CAMS: A Practical Approach Going Forward

Working with Industry by offering innovative solutions to overcome today's challanges

Wayne Robinson – May 2019

Status of SAHPRA & CAMS Regulations

MCC & SAHPRA

- SAHPRA is the **South African Health Products Regulatory Authority**
- The **Medicines and Related Substances Act,** 1965 (Act 101 of 1965), was amended by:
  - Act 72 of 2008 → Establishment of **SAHPRA**
    - This provided for the **establishment of South African Health Products Regulatory Authority (SAHPRA)**
    - Schedule 3A public entity, which operates as a separate juristic entity, outside of the National Department of Health (NDoH).
    - Focus on Medicines, Medical Devices, Veterinary Products
    - Act 72 was enacted on 1 June 2017, which then enacted Act 14 of 2015
  - Act 14 of 2015
    - Appointment of Governance Board
    - Expanded oversight of Medical Devices to include IVD's
    - Address transitional arrangements from MCC to SAHPRA
  - General Regulations published on 11 August 2017

SAHPRA

South African Health Products Regulatory Authority

SAHPRA Background

- SAHPRA is responsible for monitoring, evaluation, regulation, investigation, inspection, registration and control of medicines, clinical trials and medical devices and related matters in the public interest
- SAHPRA will:
  - Have full-time in-house capacity to support product review & approval and oversee all regulatory functions
  - Establish cooperation and information sharing with the NRAs to support implementation of best practices and timely approval of products
- SAHPRA Board Members were appointed by the Minister of Health on 9 October 2017
- Board had 3 introductory / unofficial meetings with the MCC on 24 November 2017, 13 December 2017 and 15 January 2018.
- Minister of Health called the first official SAHPRA Board Meeting on 1st February 2018:
  - MCC ceased to exist at this 1st meeting
  - Board appointed an Acting CEO after consultation with the Minister of Health
  - Board appointed committees to assist with work of the Board

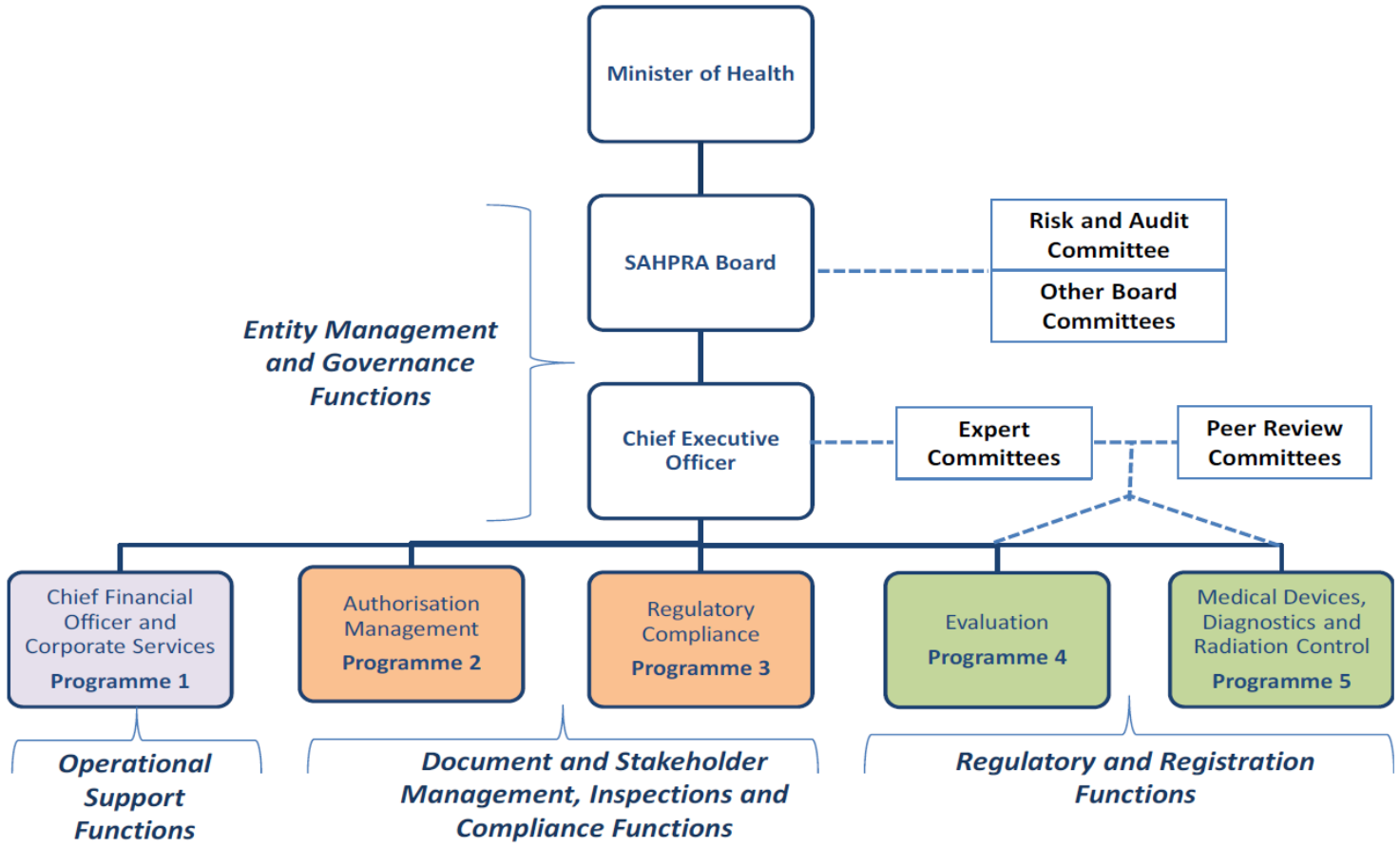
SAHPRA Board

BOARD MEMBERS AND CATEGORY OF APPOINTMENT IN TERMS OF SECTION 2C(1) OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 OF 1965), AS AMENDED

No	Name	Category of appoinment
1.	Prof. Helen Rees (Chairperson)	Section 2C(2)(a) on account of expertise in the fields of medicine, medical devices, IVD, vigilance, clinical trials, good manufacturing practice, public health or epidemiology
2.	Dr Nonhlanhla Madela - Mntla	
3.	Prof. Shabir Banoo	
4.	Dr Henry Leng	
5.	Dr Thapelo Motshudi	
6.	Prof. Kelly Chibale	
7.	Prof. Aimes Dhai	
8.	Prof. Jeffrey Mphahlele	
9.	Dr Ushma Mehta	
10.	Dr Mphane Molefe	
11.	Adv. Hasina Cassim	Section 2C(2)(b) on account of knowledge of the law
12.	Ms Mandisa Hela (Vice-Chairperson)	Section 2C(2)(c) on account of knowledge of good governance
13.	Ms Lesibana Fosu	Section 2C(2)(d) on account of knowledge of the financial matters and accounting
14.	Mr Norman Baloyi	Section 2C(2)(e) on account of knowledge of information technology
15.	Prof. Craig Household	Section 2C(2)(f) on account of knowledge of human resource management

In the interim, the Minister and the SAHPRA Board have appointed Mrs Portia Nkambule, previously a Director in the Cluster: Food Control, Pharmaceutical Trade & Product Regulation, as the Acting SAHPRA CEO.

SAHPRA Structure



SAHPRA Strategic Plan 2018-19 to 2022-23

SAHPRA Goals

- **Goal 1:** Publicly demonstrate responsiveness and accountability as an effective and efficient high performance organisation.
- **Goal 2:** Timeous regulatory decision taken on medicines and medical device applications to ensure compliance to defined standards of quality, safety, efficacy and performance.
- **Goal 3:** Re-evaluate and monitor medicines and medical devices periodically.
- **Goal 4:** Investigate, monitor, analyse, solicit and act upon existing and new adverse events, interactions, information with regard to post-marketing surveillance and vigilance.
- **Goal 5:** Ensure regulatory compliance through a process of active Inspections and investigations.
- **Goal 6:** Evaluate clinical trial protocols in accordance with defined standards.
- **Goal 7:** Evaluate the applications for sale of unregistered health products in accordance with defined standards.
- **Goal 8:** Establish and strengthen collaborative initiatives with any other regulatory authority or institutions in order to achieve the objects of the Medicines Act.
- **Goal 9:** SAHPRA is capacitated by adequate, competent and motivated Human Capital.

SAHPRA

South African Health Products Regulatory Authority

SAHPRA Strategic Plan 2018-19 to 2022-23

SAHPRA Envisaged Changes

- SAHPRA plans to have the following changes:
  - Capacity building – increased full-time in-house technical capacity
  - Expanding technical and administrative staff members
  - Improving the skills base for newer, emerging technologies
  - Improved peer review system – frequency of meetings
  - Specialized areas – retainer system for experts
  - Provisional approval on early data is being investigated
  - Reorganize the appeal process to ensure speedier outcomes
  - Website improvements and strengthen communication through dedicated unit
  - Strengthen cooperation with recognized regulatory authorities
  - Frequent engagements with stakeholders

SAHPRA

South African Health Products
Regulatory Authority

MCC vs SAHPRA

MCC	SAHPRA
• Medicines	• Medicines, Devices (incl. IVDs & Radiation control), CAMS (DS & HS)
• Within DoH	• Schedule 3A Public entity
• Under resourced?	• Sufficiently Resourced
• Limited evaluators (own 20/80)	• Increase employed evaluators (80/20)
• Traditional government business functions	• Independent business entity model & retained income (70%:30%)
• Paper driven	• System driven
• Backlogs	• Timelines-based

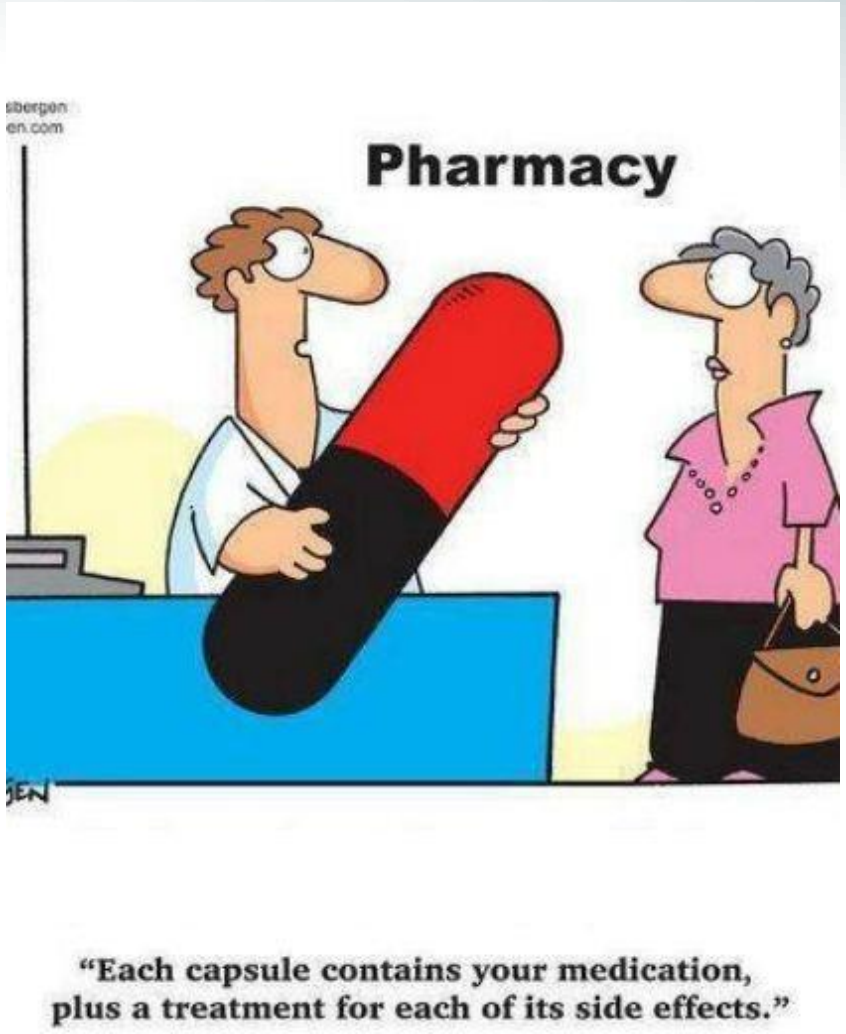
CAMS Status

Medicine Categories

Medicines and Related Substances Act, 1965
(Act 101 of 1965)
Regulation 9

- Category A
- Category B
- Category C
- Category D
  Complementary Medicines
  - 1. Discipline Specific CAMS
  - 2. Health Supplements

Use product for intended purpose



Category A Medicines

Category A Medicines are called:

- Allopathic
- Orthodox
- Western
- Modern

This is the dominant MEDICINE system in SA:

- Widespread use
- Scientific background
- Political support
- Cultural acceptability
- Biological reasoning: anatomy, physiology, biochemistry

