South Africa's experience on the regulatory framework of OTC medicines

Complementary Medicines

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Member: Medicines Control Council
Chairperson: Complementary Medicines Committee
Member: Legal Committee, Good Practices Compliance Committee

Introduction

- Contextualise SAHPRA
- Complementary Medicine in South Africa
  - Push to Regulation
  - Principles of Regulation
- CM Regulation in South Africa
  - Influence of general regulation
- Application Process
- Benefits
- Challenges

South African Health Products Regulatory Authority (SAHPRA)

Medicines and Related Substances Amendment Act, 2008 (Act 72 of 2008) – **01 June 2017**

- Medicines and Related Substances Amendment Act, 2015 (Act 14 of 2015)
- Board Structure
- Chief Executive Officer (CEO)
- Incorporation of multiple units – increased mandate
- Liaise, cooperate or exchange information with an other regulatory institution
- Enter into agreements that meet the stated objectives of SAHPRA

South African Health Products Regulatory Authority (SAHPRA)

- Concept of an Authority *vs* Council
  - Way of doing business
  - Way of making decisions
  - Way of communicating

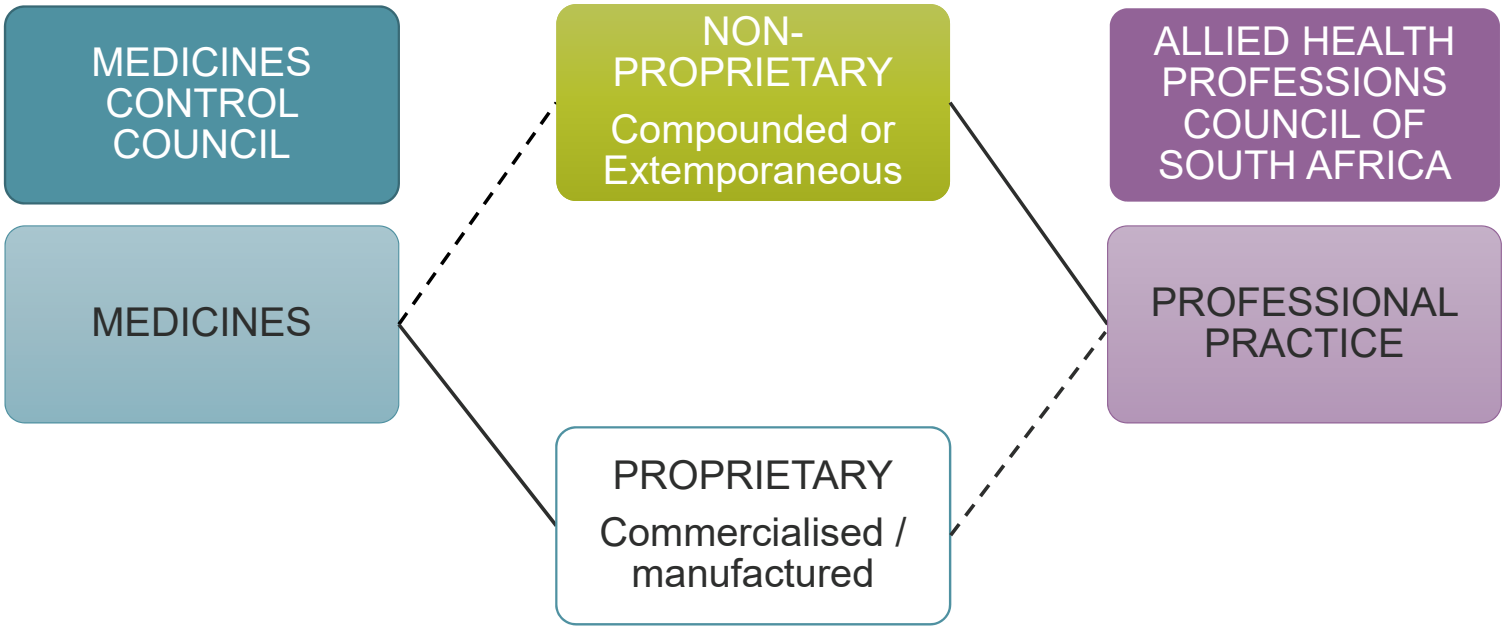
SYSTEM CHANGE?

