	Contributes to normal collagen formation for the normal function of blood vessels	An antioxidant for the maintenance of good health				
	Contributes to normal collagen formation for the normal function of bones	A factor in the maintenance of good health				
	Contributes to normal collagen formation for the normal function of cartilage	Multi-vitamin supplement/ Multi-vitamin/mineral supplement				
	Contributes to normal collagen formation for the normal function of gums					

Vitamin	Health Supplement Claim (Single Substance Products)	Health Supplement Claim (Multiple Substance Products)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Vitamin C (Ascorbic Acid) ***cont.***	Contributes to normal collagen formation for the normal function of skin					
	Contributes to normal collagen formation for the normal function of teeth					
	Contributes to normal energy-yielding metabolism					
	Contributes to normal functioning of the nervous system					
	Contributes to normal psychological function					
	Contributes to the normal function of the immune system					
	Contributes to the protection of cells from oxidative stress					
	Contributes to the reduction of tiredness and fatigue					
	Contributes to the regeneration of the reduced form of Vitamin E					
	Helps in connective tissue formation					
	Contributes to wound healing					

Vitamin	Health Supplement Claim (Single Substance Products)	Health Supplement Claim (Multiple Substance Products)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Vitamin C (Ascorbic Acid) ***cont.***	An antioxidant for the maintenance of good health					
	A factor in the maintenance of good health					
Vitamin D	Helps in the absorption and use of calcium and phosphorous	Helps in the development and maintenance of bones and teeth	**1- 13 years** 0,2 µg	≤ 25 µg	0,8 µg	≤ 1 000 I.U. (25 µg)
	Contributes to normal cell division	Helps in the absorption and use of calcium and phosphorous	**14- 18 years** 0,8 µg	≤ 25 µg		
	Contributes to normal blood calcium levels	A factor in the maintenance of good health				
	Contributes to the development and maintenance of strong bones and teeth	Calcium intake, when combined with sufficient vitamin D, a healthy diet and regular exercise, may reduce the risk of developing osteoporosis				
	Contributes to the maintenance of normal muscle function	Multi-vitamin supplement/ Multi-vitamin/mineral supplement				
	Contributes to the normal function of the immune system					
	Has a role in the process of cell division					

Vitamin	Health Supplement Claim (Single Substance Products)	Health Supplement Claim (Multiple Substance Products)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Vitamin D *cont.*	Calcium intake, when combined with sufficient vitamin D, a healthy diet and regular exercise, may reduce the risk of developing osteoporosis.					
	A factor in the maintenance of good health					
Vitamin E	Contributes to the protection of cells from oxidative stress	An antioxidant for the maintenance of good health	**1- 3 years** 0,6 mg	100 mg	1 mg	≤ 400 I.U. (273,3 mg)
	A factor in the maintenance of good health	A factor in the maintenance of good health	**4 - 8 years** 0,6 mg	150 mg		
		Multi-vitamin supplement/ Multi-vitamin/mineral supplement	**9 - 13 years** 0,6 mg	≤ 273,3 mg		
			14 - 18 years 1 mg	≤ 273,3 mg		
Vitamin K	Contributes to the maintenance of normal bones	Contributes to the maintenance of normal bones	**1 - 3 years** 3 ug	30 ug	6 ug	≤ 120 ug
	A factor in the maintenance of good health	A factor in the maintenance of good health	**4 - 8 years** 3 ug	55 ug		
			9 - 13 years 3 ug	60 ug		
			14 - 18 years 6 ug	60 ug		

Vitamin	Health Supplement Claim (Single Substance Products)	Health Supplement Claim (Multiple Substance Products)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Vitamin H (Biotin)	Helps the body to metabolise carbohydrates, fats and proteins	Helps the body to metabolise carbohydrates, fats and proteins	**1- 13 years** 1 ug	≤ 500 ug	1,8 ug	≤ 500 ug
	Contributes to normal energy-yielding metabolism	A factor in the maintenance of good health	**14 - 18 years** 1,8 ug	≤ 500 ug		
	Contributes to normal functioning of the nervous system	Multi-vitamin supplement/ Multi-vitamin/mineral supplement				
	Contributes to normal psychological function					
	Contributes to the maintenance of normal hair					
	Contributes to the maintenance of normal mucous membranes					
	Contributes to the maintenance of normal skin					
	A factor in the maintenance of good health					