CAMS Overview

- Alternative

  = another treatment for same medical issue

- Complementary

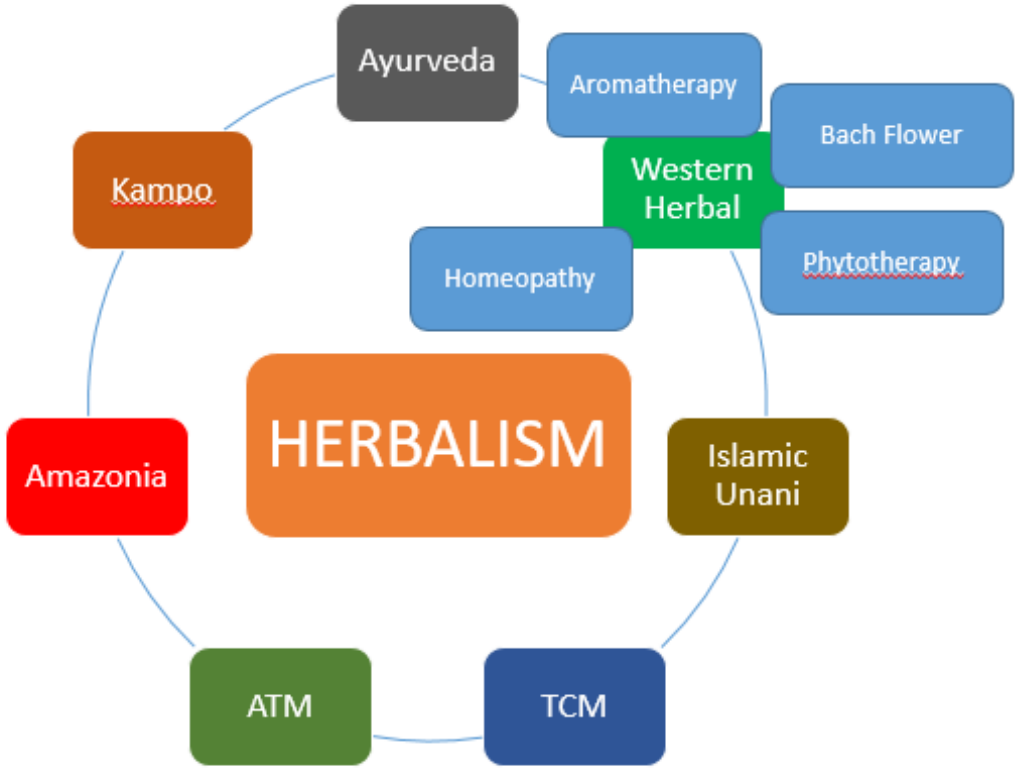
  = playing a secondary role

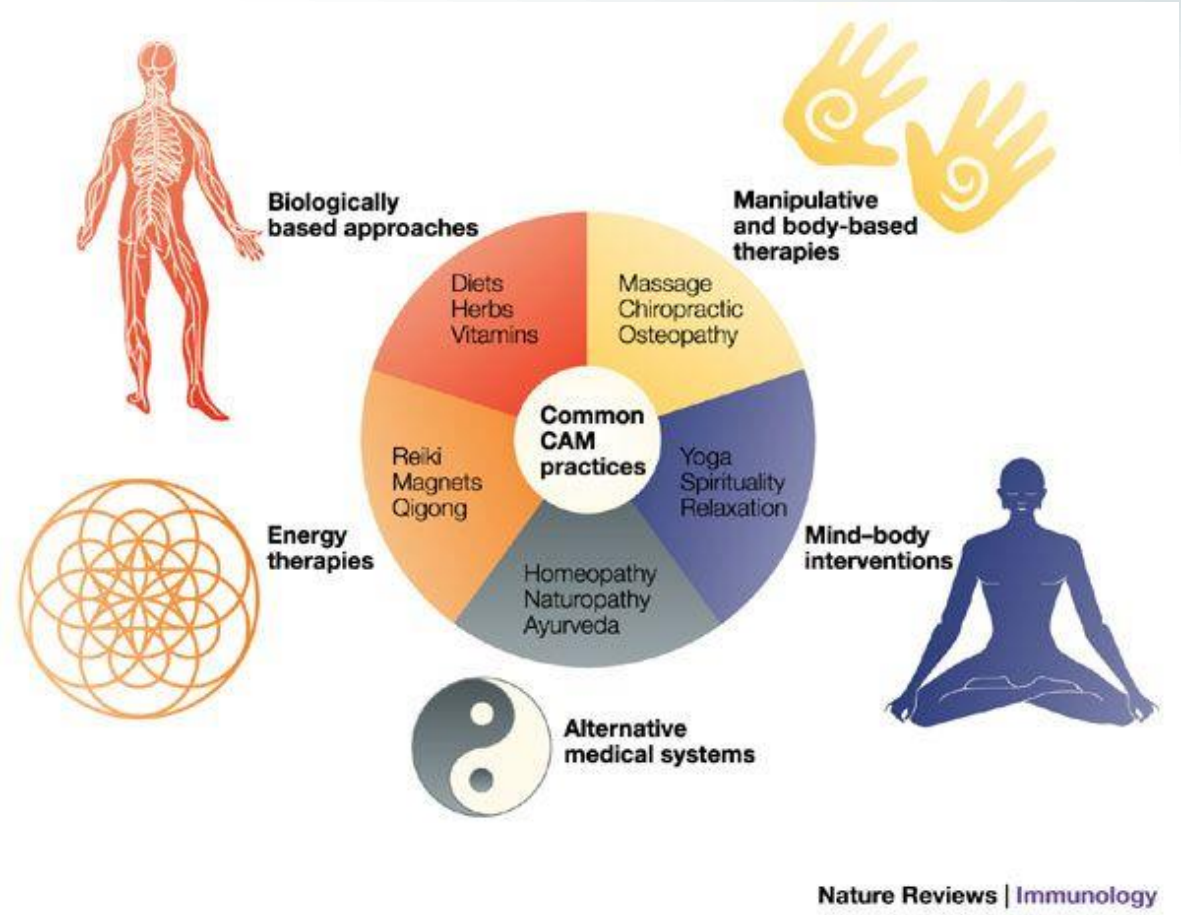
  = complements the body's natural healing tendency

Current Trend: Integrated medicine

Affords patients and prescribers more choice, but little appreciation of clashes

CAMS vs Herbalism vs Alternative Medicine





CAMS Overview

CAMS market share is substantial:

- 1996: approx. R900 million
- 2003: approx. R1.35 billion
- 2010: approx. R7.8 billion = 0.7 % global market
- 2015: R8 billion with a growth rate of 13.5 % (Health Eye)

Definition and Scope

- **CAMS** = groups of diverse treatment systems, practices and products which have historic origins outside mainstream medicine
- **Alternative :** parallel, independent system: a substitute for orthodox medicine. Not based on evidence-based scientific method
- **Complementary :** also alternative but complements i.e. possibility for use with orthodox medicine

WHO Definitions

Traditional Medicine (TM):

It is the sum total of the knowledge, skill, 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 Medicine (CM):

The terms “complementary medicine” or “alternative medicine” refer to a broad set of health care practices that are not part of that country’s own tradition or conventional medicine and are not fully integrated into the dominant health-care system. They are used interchangeably with traditional medicine in some countries.

International Trends

efsa
European Food Safety Authority

Dietary Supplements

FDA
U.S Food and Drug Administration

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

TGA Health Safety Regulation

Health Canada

SAHPRA CAMS - Definitions

Discipline Specific CAMS

i) The definition of a complementary medicine (CM) is provided as:

"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.

SAHPRA CAMS - Definitions

Health Supplements

ii) The definition of a health supplement (HS) 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 classified as schedule 0; and

b) are sold in pharmaceutical dosage forms not usually associated with a foodstuff and excludes injectables or substances schedule 1 or higher.

Combination Products

iii) The definition of a combination product is provided as:

Combination product means a single product that contains:

a) a mixture of substances of different discipline-specific origins or philosophies;

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.

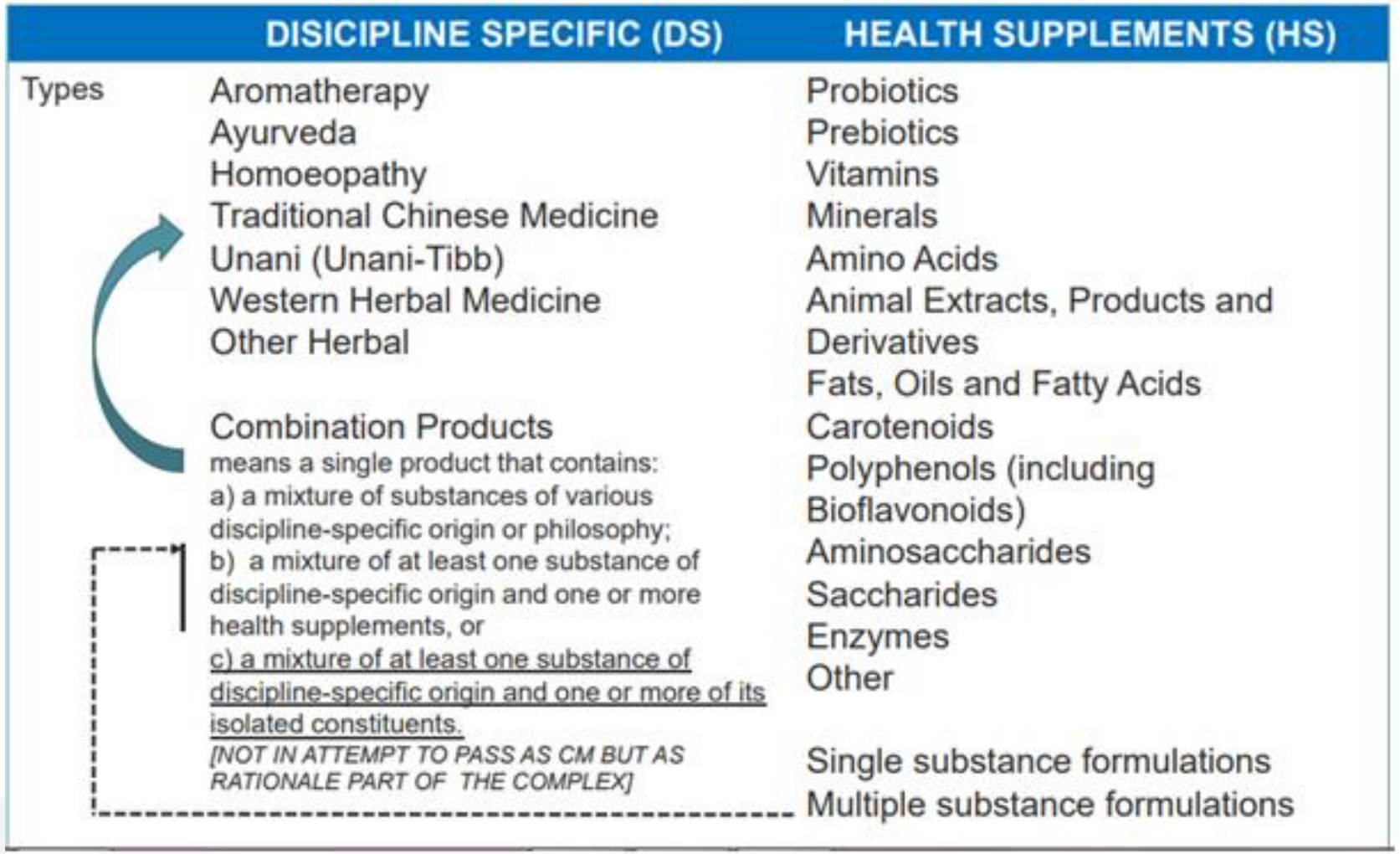
SAHPRA CAMS Disciplines

Disciplines Identified as “the CAMS that will be subject to these guidelines” (CAMS Discipline Specific Safety & Efficacy)

1. Homeopathy
2. Western Herbal Medicine
3. Traditional Chinese Medicine
4. Unani
5. Aromatherapy
6. Additional : Combination products; Other herbals
7. **Ayurveda???** →Is this still valid or meant to be put as “Other”

AND Health Supplements

Category D Medicines



High Risk

Table 1. Risk Level, type of claim and evidence required

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.

1 *Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.*
2 *All claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner".*
3 *Refer to section 5.1 i) – vi)*
4 *Refer to section 5.1 vii) – ix) and **ANNEXURE D***
5 *In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use is authenticated. Modern texts that accurately report or confirm the classical or traditional literature may be used to support claims. Traditional claims should refer to corresponding traditional descriptions of the condition(s).*
6 *Terms used must be in accordance with the practice of the associated discipline.*

Low Risk

Risk Level	Type of Claim	Evidence required to support claim
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]	• 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.