- South African Health Products Regulatory Authority (SAHPRA)
  - Regulations
  - Guidelines
  - Policies and Notices
  - Communications

REPRESENTING THE CHANGE

Complementary Medicine in South Africa

Complementary Medicine in South Africa



Complementary Medicine
…Push to Regulation

- 1996: the market share was R 900 million
- 2003: was estimated at R 1.35 billion
- 2010: SA Market size approx. R 7.8 billion - representing approx. 0.7 % of world market
- 2017: ???

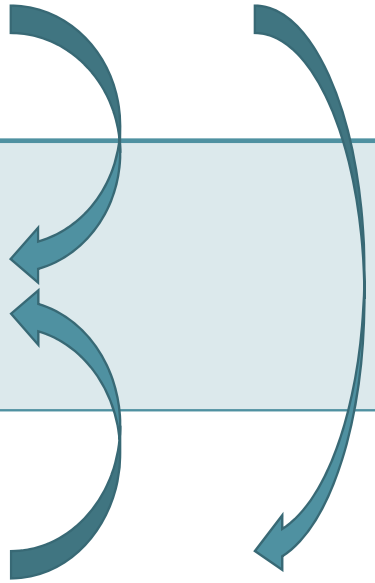
HPA. (2010). CAMs in South Africa, Alan Tomlinson; https://goo.gl/eAQB6O

Complementary Medicine
…Push to Regulation

- Past attempts to regulation the sector – since 1970s, 1980s, 1990s and 2000s
- Growth without uniformity in standards
- Patient risk
- Advertising > Effectiveness
- No handle of normally safe, abnormally unsafe, normally unsafe
- Reactive regulation
- Missing piece of the CM regulatory puzzle - accountability

Complementary Medicine
…Principles of Regulation (Risk Exposure)

Quality • Has what it should have • Does not have what it shouldn't • It lasts (expiry) • Works in way intended once taken	RISK
Safety • Safe to take • Risk – benefit ratio • Long term use • Interactions, ADRs, Contraindications	RISK
Efficacy and Effectiveness • Works in way intended / promised • Benefit • Specific product	RISK



WHO. (2014). WHO – Traditional Medicine Strategy: 2014-2023

Complementary Medicine
…Principles of Regulation

- Old / New industry
  - Treat as if a new industry
  - Acknowledge the history of the work done previously
- Appreciate and contextualise risk
  - Population specific
- Acknowledge and define traditional use

Complementary Medicine
…Principles of Regulation

- Research international practice
  - WHO
  - Australia
  - Canada
  - Europe
  - United Kingdom
  - Malaysia
  - Singapore

et al.

Continues…

Complementary Medicine
…Principles of Regulation

- Defining “what makes a medicine… a medicine”
  - Legislation
  - Precedent
  - Perception
- Nomenclature

Alignment with WHO Definitions
Traditional *vs* Complementary Medicine

Traditional medicine

AFRICAN TRADITIONAL MEDICINE

Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and **experiences indigenous to different cultures**, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.

Complementary/alternative medicine (CAM)

NON-INDIGENOUS DISCIPLINES

The terms "complementary medicine" or ~~"alternative medicine"~~ are used inter-changeably with traditional medicine in some countries. They refer to a broad set of health care practices **that are not part of that country's own tradition** and are not integrated into the dominant health care system.

WHO. (2017). Traditional Medicine: Definitions. http://who.int/medicines/areas/traditional/definitions/en/

Complementary Medicine Regulation
Regulatory Compliance

15 Sep 2014; 25 Jul 2016; 16 Jan 2017

Comment periods of 3 months each

15 Nov 2013

Discipline Specific CMs

Continued Rights of Sale

Labelling

Comply with scheduling status

25 Aug 2017

Added: Health Supplements

Continued Rights of Sale

Labelling

Scheduled medicines off market

Function of SAHPRA global changes

31 Dec 2019

Registration submission deadline for all Discipline Specifics except combinations of DS and HS

TBC

Registration deadlines for HS

Complementary Medicine Regulation
Definitions

“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 the Authority;

(b) is used or purporting to be suitable for use or manufactured or sold for use-

(i) in maintaining, complementing or assisting the 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 the Authority;

General Regulations made in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) [Gov.Not. 859 in GG 41064 of **25 Aug 2017**]