Vitamin	Health Supplement Claim (Single Substance Products)	Health Supplement Claim (Multiple Substance Products)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Folic Acid	Contributes to maternal tissue growth during pregnancy	Helps to reduce the risk of neural tube defects when taken daily prior to becoming pregnant and during early pregnancy	**1 - 13 years** 15 µg	199 µg	30 ug	≤ 500 ug
	Helps the body to metabolise proteins	Helps the body to metabolise proteins	**14 - 18** years 30 µg	≤ 500 µg		
	Helps to form red blood cells	Helps to form red blood cells				
	Helps to reduce the risk of neural tube defects when taken daily prior to becoming pregnant and during early pregnancy	A factor in the maintenance of good health				
	A factor in the maintenance of good health	Multi-vitamin supplement/ Multi-vitamin/mineral supplement				

ANNEXURE F

Allowable Levels and Claims: Minerals

Note: Any claims provided may be used with any of the stipulated dosage ranges.
Minimum: Minimum Daily Levels Required for use of Health Supplement Claim
Maximum: Maximum Daily Levels Permitted as Health Supplement

Minerals	Health Supplement Claim (Single Substance Formulations)	Health Supplement Claim (Multiple Substance Formulations)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Boron	A factor in the maintenance of good health	A factor in the maintenance of good health			225 mg	≤ 3 mg
		Mineral supplement/ Vitamin/ Mineral supplement/ Multi-mineral supplement				
Calcium *Including the following sources:* *Bone meal* *Calcium acetate* *Calcium ascorbate* *Calcium bisglycinate* *Calcium carbonate* *Calcium chloride* *Calcium chloride, hexahydrate* *Calcium chloride dehydrate* *Calcium citrate* *Calcium citrate malate* *Calcium citrate tetrahydrate* *Calcium fumarate* *Calcium glubionate anhydrous* *Calcium glubionate monohydrate*	Contributes to the development and maintenance of bones and teeth;	Contributes to the development and maintenance of bones and teeth	**1 - 18 years** 65 mg	≤ 1 300 mg	65 mg	≤ 1 300 mg
	Contributes to normal muscle function	A factor in the maintenance of good health				
	Contributes to normal blood clotting	Mineral supplement/ Vitamin/Mineral supplement/ Multi-mineral supplement				
	Contributes to normal energy-yielding metabolism	Calcium intake, when combined with sufficient vitamin D, a healthy diet, and regular exercise, may reduce the risk of developing osteoporosis				
	Contributes to normal neurotransmission					

Minerals	Health Supplement Claim (Single Substance Formulations)	Health Supplement Claim (Multiple Substance Formulations)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Calcium gluceptate *Calcium gluconate* *Calcium gluconate monohydrate* *Calcium glutarate* *Calcium glycerophosphate* *Calcium hydrolyzed animal protein (HAP) chelate* *Calcium hydrolyzed vegetable protein (HVP) chelate* *Calcium hydroxide* *Calcium lactate* *Calcium lactate gluconate* *Calcium lactate pentahydrate* *Calcium lactate trihydrate* *Calcium lactobionate dihydrate* *Calcium levulinate* *Calcium lactate pentahydrate* *Calcium lactate trihydrate* *Calcium lactobionate dihydrate* *Calcium levulinate* *Calcium levulinate dihydrate* *Calcium malate* *Calcium oxide* *Calcium phosphate, dibasic* *Calcium phosphate, monobasic* *Calcium pidolate* *Calcium pyrophosphate*	Contributes to normal function of digestive enzymes					
	Has a role in the process of cell division and specialisation					
	Calcium intake, when combined with sufficient vitamin D, a healthy diet, and regular exercise, may reduce the risk of developing osteoporosis					
	A factor in the maintenance of good health					

Minerals	Health Supplement Claim (Single Substance Formulations)	Health Supplement Claim (Multiple Substance Formulations)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Calcium silicate *Calcium sodium lactate* *Calcium succinate* *Calcium sulfate* *Calcium sulphate dihydrate* *Coral (Whole)* *Dolomite* *Oyster (Shell)*						
Chromium	Contributes to normal macronutrient metabolism	Provides support for healthy glucose metabolism			2,2 µg	≤ 50 µg
	Contributes to the maintenance of normal blood glucose levels	Helps the body to metabolise carbohydrates and fats				
	Helps the body to metabolise carbohydrates and fats	A factor in the maintenance of good health				
	A factor in the maintenance of good health	Mineral supplement/ Vitamin/ Mineral supplement/ Multi-mineral supplement				
Copper	Contributes to normal iron transport and metabolism	Helps to produce and repair connective tissue	**1 - 3 years** 35 µg	700 µg	65 µg	≤ 4 mg
	Contributes to the protection of cells from oxidative stress	Helps to form red blood cells	**4 - 8 years** 35 µg	2 500 µg		
	Contributes to normal energy- yielding metabolism	A factor in the maintenance of good health	**9 - 18 years** 35 µg	≤ 4 000 µg		
	Contributes to normal functioning of the nervous system	Mineral supplement/ Vitamin/ Mineral supplement/ Multi-mineral supplement				