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2 *All claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner".*
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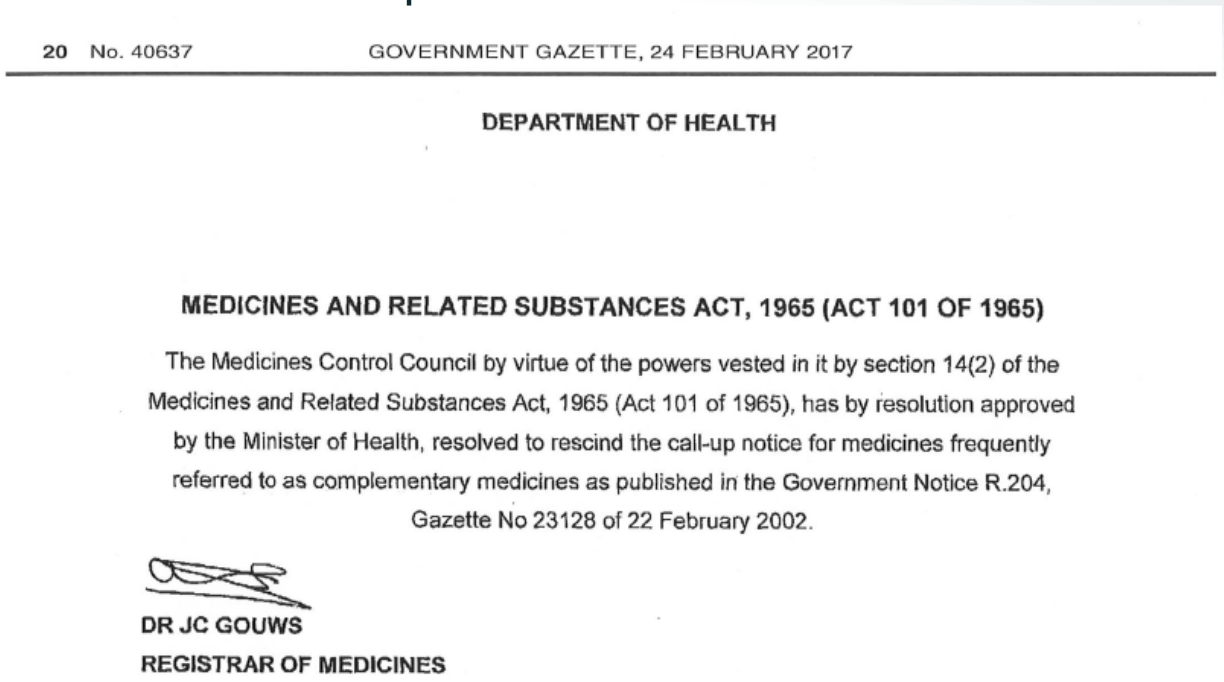
2017 Government Gazettes

On 24 Feb 2017 the MCC published GG No 40637:



20 No. 40637 GOVERNMENT GAZETTE, 24 FEBRUARY 2017

DEPARTMENT OF HEALTH

MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 OF 1965)

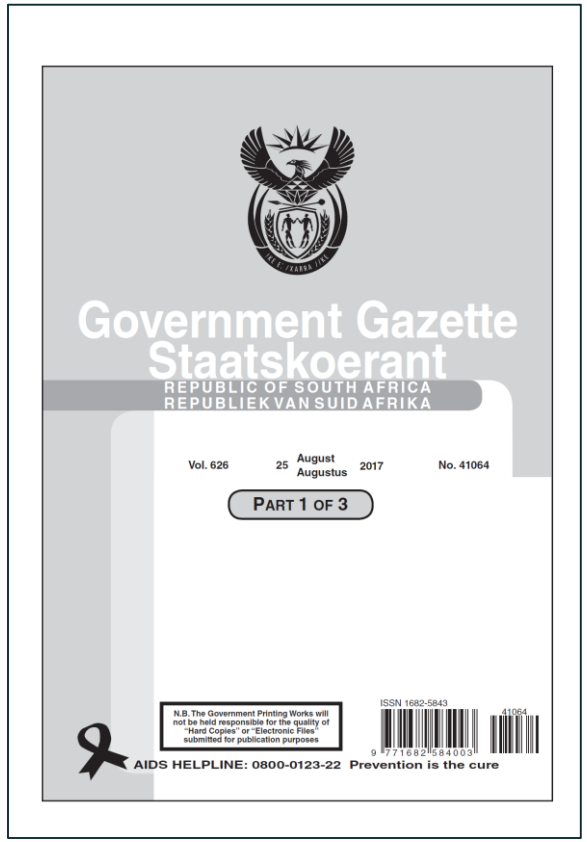
The Medicines Control Council by virtue of the powers vested in it by section 14(2) of the Medicines and Related Substances Act, 1965 (Act 101 of 1965), has by resolution approved by the Minister of Health, resolved to rescind the call-up notice for medicines frequently referred to as complementary medicines as published in the Government Notice R.204, Gazette No 23128 of 22 February 2002.

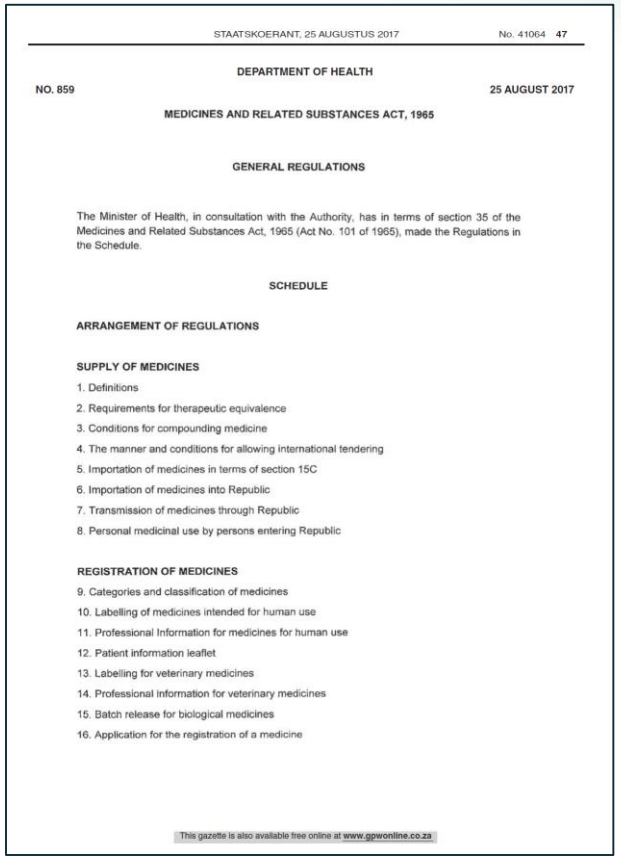
DR JC GOUWS
REGISTRAR OF MEDICINES

This understandably caused confusion and concern in the industry, especially for importers

2017 Regulations

On August 2017 the MCC published GG41064 No 859:





STAATSKOERANT, 25 AUGUSTUS 2017 No. 41064 47

DEPARTMENT OF HEALTH

NO. 859 25 AUGUST 2017

MEDICINES AND RELATED SUBSTANCES ACT, 1965

GENERAL REGULATIONS

The Minister of Health, in consultation with the Authority, has in terms of section 35 of the Medicines and Related Substances Act, 1965 (Act No. 101 of 1965), made the Regulations in the Schedule.

SCHEDULE

ARRANGEMENT OF REGULATIONS

SUPPLY OF MEDICINES

1. Definitions
2. Requirements for therapeutic equivalence
3. Conditions for compounding medicine
4. The manner and conditions for allowing international tendering
5. Importation of medicines in terms of section 15C
6. Importation of medicines into Republic
7. Transmission of medicines through Republic
8. Personal medicinal use by persons entering Republic

REGISTRATION OF MEDICINES

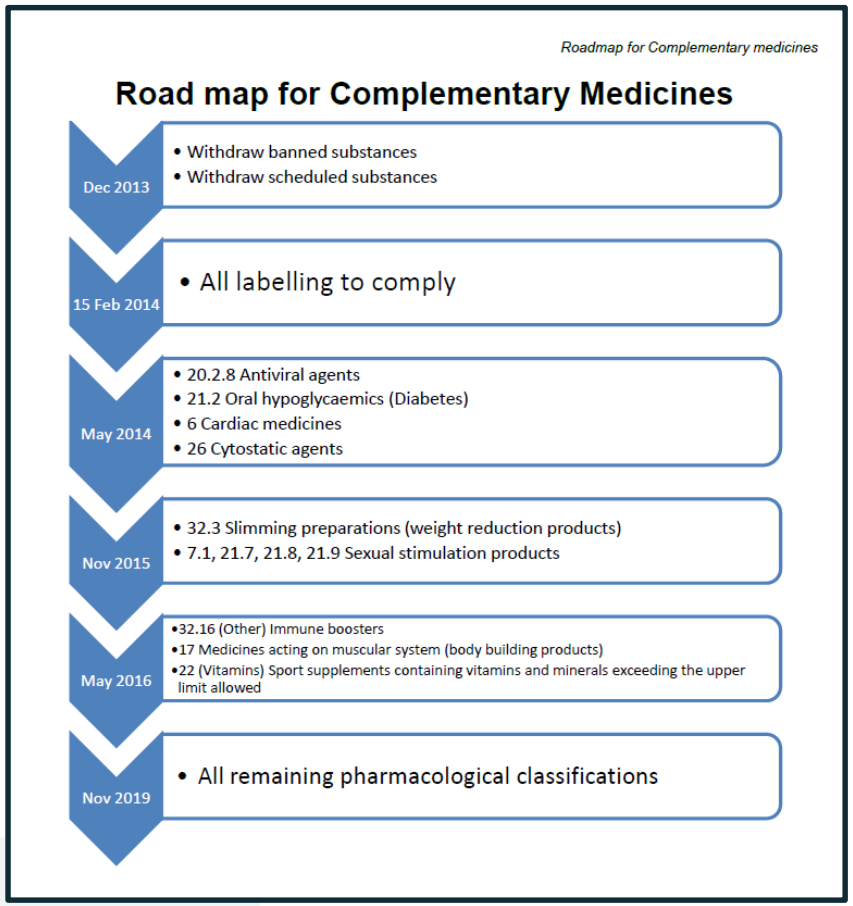
9. Categories and classification of medicines
10. Labelling of medicines intended for human use
11. Professional Information for medicines for human use
12. Patient information leaflet
13. Labelling for veterinary medicines
14. Professional information for veterinary medicines
15. Batch release for biological medicines
16. Application for the registration of a medicine

This gazette is also available free online at www.gpwonline.co.za

This “created” SAHPRA and also regulated Health Supplements as CAMS.

Section 48C – CAMS Road Map

SAHPRA Roadmap vs Current situation



VS **???**

No. 859 General Regulations - Medicines and Related Substances Act, 1965 (GG41064) on 25 August 2017 resulted in previous roadmap being rescinded or DELETED.
This has left the industry in a grey area regarding the call-ups on Discipline Specific CAMS and Health Supplements

Which Way forward

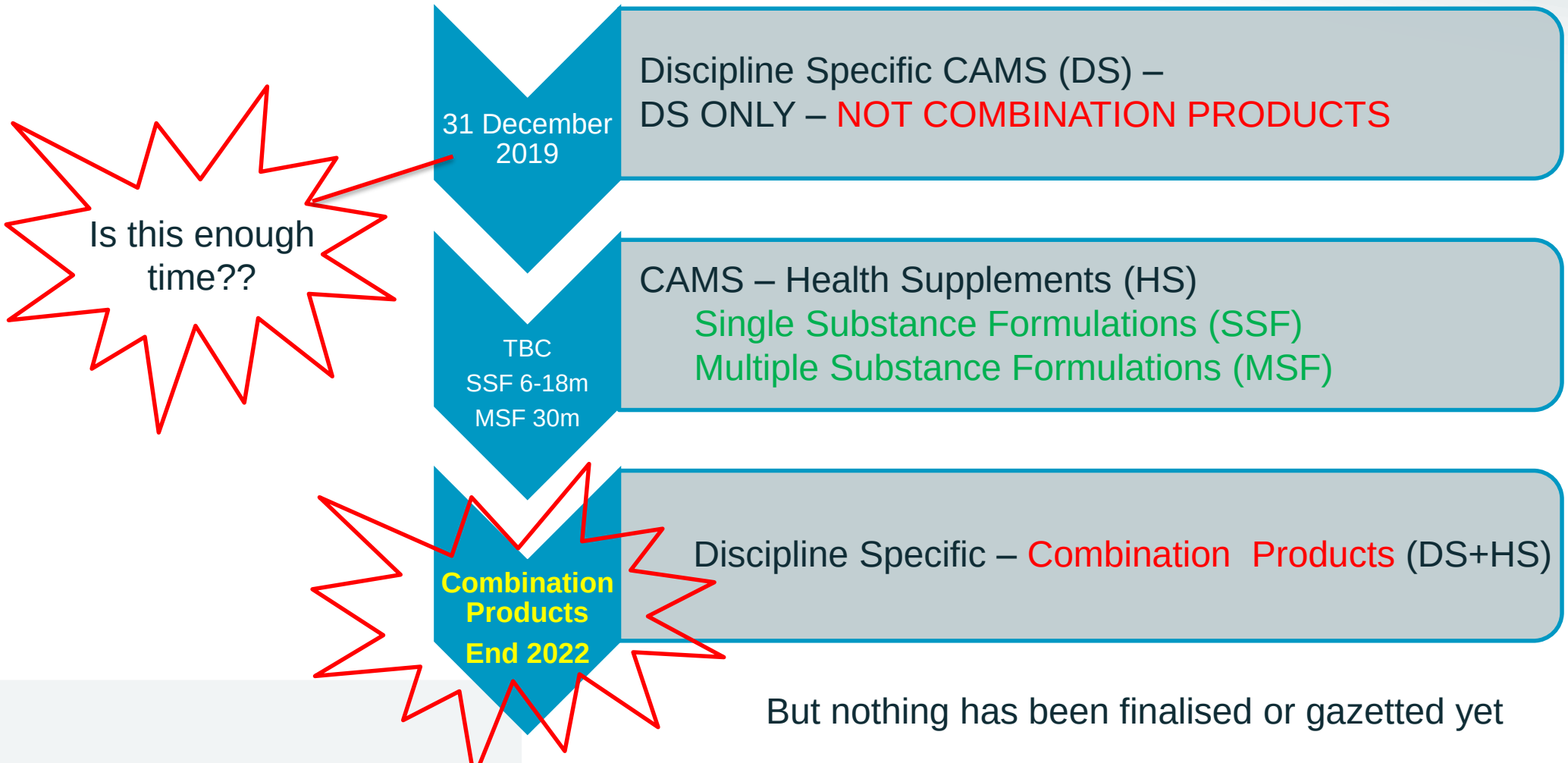
SAHPRA Meeting with CAMS CEOs

- SAHPRA hosted a meeting with the CAMS CEOs on 12 June 2018.
- At this meeting the Acting CEO, Mrs Portia Nkambule, gave an update on SAHPRA.
- Dr Neil Gower also gave a presentation on Complementary Medicines:

