COMPLETION OF THE CTD IN APPLICATION FOR A COMPLEMENTARY MEDICINE

MCC WORKSHOP

31 AUGUST 2015

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MEMBER: MEDICINES CONTROL COUNCIL (MCC)

CHAIRPERSON: COMPLEMENTARY MEDICINES COMMITTEE (CMC)

Introduction

- CMC Members
- Overview and Intention
- Current Status
  - Associated Definitions
  - Discipline Specific Substances
  - Health Supplements
- Further Development
- General Principles
- Modules 1.3 and 1.5
- Modules 4 and 5

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Overview and Intention

- Intention: CTD as a format for application
  - Clarification on its use as a format
  - Presenting Requirements for each Module and format – *what post in which boxes*
  - Time constraints – cannot address all
  - Related matters → time permitting
  - Question → in writing submitted at end (CTD)

- Workshops – February 2014
  - Invitation for training
  - Stakeholders to identify subjects – invite speakers

Complementary Medicines

- Definitions[1]

  "complementary medicine" means any substance or mixture of substances that-

  (a) originates from plants, minerals or animals;

  (b) is used or intended to be used for, or manufactured or sold for use in assisting the innate healing power of a human being or animal to mitigate, modify, alleviate or prevent illness or the symptoms thereof or abnormal physical or mental state, and

  (c) is used in accordance with the practice of the professions regulated under the Allied Health Professions Act, 1982 (Act No. 63 of 1982);

  [Definition of "complementary medicine" inserted by GN R870/2013w.e.f. 15 November 2013]

1. General Regulations made in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965)

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Complementary Medicines

- Definitions[2]

"complementary medicine" 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**;

2. Proposed Amendments to General Regulations made in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) [15 Sep 2014]

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Complementary Medicines *(Cat. D)*

	DISICIPLINE SPECIFIC (DS)	HEALTH SUPPLEMENTS (HS)
Types	Aromatherapy Ayurveda Homoeopathy Traditional Chinese Medicine Unani Medicine (Unani-Tibb) Western Herbal Medicine Combination Products *means a single product that contains:* *a) a mixture of substances of various discipline-specific origin or philosophy;* *b) a mixture of at least one substance of discipline-specific origin and one or more health supplements, or* *c) a mixture of at least one substance of discipline-specific origin and one or more of its isolated constituents.*	Probiotics Prebiotics Vitamins Minerals Amino Acids Animal Extracts, Products and Derivatives Fats, Oils and Fatty Acids Carotenoids Bioflavonoids Aminosaccharides Saccharides Enzymes Other
		Single substance formulations Multiple substance formulations

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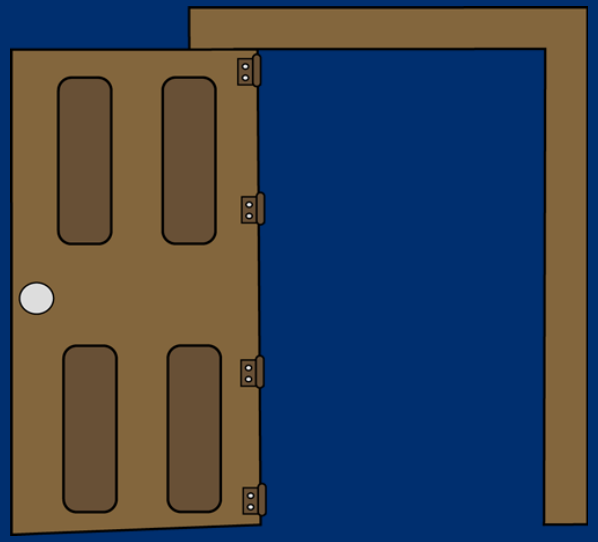
Complementary Medicines *(Cat. D)*

	DISICIPLINE SPECIFIC (DS)	HEALTH SUPPLEMENTS (HS)
Efficacy (Safety)	LOW RISK – Traditional Use <u>AND/OR</u> Clinical Evidence HIGH RISK – Traditional use <u>AND</u> Clinical Evidence	"LOW RISK" – unscheduled substances only (S0); prescribed allowable claims (single substance); prescribed guidelines on claim generation (multiple substance formulation) No treatment of diseases.
Quality	As prescribed – DS QSE	As prescribed – HS QSE
Classes	Disciplines established by Reg 25A, provided for in DS QSE	Provided for in HS QSE and amended Pharmacological Classifications (Regulations)
Call Up	1. By Risk – associated classification 2. Consider call up per discipline	1. By Single Substance as annexures become available 2. Call up combinations thereafter