Complementary Medicine Regulation
Definitions

“health supplement” means any substance, extract or mixture of substances as determined by the Authority, sold in dosage forms used or purported for use in restoring, correcting or modifying any physical or mental state by-

(a) complementing health;
(b) supplementing the diet; or
(c) a nutritional effect,

and excludes injectable preparations, medicines or substances listed as Schedule 1 or higher in the Act;

General Regulations made in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) [Gov.Not. 859 in GG 41064 of **25 Aug 2017**]

Complementary Medicine Regulation
Categorisation and Classification

Regulation 9 – Categories and classification of medicines

Category A, B, C

Category D – Complementary Medicines

Regulation 9(2) – sub-categories of Category D

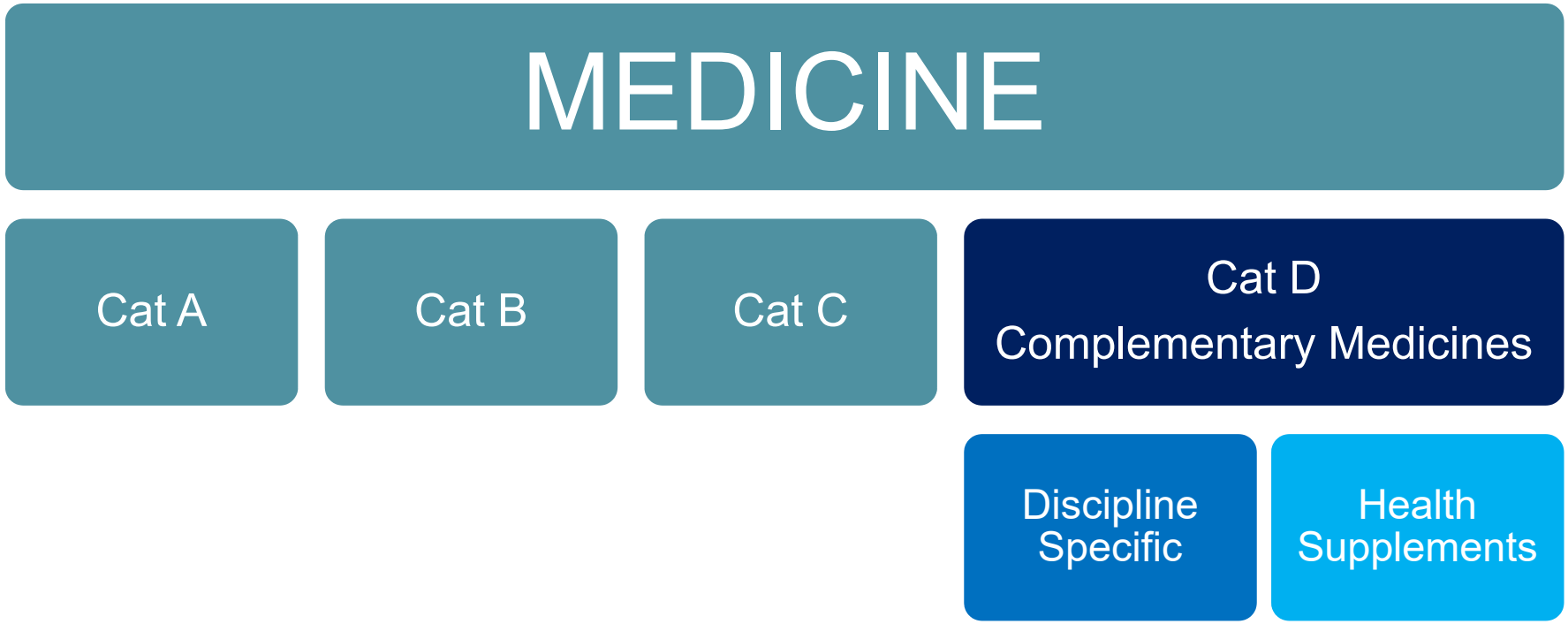
(2) Medicines in Category D shall be classified into the following sub-categories:

(a) discipline-specific medicines with such disciplines as determined by the Authority; and

(b) health supplements.

General Regulations made in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) [Gov.Not. 859 in GG 41064 of **25 Aug 2017**]

Complementary Medicine Regulation
Categorisation



Complementary Medicine Regulation
Classification

Regulation 9(3) – Classes of Medicines

(3) Medicines in Categories A and D (human complementary medicine) are subdivided into **classes** as per Annexure 1.