- This presentation highlighted a number of things to industry:
  - There is currently no Roadmap for Discipline Specific CAMS & Health Supplements
  - Health Supplements can still be launched in SA
  - SAHPRA have received approx. 246 dossiers which are being evaluated
  - However, there still has not been any CAMS product that has been registered thus far

SAHPRA Amended Roadmap

Dr Neil Gower presented the following as a proposed Amended Roadmap on 12 June 2018

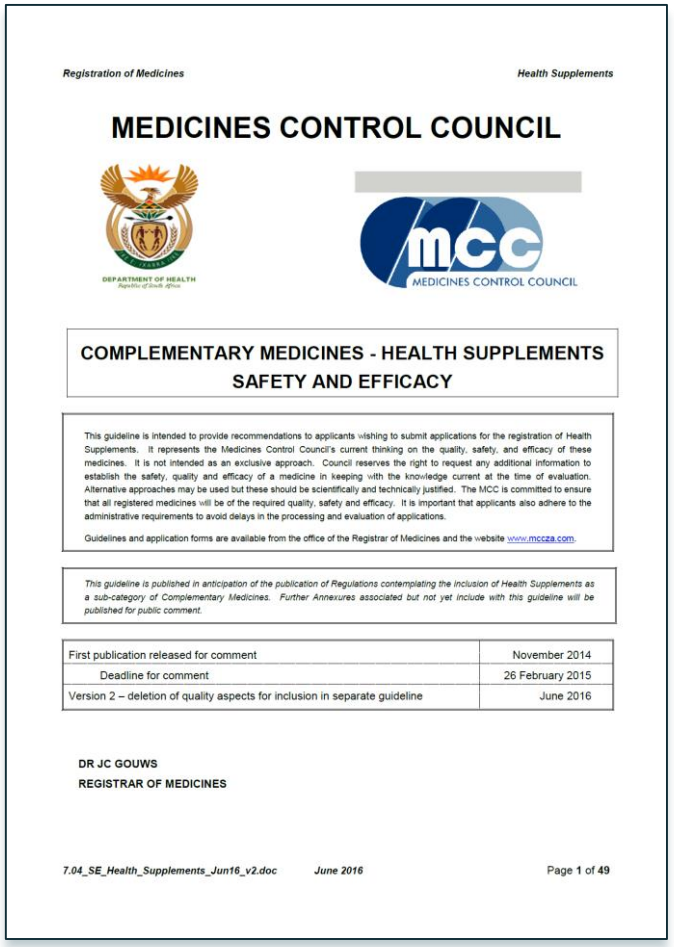


But nothing has been finalised or gazetted yet

SAHPRA's view on New Products

- Discipline Specific CAMS:
  - According to SAHPRA NO new Discipline Specific CAMS can be launched in the market as a result of the 15 November 2013 Regulations
- Health Supplements:
  - SAHPRA have confirmed that HS are not subjected to the 15 November 2013 Regulations
  - As a result there is no cut-off date that is formally prescribed (yet)
  - NOTE there are only 4 Annexures that have been finalised:
    - Annex C – Probiotics
    - Annex D – Prebiotics
    - Annex E – Vitamins
    - Annex F – Minerals
  - This would be applied to SSF, MSF and Combination (DS+HS) products
  - Risk: need to look at the HS Annexures before finalizing the formulation. If falls outside substance, limit and claims then could be considered a Category A medicine.

Health Supplement Annexures



Registration of Medicines *Health Supplements*

MEDICINES CONTROL COUNCIL

COMPLEMENTARY MEDICINES - HEALTH SUPPLEMENTS SAFETY AND 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 these medicines. 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.

This guideline is published in anticipation of the publication of Regulations contemplating the inclusion of Health Supplements as a sub-category of Complementary Medicines. Further Annexures associated but not yet include with this guideline will be published for public comment.

First publication released for comment	November 2014
Deadline for comment	26 February 2015
Version 2 – deletion of quality aspects for inclusion in separate guideline	June 2016

DR JC GOUWS
REGISTRAR OF MEDICINES

7.04_SE_Health_Supplements_Jun16_v2.doc *June 2016* Page 1 of 49

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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***

SAHPRA's Application Process

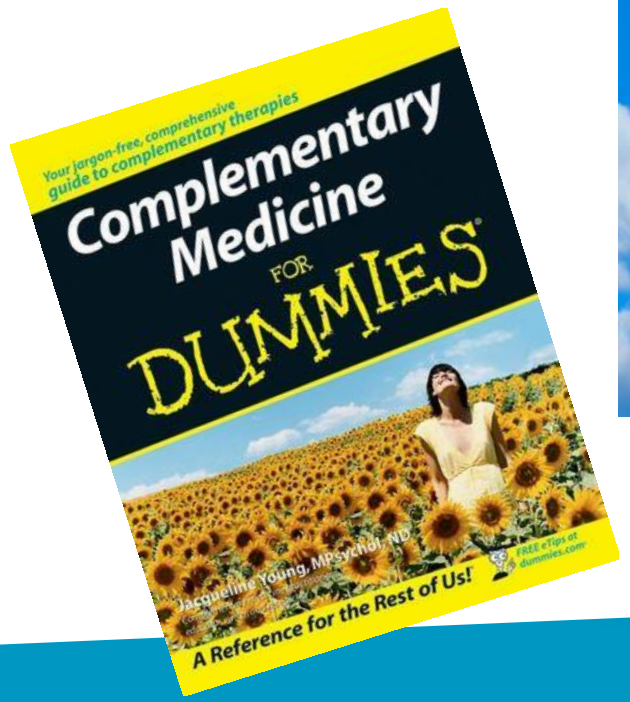
- SAHPRA is meant to be doing things differently to achieve greater results
- Being a Schedule 3A Public Entity, SAHPRA is meant to have more flexibility
- SAHPRA is investigating an electronically guided application process / dossier formulation for LOW RISK CAMS
  - HS: SSF → MSF
  - DS CAMS: Low Risk -----→ Progress to High Risk
- NB: for Tracking and evaluation of applications

- SAHPRA application process is a risk-based approach system
- Aim to minimise the HIGH RISK Claims (or substantiate):
  - Consideration of more efficient review of LOW RISK
  - Guidance on LOW RISK Clinical Info
  - Guidance on LOW RISK Quality Info
  - DS Medicine: Low risk vs High Risk
- Health Supplements: de facto listing system with application requirements focussed on quality

Industry has proposed:

- Interim Licencing System
- Appropriate GMP
- Abbreviated / Expedited HS submission
- Notification / Listing System

Problem = This has not been finalised yet and no timeline or update has been gazetted



A Practical Approach

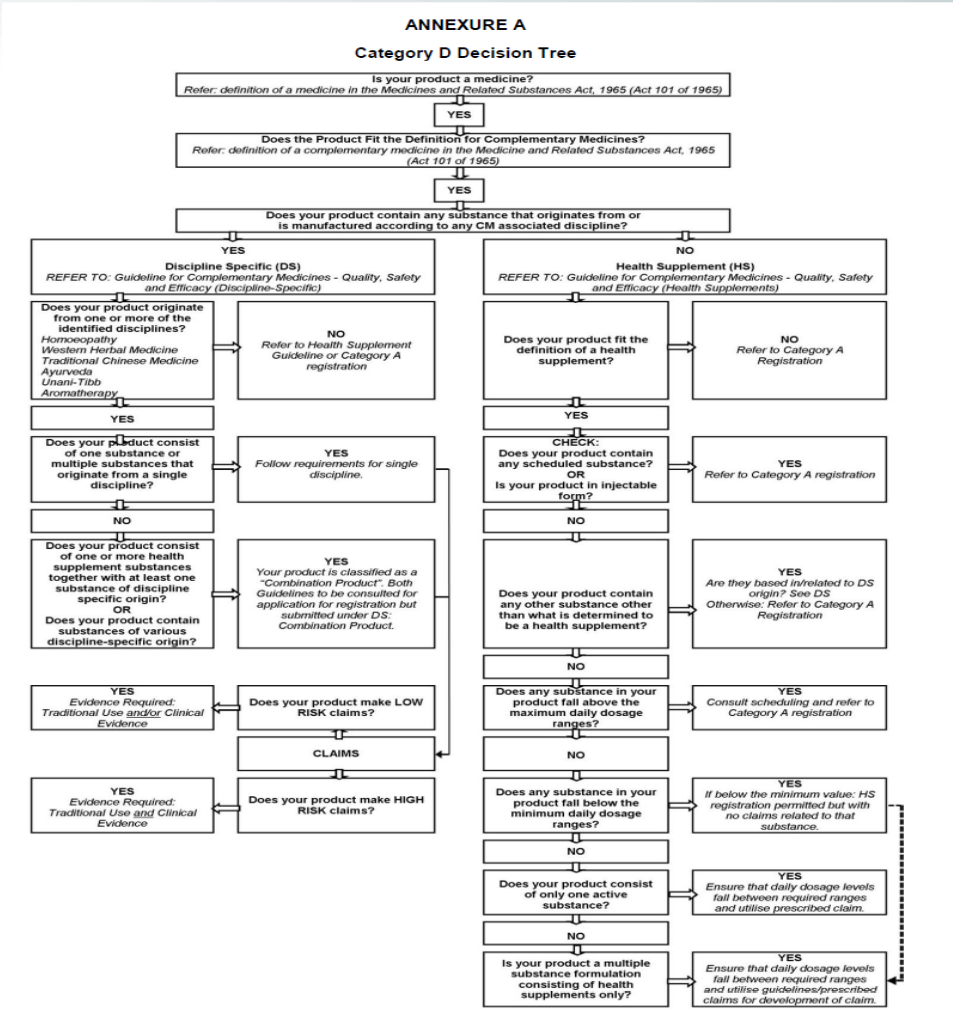
Medicine Regulation Core Principles

Practical Approach to Product Evaluation

Where to start?

- Make sure it's a CAMS or a HS!
- Use the Category D Decision Tree
- If it is not a Health Supplement – it must be

  DISCIPLINE-SPECIFIC CAMS (or Category A)
- Choose a discipline – 6 + 1 are recognised:
  - Homeopathy
  - Western Herbal Medicine
  - Unani Medicine
  - Traditional Chinese Medicine
  - Aromatherapy
  - Combination Products / Other Herbal
  - Ayurveda??



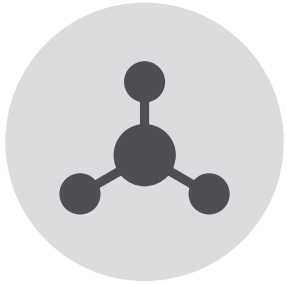
Product / Formulation Evaluation

- **Complementary Medicine – Category D medicines**
- **Discipline-specific CAMS's versus Health Supplements**
- **The importance of determining and demonstrating a discipline**
  - Is this formula congruent with the discipline?
  - Is the formulation within API limits
- **Is the dosage form suitable and stable?**
- **Low Risk versus High Risk claims – burden of proof**
  - Modules 1.5.1 & 2.5 [& Modules 1.3; 5]

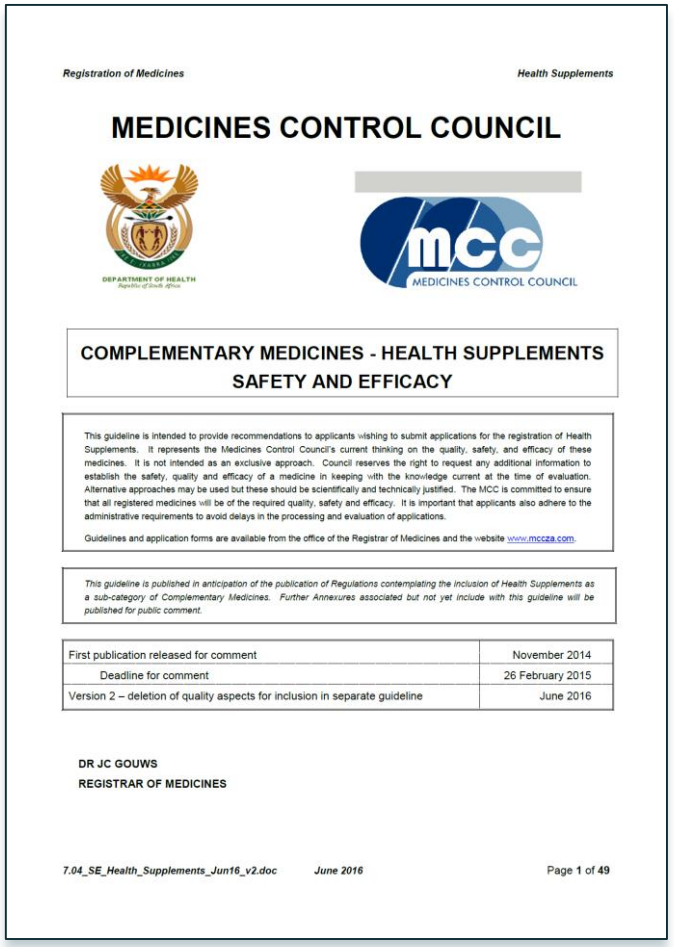
SAHPRA's Application Process

Low Risk	High Risk
Module 1 Including Application Form, PI, PIL, Label	Module 1 Including Application Form, PI, PIL, Label
Module 1.5.1 Traditional Use / Low Risk Rationale	Module 1.5.1 Traditional Use
Module 2 Relevant Summaries	Module 2 Relevant Summaries
Module 3	Module 3
Not Required Unless Necessary	Module 4
Not Required Unless Necessary	Module 5 Clinical Evidence