Current Status



- Discipline Specific
  - Traditional Use
  - Clinical Evidence
- Health Supplements
  - Substance listed in Annexures
  - Schedule 0
  - Dosage Range and Prescribed Claims
  - Annexure B: if not appearing on the list then make submission (not part of product application) to appear on the list. Review – if granted then available for use with standardised claim
  - Annexures published set by set – stakeholders to comment as published

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Current Status

- Amendment to General Regulations (Nov 2013)
  - CM Definition
  - Category D
  - Requirement for labelling
  - Implementation – Regulation 48C

- Proposed Amendment to General Regulations (Sep 2014)
  - Amended CM Definition
  - Added "health supplement"
  - Expanded pharmacological classifications

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Current Status

- Guideline: Complementary Medicines – Quality, Safety and Efficacy (Dec 2013, Feb 2014)
  - Has since become regarded as the CM "Discipline Specific (DS)"

- Guideline: Complementary Medicines – Health Supplements – Quality, Safety and Efficacy (Nov 2014) – comment until Feb 2015
  - Stakeholder comment reviewed by CMC with stakeholder hearings

- Opportunity to revise – "easier to read":
  - Guideline: CM – DS QSE, based on format of the HS Guideline
  - Guideline: CM – HS QSE, based on comment received
  - Guideline: CM – Use of the ZA-CTD Format in the Preparation of an Application

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Current Status

- Product Reviews (Discipline Specific)
  - First Call Up (May 2014)
    - 20.2.8 (Antiviral agents)
    - 21.2 (Oral hypoglycaemics),
    - 6 (Cardiac medicines),
    - 26 (Cytostatic agents)
  - Second Call Up (November 2015)
    - 32.3 (Slimming preparations)
    - 7.1, 21.7 (Male sex hormones),
    - 21.8 (Female sex hormones)
    - 21.9 (androgen-oestrogen combinations) claiming sexual stimulation and sexual dysfunction

Current Status

- Regulation Amendments
  - Impact of Health Supplements as a subset of Category D
  - Regulatory Amendments
  - Timelines for registration
  - Impact on existing Call Up
  - Requirements / implementation
  - Can see though where MCC is going

- Intention
  - Progressive realisation of goals and outcomes
  - Proactive enhancement of industry with respect to QSE

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Current Status

- Potentially the most balanced approach – recognition of origins and intentions with public safety in mind
- Utilisation of recommendations and approaches analysed across the world:
  - World Health Organisation (WHO)
  - Australia
  - Canada
  - Europe
  - United Kingdom
  - Malaysia
  - Singapore *et al.*
- Confirmed internationally

General Principles

- Regulation of Complementary Medicine industry
  - Clearly not a new industry
  - Must be treated like it is
  - ANY regulatory standard will be a new benchmark
  - Progressive realisation of these standards with minimum principles / behaviour standards

- Applicant as the Expert
  - Manufacturer / applicant has developed the product with rationale, indications, formulation, ideas, standards
  - Application: provide this rationale by providing the best available data to demonstrate you have the best possible product

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General Principles

- Avoid rumours and supposition

- Applications:
  - Requires reference to all available guidelines
  - Read them and have available to guide your product registration
  - Applicants are experts of their products for consumer benefit
  - Provide where you have evidence / data; justify where you don't and with good reason; do not ignore common sense provisions
  - MCC are not product developers – assess the validity
  - Keep public / consumer in mind – QSE

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General Principles

- SAFETY
  - "My product is completely safe"
  - What about Quality? → how does that impact safety?
  - What about claim? → how does that impact safety?
  - Patient Safety and Benefit

- Food vs Medicine
  - Food Regulations
  - Medicine Regulations
    - Cannot provide for every circumstance
    - Behaviour regulated in the open – Call Ups
  - Determine using available DEFINITIONS, documentation, guidance and reason

