CAMS: A Practical Approach Going Forward

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

Wayne Robinson – May 2019
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 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
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.

<table>
<thead>
<tr>
<th>No</th>
<th>Name</th>
<th>Category of appointment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prof. Helen Rees (Chairperson)</td>
<td>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</td>
</tr>
<tr>
<td>2</td>
<td>Dr Nonhlanhla Madela - Mntla</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Prof. Shabir Banoo</td>
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<tr>
<td>4</td>
<td>Dr Henry Leng</td>
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<tr>
<td>5</td>
<td>Dr Thapelo Motshudi</td>
<td></td>
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<tr>
<td>6</td>
<td>Prof. Kelly Chibale</td>
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<tr>
<td>7</td>
<td>Prof. Aimes Dhai</td>
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<tr>
<td>8</td>
<td>Prof. Jeffrey Mphahlele</td>
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<tr>
<td>9</td>
<td>Dr Ushma Mehta</td>
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<td>10</td>
<td>Dr Mphane Molefe</td>
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<tr>
<td>11</td>
<td>Adv. Hasina Cassim</td>
<td>Section 2C(2)(b) on account of knowledge of the law</td>
</tr>
<tr>
<td>12</td>
<td>Ms Mandisa Hela (Vice-Chairperson)</td>
<td>Section 2C(2)(c) on account of knowledge of good governance</td>
</tr>
<tr>
<td>13</td>
<td>Ms Lesibana Fosu</td>
<td>Section 2C(2)(d) on account of knowledge of the financial matters and accounting</td>
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<tr>
<td>14</td>
<td>Mr Norman Baloyi</td>
<td>Section 2C(2)(e) on account of knowledge of information technology</td>
</tr>
<tr>
<td>15</td>
<td>Prof. Craig Househam</td>
<td>Section 2C(2)(f) on account of knowledge of human resource management</td>
</tr>
</tbody>
</table>
SAHPRA Structure

Minister of Health

SAHPRA Board

Chief Executive Officer

Risk and Audit Committee

Other Board Committees

Entity Management and Governance Functions

Expert Committees

Peer Review Committees

Chief Financial Officer and Corporate Services Programme 1

Authorisation Management Programme 2

Regulatory Compliance Programme 3

Evaluation Programme 4

Medical Devices, Diagnostics and Radiation Control Programme 5

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 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
### MCC vs SAHPRA

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

MCC vs SAHPRA
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

“Each capsule contains your medication, plus a treatment for each of its side effects.”
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

HERBALISM:
- Ayurveda
- Bach Flower
- Aromatherapy
- Homeopathy
- Phytotherapy
- Kampo
- Amazonia
- Islamic Unani
- ATM
- TCM
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
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

Dietary Supplements

European Food Safety Authority

U.S Food and Drug Administration

European Medicines Agency

TGA Health Safety Regulation

Health Canada
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.
Health Supplements

i) 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.
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

<table>
<thead>
<tr>
<th>DISCIPLINE SPECIFIC (DS)</th>
<th>HEALTH SUPPLEMENTS (HS)</th>
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<tbody>
<tr>
<td>Aromatherapy</td>
<td>Probiotics</td>
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<tr>
<td>Ayurveda</td>
<td>Prebiotics</td>
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<tr>
<td>Homoeopathy</td>
<td>Vitamins</td>
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<tr>
<td>Traditional Chinese Medicine</td>
<td>Minerals</td>
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<tr>
<td>Unani (Unani-Tibb)</td>
<td>Amino Acids</td>
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<tr>
<td>Western Herbal Medicine</td>
<td>Animal Extracts, Products and Derivatives</td>
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<td>Other Herbal</td>
<td>Fats, Oils and Fatty Acids</td>
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<td>Other</td>
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**Combination Products**

A single product that contains:

1. A mixture of substances of various discipline-specific origin or philosophy.
2. A mixture of at least one substance of discipline-specific origin and one or more health supplements, or
3. 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*
<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Type of Claim</th>
<th>Evidence required to support claim</th>
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</thead>
<tbody>
<tr>
<td>HIGH RISK</td>
<td>• Treats/cures/manages any disease/disorder.</td>
<td>• Clinical data to be evaluated.</td>
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<tr>
<td></td>
<td>• Prevention of any disease or disorder.</td>
<td>AND</td>
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<tr>
<td></td>
<td>• Reduction of risk of a disease/disorder.</td>
<td>• Two of the following four sources that demonstrates adequate support for the indications claimed:</td>
</tr>
<tr>
<td></td>
<td>• Aids/assists in the management of a named symptom/disease/disorder.</td>
<td>1. Recognised Pharmacopoeia (^4),</td>
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<td></td>
<td>• Relief of symptoms of a named disease or disorder(^2)</td>
<td>2. Recognised Monograph (^4),</td>
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<td></td>
<td>• Treatment of proven vitamin or mineral deficiency diseases.</td>
<td>3. Three independent written histories of use in the classical or traditional medical literature,</td>
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<td>or</td>
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<td></td>
<td></td>
<td>4. Citations from other \textit{in vivo, in vitro} studies, case reports or others.</td>
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</table>

1. Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromise 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 (vii) – (ix) and ANNEXURE D.
4. 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.
5. Terms used must be in accordance with the practice of the associated discipline.
<table>
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<tr>
<th>Risk Level</th>
<th>Type of Claim</th>
<th>Evidence required to support claim</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW RISK</td>
<td>• General health enhancement without any reference to specific diseases¹</td>
<td>• Clinical data to be evaluated³</td>
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<tr>
<td></td>
<td>• Health maintenance, including nutritional support.</td>
<td>AND/OR:</td>
</tr>
</tbody>
</table>
|           | • Relief of minor symptoms (not related to a disease or disorder)²           | • Two of the following four sources that demonstrates adequate support for the indications claimed:
|           |                                                                                | 1 Recognised Pharmacopoeia⁴,                                                                 |
|           |                                                                                | 2 Recognised Monograph⁴;                                                                           |
|           |                                                                                | 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.                          |

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) – (x) 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.
On 24 Feb 2017 the MCC published GG No 40637:

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 SOUWS
REGISTRAR OF MEDICINES

This understandably caused confusion and concern in the industry, especially for importers
On August 2017 the MCC published GG41064 No 859:

This “created” SAHPRA and also regulated Health Supplements as CAMS.
SAHPRA Roadmap vs Current situation

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

- **31 December 2019**
  - Discipline Specific CAMS (DS) – DS ONLY – **NOT COMBINATION PRODUCTS**

- **TBC**
  - SSF 6-18m
  - MSF 30m
  - CAMS – Health Supplements (HS)
    - Single Substance Formulations (SSF)
    - Multiple Substance Formulations (MSF)

- **Combination Products End 2022**
  - Discipline Specific – **Combination Products (DS+HS)**

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

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<table>
<thead>
<tr>
<th>Supplement Type</th>
<th>Annexure</th>
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<tbody>
<tr>
<td>Probiotics</td>
<td>ANNEXURE C</td>
</tr>
<tr>
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<td>ANNEXURE D</td>
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<tr>
<td>Vitamins</td>
<td>ANNEXURE E</td>
</tr>
<tr>
<td>Minerals</td>
<td>ANNEXURE F</td>
</tr>
<tr>
<td>Amino Acids</td>
<td>To Follow</td>
</tr>
<tr>
<td>Animal Extracts, Products and Derivatives</td>
<td>To Follow</td>
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<tr>
<td>Fats, Oils and Fatty Acids</td>
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<tr>
<td>Other</td>
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</table>
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 Licensing 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
Practical Approach to Product Evaluation

Is it a DS CAMS or HS? OR Category A?

Formulation Evaluation

Research and Development

Label, PI and PIL Compliance

Innovative, safe and efficacious product for the end-user

API Sourcing and Procurement

Manufacturing (Finished products and APIs)

Quality Testing & Stability Testing

Dossier Development

Innovative, safe and efficacious product for the end-user
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]