Minerals	Health Supplement Claim (Single Substance Formulations)	Health Supplement Claim (Multiple Substance Formulations)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Copper *cont.*	Contributes to normal hair pigmentation					
	Contributes to normal skin pigmentation					
	Contributes to maintenance of normal connective tissues					
	Contributes to the normal function of the immune system					
	Helps to produce and repair connective tissue					
	Helps to form red blood cells					
	A factor in the maintenance of good health					
Iodine	Contributes to the normal production of the thyroid hormones and normal thyroid function	Contributes to the normal production of the thyroid hormones and normal thyroid function	**1 - 3 years** 6 µg	133 µg	14 µg	≤ 150 µg
	Contributes to normal cognitive function	A factor in the maintenance of good health	**4 - 13 years** 6 µg to 200 µg	≤ 150 µg		
	Contributes to normal energy-yielding metabolism	Mineral supplement/ Vitamin/ Mineral supplement/ Multi-mineral supplement	**> 14 years** 14 µg	≤ 150 µg		
	Contributes to normal functioning of the nervous system					

Minerals	Health Supplement Claim (Single Substance Formulations)	Health Supplement Claim (Multiple Substance Formulations)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Iodine *cont.*	Contributes to the maintenance of normal skin					
	A factor in the maintenance of good health					
Iron	Contributes to normal energy -yielding metabolism	Helps to form red blood cells and helps in their proper function	**0 - 18 years** 0,6 mg	≤ 24 mg	1,4 mg	≤ 24 mg
	Contributes to normal oxygen transport in the body	A factor in the maintenance of good health				
	Contributes to normal formation of red blood cells and haemoglobin and proper function	Mineral supplement/ Vitamin/ Mineral supplement/ Multi-mineral supplement				
	Contributes to normal cognitive function					
	Contributes to the reduction of tiredness and fatigue					
	Contributes to the normal functioning of the immune system					
	A factor in the maintenance of good health					

<table>
<tr><th rowspan="2">Minerals</th><th rowspan="2">Health Supplement Claim (Single Substance Formulations)</th><th rowspan="2">Health Supplement Claim (Multiple Substance Formulations)</th><th colspan="2">Children</th><th colspan="2">Adults</th></tr>
<tr><th>Minimum</th><th>Maximum</th><th>Minimum</th><th>Maximum</th></tr>
<tr><td rowspan="12">Magnesium</td><td>Contributes to normal energy -yielding metabolism</td><td>Helps to metabolise carbohydrates, fats and proteins</td><td>1 - 3 years
12 mg</td><td>65 mg</td><td rowspan="12">20 mg</td><td rowspan="12">≤ 250 mg</td></tr>
<tr><td>Contributes to normal functioning of the nervous system</td><td>Contributes to the development and maintenance of bones and teeth</td><td>4 - 8 years
12 mg</td><td>≤ 100 mg</td></tr>
<tr><td>Contributes to normal electrolyte balance</td><td>Contributes to tissue formation</td><td>9 - 13 years
12 mg</td><td>≤ 250 mg</td></tr>
<tr><td>Contributes to a reduction of tiredness and fatigue</td><td>Contributes to the maintenance of normal muscle function</td><td rowspan="10">14 - 18 years
20 mg</td><td rowspan="10">≤ 250 mg</td></tr>
<tr><td>Contributes to the maintenance of normal muscle function</td><td>A factor in the maintenance of good health</td></tr>
<tr><td>Contributes to normal protein synthesis</td><td rowspan="8">Mineral supplement/ Vitamin/ Mineral supplement/ Multi-mineral supplement</td></tr>
<tr><td>Contributes to normal psychological function</td></tr>
<tr><td>Has a role in the process of cell division</td></tr>
<tr><td>Contributes to the maintenance of normal bones</td></tr>
<tr><td>Contributes to the maintenance of normal teeth</td></tr>
</table>

Minerals	Health Supplement Claim (Single Substance Formulations)	Health Supplement Claim (Multiple Substance Formulations)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Magnesium *cont.*	Helps to metabolise carbohydrates, fats and proteins					
	Contributes to tissue formation					
	A factor in the maintenance of good health					
Manganese	Helps the body to metabolise carbohydrates, fats and protein	Helps the body to metabolise carbohydrates, fats and protein			0,13 mg	4 mg
	Contributes to the development and maintenance of normal bones	Contributes to the development and maintenance of normal bones				
	Contributes to the protection of cells from oxidative stress	A factor in the maintenance of good health				
	Contributes to normal energy-yielding metabolism	Mineral supplement/ Vitamin/ Mineral supplement/ Multi-mineral supplement				
	Contributes to the normal formation of connective tissue					
	A factor in the maintenance of good health					