Innovation & Formulation Importance

Discovery	Early development	Formulation development	Scale-up	Commercial scale supply fill / finish
				  
Active pharmaceutical ingredient	Molecule	Medicine	Product	Mass production	Commercial packaging

Using the Health Supplement Annexures available



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7.04_SE_Health_Supplements_Jun16_v2.doc *June 2016* Page 1 of 49

7.04_SE_Health_Supplements_Jun16_v2.doc

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***

Ensure your limits are within the API levels if HS

Research and Development

- Now is the time to ensure your formulation has USP benefits
- Ensure dosage form is suitable
- Check your OOS, deviations and customer complaints to improve product formulation
- Use R&D staff to evaluate formulation, dosage, API and design

Use the SAHPRA Guidelines

Complementary [6]

Type	Doc#	Title	Version	SubVersion	PublishDate	Size	Select
	7.01	Complementary Medicines - Discipline Specific Safety and Efficacy	V3		13-Jun-2016	1 MB	☐
	7.02	Road map for complementary medicines	V1		03-Dec-2013	262 KB	☐
	7.03	Complementary Medicines - Use of the ZA-CTD format in the Preparation of a Registration Application	V3		13-Jun-2016	355 KB	☐
	7.04	Complementary Medicines - Health Supplements Safety & Efficacy	V2		13-Jun-2016	966 KB	☐
	7.05	Complementary Medicines Registration Application ZA-CTD - Quality	V1		13-Jun-2016	1 MB	☐
	9.72	Complementary Medicines submitted for registration - right to sale	V1		24-Apr-2016	155 KB	☐

- 2.24 Guidance General and Module 1
- 2.25 PA CTD
- 2.05 Stability
- 2.01 General Information
- 4.01 SA Guide to GMP Herbal Annex 7

API Sourcing and Procurement

Sourcing Ingredients / APIs

- What can be in a CAMS? Combination Products?
- Extracts, concentrated extracts, standardised extracts & isolates?
- Is there a 3.2.S section? If not what next?
- GMP Status of API manufacturer vs ISO accreditation
- Does the API have monographs?

Procuring APIs

- Ensure it is from the SITE you approved
- Ensure it is the correct grade (esp botanical extractions)
- Test the incoming APIs
- Justify the sampling model you use
- Keep reccords

Initialization Road Map

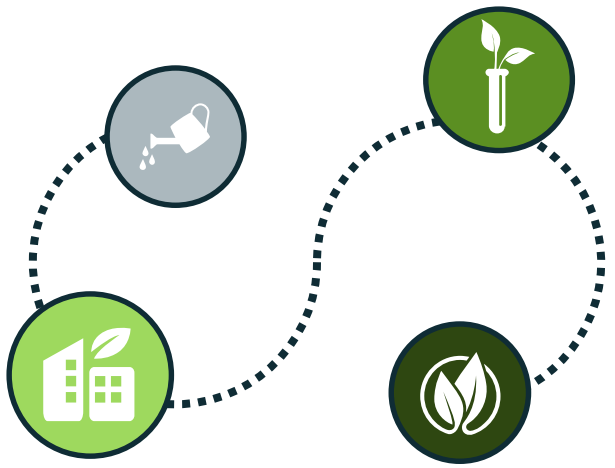
Fully-integrated product solutions

Plant Cultivation & Procurement

With a strong emphasis on reliable quality and sustainability, Our high-quality raw materials are harvested from sustainable resources and transformed into a range of innovative, industry specific active ingredients

Comprehensive Quality Control & Assurance

All incoming components undergo vigorous testing to eliminate possible quality issues early on in the process, which ultimately ensures a uncompromised final product.



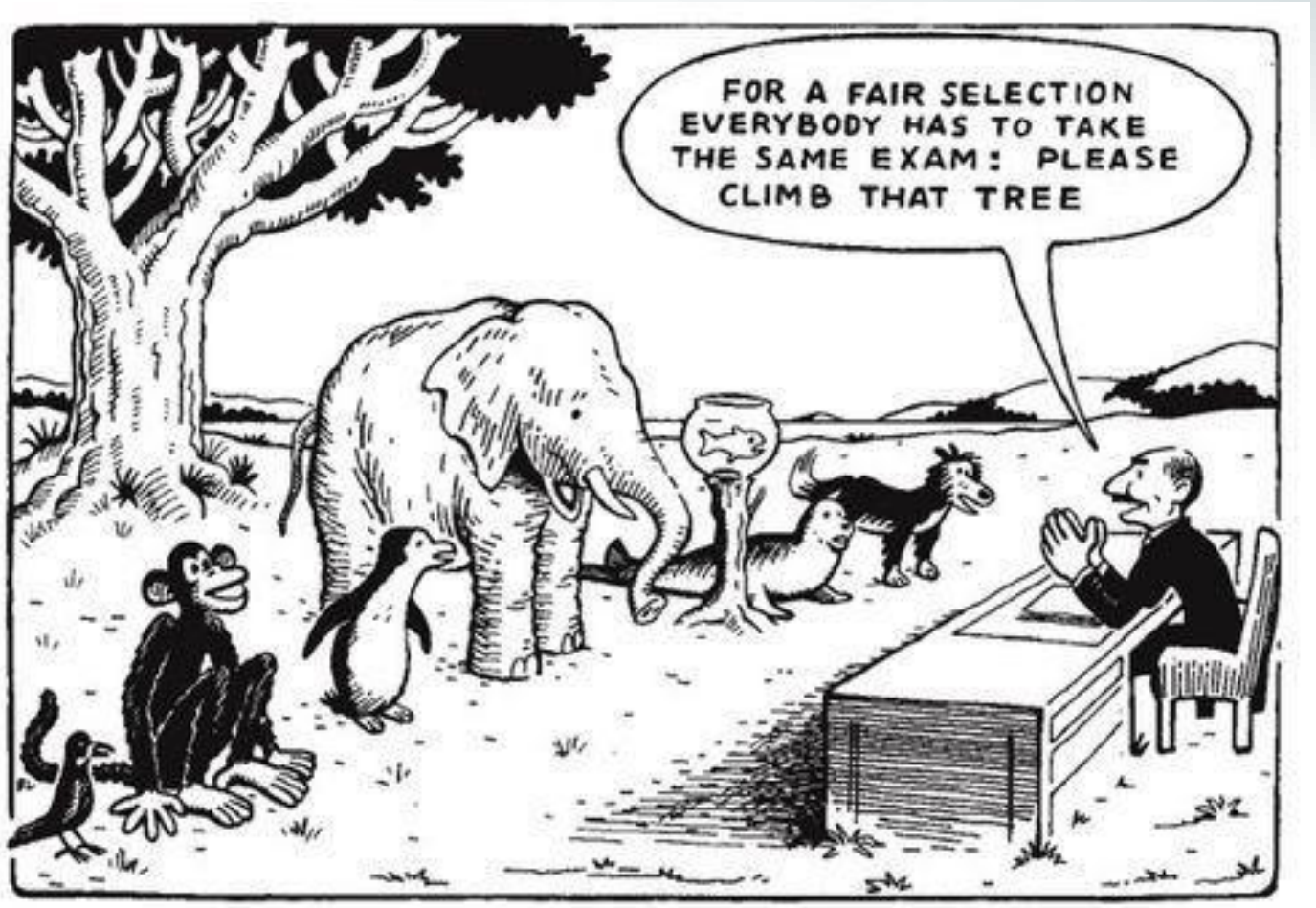
State of the art facility and processes

Our manufacturing activities are supported by our integrated Material Resource Planning (MRP) system, allowing direct access to real-time data concerning stock availability, product requirements and progress

Standardised Botanical Extracts

Our portfolio includes a range of Botanical extracts (Liquid and Powder), Plant material and Oils. By utilising our research and development capabilities, we also ventured into Active Pharmaceutical Ingredient (API) development and supporting API master files

What is Quality?



Using GMP Manufacturing Sites

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

SA GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINES

This document is intended to serve as guidance on the requirements for Good Manufacturing Practice in South Africa. This guideline is not intended as an exclusive approach. The MCC reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine. The MCC may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy standards.

Version 1	Implementation	1997
Version 1	Chapter 9 (Validation) reformatted	January 2004
Version 2	Adoption of PIC/S GMP Guide of July 2004	January 2006
Version 3	Updates to Sections in line with PIC/S Guide updates	September 2008
	Released for comment	31 January 2009
Version 4	Amendments to Annexes 3 & 7	March 2009
	Released for comment	30 June 2009
Version 5	Consolidation of comments on versions 3 & 4	November 2010
Version 6	Adoption and acknowledgement of future adaptations of the PIC/S Guide to GMP	December 2017

DR JC GOUWS
REGISTRAR OF MEDICINES

The 4 P's of GMP

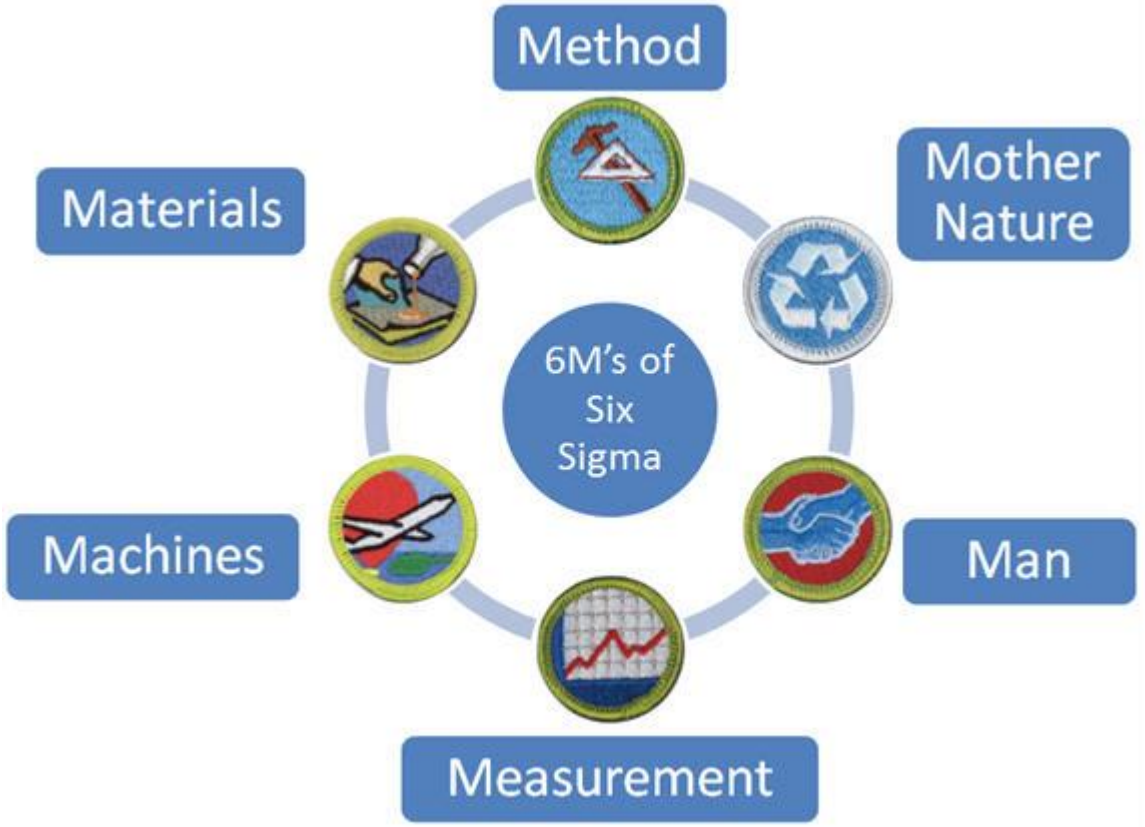
People

Premises & Equipment

Procedures & Documentation

Process

6 M’S of Six Sigma



Manufacturing - Processing Facilities

Specialised equipment for manufacturing finished products

Bulk liquid manufacturing

- Bulk batches (1,000,000 litres per annum) of plant extracts, tinctures and other medicinal liquids – (largest tank being 6,340 litres)
- AtEx (explosive atmospheres) rated area

Bulk liquid storage

- After bulk liquid manufacturing the product is placed on hold, sampled and sent to Quality Control for testing, approval and releasing
- 6 × 5,000 litres stainless steel tanks continuous stirring ability with each tank mounted on three weight load cells so as to control and reconcile bulk liquid batches

Liquid filling and packing

- State of the art liquid filling carousals for a diverse range of applications, e.g. varying viscosity and filling size
- There are three liquid filling and packing lines
- Total capacity – 8,000,000 units per annum ranging from 20 ml – 1000 ml per unit

Manufacturing - Processing Facilities

Specialised equipment for manufacturing final products

Oral solid dosage (OSD) manufacturing

- These manufacturing areas are equipped to fill gelatin capsules (size “0” & “00”) or compress tablets in various shapes and mass, complimented by 3 primary OSD counting and 3 OSD secondary packing lines

Temperature / humidity controlled warehousing

- The latest technology / energy efficient fully integrated and real time controlled
- HVAC systems
- An integrated Material Resource Planning (MRP) system ensures on-time delivery to our client base

Water treatment

- Reverse Osmosis (RO) treatment plant capable of supplying 2,000 liters of purified water per hour
- Circulated closed loop supply to 11 take-off points

Labelling, PI & PIL Requirements

Requirements for Continued Right of Sale

- Labelling / Advertising
  - Regulation 10 “Labelling of medicines intended for human use”
  - Regulation 11 “Professional information for medicines for human use”
  - Regulation 12 “Patients information leaflet”
  - Regulation 13 “Labelling of veterinary medicines”
  - Regulation 14 “ Professional information for veterinary medicines”
  - Regulation 42 “Advertising of medicines”
- Prescribed levels / indications
- No scheduled substances > S0
- Low risk indications as defined by SAHPRA
  - Complementing health
  - Supplementing the diet or
  - A nutritional effect

Quality Assurance

Quality control systems should be in line with cGMP. To keep pace with the current ZACTD regulatory requirements, some companies have invested in the necessary equipment and expanded our quality control system.