Complementary Medicine Regulation
Classes

	DISICIPLINE SPECIFIC (DS)	HEALTH SUPPLEMENTS (HS)
Types	Aromatherapy Ayurveda Homoeopathy Traditional Chinese Medicine Unani (Unani-Tibb) Western Herbal Medicine Other Herbal Combination Products	Probiotics Prebiotics Vitamins Minerals Amino Acids Animal Extracts, Products and Derivatives Fats, Oils and Fatty Acids Carotenoids Polyphenols (including Bioflavonoids) Aminosaccharides Saccharides Enzymes Other

Complementary Medicine Regulation
Classes

	DISICIPLINE SPECIFIC (DS)	HEALTH SUPPLEMENTS (HS)
Types	Aromatherapy Ayurveda Homoeopathy Traditional Chinese Medicine Unani (Unani-Tibb) Western Herbal Medicine Other Herbal Combination Products	Probiotics Prebiotics Vitamins Minerals Amino Acids Animal Extracts, Products and Derivatives Fats, Oils and Fatty Acids Carotenoids Polyphenols (including Bioflavonoids) Aminosaccharides Saccharides Enzymes Other Single substance formulations Multiple substance formulations

Complementary Medicine Regulation
Classes

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

Complementary Medicine Regulation
Classes

	DISICIPLINE SPECIFIC (DS)	HEALTH SUPPLEMENTS (HS)
Types	Aromatherapy Ayurveda Homoeopathy Traditional Chinese Medicine Unani (Unani-Tibb) Western Herbal Medicine Other Herbal	Probiotics Prebiotics Vitamins Minerals Amino Acids Animal Extracts, Products and Derivatives Fats, Oils and Fatty Acids Carotenoids Polyphenols (including Bioflavonoids) Aminosaccharides Saccharides Enzymes Other
	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	Single substance formulations Multiple substance formulations

Complementary Medicine Regulation
Classes

	DISICIPLINE SPECIFIC (DS)	HEALTH SUPPLEMENTS (HS)
Types	Aromatherapy Ayurveda Homoeopathy Traditional Chinese Medicine Unani (Unani-Tibb) Western Herbal Medicine Other Herbal	Probiotics Prebiotics Vitamins Minerals Amino Acids Animal Extracts, Products and Derivatives Fats, Oils and Fatty Acids Carotenoids Polyphenols (including Bioflavonoids) Aminosaccharides Saccharides Enzymes Other
	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. *[NOT IN ATTEMPT TO PASS AS CM BUT AS RATIONALE PART OF THE COMPLEX]*	Single substance formulations Multiple substance formulations

Complementary Medicine Regulation

Risk Level	Type of Claim	Evidence required to support claim
HIGH RISK	• Treats/cures/manages any disease/disorder. • Prevention of any disease or disorder. • Reduction of risk of a disease/disorder. • *Aids/assists in the management of a named symptom/disease/ disorder.* • *Relief of symptoms of a named disease or disorder*[2] • Treatment of proven vitamin or mineral deficiency diseases.	• Clinical data to be evaluated [3]. **AND** • Two of the following four sources that demonstrates adequate support for the indications claimed: 1 Recognised Pharmacopoeia [4]; 2 Recognised Monograph [4]; 3 Three independent written histories of use in the classical or traditional medical literature, or 4 Citations from other in vivo, in vitro studies, case reports or others.
LOW RISK	• General health enhancement without any reference to specific diseases [1] • Health maintenance, including nutritional support. • Relief of minor symptoms (not related to a disease or disorder) [2] • ***Vitamin or mineral supplementation*** *(added for purposes of presentation)*	• Clinical data to be evaluated [3] **AND/OR:** • Two of the following four sources that demonstrates adequate support for the indications claimed: 1 Recognised Pharmacopoeia [4]; 2 Recognised Monograph [4]; 3 Three independent written histories of use in the classical or traditional medical literature. [5,6], or 4 Citations from other in vivo, in vitro studies, case reports or others.