Minerals	Health Supplement Claim (Single Substance Formulations)	Health Supplement Claim (Multiple Substance Formulations)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Molybdenum	Contributes to normal sulphur amino acid metabolism	Helps the body to metabolise proteins			2,5 µg	≤ 230 µg
	Helps the body to metabolise proteins	A factor in the maintenance of good health				
	A factor in the maintenance of good health	Mineral supplement/ Vitamin/ Mineral supplement/ Multi-mineral supplement				
Phosphorus	Helps to metabolise carbohydrates, fats and proteins	Helps to metabolise carbohydrates, fats and proteins	**1 years - 18 years** 62 mg	≤ 250 mg	62 mg	≤ 250 mg
	Contributes to the development and maintenance of normal bones	Contributes to the development and maintenance of normal bones and teeth				
	Contributes to normal function of the cell membranes	A factor in the maintenance of good health				
	Contributes to energy-yielding metabolism	Mineral supplement/ Vitamin/ Mineral supplement/ Multi-mineral supplement				
	Contributes to the development and maintenance of normal teeth					
	Helps to metabolise carbohydrates, fats and proteins					
	A factor in the maintenance of good health					

Minerals	Health Supplement Claim (Single Substance Formulations)	Health Supplement Claim (Multiple Substance Formulations)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Potassium	Contributes to normal functioning of the nervous system	A factor in the maintenance of good health			75 mg	≤1 500 mg
	Contributes to normal muscle function	Mineral supplement/ Vitamin/ Mineral supplement/ Multi-mineral supplement				
	Contributes to the maintenance of normal blood pressure					
	A factor in the maintenance of good health					
Selenium	Contributes to the protection of cells from oxidative stress	An antioxidant for the maintenance of good health			3,5 µg	≤ 60 µg
	Contributes to normal spermatogenesis	A factor in the maintenance of good health				
	Contributes to the maintenance of normal hair	Mineral supplement/ Vitamin/ Mineral supplement/ Multi-mineral supplement				
	Contributes to the maintenance of normal nails					
	Contributes to the normal function of the immune system					
	Contributes to normal thyroid function					
	An antioxidant for the maintenance of good health					

Minerals	Health Supplement Claim (Single Substance Formulations)	Health Supplement Claim (Multiple Substance Formulations)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Selenium *cont*.	A factor in the maintenance of good health					
Vanadium	A factor in the maintenance of good health	A factor in the maintenance of good health			9,1 µg	≤ 182 µg
	Mineral supplement	Mineral supplement/ Vitamin/ Mineral supplement/ Multi-mineral supplement				
Zinc (and derivatives)	Contributes to the maintenance of immune function	Helps in connective tissue formation	**0 - 12 months** 0,2 mg	2 mg	0,7 mg	≤ 25 mg
	Contributes to the maintenance of normal skin	Helps to maintain healthy skin	**1 - 3 years** 0,4 mg	7 mg		
	Contributes to normal acid-base metabolism	Helps the body to metabolise carbohydrates, fats and proteins	**4 - 8 years** 0,4 mg	12 mg		
	Contributes to normal cognitive function	Helps to maintain immune function	**9 - 13 years** 0,4 mg	23 mg		
	Contributes to normal DNA synthesis	A factor in the maintenance of good health	**14 - 18 years** 0,7 mg	≤ 25 mg		
	Contributes to normal fertility and reproduction	Mineral supplement/ Vitamin/ Mineral supplement/ Multi-mineral supplement				
	Contributes to normal macronutrient metabolism					
	Contributes to normal metabolism of Vitamin A					

Minerals	Health Supplement Claim (Single Substance Formulations)	Health Supplement Claim (Multiple Substance Formulations)	Children		Adults	
			Minimum	Maximum	Minimum	Maximum
Zinc (and derivatives) *cont.*	Contributes to the maintenance of normal nails					
	Contributes to the maintenance of normal bones					
	Contributes to the maintenance of normal hair					
	Contributes to the maintenance of normal testosterone levels in the blood					
	Contributes to the maintenance of normal vision					
	Contributes to the protection of cells from oxidative stress					
	Has a role in the process of cell division					
	Contributes to connective tissue formation					
	Helps the body to metabolise carbohydrates, fats and proteins					
	A factor in the maintenance of good health					