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General Principles

- Review of Applications
  - Relevant sections reviews by relevant experts and committees
  - Appreciation for context of type of medicine

Module 1.3

- South African Labelling and Packaging

*"**label**", when used as a verb, means brand, mark or otherwise designate or describe, and when used as a noun, means any brand or mark or any written, pictorial or other descriptive matter appearing on or attached to or packed with and referring to any article or the package containing any article;* [3]

- Therefore, inclusive of PI and PIL

3. *Medicines and Related Substances Act, 1965 (Act 101 of 1965)*

Module 1.3.1

- South African Package Insert
- **Regulation 9** of the General Regulations to the Medicines and Related Substances Act, 1965 (Act 101 of 1965)
  - Regulation 9(1) reads: "*…under the headings and in the format specified in this regulation, and which shall contain the following particulars*"
- **Two languages** (English plus another official lang.)
- Look up the format and headings – latest regulations
- Consider indications, contraindications, warning, interactions or pregnancy and lactation guidance from existing international licensing / registrations and also other relevant monographs.
- Reg. 9(1)(d) – Pharmacological Classification

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Module 1.3.1

- South African Package Insert
- **NOTE:**
  - Reg. 9(1)(h) - Warnings and special precautions;

    (amended from "Warnings")
  - Reg. 9(1)(l) - Side effects;

    (amended from "Side effect and special precautions")
- In the case of a CM
  - Reg. 8(1)(t)(i) - Discipline of the Medicine
  - Reg. 8(1)(t)(ii) – Disclaimer as prescribed (if not registered)

Module 1.3.1.2

- South African Package Insert
- Standard References
  - References listed that justify the medicine in terms of efficacy or safety claims.
  - Traditional Use
  - Clinical Evidence

Module 1.3.2

- Patient Information Leaflet
- **Regulation 10** of the General Regulations to the Medicines and Related Substances Act, 1965 (Act 101 of 1965)
  - Regulation 10 reads: "…*must contain the following information with regard to the medicine*…"
- **Two languages** (English plus another official lang.)
- Look up the format and headings – latest regulations
- Consider indications, contraindications, warning, interactions or pregnancy and lactation guidance from existing international licensing / registrations and also other relevant monographs.
- Inclusion of prescribed general statements: 10(1)(e)(v)
- Reg. 10(1)(f)-(h) – as indicated plus general statements

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Module 1.3.2

- Patient Information Leaflet
- **NOTE:**
  - Reg. 10(1)(e)(ii) – Precautions and warnings;

    (amended from "Precautions")
  - Reg. 10(1)(e)(v) – amended general statements
  - Reg. 10(1)(g) – amended general statement for side effects
- In the case of a CM
  - Reg. 10(1)(n)(i) - Discipline of the Medicine
  - Reg. 10(1)(n)(ii) – Disclaimer as prescribed (if not registered)

Module 1.3.3

- Labels
- **Regulation 8** of the General Regulations to the Medicines and Related Substances Act, 1965 (Act 101 of 1965)
  - **Two languages** (English plus another official lang.)
  - Look up the format and headings – latest regulations
  - Regulation 8(1) refers to the immediate container label
  - Regulation 8(2) refers to the outer label where 8(1) applies with proviso for then sufficient information on immediate container label
  - Reg. 8(1)(z) - Category of Medicine preceding registration number / application number
  - Reg. 8(1)(aa) - Pharmacological Classification

Module 1.3.3

- Labels
  - PLUS in case of CM:
  - Reg. 8(1)(bb)(i) - statement of discipline
  - Reg. 8(1)(bb)(ii) - Disclaimer **IF NOT REGISTERED**:

"This medicine has not been evaluated by the Medicines Control Council. This medicine is not intended to diagnose, treat, cure or prevent any disease."

ROADMAP: February 2014 with extension to August 2014

Can be added on as a sticker.

- Reg. 8(3) - (3) The Council may authorise the inclusion on the label of a medicine of any special information that is not required by this regulation to be so included.