7.01 – MCC Guideline – Complementary Medicines – Discipline Specific - Safety and Efficacy (2016) V3

Complementary Medicine Regulation

<table>
<tr><th></th><th colspan="2">DISICIPLINE SPECIFIC (DS)</th><th>HEALTH SUPPLEMENTS (HS)</th></tr>
<tr><td rowspan="3">Efficacy
&
Safety</td><td colspan="2">LOW RISK
“Traditional Use”
<u>AND/OR</u>
Clinical Evidence</td><td rowspan="2">LOW RISK
Schedule 0 only
Prescribed indications (single substance)
Prescribed guidelines on claim generation (multiple substance formulation)
No treatment of disease.</td></tr>
<tr><td colspan="2">No isolates (other than as prescribed)</td></tr>
<tr><td colspan="2">HIGH RISK
“Traditional use” <u>AND</u> Clinical Evidence</td><td></td></tr>
<tr><td>Quality</td><td colspan="3">As prescribed – Guideline CM Quality</td></tr>
<tr><td>Classes</td><td colspan="2">Disciplines:
• established by Reg 9;
• provided for in Guideline CM DS: SE; and
• Class (old Pharmacological Classification) of medicines</td><td>Health Supplements:
• provided for in Guideline CM HS: SE; and
• Class (old Pharmacological Classification): Annexure 1 and 2 (of Gen Regulations)</td></tr>
<tr><td>Registration</td><td colspan="2">1. Registration deadlines (Reg 48C) prescribed by risk – associated classification
2. Consider call up per discipline</td><td>1. By Single Substance as annexures available
2. Call up combinations</td></tr>
</table>

Complementary Medicine Regulation
Original Roadmap

Registration Submission Deadline	Class
15 May 2014:	20.2.8 (Antiviral agents) 21.2 (Oral hypoglycaemics) 6 (Cardiac medicines) 26 (Cytostatic agents)
15 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
15 May 2016:	32.16 (Other) and claiming immune stimulation or expressions of similar connection 17 (Medicines acting on muscular system) 22 (Vitamins) claiming to be sport supplements and exceeding the upper limit of vitamins and minerals as published by Council
15 May 2019:	All CMs submitted

Complementary Medicine Regulation
Roadmap Addition

Registration Submission Deadline	Class
TBC	**1. Complementary Medicine (CM) - Health Supplement (HS)** ***- Single Substance Formulations (SSF)*** ***- Multiple Substance Formulations (MSF)*** **2. Discipline-Specific** ***- Combination Products*** Vitamins Minerals Probiotics Prebiotics Amino acids Carotenoids Fats, Oils and Fatty Acids Aminosaccharides Animal Extracts, Products and Derivatives Enzymes Polyphenols (including Bioflavonoids) Other

Complementary Medicine Regulation
Regulatory Compliance

- **10. LABELLING OF MEDICINES INTENDED FOR HUMAN USE**
  - **10(1)(*cc*)** Complementary Medicines:
    - **(i)** The words **"Complementary Medicine"**
    - **(ii)** A statement identifying the **discipline** or the words **"Health Supplement"**
    - **(iii) "This unregistered medicine has not been evaluated by the SAHPRA for its quality, safety or intended use."**
    - **(iv)** containing at least 5 percent of genetically modified organisms the following warning "contains genetically modified organisms".

General Regulations made in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) [Gov.Not. 859 in GG 41064 of **25 Aug 2017**]

Complementary Medicine Regulation
Regulatory Compliance

- **11. PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE**
  - **11(1)(*a*)** PI shall be made available in hard copy or **electronically** (provided that details of how to access to the PI are provided for in the PIL)
    - The PI is still an integral part of any application and use of the product by prescribers regardless of scheduling status. Therefore it must still be part of the CTD dossier and assessed as such.
  - **11(1)(*b*)** English
  - **11(1)(*t*)** Complementary Medicine
    - Same requirements as for **labelling**
  - **11(5)** Nothing contained in subregulation (4) *"shall be construed as prohibiting the inclusion of professional information with any medicine."*

INFLUENCE OF CM REGULATION → OTC → ALL

General Regulations made in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) [Gov.Not. 859 in GG 41064 of **25 Aug 2017**]

Complementary Medicine Regulation
Regulatory Compliance

- **12. PATIENT INFORMATION LEAFLET**

12(1) Each medicine shall have a PIL

12(2) English and another official language

12(2)(*n*) Complementary Medicine

- Same requirements as for **labelling**

12(2)(*p*) the manner in which the corresponding professional information as per regulation 11 may be obtained.