Chemical Specifications

Parameter	Specification
Identification (FT-IR)	≥ 95.00 % similarity to reference
Identification (TLC)	The chromatogram Rf measurement of the sample bands corresponds to the Rf time of the reference standard bands.
Loss on drying	≤ 12.0 % (m/ m)
Foreign matter	≤ 2.0% (m/m)
Pesticides	Complies to Table 2.8.13-1 EU Pesticide Database

Aflatoxins Specifications

Parameter	Specification
Aflatoxin B1	<2.0 ppb
Aflatoxin total	<4.0 ppb

Microbial Specifications

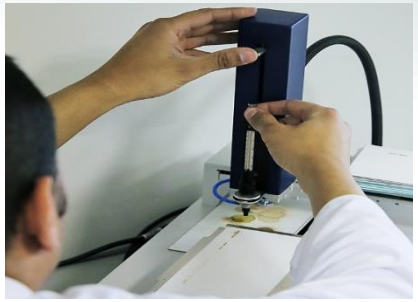
Parameter	Specification
Total aerobic plate Count	≤ 10 000 000 cfu/ g
Combined Yeast and Mould	≤ 100 000 cfu/ g
Escherichia coli	≤ 1000 cfu/g
Bile tolerant gram negative bacteria	≤100 000 cfu/g
Salmonella	Absent/ 125 g

Heavy Metals Specifications

Parameter	Specification
Arsenic	<1.0 ppm
Cadmium	<1.0 ppm
Lead	<5.0 ppm
Mercury	<0.05 ppm

Storage	
Shelf life	36 Months
Recommended storage conditions	Closed safely, protect from moisture, light and high temperature

Specialized QC Testing



General Chemistry Lab

- FT/IR identification
- Viscosity
- pH
- Conductivity
- SG
- Loss on drying
- Dissolution, Solubility
- Disintegration of capsules and tablets

Instrument Lab

- High-performance liquid chromatography
- Thin layer chromatography and fingerprinting
- Gas chromatography

Specialized QC Testing

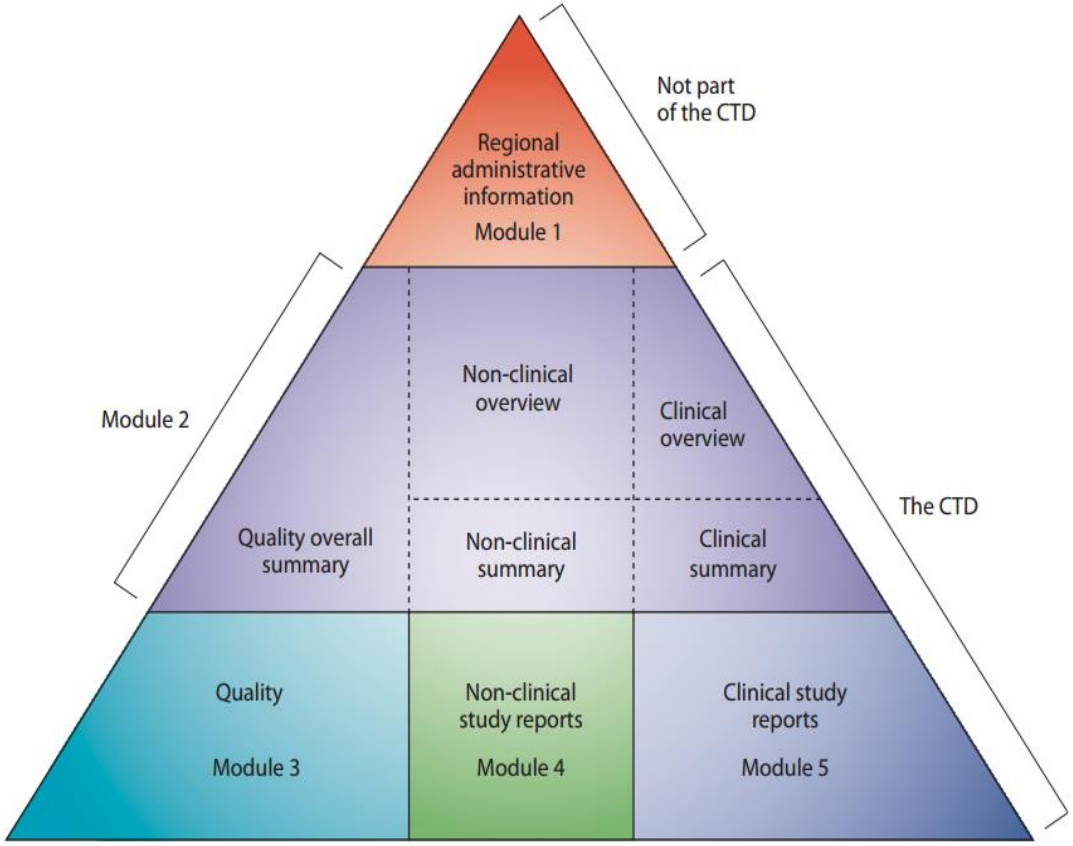
Microbial Lab

- Total plate count
- Yeast & Moulds
- E.coli (quantitative analyses)
- Salmonella (quantitative analyses)
- Bile-tolerance estimations

Stability Room

- Long term stability chambers
- Short term stability chambers
- Accelerated stability chambers

Dossier: Common Technical Document Format- Multisource products



"Registration Dossier" – Common Technical Document (CTD) is the document that contains all the technical data (administrative, quality, nonclinical and clinical) of a pharmaceutical product to be approved / registered / marketed in a country

- DMF: Drug Master File DATA proving; Quality, Efficacy, Safety
- 3.2S: Active Ingredient **(Active Pharmaceutical Ingredient)**
- 3.2P: Final pharmaceutical product

Extensive technical documents for CAMS regulations

CTD value-adding capabilities

Module 1

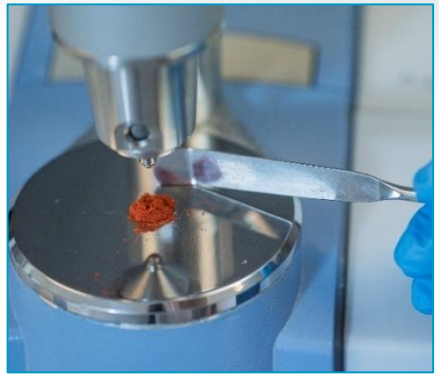
- Administrative information
- Completion of application documentation

Module 2

- Overview of application
- Formulation
- PI/PIL

Module 3

- Stability data
- Raw material information
- Pharmaceutical and analytical



Module 4

- Pre-clinical studies
- Data analysis
- Result publication

Module 5

- Clinical studies
- Data analysis
- Results publication

CAMS Future

SAHPRA Relocation to CSIR

Communication to all stakeholders *Relocation of SAHPRA*

SAHPRA
SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

25 January 2019

INTERIM RELOCATION OF SAHPRA TO CSIR

To all Stakeholders

Further to our communication of 31 October 2018 regarding the protest action at the Civitas Building, and the instruction from the Director-General Health regarding the vacating of the building, we can now confirm that interim new premises have been rented on the CSIR campus, Brummeria, Pretoria.

This is an interim relocation due to the emergency situation, while the process to procure new premises for SAHPRA is in progress.

SAHPRA is located in the following buildings on the CSIR campus:

Accessed from the Visitor's Centre, North Gate (opposite the Sasol garage):

- **Building 10f**
- **Building 16**

Accessed from the Visitor's Centre, South Gate:

- **Building 41**
- **Building 42**

Outside, to the left of the gate to the Convention Centre (South Gate):

- **Building 38a – Reception**

Please note that telephone landlines are not currently available. The cellphone contact numbers under Key Contacts on the website should be used.

Reception in building 38a will open on Friday, 01 February 2019.

Please note the following regarding deliveries to SAHPRA:

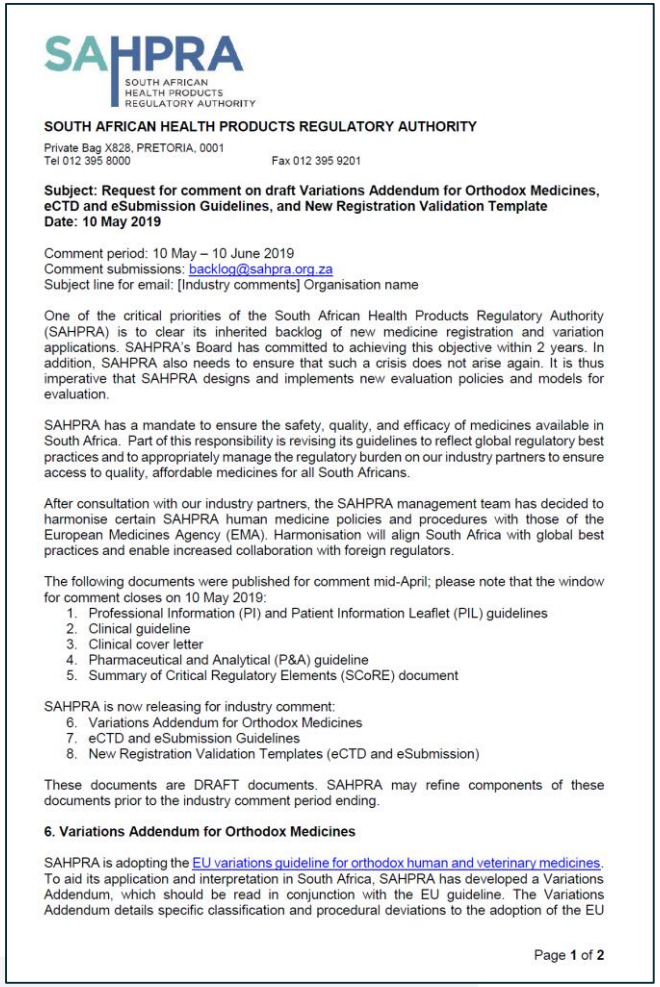
- The trading hours will be as follows:
  - Deliveries: Monday to Thursday: 08h30 – 15h15
    Friday: 08h30 – 12h00
  - Collection of certificates, permits, licences: Tuesday & Thursday 10h00 – 12h00
- Applicants will be contacted when certificates, permits, and licences are ready for collection. These should then be collected at the next designated time, as indicated above.
- Please refer to the communication 9.113 for the submission procedure for Section 21 authorisations (orthodox medicines for human use only), and communication 9.114 regarding the submission of post-marketing pharmacovigilance correspondence. Both documents are available on the SAHPRA website under Publications, Communications.

Please note that access to the other buildings is by appointment only. The relevant official to be visited will advise which building when the appointment is made. The visitor then has to report to the CSIR Visitor's Centre at the closest gate, as indicated above. The visitor's driver's licence or ID document will be required, otherwise the visitor will not be allowed onto the campus. Assets such as laptops taken into the CSIR will also have to be declared.

Ms P Nkambule
Acting Chief Executive Officer

9.120_SAHPRA_Relocation_Jan19_v1 *Jan 2019* Page 1 of 1

Recent Guidelines for Review



SAHPRA
SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

Private Bag X828, PRETORIA, 0001
Tel 012 395 8000 Fax 012 395 9201

Subject: Request for comment on draft Variations Addendum for Orthodox Medicines, eCTD and eSubmission Guidelines, and New Registration Validation Template
Date: 10 May 2019

Comment period: 10 May – 10 June 2019
Comment submissions: backlog@sahpra.org.za
Subject line for email: [Industry comments] Organisation name

One of the critical priorities of the South African Health Products Regulatory Authority (SAHPRA) is to clear its inherited backlog of new medicine registration and variation applications. SAHPRA's Board has committed to achieving this objective within 2 years. In addition, SAHPRA also needs to ensure that such a crisis does not arise again. It is thus imperative that SAHPRA designs and implements new evaluation policies and models for evaluation.

SAHPRA has a mandate to ensure the safety, quality, and efficacy of medicines available in South Africa. Part of this responsibility is revising its guidelines to reflect global regulatory best practices and to appropriately manage the regulatory burden on our industry partners to ensure access to quality, affordable medicines for all South Africans.