Modules 1.5.1 & 2.5 [ & Modules 1.3; 5]
# SAHPRA’s Application Process

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Module 1</strong>&lt;br&gt;Including Application Form, PI, PIL, Label</td>
<td><strong>Module 1</strong>&lt;br&gt;Including Application Form, PI, PIL, Label</td>
</tr>
<tr>
<td><strong>Module 1.5.1</strong>&lt;br&gt;Traditional Use / Low Risk Rationale</td>
<td><strong>Module 1.5.1</strong>&lt;br&gt;Traditional Use</td>
</tr>
<tr>
<td><strong>Module 2</strong>&lt;br&gt;Relevant Summaries</td>
<td><strong>Module 2</strong>&lt;br&gt;Relevant Summaries</td>
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<tr>
<td><strong>Module 3</strong></td>
<td><strong>Module 3</strong></td>
</tr>
<tr>
<td><strong>Not Required</strong>&lt;br&gt;Unless Necessary</td>
<td><strong>Module 4</strong></td>
</tr>
<tr>
<td><strong>Not Required</strong>&lt;br&gt;Unless Necessary</td>
<td><strong>Module 5</strong>&lt;br&gt;Clinical Evidence</td>
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</tbody>
</table>
Innovation & Formulation Importance

- **Discovery**
  - Active pharmaceutical ingredient

- **Early development**
  - Molecule

- **Formulation development**
  - Medicine

- **Scale-up**
  - Product

- **Commercial scale supply fill / finish**
  - Mass production

  - Commercial packaging
Using the Health Supplement Annexures available

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<table>
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<tbody>
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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

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- **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 records
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 rigorous testing to eliminate possible quality issues early 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 utilizing our research and development capabilities, we also ventured into Active Pharmaceutical Ingredient (API) development and supporting API master files.
What is Quality?
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

<table>
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<tr>
<th>Parameter</th>
<th>Specification</th>
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</thead>
<tbody>
<tr>
<td>Identification</td>
<td>HPLC or purity test(s)</td>
</tr>
<tr>
<td>Identification (HPLC)</td>
<td>The chromatogram and measurement of the sample bands correspond to the reference standard bands.</td>
</tr>
<tr>
<td>Less than 0.5%</td>
<td>≤ 0.5% (w/v)</td>
</tr>
<tr>
<td>Foreign matter</td>
<td>≤ 2.0% (w/v)</td>
</tr>
<tr>
<td>Pesticides</td>
<td>Conforms to Table 2 of the Official Pesticide Database</td>
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### Microbial Specifications

<table>
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<th>Parameter</th>
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<tr>
<td>Total aerobic plate count</td>
<td>≤ 10,000 CFU/g</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>≤ 1000 CFU/g</td>
</tr>
<tr>
<td>Sphingomonas</td>
<td>Absent/ &lt;125 CFU/g</td>
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</table>

### Heavy Metals Specifications

<table>
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<th>Parameter</th>
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<tbody>
<tr>
<td>Arsenic</td>
<td>&lt;1.0 ppm</td>
</tr>
<tr>
<td>Cadmium</td>
<td>&lt;1.0 ppm</td>
</tr>
<tr>
<td>Lead</td>
<td>&lt;5.0 ppm</td>
</tr>
<tr>
<td>Mercury</td>
<td>&lt;0.05 ppm</td>
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### Aflatoxin Specifications

<table>
<thead>
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<th>Parameter</th>
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<tbody>
<tr>
<td>Aflatoxin B1</td>
<td>&lt;0.5 ppm</td>
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<tr>
<td>Aflatoxin total</td>
<td>&lt;4.8 ppm</td>
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### Storage

- **Shelf life**: 36 Months
- **Recommended storage conditions**: Room temperature, 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
“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
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
The Future
NEXT EXIT

CAMS Future
SAHPRA Relocation to CSIR

To all Stakeholders

Further to our communication of 31 October 2019 regarding the planned move to the Olds Building, and the instruction from the Director-General Health regarding the vacating of the building, we can now confirm that SAHPRA has moved into the CSIR campus, 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:

- Building 10
- Building 18

Accessed from the Visitor’s Centre, North Gate (opposite the SAoK panpipe):
- Building 1
- Building 2

Outside, to the left of the gate to the Convent House (South Gate):
- Building 3
- Building 4

Please note:

- The telephone landlines are not currently available. The telephone contact numbers under Key Contacts on the website should be used.
- Reception in building 3B will open on Friday, 01 February 2019.

Please note the following regarding activities for SAHPRA:

- The opening hours of the reception will be as follows:
  - Monday to Thursday: 09:00 – 12:15
  - Monday to Thursday: 13:00 – 16:00

- Collection of certificates, permits, licences: Tuesday & Thursday 10:00 – 12:00

- 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 9.151 for the submission procedure for Section 21 authorisations (medical devices for human use only) and communication 9.14 for the submission of product marketing/pharmaceutical correspondences. 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 closed 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 still have to be declared.