General Regulations made in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) [Gov.Not. 859 in GG 41064 of **25 Aug 2017**]

Complementary Medicine Regulation
Regulatory Compliance

- **42. ADVERTISING OF MEDICINES**

  42(5)(*c*) in the case of a—

  - complementary medicine—
    - a statement identifying the **discipline** of the medicine where relevant;
    - an indication that the medicine must be used in accordance with the applicable complementary discipline and principles where relevant; and
    - if the medicine has not received registration with the Authority the following disclaimer:

  "This unregistered medicine has not been evaluated by the SAHPRA for its quality, safety or intended use.";

General Regulations made in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) [Gov.Not. 859 in GG 41064 of **25 Aug 2017**]

Application Process

- Licensed manufacturer, wholesaler, distributor
  - Licensing support phase over 5 years to compliance
- Follow all relevant Guidelines on Application
  - **SE Guideline for CM: DS (Jun 2016)**
  - **SE Guideline for CM: HS (Jun 2016)**
  - **Quality Guideline for CM (Jun2016)**
  - Other Guidance: application costs, checklists
- CTD Format – requirements as per guidelines (Low vs High Risk)

Run Off…

- Consideration of risk-based approach for Category A OTC medicines (?)
- Consideration of risk-based approach for Clinical Trials (?)
- Vigilance expansion
- Regional labelling
- Regulator’s way of doing things

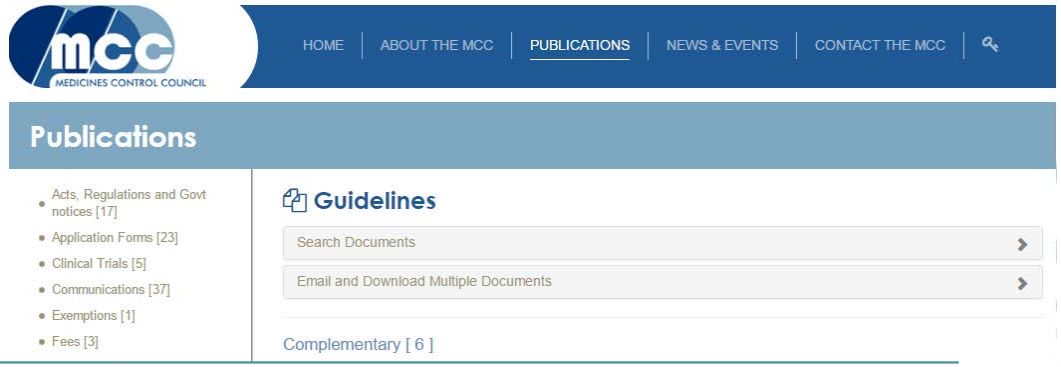
Benefits

- Better quality products
- Retraction of high risk indications
- Increased oversight within the market
- Involvement of qualified professionals with the market
- Increased confidence by consumers
- Industry development and market development
- Completed circle for CM professionals / prescribers
- Involvement of CM professionals areas of cross-over

Challenges

- LOW vs HIGH Risk
  - Future intentions / grading
- Maintenance of functional review turnaround times
- Policy Maintenance
- Use of DS substances in food
  - Guidance
- Veterinary Products
- Platform for Pharmacovigilance
  - AHPCSA

Guidelines



Name	Guideline
Complementary Medicines – **Discipline-Specific** – Safety and Efficacy	7.01_CMs_SE_DS_Jun16_v3 MCC
Complementary Medicines – Road Map	7.02_Roadmap_for_CAMs_Dec13_v1
Complementary Medicines – ZA-CTD Format	7.03_CAMs_ZACTD_Jun16_v3 MCC
Complementary Medicines – **Health Supplements** – Safety and Efficacy	7.04_SE_Health_Supplements_Jun16_v2 MCC
Complementary Medicines – **Quality**	7.05_CMs_Quality_Jun16_v1 MCC

ZA-CTD orientation built into the guidelines to assist registration

www.mccza.com

Thank you

Dankie

Ngiyabonga

Enkosi

Siyabonga kakulu

Ke a leboga

Ke a leboha

Ndi a livhuwa

dzi khense ngopfu