After consultation with our industry partners, the SAHPRA management team has decided to harmonise certain SAHPRA human medicine policies and procedures with those of the European Medicines Agency (EMA). Harmonisation will align South Africa with global best practices and enable increased collaboration with foreign regulators.

The following documents were published for comment mid-April; please note that the window for comment closes on 10 May 2019:

1. Professional Information (PI) and Patient Information Leaflet (PIL) guidelines
2. Clinical guideline
3. Clinical cover letter
4. Pharmaceutical and Analytical (P&A) guideline
5. Summary of Critical Regulatory Elements (SCoRE) document

SAHPRA is now releasing for industry comment:

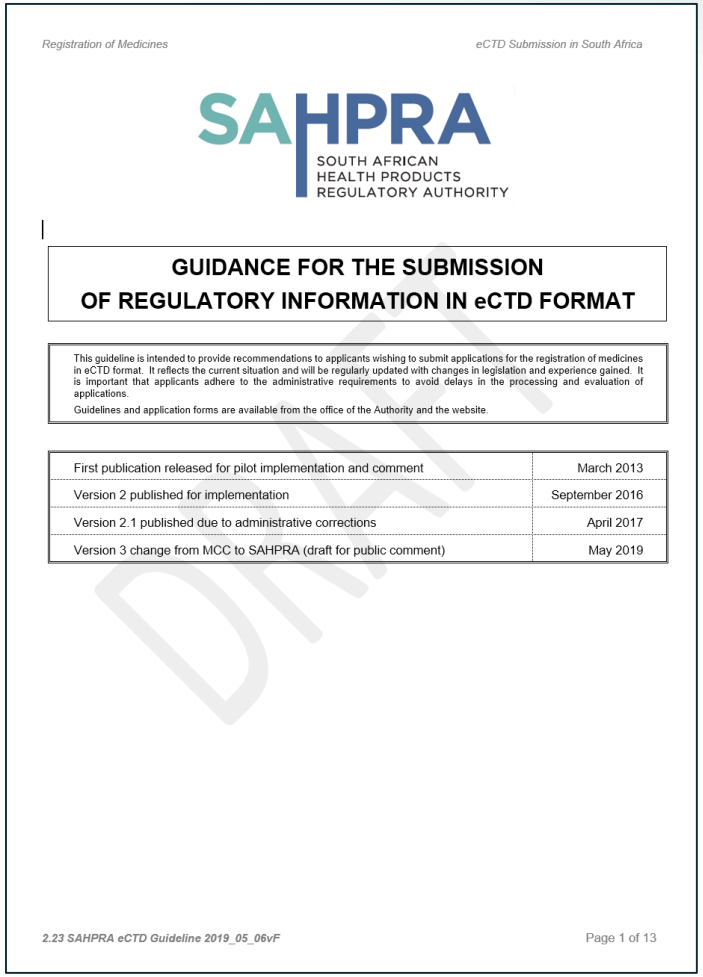
6. Variations Addendum for Orthodox Medicines
7. eCTD and eSubmission Guidelines
8. New Registration Validation Templates (eCTD and eSubmission)

These documents are DRAFT documents. SAHPRA may refine components of these documents prior to the industry comment period ending.

6. Variations Addendum for Orthodox Medicines

SAHPRA is adopting the EU variations guideline for orthodox human and veterinary medicines. To aid its application and interpretation in South Africa, SAHPRA has developed a Variations Addendum, which should be read in conjunction with the EU guideline. The Variations Addendum details specific classification and procedural deviations to the adoption of the EU

Page **1** of **2**



Registration of Medicines *eCTD Submission in South Africa*

SAHPRA
SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

GUIDANCE FOR THE SUBMISSION OF REGULATORY INFORMATION IN eCTD FORMAT

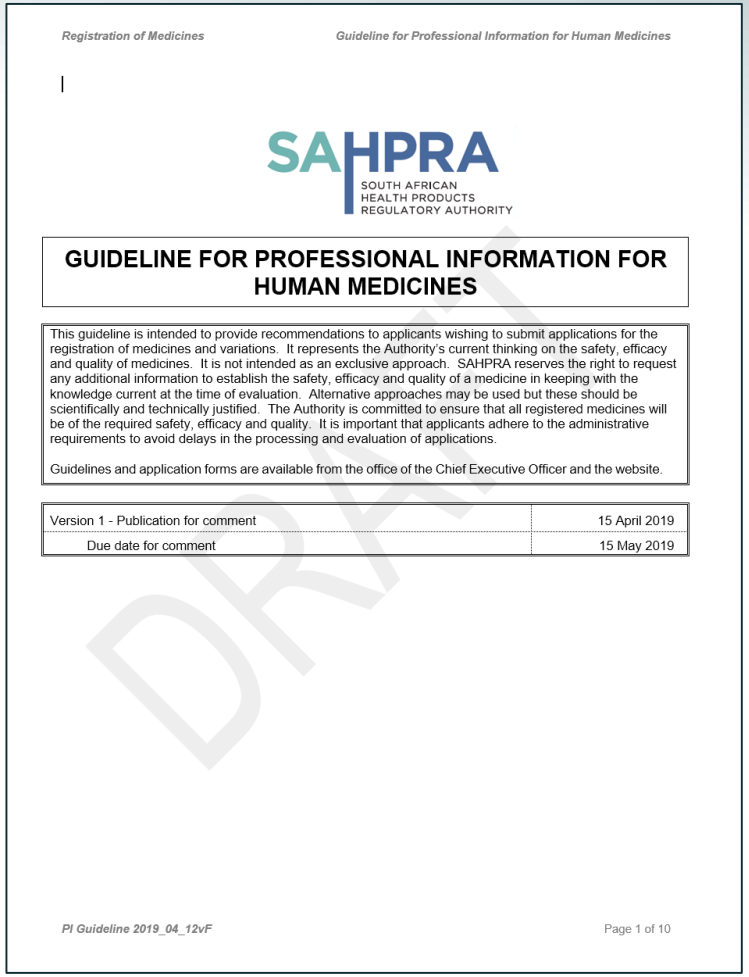
This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines in eCTD format. It reflects the current situation and will be regularly updated with changes in legislation and experience gained. It is important that applicants adhere 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 Authority and the website.

First publication released for pilot implementation and comment	March 2013
Version 2 published for implementation	September 2016
Version 2.1 published due to administrative corrections	April 2017
Version 3 change from MCC to SAHPRA (draft for public comment)	May 2019

DRAFT

2.23 SAHPRA eCTD Guideline 2019_05_06vF Page 1 of 13



Registration of Medicines *Guideline for Professional Information for Human Medicines*

SAHPRA
SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

GUIDELINE FOR PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines and variations. It represents the Authority's current thinking on the safety, efficacy and quality of medicines. It is not intended as an exclusive approach. SAHPRA reserves the right to request any additional information to establish the safety, efficacy and quality 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 Authority is committed to ensure that all registered medicines will be of the required safety, efficacy and quality. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

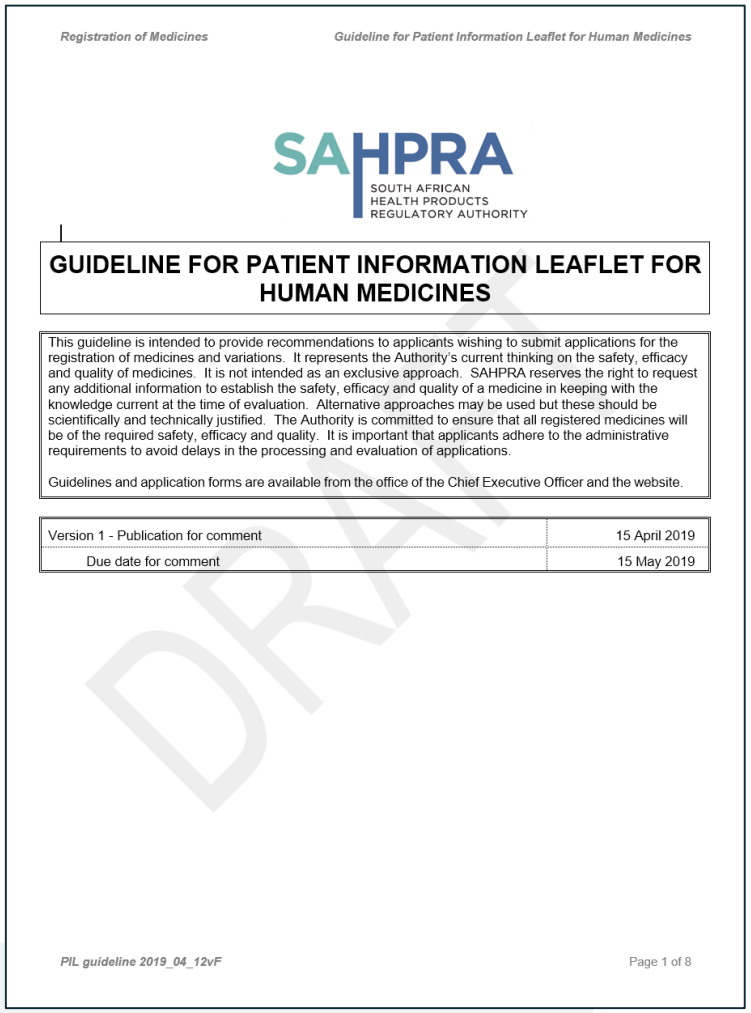
Guidelines and application forms are available from the office of the Chief Executive Officer and the website.

Version 1 - Publication for comment	15 April 2019
Due date for comment	15 May 2019

DRAFT

PI Guideline 2019_04_12vF Page 1 of 10

Recent Guidelines for Review



Registration of Medicines *Guideline for Patient Information Leaflet for Human Medicines*

SAHPRA
SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

GUIDELINE FOR PATIENT INFORMATION LEAFLET FOR HUMAN MEDICINES

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines and variations. It represents the Authority's current thinking on the safety, efficacy and quality of medicines. It is not intended as an exclusive approach. SAHPRA reserves the right to request any additional information to establish the safety, efficacy and quality 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 Authority is committed to ensure that all registered medicines will be of the required safety, efficacy and quality. It is important that applicants 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 Chief Executive Officer and the website.

Version 1 - Publication for comment	15 April 2019
Due date for comment	15 May 2019

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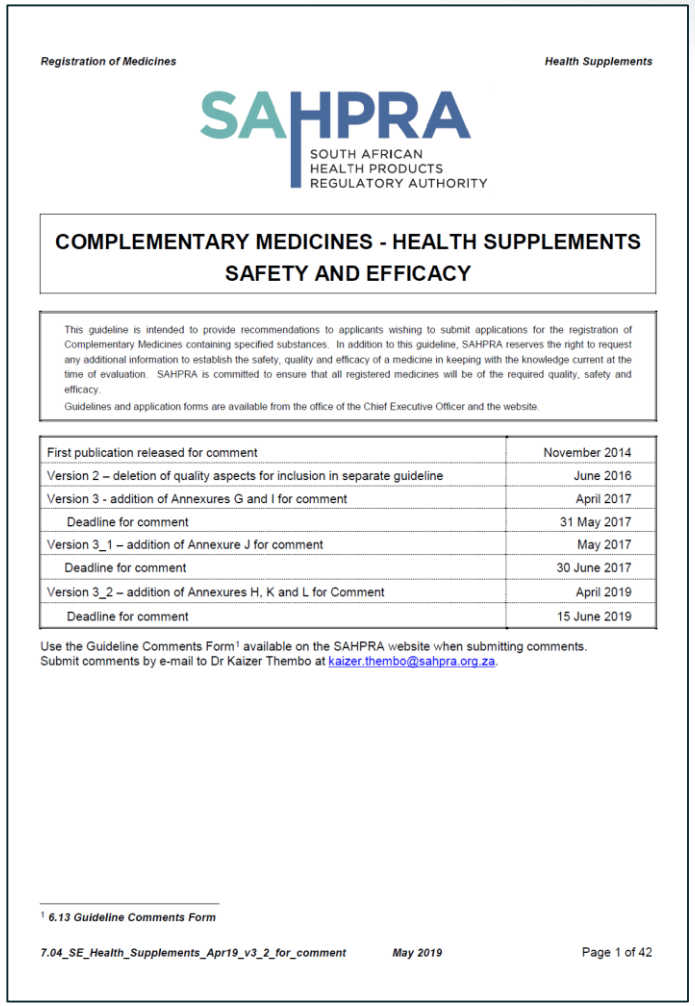
PIL guideline 2019_04_12vF Page 1 of 8



Registration of Medicines *Health Supplements*

SAHPRA
SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

COMPLEMENTARY MEDICINES - HEALTH SUPPLEMENTS SAFETY AND EFFICACY

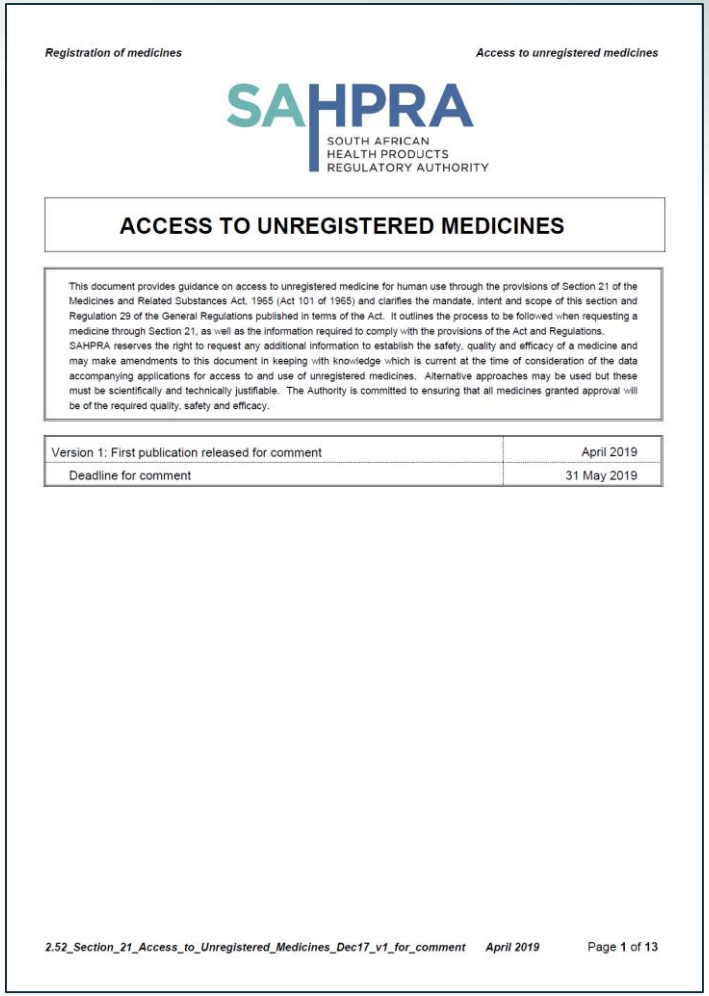
This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of Complementary Medicines containing specified substances. In addition to this guideline, SAHPRA reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. SAHPRA is committed to ensure that all registered medicines will be of the required quality, safety and efficacy.
Guidelines and application forms are available from the office of the Chief Executive Officer and the website.