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Module 1.3

- Pharmacological Classification
  - Discipline Specific Medicines (Traditional Use)
    - The CLASSIFICATION is linked to the primary claim
    - Do not confuse with Pharmacological Action which is required in the PI
      - If claim is treatment of hypertension:

        7.1.3 Other hypotensives
    - CHALLENGE:

      traditional CLAIMS – arising out of Traditional Chinese Medicine or Ayurveda

      OR

      Multiple claims from single / multiple substance formulation or combination product

      Steer toward primary classification associated with its action or list as OTHER

Module 1.3

- Pharmacological Classification
  - Health Supplements
    - The CLASSIFICATION will be linked to the type of substance
    - New classifications proposed in draft amendments to the General Regulations to the Medicines and Related Substances Act, 1965 (Act 101 of 1965)
      - 30.4 Prebiotics and Probiotics
      - 33. Minerals; 34. Animal Extracts, Products and Derivatives; 35. Fats, Oils and Fatty Acids; 36. Carotenoids; 37. Bioflavonoids; 38. Aminosaccharides; 39. Saccharides
    - CHALLENGE:

    Multiple substance formulations or combination products: reference other or dominant substance formulation. Check final classifications when published in the Regulations.

Module 1.5

- Specific Requirement for Different Types of Applications
  - 1.5.1 Literature Based Submissions (DS)

Brief statement as to why the product meets the requirements for traditional use registration and addressing the evidence of long standing use of the product, expanded in Module 2.5

Where a herbal monograph exists that is relevant to the proposed preparation, applicants should outline this fact in this section of the dossier and expand on it in Module 2.5.

Module 1.5

- Specific Requirement for Different Types of Applications
  - 1.5.1 Literature Based Submissions (HS)

Brief statement as to the justification of the claim (multiple substance formulation and/or combination products) and of the safety of the product.

Module 2.5

- Clinical Overview (Discipline Specific)

  A bibliographical evidence or expert evidence to the effect that the medicinal product in question, or its ingredients or a corresponding product, has a history of traditional medicinal use (as per the definition in the guideline) within the Republic of South Africa or within a country, the regulatory authority of which the MCC aligns itself with.

  In addition, the plausibility of pharmacological effects or efficacy of the medicinal product as well as information on the safety of use should be addressed in this section. A summary of clinical evidence should also be included where required.

  - Do not over state the evidence provided by traditional use – give sufficient reference and guidance as related to the claim and as per guideline.

Module 2.5

- Traditional Use

Use of a designated active ingredient that is well-documented, or otherwise reliably established, according to the accepted philosophy or accumulated experience of a particular discipline that may be verified in any of the listed accepted references which may apply to each discipline and accords with well-established traditional procedures of preparation, application and dosage. New combinations of active ingredients previously used separately or in different combinations, must be suitably justified according to the philosophy / principles of the associated discipline. [4]

4. MCC Guideline – **Complementary Medicines** - Quality, Safety, Efficacy

Module 2.5

- Clinical Overview
  - *Two of the following four sources that demonstrates adequate support for the indications claimed[5]:*
    1. *Recognised Pharmacopoeia;*
    2. *Recognised Monograph;*
    3. *Three independent written histories of use in the classical or traditional medical literature.*
    4. *Citations from other in vivo, in vitro studies, case reports or others.*

1-3: Traditional / historical / philosophical

4: Modern use

Module 2.5

- Monographs
  - Monographs of equivalent standing to those specifically listed may be used.
  - Monographs may be quoted but applicants must provide copies of the relevant monograph.
  - Demonstration of how the product accords with such monograph must be made.
- Pharmacopoeias
  - Copies of the relevant extract from the necessary pharmacopoeia.

Module 2.5

- Clinical Overview (Health Supplement)

  A bibliographical evidence or expert evidence to the effect that the medicinal product in question, or its ingredients or a corresponding product, accords with the claims and dosage levels as provided for in the annexures to the guideline.

  In addition, the plausibility of pharmacological effects or efficacy of the medicinal product as well as information on the safety of use should be addressed in this section.

Modules 4 and 5

- Module 4 - Non-Clinical Study Reports

  Any reports or studies referenced should be provided in full. Product specific study reports.

- Module 5 - Clinical Study Reports

  Any reports or studies referenced should be provided in full. As summarised in Module 2.5.

  Product specific study reports.