Wia P. Hutton
Acting Chief Executive Officer

Page 1 of 1
Recent Guidelines for Review

GUIDANCE FOR THE SUBMISSION OF REGULATORY INFORMATION in eCTD FORMAT

This guideline is intended to provide recommendations to applicants seeking to submit applications for the registration of medicines in eCTD format. It influences the content and structure of regulatory information that is submitted and includes principles and requirements that are consistent with International Conference on Harmonisation (ICH) guidelines and 5th Edition of the ICH guideline on electronic submission of clinical trials data (E6). 3.1.1.2 Estimation of significant safety in the processing and evaluation of applications

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

Registration of Medicines

GUDILINE FOR PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

This guideline is intended to provide recommendations to applicants seeking to submit applications for the registration of medicines in South Africa. It influences the content and structure of regulatory information that is submitted and includes principles and requirements that are consistent with International Conference on Harmonisation (ICH) guidelines and 5th Edition of the ICH guideline on electronic submission of clinical trials data (E6). 3.1.1.2 Estimation of significant safety in the processing and evaluation of applications

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

Registration of Medicines

SAHPRA

SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

PO Box 233, PRETORIA, 0001
Tel: 012 355 6200
Fax: 012 355 6211

Subject: Request for comment on draft Variations Addendum for Orthodontic Medicines, eCTD and eSubmission Guidelines, and New Registration Validation Template

Date: 10 May 2019

Comment period: 10 May – 10 June 2019

Comment submissions: feedback@sahealth.org.za

Subject line for email: [Industry commenting] Organisation name

One of the critical priorities of the South African Health Products Regulatory Authority (SAHPRA) is to drive the enhanced backing of new medicine registration and regulation. In this context, SAHPRA has developed a new registration process that builds on a focus on safety. 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 publications 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 in 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 Trial Manual
4. Pharmaceutical and Analytical (P&A) guidelines
5. Summary of Critical Regulatory Elements (SCARE) document
6. SAHPRA is now releasing for industry comment,
7. Variations Addendum for Orthodontic Medicines
8. eCTD and eSubmission Guidelines
9. New Registration Validation Template (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 Orthodontic Medicines

SAHPRA is amending the EU variations applicable for orthodontic device and treatment medicines.

To aid its application and implementation in South Africa, SAHPRA has developed a Variations Addendum that covers the regulatory changes to the existing EU regulations. The Addendum identifies specific classification and procedural deviations to the adoption of the EU
Recent Guidelines for Review

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 vaccines. 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 assessing the knowledge current at the time of evaluation. Alternative approaches may be used but those should be scientifically and technologically valid. The Authority in consultation with all interested parties will accept and consider all relevant information available 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 released for comment
15 April 2019
Due date for comment
15 May 2019

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 an application is being with the knowledge current at the time of evaluation. SAHPRA is committed to ensure that all registered medicines will be at 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 1: draft of key aspects for initiation in separate guideline
June 2016
Version 2: addition of Annexures 3 and 4 for comment
April 2017
Deadline for comment
31 May 2017
Version 3: 1st addition of Annexures 5 for comment
May 2017
Deadline for comment
30 June 2017
Version 3: 2nd addition of Annexures H, K and L for comment
April 2019
Deadline for comment
15 June 2019

Use the Guidelines Comments Form available on the SAHPRA website when submitting comments.
Submit comments by email to CK Kaiser Thento of kaiser.kaiser@sahealth.gov.za.

ACCESS TO UNREGISTERED MEDICINES

This document provides guidance on access to unregistered medicine for human use through the provisions of Section 11 of the Medicines and Related Substances Act, 1997 (Act 101 of 1997) read together with the provisions of paragraph 34 of Schedule 2 of the Geneva Regulations. Under terms of the Act, it reserves the right to request any additional information to establish safety, quality and efficacy of a medicine and may make amendments to this document in response to any reasonable request of the time of submission of the data accompanying applications for access to and use of unregistered medicines. Alternative approaches may be used but those must be scientifically and technologically valid. The Authority is committed to ensuring that all relevant parties are informed of the draft guideline and are provided with an opportunity to comment on the draft guidelines before publication.

Version 1: First publication released for comment
April 2010
Deadline for comment
31 May 2010
SAHPRA Job Adverts
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.
Laughter is the best medicine... except for treating diarrhea.
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