First publication released for comment	November 2014
Version 2 – deletion of quality aspects for inclusion in separate guideline	June 2016
Version 3 - addition of Annexures G and I for comment	April 2017
Deadline for comment	31 May 2017
Version 3_1 – addition of Annexure J for comment	May 2017
Deadline for comment	30 June 2017
Version 3_2 – addition of Annexures H, K and L for Comment	April 2019
Deadline for comment	15 June 2019

Use the Guideline Comments Form[1] available on the SAHPRA website when submitting comments.
Submit comments by e-mail to Dr Kaizer Thembo at kaizer.thembo@sahpra.org.za.

[1] *6.13 Guideline Comments Form*

7.04_SE_Health_Supplements_Apr19_v3_2_for_comment *May 2019* Page 1 of 42



Registration of medicines *Access to unregistered medicines*

SAHPRA
SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

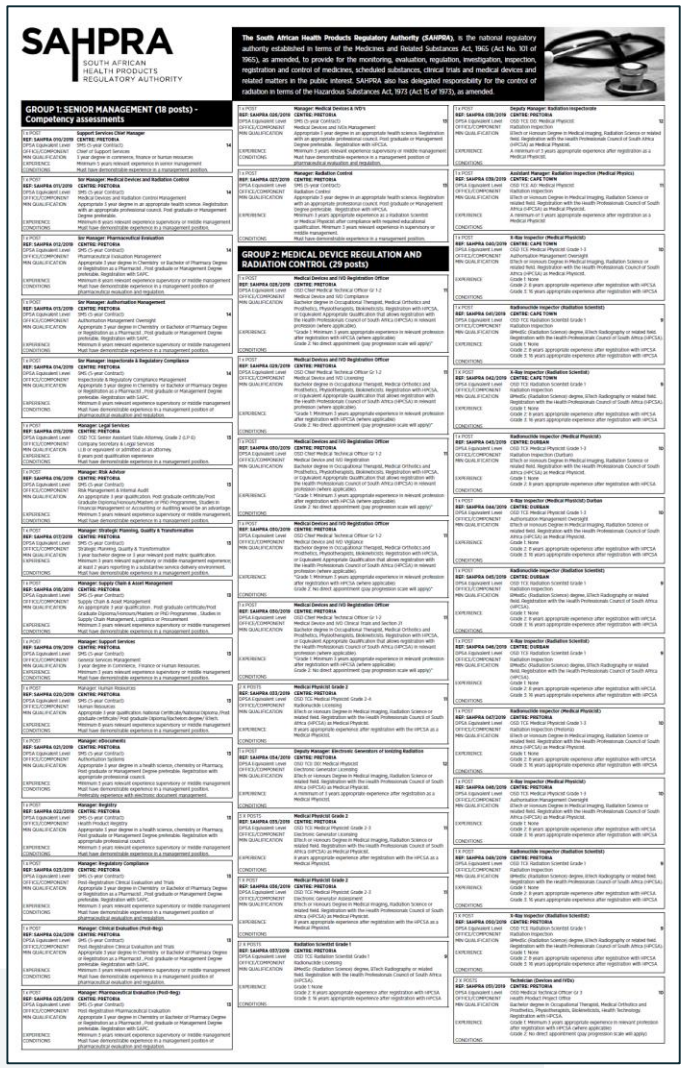
ACCESS TO UNREGISTERED MEDICINES

This document provides guidance on access to unregistered medicine for human use through the provisions of Section 21 of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) and clarifies the mandate, intent and scope of this section and Regulation 29 of the General Regulations published in terms of the Act. It outlines the process to be followed when requesting a medicine through Section 21, as well as the information required to comply with the provisions of the Act and Regulations.
SAHPRA reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine and may make amendments to this document in keeping with knowledge which is current at the time of consideration of the data accompanying applications for access to and use of unregistered medicines. Alternative approaches may be used but these must be scientifically and technically justifiable. The Authority is committed to ensuring that all medicines granted approval will be of the required quality, safety and efficacy.

Version 1: First publication released for comment	April 2019
Deadline for comment	31 May 2019

2.52_Section_21_Access_to_Unregistered_Medicines_Dec17_v1_for_comment *April 2019* Page 1 of 13

SAHPRA Job Adverts

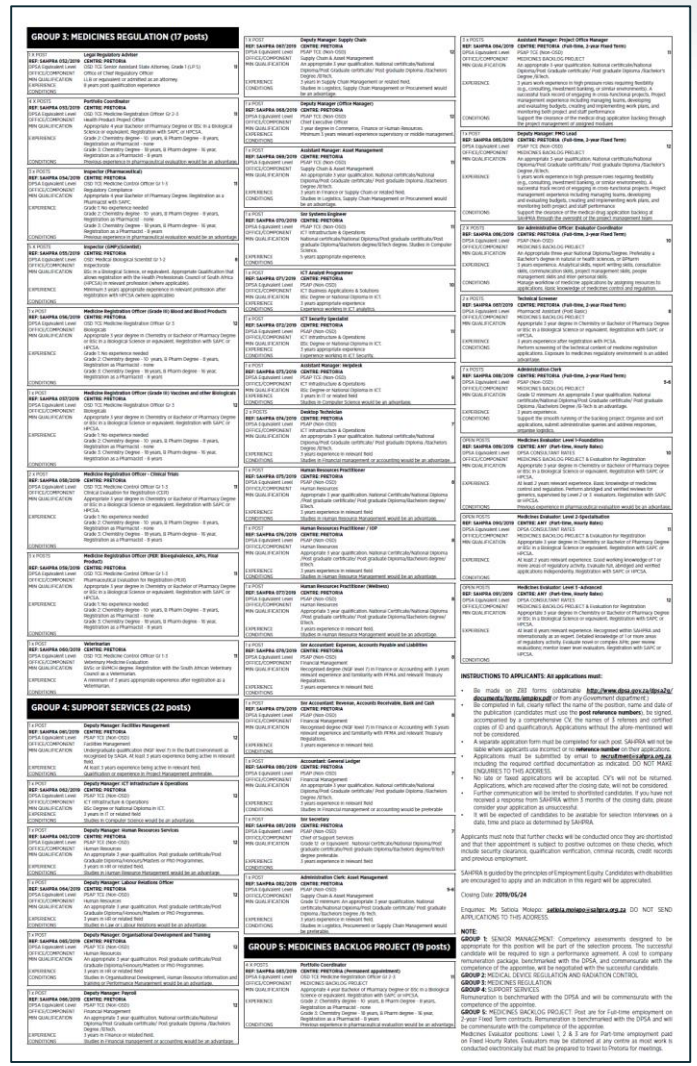


SAHPRA
SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

The South African Health Products Regulatory Authority (SAHPRA), is the national regulatory authority established in terms of the Medicines and Related Substances Act, 1965 (Act No. 101 of 1965), as amended, to provide for the monitoring, evaluation, regulation, investigation, inspection, registration and control of medicines, scheduled substances, clinical trials and medical devices and related matters in the public interest. SAHPRA also has delegated responsibility for the control of radiation in terms of the Hazardous Substances Act, 1973 (Act 15 of 1973), as amended.

GROUP 1: SENIOR MANAGEMENT (18 posts) - Competency assessments

GROUP 2: MEDICAL DEVICE REGULATION AND RADIATION CONTROL (29 posts)



GROUP 3: MEDICINES REGULATION (17 posts)

GROUP 4: SUPPORT SERVICES (22 posts)

GROUP 5: MEDICINES BACKLOG PROJECT (19 posts)

INSTRUCTIONS TO APPLICANTS: All applications must:

- Be made on Z83 forms (obtainable http://www.dpsa.gov.za/dpsa2g/documents/acts_regs/regs.pdf or from any eGovernment department)
- Be completed in full, clearly reflect the name of the position, name and date of the publication (candidates must use the **post reference numbers**). Be signed, accompanied by a comprehensive CV, the names of 3 referees and certified copies of ID and qualifications. Applications without the afore-mentioned will not be considered.
- A separate application form must be completed for each post. SAHPRA will not be liable where applicants use incorrect or no **reference number** on their applications.
- Applications must be submitted by email to **recruitment@sahpra.org.za** including the required certified documentation as indicated. DO NOT MAKE ENQUIRIES TO THIS ADDRESS.
- No late or faxed applications will be accepted. CV's will not be returned. Applications, which are received after the closing date, will not be considered.
- Further communication will be limited to shortlisted candidates. If you have not received a response from SAHPRA within 5 months of the closing date, please consider your application as unsuccessful.
- It will be expected of candidates to be available for selection interviews on a date, time and place as determined by SAHPRA.

Applicants must note that further checks will be conducted once they are shortlisted and that their appointment is subject to positive outcomes on these checks, which include security clearance, qualification verification, criminal records, credit records and previous employment.

SAHPRA is guided by the principles of Employment Equity. Candidates with disabilities are encouraged to apply and an indication in this regard will be appreciated.

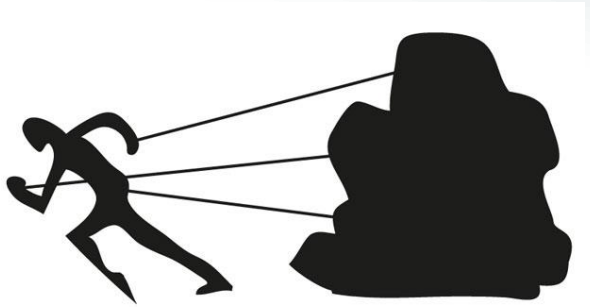
Closing Date: **2019/05/24**

Enquiries: Ms Sonisia Mokgoro: **sonisia.mokgoro@sahpra.org.za** DO NOT SEND APPLICATIONS TO THIS ADDRESS.

NOTE:
GROUP 1: SENIOR MANAGEMENT: Competency assessments designed to be appropriate for this position will be part of the selection process. The successful candidate will be required to sign a performance agreement. A cost to company remuneration package, benchmarked with the DPSA, and commensurate with the competence of the appointee, will be negotiated with the successful candidate.
GROUP 2: MEDICAL DEVICE REGULATION AND RADIATION CONTROL
GROUP 3: MEDICINES REGULATION
GROUP 4: SUPPORT SERVICES
Remuneration is benchmarked with the DPSA and will be commensurate with the competence of the appointee.
GROUP 5: MEDICINES BACKLOG PROJECT: Post are for Full-time employment on 2-year Fixed Term contracts. Remuneration is benchmarked with the DPSA and will be commensurate with the competence of the appointee.
Medicines Evaluator positions: Level 1, 2 & 3 are for Part-time employment paid on Fixed Hourly Rates. Evaluators may be stationed at any centre as most work is conducted electronically but must be prepared to travel to Pretoria for meetings.

SAHPRA Challenges

- SAHPRA will need to overcome the following challenges in order to be successful:
  - Communication & Interaction with Stakeholders
  - National Health Insurance – seen as a priority
  - National Drug Policy
  - Antimicrobial Resistance National Strategy Framework
  - Regulatory Pipeline or Backlog Project for Category A Medicines
  - Resource Constraints
  - Database & Infrastructure
  - Organizational culture – recent strikes and fires
  - Timing and Result Driven



- Although SAHPRA is made up of the same people from DoH/MCC, it is important to remember that it is still very new and thus will likely experience “teething” issues during the next few months.
- I believe it is the CAMS Industries responsibility to work with SAHPRA to ensure we have a regulatory framework that is appropriate and adds value not only to the public but also to all the stakeholders.

Remember …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except for
treating diarrhea..
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